260. *The Constituents of Natural Phenolic Resins. Part XVI. A Route to the Synthesis of Lignan Diols.*

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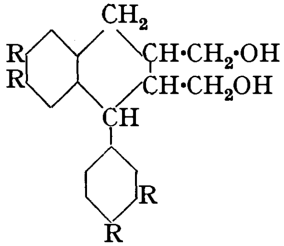
Optically inactive diols of types (I) and (II) have been prepared by Bouveault–Blanc reduction of esters of dibasic acids of types (III) and (IV) respectively. The configurations of the esters of the dibasic acids are modified by the influence of mineral acids and also by the conditions of the reduction. The constitutions of the diols of types (I) and (II) have been established by conversion into dehydroanhydro*iso*lariciresinol dimethyl ether and *dl*-matairesinol dimethyl ether respectively.

In Part IX (J., 1937, 1645) the results of preliminary experiments on the synthesis of lignan diols were reported. These experiments have been continued, and optically inactive forms of diols of types (I) and (II) have been prepared by reducing esters of dibasic acids of types (III) and (IV) respectively by the Bouveault–Blanc method.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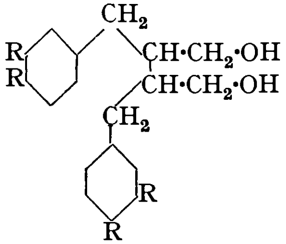
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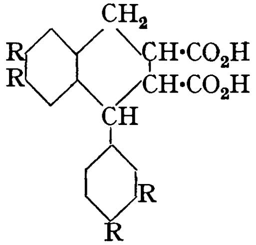
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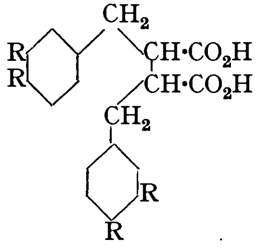
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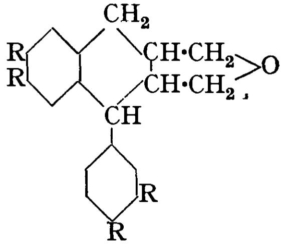
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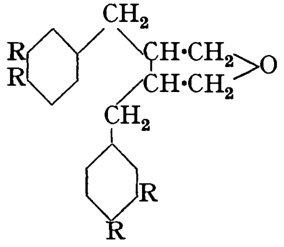
(VI.)

The first experiments were made with acids of type (III). 1-Phenylnaphthalene-2 : 3-dicarboxylic acid (Michael and Bucher, *Amer. Chem. J.*, 1898, **20**, 89) was reduced by sodium amalgam to a mixture, m. p. 170—180°, of stereoisomeric modifications of the tetrahydro-derivative (III; R = H). A homogeneous form, m. p. 209° (decomp.), was obtained by repeated crystallisation of the mixture, but the separation was tedious and wasteful, and, as in the case of analogous acids, described later, it has not been possible to isolate stereochemically pure forms, most of our experiments have been carried out with the crude acid, m. p. 170—180°. Esterification with methyl alcohol in presence of mineral acids, diazomethane or by the action of methyl iodide on the silver salt, yielded a mixture of crystalline and liquid *methyl* esters. The ratio of the two forms was constant when neutral esterification methods were employed, but varied considerably with the duration of the reaction in presence of hydrions, and it is evident that the configuration of the ester is modified by mineral acids. When the methyl ester, either the crystalline or the liquid variety, was reduced with sodium and alcohol a 20% yield of a neutral oil was obtained, and slightly increased yields resulted from the reduction of the liquid *ethyl* ester of the dibasic acid (III; R = H). The neutral oil probably contains a mixture of stereoisomeric forms of the diol (I; R = H); attempts to crystallise the oil or to prepare characteristic formyl, acetyl, or benzoyl derivatives failed, but when heated with potassium hydrogen sulphate at 180° the oil was converted into a crystalline *anhydro*-derivative (V; R = H), m. p. 103—104°. The stereoisomeric forms which probably occur in the mother-liquors have not been isolated in a pure condition.

In a similar manner 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxybenzyl)naphthalene-2 : 3-dicarboxylic acid (J., 1935, 636) was reduced in 75% yields to a mixture of stereoisomeric forms of the *tetrahydro*-derivative (III; R = OMe), from which a small amount of a homogeneous *acid*, m. p. 155—157°, was isolated by prolonged fractional crystallisation. The mixed acids gave an oily anhydride and esterification yielded the *methyl* ester in two crystalline modifications and the *ethyl* ester in a crystalline and a liquid form. Bouveault–Blanc reduction, preferably on the ethyl ester, yielded a mixture of *diols* (I; R = OMe), from which a homogeneous form, m. p. 156—158°, has been separated. This substance represents a racemic modification of *iso*lariciresinol dimethyl ether; there is a distinct resemblance in general solubility properties, and the synthetic diol gave an *anhydro*-derivative (V; R = OMe), m. p. 126—127°, which was converted into dehydroanhydro-*iso*lariciresinol dimethyl ether (J., 1937, 1645) on dehydrogenation with lead tetra-acetate. A similar dehydrogenation of the unsubstituted anhydro-derivative (V; R = H) could not be effected, and it is possible that dehydrogenation with lead tetra-acetate depends upon the activating influence of methoxyl groups upon the methylene groups adjoining the aromatic nuclei.

In connexion with other experiments, information was required concerning the stability of methylenedioxy-groups in compounds of this series to the conditions of the Bouveault–Blanc process, and in order to test this point a similar series of experiments has been made with 6 : 7-methylenedioxy-1-(3′ : 4′-methylenedioxybenzyl)naphthalene-2 : 3-dicarboxylic acid (J., 1936, 746). Reduction with sodium amalgam gave an inseparable mixture of *tetrahydro-acids* (III; RR = CH_2O_2), yielding a liquid *ethyl* ester which was converted into an oily *diol* (I; RR = CH_2O_2) by Bouveault–Blanc reduction. Repeated crystallisation gave a homogeneous form, m. p. 187°, which was converted in the usual way into the *anhydro*-derivative (V; RR = CH_2O_2), m. p. 137°.

As mentioned above, the configuration of acids of type (III) is modified by esterification in the presence of hydrions, and in view of the observed conversion of *cis*-hexahydrophthalic ester into the *trans*-form under the influence of sodium ethoxide (Hückel and Goth, *Ber.*, 1925, **58**, 4471), further configurational change under the conditions of the Bouveault–Blanc reduction was anticipated. This has been confirmed by experiments on dibasic acids of type (IV), which are available in *meso*-, *dl*-, *d*-, and *l*-forms. The *ethyl* esters of the four forms of bis-(3 : 4-dimethoxybenzyl)succinic acid (IV; R = OMe), prepared by the silver salt method, have been reduced by sodium and alcohol to an oily optically inactive *diol* (II; R = OMe), and the identity of the products from the four esters has been established by the preparation of crystalline *formyl* and *anhydro* (VI; R = OMe) derivatives, m. p.

132° and 119° respectively. It has also been observed that the ester which escapes reduction during the Bouveault–Blanc process undergoes stereochemical change, and the acidic products recovered from the reduction of the *meso*- and the *dl*-form of the ester of the acid (IV; R = OMe) contain approximately 35 and 15% of the *meso*-form of the acid. The diol (II; R = OMe) was oxidised by sodium hypobromite to *dl*-matairesinol dimethyl ether, m. p. 115°. The latter probably possesses a *trans*-configuration (J., 1938, 1985; this vol., p. 154) but the conversion cannot be used as an argument in favour of a *trans*-configuration for the diol (II; R = OMe) because of the instability of *cis*-matairesinol dimethyl ether (J., 1938, 797) under the alkaline conditions of the oxidation experiment.

Attempts to solve the stereochemical problem and to synthesise optically active diols of the lignan series are now in progress together with applications of the experiments described in this communication to the synthesis of the olivil and cubebin structures.

EXPERIMENTAL.

1-*Phenyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2 : 3-*dicarboxylic Acid* (III; R = H).—4% Sodium amalgam (1200 g.) was added to a solution of 1-phenylnaphthalene-2 : 3-dicarboxylic anhydride (26·2 g.) in hot water (600 c.c.) containing sodium hydroxide (10 g.). The stirred mixture was heated on the water-bath, and carbon dioxide passed in during 12 hours. Acidification of the filtered solution precipitated the crude acid (III; R = H) (27·5 g.), m. p. 170—180° (Found, after washing with water and drying at 100°: C, 72·7; H, 5·6. Calc. for $C_{18}H_{16}O_4$: C, 73·0; H, 5·4%). Repeated crystallisation from acetone yielded a homogeneous acid in colourless prisms (14 g.), m. p. 209° (decomp.) (Found: C, 73·3; H, 5·5%) [Michael and Bucher, *loc. cit.*, and Stobbe, *Ber.*, 1907, **40**, 3372, give 200—202° (decomp.) and 204° (decomp.) respectively]. The anhydride, prepared in 90% yields by heating the acid, m. p. 209° (decomp.), with acetyl chloride (15 parts), separated from benzene–acetone in hexagonal prisms, m. p. 155—156° (Found: C, 77·9; H, 5·0. Calc. for $C_{18}H_{14}O_3$: C, 77·7; H, 5·0%) (Michael and Bucher, *loc. cit.*, and Stobbe, *loc. cit.*, give 145—150° and 155° respectively). Unlike the anhydride of 1-phenylnaphthalene-2 : 3-dicarboxylic acid (Stobbe, *loc. cit.*), that of the tetrahydro-acid (III; R = H) was sulphonated and not converted into a ketonic acid by the action of cold concentrated sulphuric acid, and contrary to previous observations, alkaline hydrolysis of the anhydride yielded, not the original acid, m. p. 209° (decomp.), but an isomeric modification which crystallised from acetone–benzene in small prisms, m. p. 219° (Found: C, 72·9; H, 5·5%), depressed to 205—208° on admixture with the form, m. p. 209° (decomp.). Esterification of the acid (III; R = H), m. p. 170—180°, was effected (*a*) by refluxing for 4 hours with alcoholic hydrogen chloride (10 parts) or 10% alcoholic sulphuric acid and (*b*) by refluxing a suspension of the dry silver salt, precipitated by addition of silver nitrate to a hot solution of the ammonium salt of the acid (1 part), in ether (10 parts) with an alkyl halide (3 parts) for 6 hours. The *methyl* ester was obtained as a semi-solid product, about half of which was obtained in the form of long prisms, m. p. 106—109° (Found: C, 73·9; H, 6·3. $C_{20}H_{20}O_4$ requires C, 74·1; H, 6·2%). Distillation of this crystalline modification or 12 hours' esterification by method (*a*) gave a liquid methyl ester, b. p. 190—195°/1 mm. (Found: C, 74·0; H, 6·2%). The *ethyl* ester was an oil, b. p. 210—215°/1·5 mm. (Found: C, 74·9; H, 7·0. $C_{22}H_{24}O_4$ requires C, 75·0; H, 6·8%).

6 : 7-*Dimethoxy*-1-(3′ : 4′-*dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2 : 3-*dicarboxylic Acid* (III; R = OMe).—Repeated crystallisation from acetone–benzene of the crude *acid*, m. p. 140—155° (Found: C, 63·8; H, 6·0. $C_{22}H_{24}O_8$ requires C, 63·5; H, 5·8%), obtained in 90% yields by reduction of 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)naphthalene-2 : 3-dicarboxylic acid, yielded small prisms, m. p. 155—157° (Found: C, 63·9; H, 5·8%). The purification was extremely wasteful and the crude acid, m. p. 140—155°, was employed in further experiments. Esterification with methyl-alcoholic hydrogen chloride or 10% methyl-alcoholic sulphuric acid gave 80% yields of a solvated *methyl* ester, which separated from methyl alcohol–chloroform in stout prisms, m. p. 110° (Found: C, 63·2; H, 6·6. $C_{24}H_{28}O_8,CH_3{\cdot}OH$ requires C, 63·0; H, 6·7%). The action of methyl iodide on the silver salt gave 80% yields of a *methyl* ester which crystallised from methyl alcohol in long slender prisms, m. p. 146° (Found: C, 64·9; H, 6·4. $C_{24}H_{28}O_8$ requires C, 64·9; H, 6·3%). The *ethyl* ester, prepared by the alcoholic sulphuric acid method,* was resolved into (*a*) slender prisms (20% yield) from methyl alcohol,

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* An *ethyl hydrogen* ester, which separated from benzene in small prisms, m. p. 122° (Found: C, 64·8; H, 6·3. $C_{24}H_{28}O_8$ requires C, 64·6; H, 6·4%), was isolated from the sodium bicarbonate extract of the esterification mixture.

m. p. 116—117° (Found: C, 66·2; H, 6·5. $C_{26}H_{32}O_8$ requires C, 66·1; H, 6·8%), and (*b*) an oil (50% yield), b. p. 270—275°/3 mm. (Found: C, 66·1; H, 6·7%).

6 : 7-*Methylenedioxy*-1-(3′ : 4′-*methylenedioxyphenyl*)-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2 : 3-*dicarboxylic Acid* (III; RR = CH_2O_2).—The crude reduction product had a very indefinite m. p. and attempts to obtain a homogeneous modification were unsuccessful. The *ethyl* ester, prepared by the action of 10% alcoholic sulphuric acid, was a viscous oil, b. p. 260—265°/1·5 mm. (Found: C, 65·3; H, 5·5. $C_{24}H_{24}O_8$ requires C, 65·4; H, 5·4%).

1-*Phenyl*-2 : 3-*di*(*hydroxymethyl*)-1 : 2 : 3 : 4-*tetrahydronaphthalene* (I; R = H).—A solution of the ethyl ester (6·2 g.) of the acid (III; R = H) in absolute alcohol (10 c.c.) was added rapidly to molten sodium (3·76 g.) maintained at 180°. After ½ hour, four portions of alcohol (3 c.c. each) were added during the course of 1 hour. When the sodium had reacted completely, most of the alcohol was evaporated, water was added, and the removal of the alcohol was completed under reduced pressure. Ether extraction of the residue yielded an oil (1·5 g.), which has not been obtained crystalline. This oil (1 g.) and potassium hydrogen sulphate (2 g.) were heated at 180° for ½ hour; the product was isolated with ether, dissolved in light petroleum (b. p. 40—60°) (carbon), filtered, and the solvent removed. The residue was distilled, and the fraction (0·7 g.), b. p. 180°/1·5 mm., crystallised on the addition of light petroleum (b. p. 40—60°). This *anhydro*-derivative (V; R = H) (0·5 g.), m. p. 85—88° (Found: C, 85·9; H, 7·2. $C_{18}H_{18}O$ requires C, 86·4; H, 7·2%), probably consists of a mixture of stereoisomerides, and repeated crystallisation from methyl alcohol yielded colourless prisms (0·1 g.), m. p. 103—104° (Found: C, 86·2; H, 7·2%), unchanged by further crystallisation.

1-(3′ : 4′-*Dimethoxyphenyl*)-2 : 3-*dihydroxymethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (I; R = OMe).—The neutral oil, obtained in 40% yields by reducing the ethyl ester of the dibasic acid (III; R = OMe) as described above, slowly deposited crystals, m. p. 134—145° (yield = 10% of oil), from its ethereal solution (A; see below). Repeated crystallisation from ether–methyl alcohol yielded slender needles, m. p. 155—158° (yield = 5% of oil) (Found: C, 67·6; H, 7·5. $C_{22}H_{28}O_6$ requires C, 68·0; H, 7·2%). The *anhydro*-derivative (V; R = OMe), prepared in 90% yields by the action of potassium hydrogen sulphate on the diol, m. p. 155—158°, separated from methyl alcohol in rosettes of long prisms, m. p. 126—127° (Found: C, 71·2; H, 7·2. $C_{22}H_{26}O_5$ requires C, 71·4; H, 7·0%). Dehydrogenation with lead tetra-acetate (2 parts) in glacial acetic acid (8 parts) at 70° for 1½ hours yielded dehydroanhydro*iso*lariciresinol dimethyl ether, which crystallised from methyl alcohol–chloroform in stout prisms, m. p. 200—201° (Found: C, 72·0; H, 6·0. Calc. for $C_{22}H_{22}O_5$: C, 72·1; H, 6·1%), unaltered by admixture with a specimen prepared from *d*-lariciresinol (J., 1937, 1645). The ethereal mother-liquors (A) were evaporated, dehydrated with potassium hydrogen sulphate at 180°, and the crude product dehydrogenated with lead tetra-acetate; dehydroanhydro*iso*lariciresinol dimethyl ether was obtained in a yield of 40% of the oil, thus indicating the presence in the mother-liquors (A) of stereoisomeric forms of the diol (I; R = OMe).

6 : 7-*Methylenedioxy*-1-(3′ : 4′-*methylenedioxyphenyl*)-2 : 3-*dihydroxymethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (I; RR = CH_2O_2).—An ethereal solution of the neutral oil, obtained in 37% yields by Bouveault–Blanc reduction of the ethyl ester of the dibasic acid (III; RR = CH_2O_2), deposited the diol (I; RR = CH_2O_2) in 5% yields. Crystallisation from methyl alcohol–chloroform or ethyl alcohol gave rosettes of long prisms, m. p. 183—184° (Found: C, 67·6; H, 5·9. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·6%). The *anhydro*-derivative (V; RR = CH_2O_2), prepared in the usual manner, separated from methyl alcohol in rosettes of colourless prisms, m. p. 137° (Found: C, 70·8; H, 5·2. $C_{20}H_{18}O_5$ requires C, 71·0; H, 5·3%).

Esters of Bis-(3 : 4-*dimethoxybenzyl*)*succinic Acid* (IV; R = OMe).—These were prepared from the four modifications of the acid (IV; R = OMe) (this vol., p. 154) by the silver salt method. The meso-*methyl* ester crystallised from methyl alcohol–chloroform in slender prisms, m. p. 136—137° (Found: C, 64·7; H, 7·0. $C_{24}H_{30}O_8$ requires C, 64·6; H, 6·7%), and the meso-*ethyl* ester separated from alcohol in rectangular prisms, m. p. 114—115° (Found: C, 65·5; H, 7·3. $C_{26}H_{34}O_8$ requires C, 65·8; H, 7·2%). The dl-*methyl* ester crystallised from a small amount of methyl alcohol in solvated prisms, m. p. 65—66° (Found: C, 59·8; H, 7·6. $C_{24}H_{30}O_8,3CH_3{\cdot}OH$ requires C, 60·0; H, 7·7%), and the dl-*ethyl* ester was an oil (Found, after drying over phosphoric oxide in a vacuum: C, 65·4; H, 7·3%). The d- and the l-*ethyl* ester crystallised from ether in rosettes of slender prisms, m. p. 65—66° (Found, for *d*-ester: C, 65·6; H, 7·2%; for *l*-ester: C, 65·5; H, 7·1%). In chloroform (*c*, 1·030) they gave $[\alpha]_D^{17°}$ 26·4° and — 26·2° respectively.

αδ-*Bis*-(3 : 4-*dimethoxyphenyl*)-βγ-*di*(*hydroxymethyl*)*butane* (II; R = OMe).—The Bouveault–Blanc reductions were carried out as follows. The ethyl ester (1·2 g.) was dissolved in boiling alcohol (5, 10, and 5 c.c. for the *dl*-, *meso*-, and *d*- or *l*-forms respectively) and added to sodium (0·5 g.) heated to 180°. After ¼ hour, alcohol (5 c.c.) was added, and the mixture heated for ½ hour. The alcohol was removed, water added, and neutral material extracted with ether and dried. Removal of the ether left the diol (II; R = OMe) (0·7 g.). In experiments with the *meso*- and the *dl*-ester the aqueous alkaline liquors were acidified, shaken with chloroform (5 c.c.), and the sparingly soluble *meso*-acid (0·40 g. and 0·11 g. respectively), m. p. 223°, was collected; crude *trans*-acid was recovered from the chloroform filtrate (0·25 and 0·36 g. respectively). In all cases the *diol* (II; R = OMe) was obtained as an oil which showed no optical activity in alcoholic solution. It distilled unchanged at 2 mm. (Found: C, 67·4; H, 8·0. $C_{22}H_{30}O_6$ requires C, 67·7; H, 7·7%). This diol (II; R = OMe), oxidised with sodium hypobromite as described previously for the *l*-form (this vol., p. 154), yielded *dl*-matairesinol dimethyl ether, m. p. 113—115°, undepressed by admixture with an authentic specimen. The *diformyl* derivative, prepared by boiling with 80% formic acid for 15 minutes, crystallised from ether or methyl alcohol in large plates, m. p. 131—132° (Found: C, 64·9; H, 6·6. $C_{24}H_{30}O_8$ requires C, 64·6; H, 6·7%); the diol liberated by hydrolysis of the diformyl derivative was an oil. The *anhydro*-derivative (VI; R = OMe) crystallised from methyl alcohol in nacreous laminæ, m. p. 118—119° (Found: C, 70·8; H, 7·6. $C_{22}H_{28}O_5$ requires C, 71·0; H, 7·5%).

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