153. *The Constituents of Natural Phenolic Resins. Part X. Structure of l-Matairesinol Dimethyl Ether and Observations on the Condensation of Reactive Methylene Groups with O-Methyleugenol Oxide.*

By Robert D. Haworth and John R. Atkinson.

By subjecting *l*-matairesinol dimethyl ether (I; $R^1 = R^2$ = veratryl) to prolonged alkaline treatment, it has been converted into d-iso*matairesinol dimethyl ether*. This *d*-lactone is not the optical antipode of *l*-matairesinol dimethyl ether, but it is rapidly and completely converted into the latter by mild alkaline treatment. It is suggested that these isomerisations involve the asymmetric centre in the α-position with respect to the carbonyl group, that the rapid change from *d-iso-* to *l*-forms occurs without fission of the lactone ring, but the conversion of *l-* into the *d-iso*-form occurs *via* the corresponding hydroxy-acids. The hydroxy-acid corresponding to the *d-iso*-form is lactonised much less readily than the acid from the *l*-isomer, and it is concluded that *d-iso-* and *l*-matairesinol dimethyl ether represent the *cis-* and the *trans*-form respectively of (I; $R^1 = R^2$ = veratryl).

In previous work (J., 1936, 725) a lactone, believed to be structurally identical with *l*-matairesinol dimethyl ether, was prepared by two methods, and improvements have been made in one of the syntheses. The synthetic lactone differs from *d-iso-* and *l*-matairesinol dimethyl ether in crystal structure and in behaviour with lead tetra-acetate and the corresponding hydroxy-acids show wide differences in rates of lactonisation. The differences cannot be accounted for on stereochemical grounds and it is concluded that the synthetic lactone has structure (IV; R = veratryl). This structure has been established by alkaline hydrolysis of the condensation product of ethyl acetoacetate with *O*-methyleugenol oxide; the lactone (VI; R^1 = OMe, R^2 = H) was obtained and the constitution was proved by an independent synthesis. It follows that lactones previously regarded as α-benzylbutyrolactones are actually γ-benzylbutyrolactones and a list of corrected formulæ is included.

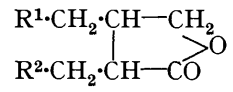
The principle reason for the previous assignation of the α-benzylbutyrolactone structure was based on the facile conversion into naphthalene derivatives. The naphthalene structures have been confirmed, new examples of such conversions are recorded, and it is suggested that the naphthalenes arise from the γ-benzylbutyrolactones by a pinacolinic change during the cyclisation with acidic reagents.

These new observations do not affect previous conclusions with regard to the structure of natural products of the lignan group.

In Part V (J., 1936, 725) the synthesis of a compound believed to be a racemic modification of matairesinol dimethyl ether (I; $R^1 = R^2$ = veratryl) was described. The synthetic product resembles the naturally occurring *l*-lactone in absorption spectra and in its behaviour towards bromine, nitric acid, potassium permanganate, and sodium hypobromite, but the synthetic lactone, unlike the *l*-lactone, could not be converted into the *cyclo*dehydro-lactones (II) and (III) by the action of lead tetra-acetate. A compound of stucture (I) can exist in two racemic (*cis* and *trans*) forms, and in Part V (*loc. cit.*) it was suggested that the inconsistency with lead tetra-acetate might be attributed to stereochemical differences. Later (J., 1937, 387) it was suggested that the *l-* and the synthetic lactone represented the *trans-* and the *cis*-form respectively of (I; $R^1 = R^2$ = veratryl).

A more detailed examination of the action of lead tetra-acetate on the synthetic racemate has confirmed the previous observation that the *cyclo*dehydro-lactones (II) and (III) are not

produced. The product has been resolved into two crystalline *diacetates*, $C_{26}H_{30}O_{10}$ and $C_{26}H_{30}O_9$, which yield the *lactones* $C_{22}H_{24}O_7$ and $C_{22}H_{26}O_8$, respectively, on hydrolysis.



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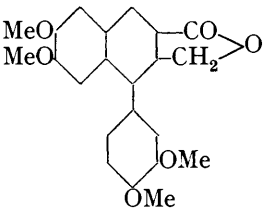

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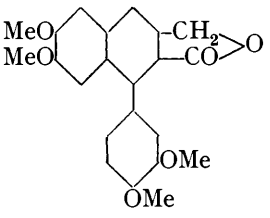
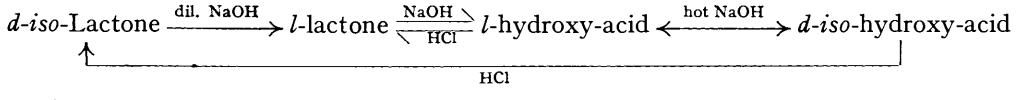


(III.)

The structure of these compounds has not been ascertained, but it is unlikely that they represent 1-phenylnaphthalene derivatives because the lactones $C_{22}H_{24}O_7$ and $C_{22}H_{26}O_8$ both yield 3 : 4-dinitroveratrole and veratric acid on treatment with nitric acid and permanganate respectively. The formation of 3 : 4-dinitroveratrole indicates the presence of an oxygenated veratrole group, but the yields were insufficient to establish the presence of two such groups. In view of the irregular behaviour observed with lead tetra-acetate in other cases (following paper) these observations do not rigidly exclude the suggested stereochemical relationship between the *l*- and the synthetic lactone.

A crystallographic comparison, made by Miss D. M. Crowfoot, shows that there is no direct relationship between the crystal structures of the *l*- and the synthetic lactone and this may be attributed either to structural or to stereochemical differences between the two compounds. It is not possible to decide from the crystal structures whether the lactones belong to the *cis*- or the *trans*-series. Details of the crystallographic examination will be published in a later communication.

The rates of hydrolysis of the *l*- and the synthetic lactone are indistinguishable, but the hydroxy-acid obtained from the *l*-lactone is lactonised much more rapidly than the hydroxy-acid corresponding to the synthetic lactone. Similar observations have been made with *l*-hinokinin and the synthetic isomer previously (J., 1936, 725) regarded as (I ; $R^1 = R^2$ = piperonyl). When *l*-matairesinol dimethyl ether (I ; $R^1 = R^2$ = veratryl), $[\alpha]_D^{19°}$ −35°, was subjected to the prolonged action of boiling concentrated potassium hydroxide solution, boiling alcoholic sodium ethoxide solution, or dilute sodium hydroxide solution at 180°, it was converted into a mixture of hydroxy-acids, yielding a crude lactone, $[\alpha]_D^{17°}$ + 18°. This crude lactone was resolved by repeated crystallisation into *l*-matairesinol dimethyl ether and d-iso*matairesinol dimethyl ether*, $[\alpha]_D^{19°}$ + 78°, from which crystalline *dinitro*- and *dibromo*-derivatives have been prepared. This *d-iso*-lactone is probably formed by inversion of the asymmetric carbon atom in the α-position with respect to the carbonyl group, and if the *l*- and the synthetic lactone differ only in sterochemical configuration the synthetic lactone must be *dl-iso*matairesinol dimethyl ether. After the *d-iso*-lactone had been heated at 180° with dilute sodium hydroxide solution, the equilibrium mixture of lactones with $[\alpha]_D^{17°}$ + 18° was regenerated, but when the *d-iso*-lactone was treated with cold methyl-alcoholic potassium hydroxide, complete inversion to *l*-matairesinol dimethyl ether occurred. It is well known that Walden inversions at α-asymmetric centres usually occur more rapidly with esters than with the anions of the corresponding carboxylic acids. The above results are explicable on the assumption that complete inversion of the *d-iso*-lactone with cold alkali is due to a Walden inversion of the α-asymmetric centre of the lactone, and the equilibration of the *d-iso*-lactone under the more drastic alkaline conditions follows its complete inversion to the *l*-lactone in accordance with the following sequence of changes :



The rates of hydrolysis of the *d-iso*-lactone and the *l*-lactone were identical in accordance with the above hypothesis, but, as the *d-iso*-lactone was converted into the hydroxy-acid

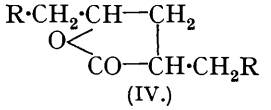
corresponding to the *l*-lactone, special conditions were necessary in order to determine the rate of lactonisation of the *d-iso*-hydroxy-acid. When the mixture of *d-iso*- and *l*-hydroxy-acids, obtained by addition of acetic acid to the equilibrium mixture of the sodium salts, was refluxed with alcohol, the *l*-acid was preferentially lactonised and the d-iso-*hydroxy-acid*, $[\alpha]_D$ −23°, could be isolated; its rate of lactonisation proved to be much slower than that of the *l*-acid and agreed more closely with the rate observed with the hydroxy-acid obtained from the synthetic lactone. As *d-iso*matairesinol dimethyl ether yielded the *cyclo*dehydro-lactones (II) and (III) on treatment with lead tetra-acetate, the failure to obtain these products from the synthetic lactone can no longer be explained by differences in stereo-chemical configuration. Furthermore, the synthetic racemate, m. p. 107°, unlike *d-iso*-matairesinol dimethyl ether, was stable to mild alkaline treatment. Drastic alkaline conditions converted it partly into an isomeric form; the m. p. of the recovered lactone was 97—99°, but fractional crystallisation yielded the synthetic racemate, m. p. 107°, and attempts to isolate the isomer from the mother-liquors have been unsuccessful. The crude lactone was indistinguishable from the original synthetic racemate in behaviour towards lead tetra-acetate, rate of hydrolysis, and rate of lactonisation of the derived hydroxy-acid. No conventional stereochemical explanation can be offered for the observed differences and it is now concluded that the synthetic racemate and *l*-matairesinol dimethyl ether differ structurally.

After the above experiments were completed Omaki (*J. Pharm. Soc. Japan*, 1937, **57**, 89) described the preparation of *d-iso*matairesinol dimethyl ether, $[\alpha]_D$ + 145°, by methylating *d-iso*arctigenin, obtained by the action of alkali on *l*-arctigenin (I; R^1 = veratryl, R^2 = vanillyl). The high rotation value suggested that our specimen of *d-iso*matairesinol dimethyl ether might be impure, but repeated crystallisation failed to alter the α_D value and we are unable to account for the discrepancy. Omaki also found that the hydroxy-acid obtained from the *l*-lactone is lactonised by boiling methyl alcohol more rapidly than the *d-iso*-hydroxy-acid, and concludes that the *d-iso*- and the *l*-lactone are *trans*- and *cis*-forms respectively. The reasons for this conclusion are not apparent and our conclusions, made from essentially the same observations, are the reverse. Inspection of the formulæ or models shows that a maximum repulsion of like groups results in a greater separation of the hydroxymethyl and carboxyl groups in the case of the hydroxy-acid derived from the *cis*-lactone. Consequently it may be argued that the hydroxy-acid which lactonises the more readily will have the *trans*-configuration and it is therefore concluded that the *d-iso*- and the *l*-lactone are *cis*- and *trans*-forms respectively. This conclusion is consistent with that arrived at previously (J., 1937, 387) on biogenetic grounds.

One of the methods, namely, that based upon the condensation of *O*-methyleugenol oxide with methyl sodio-3 : 4-dimethoxybenzyl-α-cyanoacetate, used previously (*loc. cit.*) for the preparation of the synthetic lactone, is ambiguous; lactones (I; $R^1 = R^2$ = veratryl) or (IV; R = veratryl) could arise by reaction of the cyanoacetate anion with the β- or the γ-carbon atom respectively of the oxide chain. The synthetic lactone was also obtained, in small yield, by the action of 3 : 4-dimethoxybenzyl chloride on the lactonic condensation product of ethyl acetoacetate with *O*-methyleugenol oxide. This second method has now been improved considerably from the preparative point of view, and more convincing evidence has been obtained of the identity of the product obtained by the two methods. In addition the second method of synthesis has been applied to the methylenedioxy-analogue and a lactone, identical with the lactone previously regarded as *dl*-cubebinolide (J., 1936, 725), has been obtained. It follows, therefore, that the anions of ethyl acetoacetate and substituted benzylcyanoacetates unite with the same atom of the oxide chain in compounds of the *O*-methyleugenol oxide type.

Formula (V; R^1 = OMe, R^2 = CO·CH_3) was preferred to (VI) for the condensation product of ethyl acetoacetate with *O*-methyleugenol oxide because it gave a simple interpretation of the formation of naphthalene derivatives (see p. 801), and important results have been obtained from a further examination of this condensation product. Hydrolysis with concentrated sodium hydroxide solution resulted in deacetylation with the formation of a crystalline lactone, $C_{13}H_{16}O_4$, which was also prepared from *O*-methyl-

eugenol oxide and ethyl malonate, and (V; R^1 = OMe, R^2 = H), (VI; R^1 = OMe, R^2 = H) and (VII) were considered as possible structures for the lactone $C_{13}H_{16}O_4$.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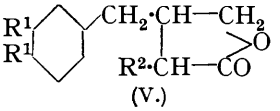
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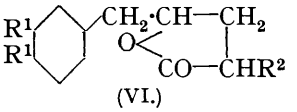
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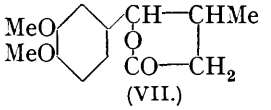
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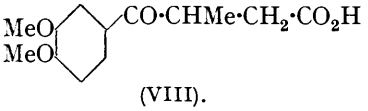
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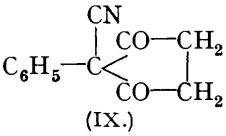
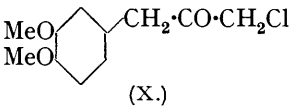

(IX.)

Structure (VII) was excluded by an independent synthesis; β-veratroyl-*n*-butyric acid (VIII) was reduced to the corresponding hydroxy-acid, which yielded *γ-veratryl-β-methylbutyrolactone* (VII) on lactonisation. An unambiguous synthesis of (V; R^1 = OMe, R^2 = H) has not yet been realised, but some experiments in this direction are described in the experimental section. Numerous failures were encountered in attempts to prepare (VI; R^1 = OMe, R^2 = H). Preliminary attempts to prepare γ-keto-δ-phenylvaleric acid by the action of ethyl succinate on phenylacetonitrile yielded an oil which gave 2-*cyano*-2-*phenyl*cyclo*pentane*-1 : 3-*dione* (IX) on distillation, but difficulties experienced in the hydrolysis of this nitrile led to the abandonment of the method. *γ-Chloro-α-veratrylacetone* (X) has been prepared by the action of diazomethane on veratrylacetyl chloride and subsequent treatment with dry hydrogen chloride, but smooth condensation of (X) with malonic, cyanoacetic, or acetoacetic ester was not effected. No obvious explanation can be offered for these failures and an attempt to prepare the methylenedioxy-analogue of (X) under precisely the same conditions yielded a *dichloro*-compound, $C_{10}H_8O_3Cl_2$. One of the chlorine atoms was hydrolysed with alcoholic potassium hydroxide and it is possible that the dichloro-compound has structure (XI) and that it arises by dismutation in the presence of hydrogen chloride (see Krohnke, *Ber.*, **1936**, **69**, 921). Eventually *γ-keto-δ-veratrylvaleric* acid (XII; R = OMe) was prepared by an application of Mrs. G. M. Robinson's method (J., **1930**, 745); veratrylacetyl chloride was condensed with ethyl sodioacetosuccinate in ethereal solution and hydrolysis of the neutral product gave a small yield of the acid (XII; R = OMe). This keto-acid was reduced by means of sodium and alcohol to the corresponding hydroxy-acid, which was lactonised to *γ-(3 : 4-dimethoxybenzyl)butyrolactone* (VI; R^1 = OMe, R^2 = H), identical in all respects with the lactone obtained by deacetylating the condensation product of ethyl acetoacetate and *O*-methyleugenol oxide. The corresponding methylenedioxy-lactone (VI; R^1R^1 = CH_2O_2, R^2 =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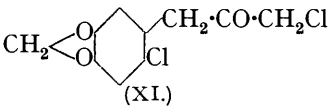
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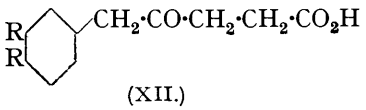
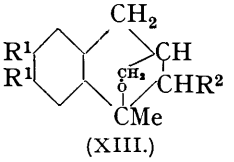

(XII.)

H), obtained similarly from piperonylacetyl chloride, was prepared from piperic acid by Fittig and Weinstein (*Annalen*, 1885, **227**, 38, 47), who describe it as an oil, yielding a crystalline hydroxy-acid, m. p. 95°. Our product is an oil, yielding the hydroxy-acid, m. p. 95°, and a crystalline *nitro*-derivative, and with the aid of these derivatives the identity of this lactone with the lactone obtained previously by deacetylating the condensation product of ethyl acetoacetate and safrole oxide (J., **1936**, 351) has been established.

These important observations prove that the anions of ethyl acetoacetate, malonate, or substituted benzylcyanoacetates react with the γ-carbon atom of *O*-methyleugenol and safrole oxide, giving γ-substituted butyrolactones of type (VI; R^2 = $CO{\cdot}CH_3$, CO_2Et, or $C_6H_5{\cdot}CH_2$) and not β-substituted butyrolactones of type (V) as previously suggested. Consequently the products formerly regarded as *dl*-matairesinol dimethyl ether (I; R^1 = R^2 = veratryl) and *dl*-cubebinolide (*dl*-hinokinin) (I; R^1 = R^2 = piperonyl) must possess the formulæ (IV; R = veratryl) and (IV; R = piperonyl) respectively, and the differences in behaviour of the natural and the synthetic lactone towards lead tetra-acetate, hydrolytic and lactonising agents are readily understandable.

As mentioned earlier in this communication, the numerous conversions of the condens-

ation product of ethyl acetoacetate with safrole or *O*-methyleugenol oxide into naphthalene derivatives constituted a powerful argument for the earlier selection of structure (V; R^2 = $CO{\cdot}CH_3$) in preference to (VI; R^2 = $CO{\cdot}CH_3$). A critical review of our previous results (J., 1935, 636; 1936, 348, 725, 998; 1937, 1646; see also following paper) and further observations made during the course of the present work have strengthened the evidence that the naphthalene structure assigned to these products is correct. When α-acetyl-γ-3 : 4-dimethoxybenzylbutyrolactone (VI; R^1 = OMe, R^2 = $CO{\cdot}CH_3$) was treated with methyl-alcoholic hydrogen chloride, it was converted into *methyl* 6 : 7-*dimethoxy*-3 : 1-endo*methyleneoxy*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-*carboxylate* (XIII; R^1 = OMe, R^2 = CO_2Me), and the corresponding *acid* (XIII; R^1 = OMe, R^2 = CO_2H) was prepared either by alkaline hydrolysis of the methyl ester, or directly from (VI; R^1 = OMe, R^2 = $CO{\cdot}CH_3$) by the action of a mixture of acetic and hydrochloric acids. The acid (XIII; R^1 = OMe, R^2 = CO_2H) was converted into 6 : 7-*dimethoxy*-1 : 3-*dimethylnaphthalene* (XVI) by heating with selenium at 280°, and the *endo*methyleneoxy-structures, or alternatives based upon the oxide structure (XIV), are necessary to explain the Zerewitinoff determinations, which proved the presence of one active hydrogen atom in the acid (XIII; R^1 = OMe, R^2 = CO_2H) and the absence of active hydrogen atoms in the methyl ester (XIII; R^1 = OMe, R^2 = CO_2Me). The lactone



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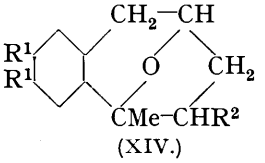

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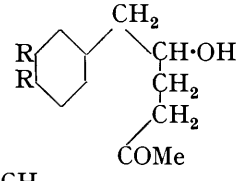

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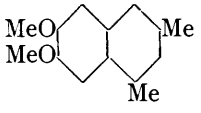
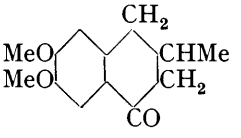
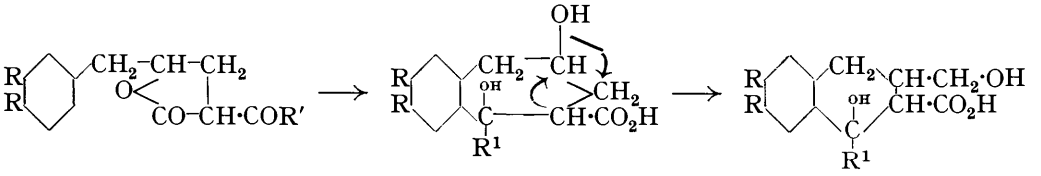




(XVII.)

(VI; R^1 = OMe, R^2 = $CO{\cdot}CH_3$) was hydrolysed by dilute sodium hydroxide solution to give *methyl γ-hydroxy-δ-veratrylbutyl ketone* (XV; R = OMe). This oily ketone was converted by a mixture of acetic and hydrochloric acids into 6 : 7-*dimethoxy*-3 : 1-endo-*methyleneoxy*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (XIII; R^1 = OMe, R^2 = H), which contained no active hydrogen atom and yielded 6 : 7-dimethoxy-1 : 3-dimethylnaphthalene (XVI) on dehydrogenation with selenium. The structure of the dehydrogenation product (XVI) was proved by a synthesis from β-veratroyl-*n*-butyric acid (VIII). The crude Clemmensen reduction product of (VIII) was cyclised to 1-*keto*-6 : 7-*dimethoxy*-3-*methyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (XVII), which was converted into (XVI) by condensation with methylmagnesium iodide and subsequent dehydrogenation with selenium. The methylenedioxy-derivatives (VI; R^1R^1 = CH_2O_2, R^2 = $CO{\cdot}CH_3$) and (XV; RR = CH_2O_2), described in Part IV (J., 1936, 351), have been converted similarly into the endo*methyleneoxy*-derivatives (XIII; R^1R^1 = CH_2O_2, R^2 = CO_2H), (XIII; R^1R^1 = CH_2O_2, R^2 = CO_2Me) and (XIII; R^1R^1 = CH_2O_2, R^2 = H), but the dehydrogenation of these compounds has not been examined.

Reference to other communications of this series shows that the formation of naphthalene derivatives does not demand the application of the selenium dehydrogenation reaction, but all cases of naphthalene formation, observed in this and previous work, involve the use of acidic cyclising agents. This suggested that the conversion of compounds of type (VI) into naphthalene derivatives involves a pinacolinic transformation and the following general mechanism is now advanced.



The scheme is applicable to lactones where R^1 may be a methyl or a substituted phenyl group, and the conversion of keto-alcohols of type (XV) into naphthalenes may be formulated in a similar manner. It is noteworthy that the formation of naphthalene derivatives has not been observed with the lactone (VI; R^1 = OMe, R^2 = H); here R^1·CO is replaced by H, and as the synthetic lactone (IV; R = veratryl) differs structurally from, and is not converted by acidic reagents into either *iso*- or matairesinol dimethyl ether, it is probable that the pinacolinic change is dependent upon a cyclisation reaction. The above scheme represents a typical pinacolinic transformation and there is evidence from the chemistry of the azulenes (Pfau and Plattner, *Helv. Chim. Acta*, 1936, **19**, 858) that the *cyclo*pentane*cyclo*heptane ring system is capable of rearrangement to naphthalene compounds.

All experimental observations in this and in other papers of this series are in complete harmony with this modified interpretation of the reactions. The structures formerly assigned to the naphthalene derivatives remain undisturbed, and previous conclusions with regard to the structure of natural products of the lignan family are not invalidated. It is necessary to modify the structures of the butyrolactones which were previously regarded as substituted β-benzylbutyrolactones of type (V), to the corresponding substituted γ-benzylbutyrolactone structure (VI). In the same way keto-alcohols previously formulated as primary alcohols of the methyl (or phenyl) β-hydroxymethyl-γ-phenylpropyl ketone type must be altered to the secondary alcoholic, methyl (or phenyl) γ-hydroxy-δ-phenylbutyl ketone structure (as XV). A list of corrected structures is appended together with references to the erroneous formulations.

γ-(3 : 4-Methylenedioxybenzyl)butyrolactone, J., 1936, 349, 351 (V; R = H).

α-Acetyl-γ-(3 : 4-methylenedioxybenzyl)butyrolactone, *ibid.* (V; R = CO·CH_3).

Ethyl γ-(3 : 4-methylenedioxybenzyl)butyrolactone-α-carboxylate, *ibid.* (V; R = CO_2Et).

α-Acetyl-α-(3 : 4 : 5-trimethoxybenzoyl)-γ-(3 : 4-methylenedioxybenzyl)butyrolactone, *ibid.* (VII; R = CO·CH_3).

Ethyl α-acetyl-α-(3 : 4 : 5-trimethoxybenzoyl)-γ-(3 : 4-methylenedioxybenzyl)butyrolactone-α-carboxylate, *ibid.* (VII; R = CO_2H).

α-(3 : 4 : 5-Trimethoxybenzoyl)-γ-(3 : 4-methylenedioxybenzyl)butyrolactone, *ibid.* (VII; R = H).

Methyl γ-hydroxy-δ-piperonylbutyl ketone, *ibid.* (VIII).

α-Acetyl-γ-(3 : 4-dimethoxybenzyl)butyrolactone, J., 1936, 725, 727 (IV).

α-Veratroyl-γ-(3 : 4-dimethoxybenzyl)butyrolactone, *ibid.* (V) and J., 1937, 1646, 1648.

α-Piperonyl-γ-(3 : 4-methylenedioxybenzyl)butyrolactone, J., 1936, 727.

α-Acetyl-αγ-bis-(3 : 4-dimethoxybenzyl)butyrolactone, *ibid.*, pp. 725, 728 (VIII).

αγ-Bis-(3 : 4-dimethoxybenzyl)butyrolactone, *ibid.* (III; R = OMe).

αγ-Bis-(3 : 4-methylenedioxybenzyl)butyrolactone, *ibid.*, pp. 727, 729 (III; RR = CH_2O_2).

α-Acetyl-γ-(3-methoxy-4-ethoxybenzyl)butyrolactone, J., 1936, 999, 1001.

α-Veratroyl-γ-(3-methoxy-4-ethoxybenzyl)butyrolactone, *ibid.*, p. 1001.

α-(3-Methoxy-4-ethoxybenzoyl)-γ-(3 : 4-dimethoxybenzyl)butyrolactone, *ibid.*, p. 1001

α-(3-Methoxy-4-ethoxybenzyl)-γ-(3 : 4-dimethoxybenzyl)butyrolactone, *ibid.*, pp. 999, 1001 (I).

α-(3 : 4-Dimethoxybenzyl)-γ-(3-methoxy-4-ethoxybenzyl)butyrolactone, *ibid.* (II).

Veratryl γ-hydroxy-δ-veratrylbutyl ketone, J., 1937, 1646, 1648 (IX).

Experimental.

αγ-Bis-(3 : 4-methylenedioxybenzyl)butyrolactone (IV; R = piperonyl).—*α-Acetyl-αγ-bis-(3 : 4-methylenedioxybenzyl)butyrolactone* (4·1 g.) was prepared from 3 : 4-methylenedioxybenzyl chloride (3·5 g.) and the sodio-derivative of α-acetyl-γ-(3 : 4-methylenedioxybenzyl)butyrolactone (4 g.) (VI; R^1R^1 = CH_2O_2, R^2 = CO·CH_3) exactly as described (J., 1936, 728) in the case of the corresponding 3 : 4-dimethoxybenzyl derivative. The product was an

alkali-insoluble oil, b. p. 270—280°/1 mm., giving no colour with ferric chloride (Found: C, 66·8; H, 5·1. $C_{22}H_{20}O_7$ requires C, 66·7; H, 5·0%). The lactone (1 g.) was refluxed for 1 hour with alcohol (10 c.c.) and 5% sodium hydroxide solution (10 c.c.), water added, and neutral matter removed in chloroform. The alkaline liquor was acidified, lactonised by boiling for 5 minutes, and extracted with chloroform. The extract was washed with sodium bicarbonate solution and dried, and the solvent removed. The product (IV; R = piperonyl) crystallised from methyl alcohol in colourless prisms (0·4 g.), m. p. 107—108° (Found: C, 67·8; H, 5·1. Calc. for $C_{20}H_{18}O_6$: C, 67·8; H, 5·1%), which gave no depression in m. p. when mixed with the compound obtained previously (J., 1936, 729) from safrole oxide and methyl 3 : 4-methylenedioxybenzyl-α-cyanoacetate. Identity was confirmed by comparison of the dibromo- and dinitro-derivatives, m. p.'s 123° and 161° respectively.

αγ-Bis-(3 : 4-dimethoxybenzyl)butyrolactone (IV; R = veratryl).—α-Acetyl-αγ-bis-(3 : 4-dimethoxybenzyl)butyrolactone (1·8 g.) (J., 1936, 728) was hydrolysed with aqueous alcoholic sodium hydroxide as described above; the lactone (IV; R = veratryl) (0·7 g.), m. p. 106—107° (Found: C, 68·4; H, 6·9. Calc. for $C_{22}H_{26}O_6$: C, 68·4; H, 6·7%), obtained was identical with the product described previously (J., 1936, 728) and identity was confirmed by the preparation of the dibromo- and dinitro-derivatives, m. p.'s 110° and 179° respectively.

Action of Oxidising Agents on Matairesinol Dimethyl Ether (I; $R^1 = R^2$ = veratryl) *and the Synthetic Lactone* (IV; R = veratryl).—(a) *Potassium permanganate.* The synthetic lactone (IV; R = veratryl) was oxidised with potassium permanganate as described previously (J., 1935, 635) for matairesinol dimethyl ether. Veratric acid, m. p. 179—180°, was obtained in similar yield.

(b) *Sodium hypobromite.* The synthetic lactone, or matairesinol dimethyl ether (0·3 g.), was dissolved in 1% methyl-alcoholic potassium hydroxide (10 c.c.), refluxed for 10 minutes, the alcohol removed, and the hydroxy-acid salt dissolved in water (10 c.c.). A solution of bromine (0·5 c.c.) in 10% sodium hydroxide solution (12 c.c.) was added and, after refluxing for 3 hours, the solution was treated with sulphur dioxide, acidified with dilute sulphuric acid, and extracted with chloroform. The acids were removed from the extract by washing with sodium bicarbonate solution and recovered; crystallisation from hot water gave veratric acid (0·26 g.), m. p. 180°. Reduction of the amount of sodium hypobromite led to recovery of lactone and a diminution in yield of veratric acid.

(c) *Lead tetra-acetate.* The action of lead tetra-acetate on *l*-matairesinol dimethyl ether has been described (J., 1935, 635). The synthetic lactone (IV; R = veratryl) (0·5 g.) in acetic acid (5 c.c.) was treated at 70° with lead tetra-acetate (1·2 g.) in acetic acid (15 c.c.) for 20 minutes. Water was added, the product extracted with chloroform, the extract washed with sodium bicarbonate solution and dried, and the solvent removed. The residue solidified on trituration with a little methyl alcohol; the solid (0·4 g.), m. p. 140—150°, was collected and resolved by fractional crystallisation from benzene into two *diacetates*, A and B. The sparingly soluble compound, A, separated from benzene in colourless slender needles, m. p. 150—151° (Found: C, 64·4, 64·5; H, 6·1, 6·4; $CH_3{\cdot}CO$, 16·7, 17·7. $C_{26}H_{30}O_9$ requires C, 64·2; H, 6·2; $2CH_3{\cdot}CO$, 17·7%). B crystallised from benzene–ether in colourless prisms, m. p. 158—159° (Found: C, 62·4, 62·5; H, 5·9, 6·0; $CH_3{\cdot}CO$, 17·7, 18·0. $C_{26}H_{30}O_{10}$ requires C, 62·2; H, 6·0; $2CH_3{\cdot}CO$, 17·1%). The substance A (0·1 g.) was hydrolysed with 2% methyl-alcoholic sodium hydroxide (10 c.c.) on the water-bath for 10 minutes. The alcohol was removed, water (10 c.c.) added, and the solution acidified and heated on the water-bath for ½ hour; the product, C, isolated with chloroform, separated from methyl alcohol in slender prisms, m. p. 101—103° (Found: C, 63·2, 63·4; H, 6·2, 6·4. $C_{22}H_{26}O_8$ requires C, 68·2; H, 6·3%). In the same way, hydrolysis of B gave D, which crystallised from methyl alcohol in slender prisms, m. p. 147—148° (Found: C, 66·1, 66·3; H, 6·1, 6·2. $C_{22}H_{24}O_7$ requires C, 66·0; H, 6·0%). The compounds C and D contained no acetyl groups, gave no colour with tetranitromethane, and on oxidation with potassium permanganate in faintly alkaline solution they (0·2 g.) yielded veratric acid (0·05 g.). C or D (0·1 g.) was boiled with concentrated nitric acid (1 c.c.) for 5 minutes, and water added; the neutral product, isolated with ether, crystallised from methyl alcohol in pale yellow needles (0·02 g.), m. p. 126—127°, not depressed by 4 : 5-dinitroveratrole. The new formula (IV; R = veratryl) for the synthetic lactone does not simplify the interpretation of the structures of A, B, C, and D.

d-iso*Matairesinol Dimethyl Ether* (I; $R^1 = R^2$ = veratryl). (a) *l*-Matairesinol dimethyl ether (5 g.), $[\alpha]_D^{19°}$ −36°, was warmed for 5 minutes with a solution of sodium methoxide (from 0·64 g. of sodium) in methyl alcohol (25 c.c.), and the solution evaporated to dryness under reduced pressure. The sodium salt of the hydroxy-acid was dissolved in water (40 c.c.) and

heated in a sealed tube at 180° for 24 hours. The solution was acidified with dilute hydrochloric acid, lactonised by boiling for 5 minutes, and extracted with chloroform, and the extract washed with 1% sodium hydroxide solution. Removal of the solvent yielded a crude lactone (4·5 g.), m. p. 102—109°, $[\alpha]_D^{17°}$ +18·7° in chloroform (c = 7·91).

(b) *l*-Matairesinol dimethyl ether (5 g.), boiled with 50% potassium hydroxide solution (25 c.c.) for 24 hours, afforded a crude lactone (4·0 g.), $[\alpha]_D^{17°}$ +18·4° in chloroform (c = 9·24).

(c) *l*-Matairesinol dimethyl ether (5 g.), refluxed with a solution of sodium (2 g.) in absolute alcohol (20 c.c.) in a nitrogen atmosphere for 5 days, gave a crude lactone (3·5 g.), $[\alpha]_D^{17°}$ +17·9° in chloroform (c = 5·25).

Fractional crystallisation from methyl alcohol resolved the crude lactone (4·5 g.) into head and tail fractions, from which pure *l*-matairesinol dimethyl ether (2·1 g.) and d-iso*matairesinol dimethyl ether* (1·7 g.) respectively were isolated. During the separation frequent use was made of the greater speed of solution of the *d-iso*-form in methyl alcohol. *d-iso*Matairesinol dimethyl ether separated from methyl alcohol in long, feathery needles, m. p. 111—112°, $[\alpha]_D^{19°}$ +78° in chloroform (c = 4·01), and this value was unchanged after further crystallisations (Found : C, 68·4; H, 6·8. $C_{22}H_{26}O_6$ requires C, 68·4; H, 6·7%). Attempts to convert *d-iso*matairesinol dimethyl ether into the corresponding hydroxy-acid by the action of cold methyl-alcoholic potassium or barium hydroxide resulted in a quantitative recovery of *l*-matairesinol dimethyl ether. When heated with dilute sodium hydroxide solution at 180° for 24 hours, the *d-iso*-lactone was converted into the equilibrium mixture with $[\alpha]_D^{17°}$ +18°. *d-iso*Matairesinol dimethyl ether was converted into the *cyclo*dehydro-lactones (II) and (III) by the action of lead tetra-acetate as described previously (J., 1935, 633) for the *l*-lactone.

Dibromo-d-iso*matairesinol dimethyl ether*, prepared in acetic acid solution, separated from alcohol in long needles, m. p. 144°, $[\alpha]_D^{20°}$ +18·8° (c = 1·15) in chloroform (Found : C, 48·2; H, 4·2. $C_{22}H_{24}O_6Br_2$ requires C, 48·5; H, 4·5%). *Dinitro*-d-iso*matairesinol dimethyl ether*, prepared in acetic acid solution, separated from alcohol–chloroform in pale yellow plates, m. p. 161—162°, $[\alpha]_D^{20°}$ +105·5° in chloroform (c = 1·20) (Found after drying at 100° : C, 55·4; H, 5·2. $C_{22}H_{24}O_{10}N_2$ requires C, 55·4; H, 5·0%). The crystals probably contain solvent of crystallisation which is lost at 100° with modification of the crystalline form.

Rates of Hydrolysis of Lactones.—Excess of N/20-barium hydroxide was added to N/100-methyl-alcoholic solutions of the lactones and the rates of hydrolysis at 15° were determined by titrating aliquot portions with N/20-hydrochloric acid at suitable intervals. No special accuracy was aimed at, but the figures in Table I were reproducible to within 5% of the values given.

TABLE I.

	Time in hours :	0·5.	1·5.	3.	6.	8.	12.	17.
% Hydrolysis at 15°.	*l*-Matairesinol dimethyl ether	21	42	58	76	85	94	97
	*d-iso*Matairesinol dimethyl ether	21	40	56	76	84	94	—
	αγ-Bis-(3 : 4-dimethoxybenzyl)-butyrolactone	23	41	60	78	86	—	—
	l-Hinokinin	17	34	58	80	88	—	—
	αγ-Bis-(3 : 4-methylenedioxybenzyl)-butyrolactone	17	35	57	79	87	—	—

l-*Matairesinolic Acid Dimethyl Ether.*—*l*-Matairesinol dimethyl ether (1 g.) was warmed for 5 minutes with sodium methoxide (from 0·08 g. of sodium) in methyl alcohol (10 c.c.). The alcohol was removed, the sodium salt dissolved in water (15 c.c.), and the well-cooled solution carefully acidified with dilute acetic acid. The precipitate was collected, washed with water, and dissolved in a little cold acetone, and water gradually added; the *hydroxy-acid* separated in long prisms, which melted at 90—95° with loss of water, resolidified, and melted again at 127° (Found after drying over phosphoric oxide : C, 65·5; H, 7·0. $C_{22}H_{28}O_7$ requires C, 65·3; H, 6·9%). $[\alpha]_D^{18°}$ −32° in alcohol (c = 1·00).

γ-Hydroxy-αγ-bis-(3 : 4-dimethoxybenzyl)butyric acid, obtained similarly from the synthetic lactone (IV; R = veratryl) and isolated with chloroform, was an oil (Found after drying in a desiccator : C, 65·1; H, 7·1. $C_{22}H_{28}O_7$ requires C, 65·3; H, 6·9%).

d-iso*Matairesinolic Acid Dimethyl Ether.*—*l*-Matairesinol dimethyl ether was heated in a sealed tube with sodium hydroxide solution at 180° as described on p. 803. The mixed hydroxy-acids, precipitated with acetic acid, were dried in a desiccator, dissolved in alcohol, and boiled for 2 hours. The alcohol was removed, sodium bicarbonate solution added, and lactonic matter removed with chloroform. Addition of acetic acid to the bicarbonate liquor precipitated a gum, which slowly solidified and crystallised from aqueous alcohol in

small prisms, m. p. 160° (Found: C, 65·4; H, 6·8. $C_{22}H_{28}O_7$ requires C, 65·3; H, 6·9%). $[\alpha]_D^{18°}$ −23° in alcohol (c = 1·03). Lactonisation with hot dilute mineral acid yielded *d-iso*-matairesinol dimethyl ether, m. p. 111°. $[\alpha]_D^{19°}$ +78°.

Rates of Lactonisation of Hydroxy-acids.—Two methods were employed: (a) Excess of N/20-barium hydroxide was added to N/100-methyl-alcoholic solutions of the lactones. After 24 hours at 15° the concentration of the hydroxy-acid was determined by neutralisation with N/20-hydrochloric acid. An additional quantity of N/20-hydrochloric acid was then added to liberate the hydroxy-acid from its barium salt; a slight deficiency was used to prevent catalysis by free mineral acid. The solution was heated at 59° under reflux, and aliquot portions titrated at intervals with N/20-barium hydroxide (Table II). (b) As method (a) was not applicable for the *d-iso*-hydroxy-acid, the following was adopted. An N/100-solution of the hydroxy-acid in alcohol (250 c.c.) was diluted to 350 c.c. with water and heated at 59°. Aliquot portions were titrated at intervals with N/20-barium hydroxide (Table III). Results (*) in Table III illustrate the catalytic influence of mineral acids; the measurements were made with N/100-methyl-alcoholic solutions of the hydroxy-acids (250 c.c.), made up to 350 c.c. with N/40-hydrochloric acid. The figures in Tables II and III were reproducible to within 4% of the values recorded.

TABLE II.

	Time in hours:	1.	2.	4.	6.	10.	20.
% Lactonisation at 59°.	*l*-Matairesinol dimethyl ether or *d-iso*matairesinol dimethyl ether	11	17	25	31	44	74
	αγ-Bis-(3 : 4-dimethoxybenzyl)-butyrolactone; either before or after action of alkali at 180°	8·5	11	12	14	19	24
	l-Hinokinin	19	27	37	43	53	—
	αγ-Bis-(3 : 4-methylenedioxybenzyl)-butyrolactone	13	15	18	—	24	29

TABLE III.

	Time in hours:	1.	2.	4.	6.	10.	20.
% Lactonisation at 59°.	*l*-Matairesinolic acid dimethyl ether	6	11	19	24	31	42
		* 95·5	97	98	—	—	—
	*d-iso*Matairesinolic acid dimethyl ether	3	4	5	6	7	9
		* 35	54	75	87	—	—
	γ-Hydroxy-αγ-bis-(3 : 4-dimethoxybenzyl)butyric acid	4	6	8·5	10	12	13

γ-Veratryl-β-methylbutyrolactone (VII).—β-Veratroyl-*n*-butyric acid (VIII) (1 g.) (this vol., p. 811) in absolute alcohol (25 c.c.) was gradually added to molten sodium (4 g.) in an oil-bath at 160°. After heating for 1 hour at 160—180°, the solution was cooled and diluted with water, the alcohol removed, and the mixture acidified and lactonised by boiling for 15 minutes. The product was extracted with chloroform, the extract washed with sodium bicarbonate solution, and the chloroform removed; the residue crystallised from ether–light petroleum in colourless prisms, m. p. 112—113° (Found: C, 66·3; H, 7·1. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%).

2-Cyano-2-phenylcyclopentane-1 : 3-dione (IX).—Phenylacetonitrile (5·8 g.), ethyl succinate (8·7 g.), and sodium ethoxide (from 1·15 g. of sodium) in alcohol (25 c.c.) were refluxed for 4 hours. After addition of water and removal of neutral matter with ether, the alkaline solution was acidified. The product, isolated with ether, was an oil, which on distillation at 1 mm. yielded a fraction (3 g.), b. p. about 120°, and a fraction (4·5 g.), b. p. 180—190°/1 mm. The latter solidified and crystallised from methyl alcohol–chloroform in long flat prisms, m. p. 149° (Found: C, 72·5; H, 4·5. $C_{12}H_9O_2N$ requires C, 72·3; H, 4·6%). The compound contained nitrogen and gave no coloration with ferric chloride.

γ-Chloro-α-veratrylacetone (X).—Pure veratrylacetic acid (2·5 g.) was warmed gently with pure thionyl chloride (5 g.) for 20 minutes; the excess of thionyl chloride was removed under reduced pressure, the final traces were eliminated by two additions and subsequent removals of benzene, and the residual acid chloride was dissolved in ether (10 c.c.) and gradually added with cooling to a solution of diazomethane (from 6 c.c. of nitrosomethylurethane) in ether (30 c.c.). After 3 hours, ethereal hydrogen chloride was added until evolution of nitrogen ceased, the solution was washed, first with water and then with sodium bicarbonate solution, and dried, and the solvent removed. The residual oil crystallised from ether–light petroleum in colourless needles (2·3 g.), m. p. 52° (Found: C, 57·7; H, 5·4; Cl, 15·0. $C_{11}H_{13}O_3Cl$ requires C, 57·7; H, 5·7; Cl, 15·5%), which rapidly deposited sodium chloride on addition to alcoholic sodium ethoxide.

α-(2-Chloropiperonyl)-γ-chloroacetone (XI).—Piperonylacetic acid (5·0 g.), treated in precisely the same way, gave a *dichloro*-compound, possibly (XI), which crystallised from ether–light petroleum in colourless needles (4 g.), m. p. 107—108° (Found : C, 48·5; H, 3·3; Cl, 28·0. $C_{10}H_8O_3Cl_2$ requires C, 48·2; H, 3·2; Cl, 28·7%). This dichloro-compound was boiled with excess of 10% methyl-alcoholic potassium hydroxide for 3 hours; the alcohol was removed, neutral matter extracted with ether, the alkaline liquor acidified with nitric acid, and the hydrolysable chlorine estimated volumetrically (Found : Cl, 14·6. $C_{10}H_8O_3Cl_2$ requires 1Cl, 14·4%).

γ-(3 : 4-Dimethoxybenzyl)butyrolactone (VI; R^1 = OMe, R^2 = H).—(a) α-Acetyl-γ-(3 : 4-dimethoxybenzyl)butyrolactone (VI; R^1 = OMe, R^2 = $CO{\cdot}CH_3$) (1 g.) (J., 1936, 727) was heated on a water-bath for 5 hours with 20% methyl-alcoholic potassium hydroxide (10 c.c.). Water was added, the methyl alcohol removed, and neutral products containing methyl γ-hydroxy-δ-veratrylbutyl ketone (see p. 807) extracted with ether. The alkaline liquor was acidified and lactonised, and the product, isolated with ether, crystallised from ether–methyl alcohol; yield, 0·3 g.

(b) *O*-Methyleugenol oxide (3·9 g.) was added to a solution of ethyl sodiomalonate (from 0·46 g. of sodium and 3·2 g. of ethyl malonate) in alcohol (20 c.c.). After 4 days the crystalline sodio-derivative was collected, washed with a little alcohol and ether, and decomposed with dilute sulphuric acid. The product, isolated with ether, was boiled with a slight excess of 10% methyl-alcoholic potassium hydroxide for 30 minutes and after removal of the alcohol, the solution was acidified, lactonised, and extracted with chloroform. The extract was washed with sodium bicarbonate solution, the solvent removed, and the residue distilled (b. p. 190—200°/1 mm.) and crystallised; yield, 0·8 g.

(c) A solution of veratrylacetyl chloride (prepared from 10 g. of the acid as described on p. 805) in ether (50 c.c.) was added slowly with stirring to an ice-cold solution of ethyl sodioacetosuccinate (from 1·3 g. of sodium and 12 g. of the ester) in ether (50 c.c.). After 12 hours, the mixture was refluxed for 15 minutes and poured into water. The ethereal layer was rapidly washed with 1% sodium hydroxide solution and then shaken for 4 hours with 4% sodium hydroxide solution (120 c.c.). The alkaline layer was acidified and extracted with ether, the extract dried, and the solvent removed. The residual oil, which gave a red ferric test, was boiled for 12 hours with 5% sulphuric acid (80 c.c.) and the acidic products, isolated with ether, were taken up in sodium hydroxide solution and saturated with sulphur dioxide. After removal of impurities in ether, the aqueous layer was acidified, heated on the water-bath for 30 minutes, and extracted with ether. Removal of the ether yielded *γ-keto-δ-veratrylvaleric acid* (XII; R = OMe) (1·2 g.) as an oil (Found after drying in a desiccator : C, 62·1; H, 6·6. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%). The keto-acid (XII; R = OMe) (1 g.) was dissolved in absolute alcohol (30 c.c.) and added gradually to sodium (4 g.) at 180°. After 3 hours, the lactone was isolated as described in a similar case (p. 805) and was purified first by distillation at 1 mm. and then by crystallisation; yield, 0·6 g.

γ-(3 : 4-Dimethoxybenzyl)butyrolactone (VI; R^1 = OMe, R^2 = H) obtained by methods (a), (b), and (c), crystallised from ether–methyl alcohol in colourless needles, m. p. 83—84° (Found : C, 66·2; H, 7·0. $C_{13}H_{16}O_4$ requires C, 66·0; H, 6·8%). The *nitro*-derivative, prepared in acetic acid solution, separated from methyl alcohol in pale yellow prisms, m. p. 115—116° (Found : C, 55·5; H, 5·5. $C_{13}H_{15}O_6N$ requires C, 55·5; H, 5·4%). Oxidation with sodium hypobromite or potassium permanganate converted the lactone (VI; R^1 = OMe, R^2 = H) into veratric acid, and the lactone was recovered from attempted cyclisations with methyl-alcoholic hydrogen chloride, acetic–hydrochloric acid, and 80% sulphuric acid.

γ-(3 : 4-Methylenedioxybenzyl)butyrolactone (VI; R^1R^1 = CH_2O_2, R^2 = H).—This compound, obtained previously (J., 1936, 351) (a) from ethyl malonate and safrole oxide and (b) by hydrolysis of α-acetyl-γ-(3 : 4-methylenedioxybenzyl)butyrolactone (VI; R^1R^1 = CH_2O_2, R^2 = $CO{\cdot}CH_3$), is an oil. Condensation of piperonyl chloride (10 g.) and ethyl sodioacetoglutarate, and hydrolysis of the product as described above for the dimethoxy-analogue, yielded γ-keto-δ–piperonylvaleric acid (XII; RR = CH_2O_2) (1·3 g.), which crystallised from ether–light petroleum in long needles, m. p. 87° (Fittig and Weinstein, *loc. cit.*, give 87°) (Found : C, 60·9; H, 5·2. Calc. for $C_{12}H_{12}O_5$: C, 61·0; H, 5·1%). Reduction of this keto-acid (1 g.) with sodium and alcohol as described above yielded the lactone (VI; R^1R^1 = CH_2O_2, R^2 = H) as an oil (0·8 g.), b. p. 170—180°/0·1 mm. The identity of the oil prepared by the three methods has been established by comparison of crystalline derivatives. The *nitro*-derivative, prepared in acetic acid solution, crystallised from methyl alcohol in pale yellow prisms, m. p. 98—99° (Found : C, 54·2; H, 4·3. $C_{12}H_{11}O_6N$ requires C, 54·3; H, 4·2%). The hydroxy-acid, prepared by hydrolysis with barium hydroxide, crystallised from ether–light petroleum in

colourless plates, m. p. 95° (Fittig and Weinstein, *loc. cit.*, give 95°) (Found: C, 60·8; H, 5·7. Calc. for $C_{12}H_{14}O_5$: C, 60·6; H, 5·9%).

Methyl γ-hydroxy-δ-veratrylbutyl ketone (XV; R = OMe) was obtained as an oil, b. p. 185—188°/0·3 mm. (Found: C, 66·4; H, 8·2. $C_{14}H_{20}O_4$ requires C, 66·7; H, 8·0%), by the action of 2% sodium hydroxide solution on α-acetyl-γ-(3 : 4-dimethoxybenzyl)butyrolactone (VI; R^1 = OMe, R^2 = CO·CH_3) as described previously (J., 1936, 351) for the methylenedioxy-analogue.

6 : 7-*Dimethoxy*-3 : 1-endo*methyleneoxy*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (XIII; R^1 = OMe, R^2 = H).—Concentrated hydrochloric acid (9 c.c.) was added to a solution of the above keto-alcohol (XV; R = OMe) (1 g.) in glacial acetic acid (5 c.c.) and after 24 hours the mixture was diluted with water and extracted with ether; the extract was washed with sodium bicarbonate solution and dried, and the solvent removed. The residue crystallised from light petroleum in compact prisms (0·75 g.), m. p. 96° (Found: C, 71·6; H, 7·8. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). Zerewitinoff determinations showed the absence of hydroxyl groups and the compound was recovered after heating with potassium hydrogen sulphate at 180°.

6 : 7-*Methylenedioxy* - 3 : 1 - endo*methyleneoxy* - 1 - *methyl* - 1 : 2 : 3 : 4 - *tetrahydro* - *naphthalene* (XIII; R^1R^1 = CH_2O_2, R^2 = H), obtained similarly from methyl γ-hydroxy-δ-piperonylbutyl ketone (XV; RR = CH_2O_2) (J., 1936, 351) and acetic–hydrochloric acid, separated from light petroleum in colourless prisms, m. p. 85—86° (Found: C, 71·3; H, 6·4. $C_{13}H_{14}O_3$ requires C, 71·6; H, 6·5%). Hydroxyl groups were absent and the compound was not dehydrated with potassium hydrogen sulphate at 180°.

6 : 7-*Dimethoxy*-3 : 1-endo*methyleneoxy*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-*carboxylic Acid* (XIII; R^1 = OMe, R^2 = CO_2H).—Concentrated hydrochloric acid (9 c.c.) was added to a solution of α-acetyl-γ-(3 : 4-dimethoxybenzyl)butyrolactone (VI; R^1 = OMe, R^2 = CO·CH_3) (1 g.) in glacial acetic acid (10 c.c.) and after 24 hours the mixture was diluted with water and extracted with chloroform; the extract was washed several times with water, and the solvent removed. The residue separated from ether–light petroleum in colourless stout prisms (0·7 g.), m. p. 182—183° (Found: C, 64·5; H, 6·7; OH, 10·0. $C_{15}H_{18}O_5$ requires C, 64·7; H, 6·5; OH, 9·6%). The *methyl* ester (XIII; R^1 = OMe, R^2 = CO_2Me), prepared in 80% yield by the action of boiling methyl-alcoholic hydrogen chloride on the lactone (VI; R^1 = OMe, R^2 = CO·CH_3), and isolated with chloroform, crystallised from methyl alcohol in colourless prisms, m. p. 142° (Found: C, 65·7; H, 6·9. $C_{16}H_{20}O_5$ requires C, 65·7; H, 6·9%). This ester contained no hydroxyl groups and on hydrolysis with methyl-alcoholic potassium hydroxide yielded the acid, m. p. 182—183°.

6 : 7-*Methylenedioxy* - 3 : 1 - endo*methyleneoxy*-1-*methyl* - 1 : 2 : 3 : 4 - *tetrahydronaphthalene*-2-*carboxylic acid* (XIII; R^1R^1 = CH_2O_2, R^2 = CO_2H), obtained in 70% yield from α-acetyl-γ-(3 : 4-methylenedioxybenzyl)butyrolactone (VI; R^1R^1 = CH_2O_2, R^2 = CO·CH_3) by the action of acetic–hydrochloric acid, separated from ether–light petroleum in stout prisms, m. p. 219—220° (Found: C, 64·3; H, 5·7; OH, 11·0. $C_{14}H_{14}O_5$ requires C, 64·1; H, 5·4; OH, 10·5%). The *methyl* ester (XIII; R^1R^1 = CH_2O_2, R^2 = CO_2Me), obtained in 70% yield by the action of methyl-alcoholic hydrogen chloride on the lactone (VI; R^1R^1 = CH_2O_2, R^2 = CO·CH_3), separated from methyl alcohol in prisms, m. p. 156—157° (Found: C, 65·5; H, 6·0. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·8%). Hydroxyl groups were absent and hydrolysis gave the acid, m. p. 219—220°.

6 : 7-*Dimethoxy*-1 : 3-*dimethylnaphthalene* (XVI).—(a) The compound (XIII; R^1 = OMe, R^2 = H) or the acid (XIII; R^1 = OMe, R^2 = CO_2H) (1 part) was heated with selenium (1 part) at 280° for 12 hours. A chloroform extract of the product was evaporated, the residue extracted with light petroleum (carbon), and the solvent removed. A methyl-alcoholic solution of picric acid was added to the product, and the recrystallised picrate, m. p. 116—118°, was decomposed by shaking its ethereal solution with dilute aqueous ammonia. (b) A suspension of β-veratroyl-*n*-butyric acid (VIII) (2 g.) in concentrated hydrochloric acid (15 c.c., added in two portions) was refluxed with amalgamated zinc (12 g.) for 12 hours. The oily product (2 g.), isolated with chloroform, was heated in the water-bath for 30 minutes with 80% sulphuric acid (8 c.c.), water added, and the mixture extracted with chloroform. The extract was washed with dilute sodium hydroxide solution and dried, and the solvent removed; the residual 1-*keto*-6 : 7-*dimethoxy*-3-*methyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* crystallised from ether–light petroleum or a small amount of methyl alcohol in large prisms (1·3 g.), m. p. 132—133° (Found: C, 70·8; H, 7·5. $C_{13}H_{16}O_2$ requires C, 70·8; H, 7·4%). A solution of methylmagnesium iodide (from 0·07 g. of magnesium and 0·4 g. of methyl iodide) in ether (5 c.c.) was added to a solution of the ketone (0·5 g.) in benzene (5 c.c.); after refluxing for 30 minutes, the mixture was decomposed with

dilute hydrochloric acid and the product (0·5 g.) was dehydrogenated with selenium (1 g.) at 280° and isolated as described above.

6 : 7-*Dimethoxy*-1 : 3-*dimethylnaphthalene* (XVI), prepared by methods (a) and (b), separated from light petroleum in rosettes of long prisms, m. p. 97—98° (Found : C, 77·7; H, 7·5. $C_{14}H_{16}O_2$ requires C, 77·7; H, 7·4%). The *picrate* crystallised from methyl alcohol in red needles, m. p. 119—120° (Found : C, 53·4; H, 4·4. $C_{14}H_{16}O_2,C_6H_3O_7N_3$ requires C, 53·8; H, 4·3%).

The following compounds were prepared during the course of this research.

α-*Cyano*-β-(O-*benzylvanillyl*)*acrylic Acid.*—A 25% aqueous solution of sodium cyanoacetate (20 c.c.) was added to a warm solution of *O*-benzylvanillin (9 g.) in alcohol (5 c.c.). 20% Sodium hydroxide solution (5 c.c.) was added, and the mixture shaken with cooling for 1 hour. The pale yellow solid which rapidly separated was decomposed with hydrochloric acid, and the *acid* was collected and crystallised from methyl alcohol; yellow needles (11 g.), m. p. 202°, were obtained (Found : C, 70·1; H, 4·7. $C_{18}H_{15}O_4N$ requires C, 69·8; H, 4·9%).

Methyl α-*cyano*-β-(O-*benzylvanillyl*)*propionate* was prepared by adding 2% sodium amalgam (300 g.) with rapid stirring and ice-cooling to a suspension of the above acid (10 g.) in water (250 c.c.). Acidification yielded a gummy acid, which was isolated with chloroform and esterified by boiling with 4% methyl-alcoholic hydrogen chloride (100 c.c.) for 4 hours. The mixture was poured into water and extracted with ether, the extract washed with sodium bicarbonate solution and dried, and the ether removed. The *methyl* ester crystallised from methyl alcohol in colourless prisms (9 g.), m. p. 72° (Found : C, 70·4; H, 6·0. $C_{19}H_{19}O_4N$ requires C, 70·2; H, 5·8%).

β-*Hydroxy*-γ-*phenoxy*-α-*phenylpropane.*—α-Phenoxyphenylacetone (Pfeiffer and Willems, *Ber.*, 1929, **62**, 1243) (1 g.) was gently boiled with aluminium *iso*propoxide (4·5 g.) in *iso*propyl alcohol (12 c.c.) and the acetone was removed through a short column. After 1 hour the solvent was removed under reduced pressure, and dilute hydrochloric acid added; the product, isolated with ether, crystallised from ether–light petroleum in hexagonal plates (0·8 g.), m. p. 92° (Found : C, 78·7; H, 7·0. $C_{15}H_{16}O_2$ requires C, 78·8; H, 7·0%).

α-*Cyano*-β-*keto*-γ-*phenoxy*-α-*veratrylpropane* was prepared by boiling veratrylacetonitrile (5·3 g.) and methyl phenoxyacetate (5 g.) with sodium ethoxide (from 0·7 g. of sodium) in alcohol (15 c.c.). After 2 hours, water was added, neutral matter removed with ether, and the alkaline liquor acidified. The *cyano-ketone*, isolated with ether, crystallised from aqueous methyl alcohol in colourless prisms (6 g.), m. p. 111—112° (Found : C, 69·7; H, 5·3. $C_{18}H_{17}O_4N$ requires C, 69·5; H, 5·5%).

β-*Keto*-γ-*phenoxy*-α-*veratrylbutyramide* was prepared by hydrolysing the above cyano-ketone (5 g.) with acetic acid (120 c.c.) and fuming hydrochloric acid (80 c.c.) in the cold. After 2 days, water was added, and some of the solvent removed under diminished pressure; the product crystallised from acetic acid in colourless needles (4·8 g.), m. p. 173° (Found : C, 65·7; H, 5·6. $C_{18}H_{19}O_5N$ requires C, 65·7; H, 5·8%), which gave a red-brown ferric test.

γ-*Phenoxy*-α-*veratrylacetone*, obtained in 60% yield by boiling the above amide for 6 hours with 8% hydrochloric acid (50 parts), crystallised from ether–light petroleum or a little methyl alcohol in slender prisms, m. p. 63—64° (Found : C, 71·4; H, 6·1. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%).

β-*Hydroxy*-γ-*phenoxy*-α-*veratrylpropane*, prepared by reducing the above ketone (1·4 g.) with aluminium *iso*propoxide (5 g.) in *iso*propyl alcohol (12 c.c.), separated from ether–light petroleum in compact prisms (1 g.), m. p. 100° (Found : C, 71·0; H, 6·9. $C_{17}H_{20}O_4$ requires C, 70·8; H, 7·0%).

γ-*Veratroyl*-n-*butyric Acid.*—Veratrole (6 g.) and glutaric anhydride (5 g.) were added to aluminium chloride (12 g.) in nitrobenzene (50 c.c.) at 0°. After 12 hours, dilute hydrochloric acid was added, the nitrobenzene removed in steam, and the solid residue collected after cooling. The crude acid was dissolved in sodium bicarbonate solution, recovered, dried, and crystallised from benzene; colourless prisms (5 g.), m. p. 140—142°, were obtained (Found : C, 61·6; H, 6·5. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·3%).

δ-*Veratrylvaleric acid*, obtained by heating the above keto-acid (1 g.) with concentrated hydrochloric acid (10 c.c.) and amalgamated zinc (5 g.) for 12 hours, crystallised from benzene in colourless small prisms (0·7 g.), m. p. 78° (Found : equiv., 239. $C_{13}H_{18}O_4$ requires equiv., 238).

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