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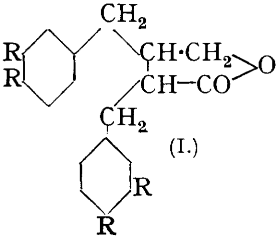
373. *The Constituents of Natural Phenolic Resins. Part XIII. The Synthesis of* dl-, d-, *and* l-*Hinokinin.*

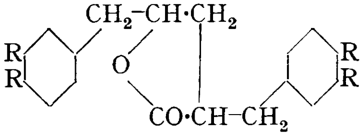
By Robert D. Haworth and David Woodcock.

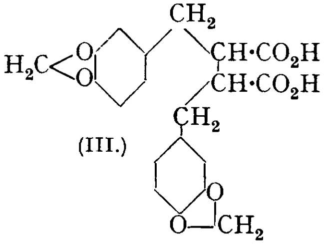
Measurements of the rates of hydrolysis and lactonisation of αβ-di-(3 : 4-methylenedioxybenzyl)butyrolactone (I; RR = CH_2O_2) (Keimatsu, Ishiguro, and Nakamura, *J. Pharm. Soc. Japan*, 1935, **55**, 185) and the corresponding hydroxy-acid respectively confirm the structure assigned to the compound.

αβ-Di-(3 : 4-methylenedioxybenzyl)succinic acid occurs in two forms, m. p. 240° and 201° (decomp.). Contrary to the views of Keimatsu, Ishiguro, and Nakamura (*loc. cit.*) the higher-melting form is the *meso*-modification and the lower-melting isomer has been resolved by means of strychnine. The d- and the l-*acid* yield active *anhydrides*, which, on reduction with amalgamated aluminium in moist ether–benzene solution, yield *d*- and *l*-αβ-di-(3 : 4-methylenedioxybenzyl)butyrolactone respectively. The *l*-form of the lactone (I; RR = CH_2O_2) is identical with natural *l*-hinokinin, and the synthesis strengthens the opinion that the natural products of this type possess the *trans*-configuration.

In Part V (J., 1936, 725) compounds considered to be αβ-di-(3 : 4-methylenedioxybenzyl)-(I; RR = CH_2O_2) and αβ-di-(3 : 4-dimethoxybenzyl)-butyrolactones (I; R = OMe) were synthesised by the condensation of appropriate allylbenzene oxides and benzylcyanoacetates. Later (this vol., p. 797), lead tetra-acetate dehydrogenation experiments and measurements of the rates of lactonisation led to the conclusion that these structures were erroneous and that the substances were derivatives of αγ-dibenzylbutyrolactone (II). While the experiments described in Part V were in progress, Keimatsu, Ishiguro, and Nakamura (*J. Pharm. Soc. Japan*, 1935, **55**, 185) prepared αβ-di-(3 : 4-methylenedioxybenzyl)butyrolactone by reducing the anhydride of αβ-di-(3 : 4-methylenedioxybenzyl)succinic acid (III) (Stobbe and co-workers, *Annalen*, 1911, **380**, 78) with amalgamated aluminium in moist ethereal solution, and the recorded melting point of the lactone coincided with that of αγ-di-(3 : 4-methylenedioxybenzyl)butyrolactone (II; RR = CH_2O_2) obtained from safrole oxide and methyl 3 : 4-methylenedioxybenzylcyanoacetate.


(I.)


(II.)


(III.)

The work of the Japanese chemists has now been repeated and mixed melting point observations have shown that their lactone was not identical with αγ-di-(3 : 4-methylenedioxybenzyl)butyrolactone. As the rate of hydrolysis of their lactone and the rate of lactonisation of the corresponding hydroxy-acid were indistinguishable from those of natural *l*-hinokinin (I; RR = CH_2O_2) and the derived hydroxy-acid respectively, the

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claim of these chemists to have effected the synthesis of αβ-di-(3 : 4-methylenedioxybenzyl)butyrolactone (*dl*-hinokinin or the diastereoisomeride, *dl-iso*hinokinin) (I ; RR = CH_2O_2) is substantiated.

Keimatsu, Ishiguro, and Nakamura (*loc. cit.*) described two forms of αβ-di-(3 : 4-methylenedioxybenzyl)succinic acid (III) melting at 236—238° and 191—193°. These yielded the same anhydride, m. p. 160—161°, which was converted into the lower-melting acid on hydration. We find that the melting point of the lower-melting acid is 201° (decomp.), but otherwise the previous results have been confirmed. Keimatsu, Ishiguro, and Nakamura (*loc. cit.*) regard the higher-melting acid as the racemate, and the lower-melting acid and the anhydride as the *meso*-forms, but we are unable to accept these stereochemical conclusions. It has been shown (this vol., p. 798) that *d-iso*matairesinol dimethyl ether, the diastereoisomeride of *l*-matairesinol dimethyl ether (I ; R = OMe), is extremely sensitive to alkaline reagents, and the observed stability of the synthetic αβ-di-(3 : 4-methylenedioxybenzyl)butyrolactone (I ; RR = CH_2O_2) towards alkali suggests that the synthetic lactone is *dl*-hinokinin and not *dl-iso*hinokinin. This conclusion is confirmed by comparison of the rates of hydrolysis and lactonisation of the lactones and derived hydroxy-acids respectively. Furthermore, if the anhydride of (III) has the *meso* (*cis*)-configuration as suggested by the Japanese chemists, and if the absence of optical inversion during reduction with amalgamated aluminium is assumed, the synthetic lactone will possess the *cis*-configuration. This conclusion is the reverse of the opinion expressed on several occasions (*Ann. Reports*, 1937, **33**, 277, footnote ; J., 1937, 387 ; this vol., p. 799) that *l*-matairesinol and *l*-hinokinin possess the *trans*-configuration. As far as can be ascertained from the publication of Keimatsu, Ishiguro, and Nakamura (*loc. cit.*), the configurations assigned to the two forms of αβ-di-(3 : 4-methylenedioxybenzyl)succinic acid (III) are based entirely upon the untrustworthy rule that the racemate possesses the higher melting point. There are numerous exceptions to this rule and in the closely analogous case of αβ-dibenzylsuccinic acid, Cordier (*Compt. rend.*, 1931, **192**, 361) has proved by resolution that the lower melting isomer is the racemate. Rigid determination of structure in these cases therefore demands resolution methods and their application has led to the disproof of the stereochemical views of Keimatsu, Ishiguro, and Nakamura (*loc. cit.*). The higher-melting form of αβ-di-(3 : 4-methylenedioxybenzyl)succinic acid (III) proved to be the *meso*-form, but the isomer, m. p. 201° (decomp.), has been resolved into optical antipodes and consequently represents the racemic modification. The resolution was easily effected by means of strychnine and d- and l-αβ-*di*-(3 : 4-*methylenedioxybenzyl*)*succinic acids*, m. p. 175°, $[\alpha]_D^{17°}$ 12·1° and − 12·4° respectively, were obtained from the *strychnine* salts. Crystallisation of an equimolecular mixture of the *d*- and the *l*-modification yielded the racemate, m. p. 201° (decomp.).

When *d*- and *l*-αβ-di-(3 : 4-methylenedioxybenzyl)succinic acid (III) were boiled with acetic anhydride, they were converted into lævo- and dextro-rotatory *anhydrides*, m. p. 144°, respectively, and crystallisation of equimolecular quantities of these *d*(−)- and *l*(+)-anhydrides yielded the racemate, m. p. 160—161°. This inversion in sign of optical rotatory power is in no way remarkable ; the active forms of hexahydrophthalic and camphoric acids show a similar inversion on anhydride formation. When, however, active anhydrides are reduced to butyrolactone derivatives by means of amalgamated aluminium in moist ether–benzene solution, a further inversion of optical rotatory power is observed. The *d*(−)- and the *l*(+)-anhydride gave d- and l-αβ-*di*-(3 : 4-*methylenedioxybenzyl*)*butyrolactone* (I ; RR = CH_2O_2), m. p. 65—66°, $[\alpha]_D^{17°}$ + 33·8° and − 34·0° respectively, and crystallisation of equimolecular quantities of the optical antipodes yielded the racemate, m. p. 108°. The identity of the *l*-lactone with *l*-hinokinin (*l*-cubebinolide *) was established by direct comparison of the lactones and their dibromo- and dinitro-substitution products,

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* It has been shown by Mameli (*Gazzetta*, 1935, **65**, 886) that cubebinolide has $[\alpha]_D^{16°}$ −33·7° and not + 33·7° as previously reported (*ibid.*, 1912, **42**, 551). Consequently cubebinolide and hinokinin are identical (see Yoshiki and Ishiguro, *loc. cit.* ; Keimatsu and Ishiguro, *J. Pharm. Soc. Japan*, 1935, **55**, 45 ; Mameli, *Gazzetta*, 1935, **65** 886 ; Briggs, *J. Amer. Chem. Soc.*, 1935, **57**, 1383) and not optical antipodes as stated in previous parts of this series (J., 1936, 727 ; 1937, 387 ; *Ann. Reports*, 1936, **33**, 273).

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and confirmed by measurements of the rates of hydrolysis of the lactones and the rates of lactonisation of the corresponding hydroxy-acids. Recently Erdtman (*Svensk Kem. Tidskr.*, 1938, **50**, 163) has encountered dimorphism in the case of dinitro*epi*pinoresinol dimethyl ether, and a similar phenomenon has been observed with dinitrohinokinin. Yoshiki and Ishiguro (*J. Pharm. Soc. Japan*, 1933, **53**, 11) and Mameli (*Gazzetta*, 1921, **51**, 353) describe *l*-dinitrohinokinin as pale yellow prisms, m. p. 184°. For a considerable period we were unable to reproduce this result; instead, both natural and synthetic *l*-hinokinin yielded the same dinitro-derivative, m. p. 163—164°. Eventually a dinitration of the synthetic lactone, carried out under apparently standard conditions, yielded the dinitro-derivative, m. p. 184—185°, which was also obtained later from natural *l*-hinokinin. The two forms are dimorphous and either could be obtained by inoculating solutions with the appropriate crystal.

The above synthesis of *l*-hinokinin strengthens the opinion, previously expressed, that the natural lactone possesses the *trans*-configuration, and a synthesis of *l*-matairesinol dimethyl ether along similar lines is in progress.

EXPERIMENTAL.

αβ-Di-(3 : 4-methylenedioxybenzylidene)succinic acid was prepared by the following modification of Stobbe's method (*loc. cit.*). A solution of piperonal (5 g.) and ethyl succinate (3 g.) in ether (30 c.c.) was added to a suspension of sodium ethoxide (from sodium, 0·8 g.) in ether (30 c.c.); a buff-coloured precipitate rapidly separated. The mixture was kept for 7 days in the ice-chest, water then added, the aqueous layer removed and acidified, and the acid collected. It crystallised from acetic acid in pale yellow prisms (3 g.), m. p. 207—208°, which contained solvent of crystallisation (Found: C, 57·2; H, 4·6; equiv., 123. Calc. for $C_{20}H_{14}O_8,2CH_3{\cdot}CO_2H$: C, 57·4; H, 4·4%; equiv., 125), or from acetone–benzene in pale yellow prisms, m. p. 228° (Found: C, 62·7; H, 3·7. Calc. for $C_{20}H_{14}O_8$: C, 62·8; H, 3·6%). The anhydride, obtained in 90% yield by refluxing the acid with acetic anhydride (5 parts) for 1 hour, crystallised from benzene in orange plates, m. p. 212—213° (Found: C, 65·7; H, 3·4. Calc. for $C_{20}H_{12}O_7$: C, 65·9; H, 3·3%). Stobbe (*loc. cit.*) gives 210° as the m. p. of both the acid and its anhydride.

meso-αβ-*Di-(3 : 4-methylenedioxybenzyl)succinic Acid* (III).—The preceding acid (8 g.) was dissolved in 1% sodium hydroxide solution (500 c.c.) and reduced by the gradual addition of 4% sodium amalgam (2400 g.) at 80—90°, carbon dioxide being passed through the solution. After 12 hours the liquid was filtered and acidified, and the crude acid (7 g.) collected. Crystallisation from acetic acid yielded the *meso*-form of the acid (III) (4 g.) in colourless prisms, m. p. 240—241° (Found: C, 62·0; H, 4·8. Calc. for $C_{20}H_{18}O_8$: C, 62·2; H, 4·7%). Attempts to resolve the acid by means of strychnine, brucine, or cinchonine were unsuccessful. A small amount of the *dl*-form of the acid (III) was obtained from the acetic acid mother-liquor, but this acid was obtained more conveniently as described below.

dl(trans)-αβ-*Di-(3 : 4-methylenedioxybenzyl)succinic Anhydride.*—The *meso*-acid (III) (2 g.) was refluxed with acetic anhydride (10 c.c.) for 1 hour, and the solution evaporated to dryness under reduced pressure. The residual oil, crystallised from a little benzene (carbon), yielded the anhydride (1·7 g.) in colourless needles, m. p. 160—161° (Found: C, 65·3; H, 4·2. Calc. for $C_{20}H_{16}O_7$: C, 65·2; H, 4·3%).

dl-αβ-*Di-(3 : 4-methylenedioxybenzyl)succinic Acid* (III).—The *dl*-anhydride (7 g.) was suspended in water and boiled during the gradual addition of 8% sodium hydroxide solution until a permanent alkaline reaction to phenolphthalein was obtained. The cooled solution was acidified, and the *dl*-acid collected; it crystallised from methyl alcohol in stout hexagonal prisms (6·5 g.), m. p. 201° (decomp.) (Found: C, 62·4; H, 4·6. Calc. for $C_{20}H_{18}O_8$: C, 62·2; H, 4·7%).

Resolution. A solution of the *dl*-acid (5·2 g.) and strychnine (9·3 g.) in boiling alcohol (300 c.c.) was diluted with hot water (400 c.c.), filtered, and allowed to cool. The *strychnine* salt of the *l*-acid, which gradually separated, was twice crystallised from 50% alcohol; large prismatic plates (7·1 g.), which gradually decomposed at 260° after softening at about 140°, were obtained (Found: C, 60·5; H, 6·5; loss in a vacuum at 115°, 13·8. $2C_{21}H_{22}O_2N_2,C_{20}H_{18}O_8,9{\cdot}5H_2O$ requires C, 60·7; H, 6·6; loss, 14·0%). In chloroform solution (*c*, 1·014) the salt had $[\alpha]_D^{18°}$ — 29·6°. Concentration of the mother-liquors gave the *strychnine* salt of the *d*-acid, which, after two crystallisations from hot water, was obtained in colourless needles (6·8 g.), gradual

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decomp. at about 240° after softening at 140° (Found : C, 66·3; H, 5·9; loss in a vacuum at 115°, 6·3. $2C_{21}H_{22}O_2N_2,C_{20}H_{18}O_8,4H_2O$ requires C, 66·1; H, 6·3; loss, 6·4%). In chloroform (*c*, 0·880) the salt had $[\alpha]_{\mathrm{D}}^{17^\circ}$ − 67·0°. The greater lævorotatory value of the strychnine salt of the *d*-acid is probably connected with inversion in optical rotatory power during salt formation. Although quantitative measurements have not been made, it has been observed that the *d*- and the *l*-acid yield lævo- and dextro-rotatory solutions respectively on neutralisation with dilute sodium hydroxide solution.

The strychnine salts were dissolved in chloroform and shaken with dilute aqueous ammonia, and the acids, precipitated by acidification of the alkaline solutions, were collected and crystallised from methyl alcohol. d-αβ-*Di*-(3 : 4-*methylenedioxybenzyl*)*succinic acid* (III) crystallised in colourless prisms, m. p. 174—175° (Found : C, 62·2; H, 4·7. $C_{20}H_{18}O_8$ requires C, 62·2; H, 4·7%). In acetone solution (*c*, 0·992) it had $[\alpha]_{\mathrm{D}}^{17^\circ}$ + 12·1°. The l-*acid*, colourless prisms, m. p. 174—175° (Found : C, 62·2; H, 4·6%), had $[\alpha]_{\mathrm{D}}^{17^\circ}$ − 12·4° in acetone solution (*c*, 1·032).

d(−)- *and* l(+)-αβ-*Di*-(3 : 4-*methylenedioxybenzyl*)*succinic anhydrides*, obtained in 90% yields by boiling the *d*- and the *l*-acid respectively with acetic anhydride as described above in the case of the *dl*-acid, crystallised from benzene in small prisms, m. p. 143—144° [Found for the *d*(−)-form : C, 65·3; H, 4·3. Found for the *l*(+)-form : C, 65·4; H, 4·3. $C_{20}H_{16}O_7$ requires C, 65·2; H, 4·3%]. In acetone solution (*c*, 1·028) the *d*(−)-form had $[\alpha]_{\mathrm{D}}^{17^\circ}$ −21·4° and the *l*(+)-form (*c*, 0·935) had $[\alpha]_{\mathrm{D}}^{17^\circ}$ + 21·5°.

dl(trans)-αβ-*Di*-(3 : 4-*methylenedioxybenzyl*)*butyrolactone* (I; RR = CH_2O_2).—The *dl*(*trans*)-anhydride (1 g.) was dissolved in a mixture of benzene (20 c.c.) and ether (30 c.c.) and mixed with amalgamated aluminium (3·5 g.), and water gradually added to the mixture during 2 days. After filtration the alumina was extracted (Soxhlet) with acetone; evaporation of the combined extract and filtrate yielded an oil, which was refluxed with 5% methyl-alcoholic potassium hydroxide (10 c.c.) for ½ hour. The methyl alcohol was removed, and the filtered solution acidified with hydrochloric acid and heated at 100° for 1 hour. Excess of sodium bicarbonate was added and after digestion on the water-bath for ½ hour the mixture was extracted with chloroform. The product crystallised from methyl alcohol (carbon) in colourless needles (0·35 g.), m. p. 108° (Found : C, 68·0; H, 5·2. Calc. for $C_{20}H_{18}O_6$: C, 67·8; H, 5·1%). Keimatsu, Ishiguro, and Nakamura (*loc. cit.*) give 106—107°. *dl*-αβ-Di(bromo-3 : 4-methylenedioxybenzyl)butyrolactone, obtained by bromination in acetic acid solution, separated from methyl alcohol in colourless rectangular prisms, m. p. 160° (Found : C, 46·8; H, 3·0. Calc. for $C_{20}H_{16}O_6Br_2$: C, 46·9; H, 3·1%). *dl*-αβ-Di(nitro-3 : 4-methylenedioxybenzyl)butyrolactone, prepared in acetic acid solution, crystallised from methyl alcohol–chloroform in pale yellow prisms, m. p. 172° (Found : C, 54·0; H, 3·8. Calc. for $C_{20}H_{16}O_{10}N_2$: C, 54·0; H, 3·6%). Keimatsu and Ishiguro (*J. Pharm. Soc. Japan*, 1936, **56**, 19) give m. p. 159—160° and 171—172° for the dibromo- and the dinitro-derivative respectively.

l(trans)-αβ-*Di*-(3 : 4-*methylenedioxybenzyl*)*butyrolactone* (l-*Hinokinin*, l-*Cubebinolide*).—This lactone, obtained similarly in 35% yields from the *l*(+)-anhydride, crystallised from methyl alcohol in large colourless prisms, m. p. 65—66° (Found : C, 67·7; H, 5·1. Calc. for $C_{20}H_{18}O_6$: C, 67·8; H, 5·1%), which gave no depression when mixed with *l*-hinokinin, m. p. 64—65°. In chloroform solution (*c*, 0·981) it had $[\alpha]_{\mathrm{D}}^{17^\circ}$ − 34·0°. Yoshiki and Ishiguro (*J. Pharm. Soc. Japan*, 1933, **53**, 11) and Mameli (*Gazzetta*, 1935, **65**, 886) give $[\alpha]_{\mathrm{D}}^{21^\circ}$ − 32·4° and − 33·7° in 2% alcohol and chloroform respectively. The dibromo-derivative separated from methyl alcohol in colourless rectangular prisms, m. p. 136° (Found : C, 46·9; H, 3·2. Calc. for $C_{20}H_{16}O_6Br_2$: C, 46·9; H, 3·1%), which gave no depression in m. p. when mixed with *l*-dibromohinokinin. In chloroform solution (*c*, 1·302) it had $[\alpha]_{\mathrm{D}}^{18^\circ}$ − 32·4°. Yoshiki and Ishiguro (*loc. cit.*) give m. p. 138° and $[\alpha]_{\mathrm{D}}^{22^\circ}$ − 26·9°. The dinitro-derivative, prepared in acetic acid solution, separated from methyl alcohol–chloroform, benzene, acetone or acetic acid in pale yellow prisms. As stated on p. **1987**, the early specimens melted at 163—164° (Found for a specimen obtained from the synthetic lactone : C, 53·7; H, 3·8. Found for a specimen obtained from natural *l*-hinokinin : C, 53·8; H, 3·7. Calc. for $C_{20}H_{16}O_{10}N_2$: C, 54·0; H, 3·6%). In chloroform solution (*c*, 1·603), the dinitro-derivatives from the synthetic and the natural lactone had $[\alpha]_{\mathrm{D}}^{17^\circ}$ − 146° and − 144° respectively. Later the dimorphous form, m. p. 183—184°, was obtained (Found for a specimen obtained from the synthetic lactone : C, 53·9; H, 3·8. Found for a specimen obtained from natural *l*-hinokinin : C, 53·7; H, 3·7%). In chloroform solution (*c*, 0·892) the dinitro-derivatives, m. p. 183—184°, from the synthetic and the natural lactone had $[\alpha]_{\mathrm{D}}^{17^\circ}$ − 143° and − 144·5° respectively. Yoshiki and Ishiguro (*loc. cit.*) give $[\alpha]_{\mathrm{D}}^{22^\circ}$ − 90·5° in acetone; we find the dinitro-derivative of natural *l*-hinokinin has $[\alpha]_{\mathrm{D}}^{18^\circ}$ − 85·9° in acetone (*c*, 0·144).

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d(trans)-αβ-*Di*-(3 : 4-*methylenedioxybenzyl*)*butyrolactone* (I; RR = CH_2O_2).—Obtained similarly in 35% yields from the *d*(−)-anhydride, this lactone separated very slowly from methyl alcohol in large colourless prisms, m. p. 64—65° (Found : C, 67·6; H, 5·1. $C_{20}H_{18}O_6$ requires C, 67·8; H, 5·1%). In chloroform solution (*c*, 0·976) it had $[\alpha]_D^{17°}$ + 33·8° and crystallisation of equimolecular proportions of the *d*- and the *l*-form from methyl alcohol yielded the *dl*-lactone, m. p. 108°. The *dibromo*-derivative separated from methyl alcohol in colourless rectangular prisms, m. p. 136° (Found : C, 46·8; H, 3·0. $C_{20}H_{16}O_6Br_2$ requires C, 46·9; H, 3·1%), which had $[\alpha]_D^{18°}$ + 31·5° in chloroform solution (*c*, 1·285). When equimolecular proportions of the *d*- and the *l*-form were crystallised from methyl alcohol, the *dl*-form separated in colourless prisms, m. p. 160°. The *dinitro*-derivative was obtained from methyl alcohol–chloroform in dimorphous forms, m. p. 161—162° and 183—184° (Found for the former : C, 54·2; H, 3·7. Found for the latter : C, 54·1; H, 3·6. $C_{20}H_{16}O_{10}N_2$ requires C, 54·0; H, 3·6%). In chloroform solution (*c*, 0·770) the lower- and the higher-melting form had $[\alpha]_D^{17°}$ + 148·7° and + 147·2° respectively. An equimolecular mixture of the *d*- and the *l*-form (m. p. either 162° or 184°) separated from methyl alcohol–chloroform as the racemate, m. p. 172°.

Rates of Hydrolysis of the Lactones.—The following results were obtained by the method described previously (this vol., p. 804) :

% Hydrolysis at 15°.

Time, hours	0·5	1·5	3	6	8	12
l-Hinokinin	18	35	61	82	90	95
l-αβ-Di-(3 : 4-methylenedioxybenzyl)butyrolactone	17	36	60	80	88	95
d- „ „ „	19	35	58	82	91	95
dl- „ „ „	18	37	61	83	89	96

Rates of Lactonisation of the Hydroxy-acids.—The following results were obtained by method (*a*) described previously (this vol., p. 805) :

% Lactonisation at 60°.

Time, hours	1	2	4	6	10	20	30
l-Hinokinin	19	26	35	41	50	80	97
l-αβ-Di-(3 : 4-methylenedioxybenzyl)butyrolactone	18	27	34	43	48	78	96
d- „ „ „	19	27	34	41	49	79	94
dl- „ „ „	20	24	37	42	51	78	95

One of the authors (D. W.) thanks the Council of King's College for a grant from the Post Graduate Studentship Fund.

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[*Received, November* 1*st*, 1938.]