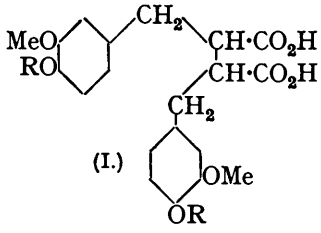
200. *The Constituents of Natural Phenolic Resins. Part XVII. A Synthesis of* l-*Matairesinol.*

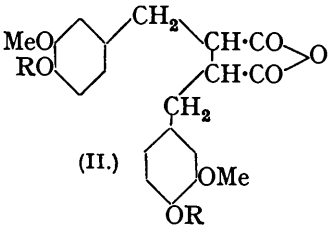
By Robert D. Haworth and Frank H. Slinger.

By protection of the phenolic group of vanillin with a benzyl group, the series of reactions previously used (J., 1939, 154) for the preparation of *d*-, *l*-, and *dl*-matairesinol dimethyl ether has now been extended to the synthesis of the naturally occurring *l*-matairesinol (III; R = H). The *d*- and the *dl*-modification of the phenol have also been obtained, but not in a crystalline state.

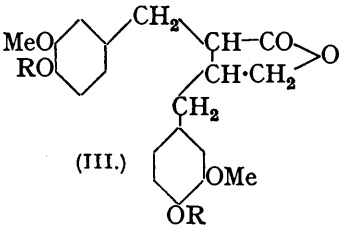
As no successful syntheses of the phenolic resinols have previously been reported, it was of interest to ascertain whether the method recently used (J., 1939, 154) for the preparation of *d*-, *l*-, and *dl*-matairesinol dimethyl ether (III; R = Me) was capable of extension to the synthesis of *d*-, *l*-, and *dl*-matairesinol (III; R = H).



(I.)



(II.)



(III.)

Suitable conditions for the preparation of (I; R = H) from vanillin could not be discovered, and it was therefore necessary to protect the phenolic group with a radical, stable towards the alkaline conditions used in some of the stages of the synthesis, but capable of ultimate removal from the molecule. The benzyl group was selected for this purpose, and although the condensation product of *O*-benzylvanillin and ethyl succinate could not be isolated in a crystalline condition, reduction of the crude product with sodium amalgam yielded meso-αβ-*di*-(4-*benzyloxy*-3-*methoxybenzyl*)*succinic acid* (I; R = CH_2Ph), m. p. 203°, in 25% yield. Debenzylation of this acid with concentrated hydrochloric acid gave meso-αβ-*di*-(4-*hydroxy*-3-*methoxybenzyl*)*succinic acid* (I; R = H), m. p. 228—229°, which on methylation yielded the dimethyl ether, identical with *meso*-αβ-di-(3 : 4-dimethoxybenzyl)-succinic acid (I; R = Me) described previously (*loc. cit.*). Attempts to convert the

O-benzyl ether (I; R = CH_2Ph) into the anhydride (II; R = CH_2Ph) by dehydration with acetic anhydride, acetyl chloride, phosphoric oxide or pyrolysis were unsuccessful. The reason for this failure is obscure; recognisable products were not obtained, but there are indications that either decarboxylation or ring closure, possibly to a 1-keto-2-benzyltetrahydronaphthalene-3-carboxylic acid, may be responsible for the abnormal results. These unexpected difficulties led to an investigation of the action of acetic anhydride on *meso*-αβ-di-(4-hydroxy-3-methoxybenzyl)succinic acid (I; R = H). An oil was obtained, which was converted into (*a*) dl-αβ-*di*-(4-*acetoxy*-3-*methoxybenzyl*)*succinic acid* (I; R = $CO{\cdot}CH_3$) by boiling with water, (*b*) dl-αβ-*di*-(4-*hydroxy*-3-*methoxybenzyl*)*succinic acid* (I; R = H), m. p. 194—195°, by hydrolysis with sodium hydroxide or preferably with hydrochloric acid, and (*c*) into *dl*-matairesinol dimethyl ether (III; R = Me) by reduction with aluminium amalgam in moist ether–benzene solution and subsequent methylation of the oily lactonic product. It is probable from these observations that the oil obtained by the action of acetic anhydride on the *meso*-acid (I; R = H) consists essentially of the *trans*-form of αβ-di-(4-acetoxy-3-methoxybenzyl)succinic anhydride (II; R = $CO{\cdot}CH_3$).

Resolution of *dl*-αβ-di-(4-hydroxy-3-methoxybenzyl)succinic acid (I; R = H) was effected by fractional crystallisation of the strychnine salt. A pure *salt*, $[\alpha]_D^{17°}$ − 18°, was isolated from the " head " fractions, but preliminary attempts to recover the acid with either sodium hydroxide or aqueous ammonia were accompanied by some racemisation. Eventually the l-*acid* (I; R = H), $[\alpha]_D^{17°}$ − 47°, was obtained by decomposing a chloroform solution of the strychnine salt with cold sodium bicarbonate solution. This *l*-acid gave, with acetic anhydride, an oily anhydride, which was converted into *l*-matairesinol (III; R = H), m. p. 116—117°, $[\alpha]_D^{16°}$ − 46°, by reduction with aluminium amalgam in moist ether–benzene solution. The identity of the product with *l*-matairesinol obtained from *Podocarpus spicatus* was established by direct comparison of the phenols and by comparison of the dimethyl ethers and *di*-p-*nitrobenzoyl* derivatives.

As the mother-liquors from the crystallisation of the strychnine salt, $[\alpha]_D^{17°}$ − 18°, did not yield a second stereochemically homogeneous salt, the acid was recovered with sodium bicarbonate and combined with brucine. A small amount of a brucine salt of constant α_D value was obtained, from which a slightly impure d-*form*, $[\alpha]_D^{15°}$ + 40°, of the acid (I; R = H) was regenerated. This *d*-acid gave an oily anhydride, which yielded *d*-matairesinol (III; R = H) on reduction with aluminium amalgam in the usual way. This optical antipode of the natural resinol has not been obtained in a crystalline state, but the oil was converted almost quantitatively into *d*-matairesinol dimethyl ether (*loc. cit.*) by the action of methyl sulphate.

Experimental.

meso-αβ-*Di*-(4-*benzyloxy*-3-*methoxybenzyl*)*succinic Acid* (I; R = CH_2Ph).—A solution of ethyl succinate (4·4 g.) and *O*-benzylvanillin (12·1 g.) in anhydrous ether (100 c.c.) was added, with cooling and shaking, to a suspension of sodium ethoxide (from sodium, 1·12 g.) in ether (50 c.c.); a yellow precipitate rapidly separated. The mixture was kept for 24 hours in the ice-chest, water (50 c.c.) then added, and the aqueous layer heated on the water-bath with 4% sodium amalgam (1000 g.) for 6 hours, excess alkalinity being destroyed by a continuous stream of carbon dioxide. The filtered solution was acidified with hydrochloric acid, and the *acid* (I; R = CH_2Ph), which separated as an oil and rapidly hardened, was collected after 12 hours and crystallised first from glacial acetic acid and then from alcohol, forming rosettes of colourless needles (3·5 g.), m. p. 203° (Found: C, 71·6; H, 5·6; equiv., 288. $C_{34}H_{34}O_8$ requires C, 71·6; H, 6·0%; equiv., 285).

The acid (I; R = CH_2Ph) (0·5 g.), boiled with acetic anhydride (5 c.c.) for periods varying from 15 minutes to 6 hours, yielded, after removal of the excess of acetic anhydride, an oil which solidified on trituration with ether. The product, m. p. 90—110° (Found: equiv., 453), could not be purified by crystallisation or distillation in a vacuum, and alkaline hydrolysis gave an intractable gum. The acid (I; R = CH_2Ph) (0·1 g.) was heated for 1 hour at 220°; the product was dissolved in benzene and washed with sodium bicarbonate solution, and the benzene removed; the residual amorphous solid did not melt at 300°. The acid (I; R = CH_2Ph) (0·5 g.) was boiled for 15 minutes with a suspension of phosphoric oxide (2 g.) in benzene (10 c.c.), and water added. After recovery of unchanged acid with sodium bicarbonate, the benzene was removed, and the residual oil crystallised from benzene–ligroin, small prisms, m. p. 148° (Found:

C, 74·2; H, 5·7%; equiv., 555), being obtained in 50% yield. Alkaline hydrolysis of this product yielded a substance, crystallising from aqueous alcohol in small prisms, m. p. 129—130° (Found: C, 71·0; H, 6·0%; equiv., 540). This product, which was soluble in sodium hydroxide but insoluble in bicarbonate solution, gave a negative ferric test and failed to couple with diazonium compounds.

meso-αβ-*Di*-(4-*hydroxy*-3-*methoxybenzyl*)*succinic Acid* (I; R = H).—After αβ-di-(4-benzyloxy-3-methoxybenzyl)succinic acid (I; R = CH_2Ph) (0·5 g.) had been boiled with a mixture of concentrated hydrochloric acid (7 c.c.) and acetic acid (20 c.c.) for 1 hour, the solution was evaporated to dryness under reduced pressure. The residue was dissolved in methyl alcohol (0·5 c.c.) and poured into acetic acid (5 c.c.); the *acid* (I; R = H) (0·27 g.) gradually separated in small rhombs, m. p. 228—229° (Found: C, 61·5; H, 5·6; equiv., 195. $C_{20}H_{22}O_8$ requires C, 61·5; H, 5·6%; equiv., 195). The *methyl* ester, prepared by the action of methyl-alcoholic hydrogen chloride, crystallised from methyl alcohol in slender prisms, m. p. 169—170° (Found: C, 63·1; H, 6·2. $C_{22}H_{26}O_8$ requires C, 63·1; H, 6·2%), which gave the *meso*-acid (I; R = H) on hydrolysis with methyl-alcoholic potassium hydroxide. Methylation of the *meso*-acid (I; R = H) with methyl sulphate in sodium hydroxide solution gave a mixture of *meso*-αβ-di-(3 : 4-dimethoxybenzyl)succinic acid, m. p. 222—223°, and the corresponding methyl ester, m. p. 137°, which were identified by comparison with authentic specimens (*loc. cit.*; J., 1939, 1240).

dl-αβ-*Di*-(4-*hydroxy*-3-*methoxybenzyl*)*succinic Acid* (I; R = H).—The *meso*-acid (I; R = H) (5 g.) was boiled with acetic anhydride (25 c.c.) for 15 minutes. Removal of the solvent under reduced pressure left an oily anhydride, which was hydrolysed by boiling with water for 1 hour to dl-αβ-*di*-(4-*acetoxy*-3-*methoxybenzyl*)*succinic acid* (I; R = $CO{\cdot}CH_3$); this, isolated with ether, crystallised from ether–benzene in stout prisms, m. p. 129—130° (Found: C, 60·2; H, 5·8; $CO{\cdot}CH_3$, 19·0. $C_{24}H_{26}O_{10}$ requires C, 60·6; H, 5·5; $CO{\cdot}CH_3$, 18·9%). The oily anhydride (1 g.) was refluxed for 1 hour with N-hydrochloric acid (25 c.c.); the dl-*acid* (I; R = H) crystallised from the hot solution in rosettes of needles (1 g.), m. p. 194—195° (Found: C, 61·3; H, 5·8; equiv., 202. $C_{20}H_{22}O_8$ requires C, 61·5; H, 5·6%; equiv., 195). Methylation of the *dl*-acid (I; R = H) with methyl sulphate yielded *dl*-αβ-di-(3 : 4-dimethoxybenzyl)succinic acid together with a small amount of the corresponding methyl ester (*loc. cit.*; J., 1939, 1240).

Resolution of the dl-*Acid* (I; R = H).—The acid (3·0 g.) and strychnine (5·1 g.) were mixed in chloroform solution. The solvent was removed and replaced by hot alcohol containing 10% of water. The stout prisms (3·83 g.) which separated on cooling were twice crystallised from aqueous alcohol; prisms (3·0 g.), shrinking at 145° and melting at 247°, were obtained (Found: C, 61·0; H, 7·1; loss in weight over P_2O_5, 13·6. $2C_{21}H_{22}O_2N_2,C_{20}H_{22}O_8,9H_2O$ requires C, 61·0; H, 6·9; loss in weight, 13·3%). In chloroform solution (*c*, 2·00) it gave $[\alpha]_D^{17°}$ − 18°. This *strychnine* salt was dissolved in chloroform and shaken with sodium bicarbonate solution; the l-*acid* (I; R = H), liberated by acidification of the bicarbonate extract and isolated with ether, crystallised from ether–benzene in rosettes of needles, m. p. 109° (Found: C, 60·9; H, 5·8. $C_{20}H_{22}O_8$ requires C, 61·5; H, 5·6%). In alcoholic solution (*c*, 2·00) it gave $[\alpha]_D^{17°}$ − 47°. The mother-liquors from the crystallisation of the strychnine salt described above were evaporated, the residue taken up in chloroform and decomposed with sodium bicarbonate, and the acid (1·7 g.) recovered. This was treated with brucine (3·4 g.) in chloroform, and the resultant salts crystallised from aqueous alcohol. After three crystallisations the " head " fractions yielded a brucine salt in colourless prisms (0·5 g.), which in chloroform solution (*c*, 2·00) gave $[\alpha]_D^{15°}$ − 54°. The d-*acid*, recovered with sodium bicarbonate in the usual way, separated from ether–benzene in rosettes of needles, m. p. 106—108° (Found: C, 61·2; H, 5·7%). In alcoholic solution (*c*, 2·00) it gave $[\alpha]_D^{16°}$ + 40°.

l-, d-, *and* dl-*Matairesinol* (III; R = H).—l-αβ-Di-(4-hydroxy-3-methoxybenzyl)succinic acid (I; R = H) (0·6 g.) was boiled with acetic anhydride (6 c.c.) for 15 minutes. After removal of the solvent in a vacuum, the residual gum was dissolved in a mixture of benzene (20 c.c.) and ether (30 c.c.) added to aluminium amalgam (3·5 g.), and reduced at room temperature by three-hourly additions of a few drops of water during 3 days. The liquid was filtered, the alumina dissolved in dilute sulphuric acid, and the remaining gum extracted with chloroform and added to the benzene–ether filtrate, which was then evaporated. The residual oil was refluxed for ½ hour with 5% methyl-alcoholic potassium hydroxide (20 c.c.), and after dilution with water the alcohol was removed. The filtered aqueous solution was acidified with hydrochloric acid and lactonised by heating at 100° for 1 hour. The product, isolated with chloroform, and washed with sodium bicarbonate, separated after two crystallisations from methyl alcohol (carbon) in stout prisms (0·06 g.), m. p. 116—117° (Found: C, 67·2; H, 6·6. Calc. for $C_{20}H_{22}O_6$:

C, 67·0; H, 6·3%), undepressed by admixture with natural *l*-matairesinol. In acetone solution (*c*, 1·00) the synthetic resinol gave $[\alpha]_D^{16°}$ — 46°, and on methylation it yielded *l*-matairesinol dimethyl ether, m. p. and mixed m. p. 125—126°. The *di*-p-*nitrobenzoate*, obtained from either the synthetic or the natural resinol by treatment with *p*-nitrobenzoyl chloride in pyridine, crystallised from methyl alcohol–chloroform in solvated slender prisms, m. p. 95—156°, and from dilute acetic acid in micro-prisms, m. p. 157—158° (Found : C, 61·9; H, 4·3. $C_{34}H_{28}O_{12}N_2$ requires C, 62·2; H, 4·3%). In chloroform solution (*c*, 1·0) it gave $[\alpha]_D^{18°}$ + 9°.

The conversion of the *d*- and the *dl*-modification of the phenolic acid (I; R = H) into *d*- and *dl*-matairesinol, respectively, was carried out under conditions similar to those described above for the *l*-acid. The products, which have so far resisted purification, yielded *d*- and *dl*-matairesinol dimethyl ether, respectively, on treatment with methyl sulphate in alkaline solution.

One of us (F. H. S.) wishes to thank the Department of Scientific and Industrial Research for a maintenance grant, and we are indebted to Imperial Chemical Industries Ltd. (Dyestuffs Group) for a grant for the purchase of chemicals.

THE UNIVERSITY, SHEFFIELD. [*Received, June 21st*, 1940.]