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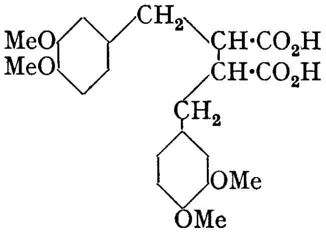
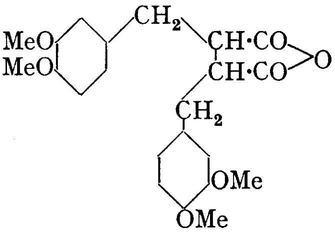
36. *The Constituents of Natural Phenolic Resins. Part XIV. The Synthesis of* dl-, d-, *and* l-*Matairesinol Dimethyl Ether.*

By Robert D. Haworth and David Woodcock.

Syntheses of *dl*-, *d*-, and *l*-αβ-di-(3 : 4-dimethoxybenzyl)butyrolactone have been effected by the method employed (J., 1938, 1985) for the corresponding methylenedioxy-derivatives. The synthetic *l*-lactone is identical with *l*-matairesinol dimethyl ether, obtained by methylation of natural *l*-matairesinol.

In a recent communication (J., 1938, 1985) the synthesis of *dl*-, *d*-, and *l*-hinokinin from αβ-di-(3 : 4-methylenedioxybenzylidene)succinic acid was reported. Attempts to extend the method to the synthesis of matairesinol dimethyl ether (III) were at first disappointing because the required αβ-di-(3 : 4-dimethoxybenzylidene)succinic acid could not be isolated from the condensation which undoubtedly occurred between veratraldehyde and ethyl succinate in the presence of sodium ethoxide. Reduction of the crude acidic fraction of the condensation product with sodium amalgam yielded a mixture, from which meso-αβ-*di*-(3 : 4-*dimethoxybenzyl*)*succinic acid* (I) was isolated by means of its sparing solubility in organic solvents. This acid (I) was converted by boiling with acetic anhydride into dl(trans)-αβ-*di*-(3 : 4-*dimethoxybenzyl*)*succinic anhydride* (II), which yielded dl(trans)-αβ-*di*-(3 : 4-*dimethoxybenzyl*)*butyrolactone* (III) on reduction with amalgamated aluminium in moist ether–benzene solution. The lactone (III) gave crystalline *dibromo*- and *dinitro*-substitution products, it was converted by lead tetra-acetate into a mixture of the lactones of 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)-3-hydroxymethylnaphthalene-2-carboxylic and 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)-2-hydroxymethylnaphthalene-3-carboxylic acid, and its rate of hydrolysis and the rate of lactonisation of the corresponding hydroxy-acid were indistinguishable from those of *l*-matairesinol dimethyl ether and the derived hydroxy-acid respectively. Consequently the synthetic lactone (III) is regarded as *dl*-matairesinol dimethyl ether.


(I.)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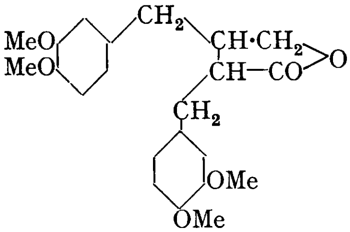
(III.)

Hydrolysis of *dl*(*trans*)-αβ-di-(3 : 4-dimethoxybenzyl)succinic anhydride (II) yielded dl-αβ-*di*-(3 : 4-*dimethoxybenzyl*)*succinic acid* (I), which was resolved by strychnine into the *d*- and the *l*-modification, $[\alpha]_{D}^{15^\circ}$ + 25·8° and — 25·3° respectively.

The *d*- and the *l*-form of αβ-*di*-(3 : 4-*dimethoxybenzyl*)*succinic acid* (I) yielded *d*(—)- and *l*(+)-anhydrides (II), m. p. 131°, $[\alpha]_{D}^{15^\circ}$ ± 38°, which were reduced with amalgamated aluminium to d- and l-αβ-*di*-(3 : 4-*dimethoxybenzyl*)*butyrolactones* (III), m. p. 126°, $[\alpha]_{D}^{15^\circ}$ ± 32° respectively. The identity of the synthetic lactone with *l*-matairesinol dimethyl ether was established by direct comparison of the lactones and their dibromo- and dinitro-substitution products. The synthetical *d*- and *l*-lactones underwent cyclodehydrogenation to a mixture of the lactones of 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)-3-hydroxymethylnaphthalene-2-carboxylic acid and 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)-2-hydroxymethylnaphthalene-3-carboxylic acid, and the rates of hydrolysis of the synthetic lactones and the rates of lactonisation of the corresponding hydroxy-acids were indistinguishable from those of *l*-matairesinol dimethyl ether and the dimethyl ether of *l*-matairesinolic acid respectively.

Experimental.

meso-αβ-*Di*-(3 : 4-*dimethoxybenzyl*)*succinic Acid* (I).—A solution of veratraldehyde (16·8 g.) and ethyl succinate (8·8 g.) in ether (50 c.c.) was added to a suspension of sodium ethoxide

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(from sodium, 2·24 g.) in ether (20 c.c.). After 4 hours, the cream-coloured precipitate was dissolved by addition of water (40 c.c.) and 4% sodium amalgam (2000 g.) was gradually added to the aqueous layer which was warmed on the water-bath for 6 hours and subjected to a continuous stream of carbon dioxide. Acidification of the filtered solution yielded a gum, which was shaken with chloroform, and the *acid* (I) which separated was collected. Crystallisation from glacial acetic acid gave slender prisms (3·7 g.), m. p. 223—224° (rapid heating) (Found : C, 63·2; H, 6·1. $C_{22}H_{20}O_8$ requires C, 63·2; H, 6·3%).

dl(trans)-αβ-*Di*-(3 : 4-*dimethoxybenzyl*)*succinic anhydride* (II), obtained in 85% yield by boiling the *meso*-acid with acetic anhydride (5 parts) for 1 hour, crystallised from benzene in rosettes of colourless prisms, m. p. 110—112° (Found : C, 65·7; H, 6·2. $C_{22}H_{24}O_7$ requires C, 66·0; H, 6·0%).

dl(trans)-αβ-*Di*-(3 : 4-*dimethoxybenzyl*)*butyrolactone* (III), obtained in 30% yield by reducing the preceding anhydride with amalgamated aluminium as described previously (*loc. cit.*) for an analogous case, crystallised from a little methyl alcohol in small prisms, m. p. 113—115° (Found : C, 68·2; H, 6·6. $C_{22}H_{26}O_6$ requires C, 68·4; H, 6·8%). The *dibromo*-derivative crystallised from methyl alcohol in colourless slender prisms, m. p. 112—113° (Found : C, 48·4; H, 4·6. $C_{22}H_{24}O_6Br_2$ requires C, 48·5; H, 4·5%), and the *dinitro*-derivative separated from methyl alcohol–chloroform in pale yellow, slender prisms, m. p. 191—192° (Found : C, 55·2; H, 4·8. $C_{22}H_{24}O_{10}N_2$ requires C, 55·5; H, 5·1%).

dl-αβ-*Di*-(3 : 4-*dimethoxybenzyl*)*succinic acid* (I), obtained in quantitative yield by hydrolysis of the above anhydride (II), separated from aqueous methyl alcohol in stout solvated prisms, melting indefinitely between 95° and 105° (Found : loss in a vacuum at 95°, 14·3. $C_{22}H_{26}O_8,4H_2O$ requires loss, 14·6%. Found for anhydrous acid : C, 62·8; H, 5·9. $C_{22}H_{26}O_8$ requires 63·1; H, 6·2%).

Resolution. A solution of the *dl*-acid (6·0 g.) and strychnine (7·5 g.) in a mixture of methyl alcohol (70 c.c.) and chloroform (30 c.c.) was boiled for 5 minutes. The chloroform was then removed by distillation and the hot residue was treated with about half its volume of hot water. The *strychnine* salt of the *l*-acid separated, and after two crystallisations from 50% methyl alcohol was obtained as large prismatic plates (6·65 g.), which shrank at 120° and decomposed at about 240° (Found : C, 67·3; H, 6·3; loss in a vacuum at 115°, 5·0. $2C_{21}H_{22}O_2N_2,C_{22}H_{26}O_8,3H_2O$ requires C, 67·4; H, 6·6; loss, 4·7%. Found for anhydrous salt : C, 70·7; H, 6·3. $2C_{21}H_{22}O_2N_2,C_{22}H_{26}O_8$ requires C, 70·8; H, 6·4%). In chloroform solution (*c*, 0·991), the salt had $[\alpha]_D^{15^\circ}$ − 27·3°. Concentration of the mother-liquors yielded a further small crop of the strychnine salt of the *l*-acid, and eventually the strychnine of salt the *d*-acid was obtained as a gum.

d- *and* l-αβ-(3 : 4-*Dimethoxybenzyl*)*succinnic Acids* (I).—The crystalline strychnine salt of the *l*-acid and the gummy salt of the *d*-acid were separately dissolved in chloroform and shaken with dilute aqueous ammonia, and the acids recovered from the alkaline layer were collected and crystallised twice from small amounts of methyl alcohol. The l-*acid*, obtained as colourless solvated prisms melting indefinitely between 95° and 105° (Found : C, 55·6; H, 6·5; loss in a vacuum at 95°, 11·3. $C_{22}H_{26}O_8,3H_2O$ requires C, 55·9; H, 6·7; loss, 11·4%), had $[\alpha]_D^{15^\circ}$ −25·3° in chloroform (*c*, 1·013). The d-*acid* separated as colourless prisms containing 3 molecules of water of crystallisation (Found : C, 55·8; H, 6·9; loss in a vacuum at 95°, 11·1. $C_{22}H_{26}O_8,3H_2O$ requires C, 55·9; H, 6·7; loss, 11·4%). In chloroform solution (*c*, 1·014) it had $[\alpha]_D^{15^\circ}$ + 25·8°. Crystallisation of equimolecular proportions of the *d*- and the *l*-acid from aqueous methyl alcohol yielded the *dl*-acid.

d(−)- and l(+)-αβ-*Di*-(3 : 4-*dimethoxybenzyl*)*succinic anhydrides*, prepared in the usual way, crystallised from benzene in colourless rectangular prisms, m. p. 131° [Found for the *d*(−)-form : C, 66·0; H, 5·8. Found for the *l*(+)-form : C, 66·2; H, 5·9. $C_{22}H_{24}O_7$ requires C, 66·0; H, 6·0%]. In acetone solution, the *d*(−)-form (*c*, 1·000) had $[\alpha]_D^{15^\circ}$ −37·6°, and the *l*(+)-form (*c*, 0·986) had $[\alpha]_D^{15^\circ}$ +38·4. Crystallisation of equimolecular proportions of the *d*(−)- and the *l*(+)-form from benzene gave the racemate, m. p. 110—112°.

l(trans)-αβ-*Di*-(3 : 4-*dimethoxybenzyl*)*butyrolactone*(*l*-matairesinol dimethyl ether) (III), obtained in 30% yield from the *l*(+)-anhydride, separated from methyl alcohol in stout colourless prisms, m. p. 127° (Found : C, 68·2; H, 6·9. $C_{22}H_{26}O_6$ requires C, 68·4; H, 6·8%), which gave no depression in m. p. with *l*-matairesinol dimethyl ether. In chloroform solution (*c*, 0·998) it had $[\alpha]_D^{15^\circ}$ −32·3°. The *dibromo*-derivative separated from ethyl alcohol in long colourless prisms, m. p. 123° (Found : C, 48·3; H, 4·6. $C_{22}H_{24}O_6Br_2$ requires C, 48·5; H, 4·5%), which gave no depression in m. p. with dibromo-*l*-matairesinol dimethyl ether. In chloroform solution (*c*, 0·828) it had $[\alpha]_D^{15^\circ}$ −39·8°. The *dinitro*-derivative crystallised from methyl alcohol–chloroform

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in pale yellow needles, m. p. 172—173° (Found : C, 55·4; H, 5·1. $C_{22}H_{24}O_{10}N_2$ requires C, 55·5; H, 5·1%), which in chloroform solution (*c*, 0·862) had $[\alpha]_{\rm D}^{15^\circ}$ $-124°$ and which gave no depression in m. p. with dinitro-*l*-matairesinol dimethyl ether.

d(trans)-αβ-*Di*-(3 : 4-*dimethoxybenzyl*)*butyrolactone*, obtained in 33% yield from the *d*(—)-anhydride, separated from methyl alcohol in stout colourless prisms, m. p. 126° (Found : C, 68·3; H, 6·7. $C_{22}H_{26}O_6$ requires C, 68·4; H, 6·8%), which in chloroform solution (*c*, 0·996) had $[\alpha]_{\rm D}^{15^\circ}$ $+ 32·2°$. Crystallisation with an equal amount of the *l*-form yielded the racemate, m. p. 113°. The *dibromo*-derivative crystallised from ethyl alcohol in colourless prisms, m. p. 123° (Found : C, 48·4; H, 4·5. $C_{22}H_{24}O_6Br_2$ requires C, 48·5; H, 4·5%), had $[\alpha]_{\rm D}^{15^\circ}$ $+ 40·2°$ in chloroform solution (*c*, 0·640) and yielded the *dl*-dibromo-derivative when crystallised with an equal weight of the corresponding *l*-form. The *dinitro*-derivative crystallised from methyl alcohol–chloroform in pale yellow needles, m. p. 173—174° (Found : C, 55·4; H, 5·0. $C_{22}H_{24}O_{10}N_2$ requires C, 55·5; H, 5·1%). It had $[\alpha]_{\rm D}^{15^\circ}$ $-126°$ in chloroform solution (*c*, 0·849) and yielded the racemate, m. p. 191—192°, when crystallised with an equal weight of the *l*-form.

Rates of Hydrolysis of the Lactones.—The method described previously (J., 1938, 804) was employed with N/200-methyl-alcoholic solutions of the lactones :

% Hydrolysis at 16°.

Time, hours	2	4	7	10	14	24	31
l-Matairesinol dimethyl ether	10	20	32	60	70	87	95
dl-*aβ*-Di-(3 : 4-dimethoxybenzyl)butyrolactone	9	18	31	59	71	85	94
l-*aβ*-Di-(3 : 4-dimethoxybenzyl)butyrolactone	9	20	29	58	71	89	96
d-*aβ*-Di-(3 : 4-dimethoxybenzyl)butyrolactone	10	18	30	60	71	84	94

Rates of Lactonisation of the Hydroxy-acids.—Method (a) described previously (*loc. cit.*) was employed with 0·9N/100-methyl-alcoholic solutions of the lactones.

% Lactonisation at 60°.

Time, hours	1	2·5	4	7	10	13·5	24	30
l-Matairesinol dimethyl ether	18	24	30	41	50	55	60	74
dl-*aβ*-Di-(3 : 4-dimethoxybenzyl)butyrolactone	19	23	29	43	50	54	60	72
l-*aβ*-Di-(3 : 4-dimethoxybenzyl)butyrolactone	19	23	31	42	49	54	59	74
d-*aβ*-Di-(3 : 4-dimethoxybenzyl)butyrolactone	19	25	30	40	50	56	61	71

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