334. *Rottlerin. Part IV.*

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The fact that neither 5 : 7-dihydroxy-6- nor 5 : 7-dihydroxy-8-β-phenylpropionyl-chroman is identical with octahydrorottlerone (Part III, *loc. cit.*), referred to in Parts I and II (*loc. cit.*) as tetrahydrorottlerone, led to a re-investigation of this substance. Whilst fission of octahydrorottlerone with hot concentrated alkali gave results identical with those previously recorded (Part II), the use of more dilute alkali has now been found to yield the keto-chroman (III). This behaviour, and the absence of *C*-methyl-phloroglucinol derivatives in the hydrolysate together with the conversion of tetra-hydrorottlerin into the diphenylmethane (I, R = H) and octahydrorottlerone, suggested that the latter had the structure type (II, R = H), which is in good agreement with the analytical results of the substance and its derivatives. This conclusion was confirmed by the synthesis of octahydrorottlerone from the keto-chroman (III) and formaldehyde. The structure of (I, R = H), which was arrived at by analysis and degradation, was also confirmed by its synthesis from *C*-methylphloracetophenone.

Re-investigation of a considerable number of rottlerin derivatives did not serve to distinguish between the empirical formulæ $C_{30}H_{28}O_8$ and $C_{31}H_{30}O_8$ for rottlerin, but the results of molecular-weight determinations appear to exclude formulæ based on C_{60} or C_{62} which might be expected on the basis of the simultaneous formation of (I, R = H) and (II, R = H) from tetrahydrorottlerin. The isolation of the azo-derivative (IX) from the latter by Boehm's reaction confirms the presence of the *C*-methylphloracetophenone residue in rottlerin. This residue is joined to the rest of the molecule by a methylene group and hence in view of the new orientation of octa-hydrorottlerone the structures of rottlerin and its tetrahydro-derivative are now regarded as being (VI, R = H) and (VII, R = H) respectively. Consideration of all the available evidence disproves the view that rottlerin contains a lactone group.

SINCE the hydrogenation product of rottlerone, hitherto referred to as tetra- but now shown to be octa-hydrorottlerone, had been found to yield only β-phenylpropionic acid and 5 : 7-dihydroxy-2 : 2-dimethylchroman on hydrolysis with concentrated alkali, it was concluded in Part II (J., 1938, 309) that this compound had the structure (III) or (IIIa), the latter of which was preferred on account of the insolubility of both rottlerone and its hydrogenation derivative in dilute aqueous sodium hydroxide. When it was subsequently found that octahydrorottlerone was not identical with either of the synthetical ketones (III) and (IIIa) (Part III, this vol., p. 1257), a re-investigation of this compound and its derivatives was undertaken. In the course of an examination of the methyl ether of octahydrorottlerone we found that the results obtained in molecular-weight determinations were consistently much higher than that demanded by the formula $C_{20}H_{18}O_4$ for rottlerone. Further, the nitrogen values obtained for the oxime of this ether and the analytical results for a reduction product of perhydrorottlerone methyl ether (unpublished work) could not be explained on the basis of this empirical formula. An extensive investigation of the hydrolytic fission of octahydrorottlerone was then carried out, but, under the conditions previously employed, only 5 : 7-dihydroxy-2 : 2-dimethylchroman and β-phenylpropionic acid were obtained and a careful search amongst the neutral residues failed to reveal the presence of even traces of a *C*-methylphloroglucinol derivative, which might have been expected on the basis of the structure type (VI, R = H) proposed in Part II for rottlerin. When, however, the hydrolysis of octahydrorottlerone was carried out under less drastic conditions, *viz.*, by heating the compound with 10% aqueous alcoholic sodium hydroxide on the water-bath, a small yield of the keto-chroman (III), identical in every way with an authentic specimen, was obtained; by the use of zinc dust in the hydrolysis this yield was somewhat increased, but the formation of resinous impurities could not be avoided. The production of (III) in this manner and the absence of *C*-methylphloroglucinol deriva-tives in the hydrolysate, along with the results of molecular-weight determinations on octahydrorottlerone methyl ether, suggested the possibility that octahydrorottlerone was composed of two keto-chroman units, *e.g.*, either a chromanyl-chroman or a dichromanyl-methane of the type (II). Because the conditions of hydrolysis employed for the production

of (III) were somewhat similar to those used by Boehm (*Annalen*, 1901, **318**, 230; 1903, **329**, 269) for the scission of polyhydroxy-keto-diphenylmethanes, the latter possibility appeared to be the more feasible, a view which also appeared to be supported by the fact that on being boiled with acetic acid tetrahydrorottlerin gave rise to a mixture of 2 : 4 : 6 : 2' : 4' : 6'-*hexahydroxy*-5 : 5'-*diacetyl*-3 : 3'-*dimethyldiphenylmethane* (I, R = H) and octahydrorottlerone (compare Brockmann and Maier, *Annalen*, 1938, **535**, 149). Consequently, having found in a model experiment that the interaction of 5 : 7-dihydroxy-8-acetyl-2 : 2-dimethylchroman and formaldehyde in alcoholic sulphuric acid gave rise to an almost theoretical yield of 5 : 7 : 5' : 7'-*tetrahydroxy*-8 : 8'-*diacetyl*-2 : 2 : 2' : 2'-*tetramethyl*-6 : 6'-*dichromanylmethane* and did not involve the extrusion of the acyl group, we effected the synthesis of (II, R = H) by this method from both synthetical and natural specimens of the keto-chroman (III). A detailed comparison of (II, R = H) and natural octahydrorottlerone showed that they possessed identical properties, including the insolubility in dilute aqueous sodium hydroxide which is characteristic of rottlerone and its hydrogenation products. Consequently, the acetate and methyl ether which have been referred to in Parts I and II (*loc. cit.*) as the diacetate and dimethyl ether of tetrahydrorottlerone respectively are clearly the tetra-acetate (II, R = Ac) and the tetramethyl ether (II, R = Me) of octahydrorottlerone and the oxime (Part I) of the latter is therefore the dioxime, with which the analytical results are in agreement. Since octahydrorottlerone can be obtained from rottlerin by way of tetrahydrorottlerin and from rottlerone, the latter substance is a dichromenylmethane represented by the expression (VIII, R = H) and in agreement with this view it has been found that on methylation by the potassium carbonate–methyl sulphate method (George and Robertson, J., 1937, 1535) rottlerone gives rise to the *tetramethyl* ether (VIII, R = Me), which on hydrogenation with a palladium–charcoal catalyst furnishes *O*-tetramethyloctahydrorottlerone.

(I.)   (II.)

(III.)   (IIIa.)   (IV.)   (V.)
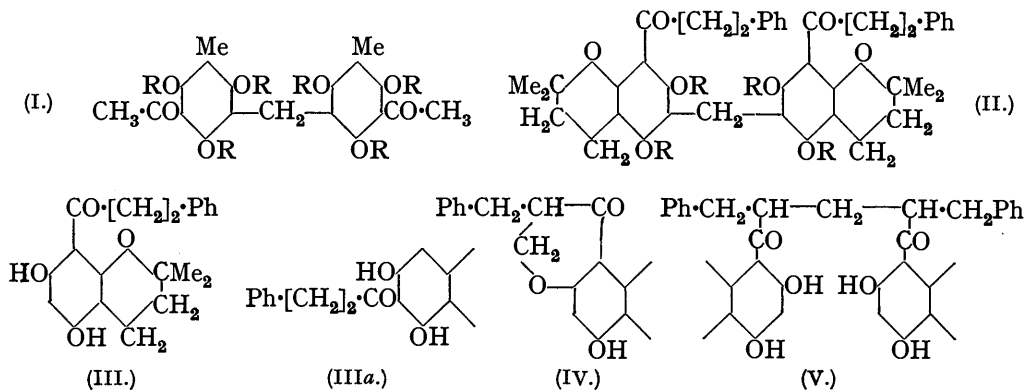
With regard to the synthesis of octahydrorottlerone (II, R = H) and the analogue having an acetyl group in the 8-position it is conceivable, owing to the presence of the ·CH$_2$·CO· group in the keto-chroman (type III), that the reaction might have taken an alternative route, *viz.*, the formaldehyde might have reacted with the methylene in the α-position to the carbonyl group, giving either the chromano-dihydro-γ-pyrone type (IV) or the bimolecular type (V). The former possibility is not supported by the analytical results and appears to be unlikely because attempts in this laboratory (unpublished work) to effect the synthesis of analogous, less complex *iso*flavanones from *o*-hydroxyphenacetophenones by this method have so far failed. Further, although on account of the instability of the chromanone system in the presence of alkaline reagents (IV) would in all probability give rise to a dimethyl ether, in the present instance the analyses and properties of *O*-tetramethyloctahydrorottlerone entirely exclude this possibility. With regard to the second alternative, this structure (V) is excluded by the results of alkaline fission, because a substance having formula (V) would be expected to give αγ-dibenzylglutaric acid and not β-phenylpropionic acid or the keto-chroman (III).

The structure of the diphenylmethane (I, R = H) obtained along with octahydro-

rottlerone by the action of hot acetic acid on tetrahydrorottlerin was established as follows : The compound was phenolic, having a strong ferric reaction, and, since *C*-methylphloroglucinol is formed in small amount when the rottlerone change is effected with alkali, it seemed likely to be a phloroglucinol derivative. On methylation by the potassium carbonate–methyl sulphate method the phenol gave a *methyl* ether, insoluble in aqueous sodium hydroxide and having a negative ferric reaction. The analytical results obtained for the parent compound and its ether were in close agreement with the empirical formulæ $C_{14}H_{14}O_6$ (forming a pentamethyl ether) and $C_{19}H_{20}O_8$ (hexamethyl ether) and of these alternatives the latter agreed better with the results of molecular-weight determinations. The former possibility appeared to be finally excluded when it was found that on treatment with diazoaminobenzene the parent phenol gave rise to 2 : 4 : 6-trihydroxy-5-acetyl-3-methylazobenzene, identified by comparison with an authentic sample. In consequence, therefore, it seemed that the new phenol had the structure (I, R = H) and this conclusion was ultimately confirmed by the synthesis of the compound by the interaction of *C*-methylphloracetophenone and formaldehyde in alcoholic sulphuric acid.

With regard to the objections raised by Ray and his collaborators (*J. Indian Chem. Soc.*, 1938, **15**, 393) to the earlier structure (III*a*) for rottlerone it may be noted, since the new structure retains this type of unit, that the hydroxy-ketone (III) and its isomeride, 5 : 7-dihydroxy-6-β-phenylpropionyl-2 : 2-dimethylchroman, do not appear to react with carbonyl reagents (Part III, *loc. cit.*). The ethers of these ketones, however, can be oximated on prolonged treatment and under similar conditions *O*-tetramethyloctahydrorottlerone forms the dioxime (Part I, *loc. cit.*, and present paper). Though so far we have been unable to determine the conditions required for the cyclisation of rottlerone and the isolation of the resulting pure dihydro-γ-pyrone derivative (*e.g.*, by boiling with acetic acid an amorphous yellow product was formed), it must be observed that under the usual conditions whereby this change is generally effected (with acidic or alkaline reagents) the chromen system would not be expected to be stable, and, further, the reaction is normally a reversible one.

In Part I (*J.*, 1937, 748) the empirical formula $C_{33}H_{30}O_9$ proposed by Perkin (*J.*, 1895, **67**, 230) was provisionally adopted for rottlerin, but it was clearly recognised at that stage that the analytical results were in reasonably good agreement with other possible formulæ, including $C_{31}H_{30}O_8$, put forward by Hoffmann and Fari (*Arch. Pharm.*, 1933, **271**, 97), and $C_{30}H_{28}O_8$ adopted in Part II (*J.*, 1938, 309). At the same time the difficulty of arriving at a final decision on this question from the results of analysis and molecular-weight determinations was clearly appreciated, a conclusion which has also been expressed by Brockmann and Maier (*loc. cit.*), who have adopted the empirical formula $C_{30}H_{28}O_8$. Ray and his collaborators (*J. Indian Chem. Soc.*, 1938, **15**, 393 ; *Current Science*, 1938, **6**, 333 ; *J. Soc. Chem. Ind.*, 1938, **57**, 134), however, maintain that rottlerin has the empirical formula $C_{31}H_{30}O_8$ of Hoffmann and Fari. On account of these conflicting views and because on the basis of the new structure now deduced from synthetical evidence for rottlerone it seemed feasible that rottlerin might possibly have approximately a C_{60}- or a C_{62}-empirical formula we have re-investigated a considerable number of rottlerin derivatives, but, though formulæ of the latter type appear to be excluded, our analytical results in themselves do not serve to distinguish between the formulæ $C_{30}H_{28}O_8$ and $C_{31}H_{30}O_8$. However, the structural formula (VI, R = H) which is now decided on for rottlerin and which accounts for its derivatives and degradation products definitely excludes the empirical formula $C_{31}H_{30}O_8$, since the extra CH_2-group which it implies cannot be accounted for.

The formation of *C*-methylphloroglucinol in small quantity in the conversion of rottlerin and tetrahydrorottlerin into rottlerone and its octahydro-derivative respectively (Part I, *loc. cit.*) indicated that the rottlerin molecule contains a *C*-methylphloroglucinol residue and in our opinion the production of 2 : 4 : 6-trihydroxy-5-acetyl-3-methylazobenzene (IX) according to Boehm's method (Brockmann and Maier, *loc. cit.*) affords substantial proof that this residue is present as a *C*-methylphloracetophenone unit attached to the rest of the molecule by a methylene group as in formula (VI, R = H). Ray and his co-workers (*loc. cit.*), who appear to have overlooked the nature of Boehm's reaction, maintain that the azo-compound is formed as the result of a deep-seated change in the rottlerin molecule

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which involves the unsaturated centre of the chromen system. The formation of the same azo-derivative (IX), however, from tetrahydrorottlerin (present work, also carried out independently by Dr. Brockmann, private communication) and from perhydrorottlerin, where in both cases the ethylenic linkage of the chromen system is absent, clearly confirms the nature and mode of attachment of the C-methylphloroglucinol residue. In this connexion also we have examined the behaviour of the di- and penta-methyl ethers of rottlerin and tetrahydrorottlerin towards warm alcoholic diazoaminobenzene and, as would be expected from the suppression of the hydroxyl groups in these compounds by methylation, we were unable to obtain an azo-compound.

(VI.) (VII.) (VIII.) (IX.) (X.) (Xa.)

$$P—CH_2—P—R—Cr—CH_2—Cr \quad (Xa.)$$
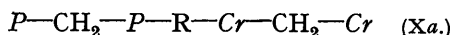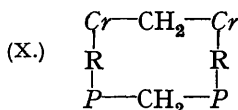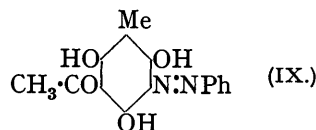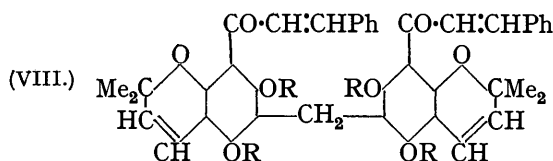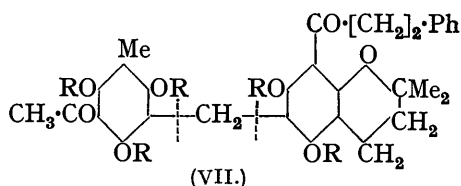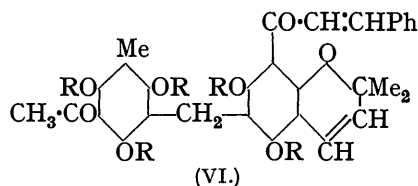
Whilst affording confirmatory evidence regarding the existence of a C-methylphloracetophenone residue in rottlerin and its tetrahydro-derivative arrived at by Boehm's reaction, the conversion of tetrahydrorottlerin into a mixture of (I, R = H) and (II, R = H) by the acetic acid method would appear to lead to the view that both the latter units were present as such in the tetrahydrorottlerin molecule, thereby implying an empirical formula based on C_{60} or C_{62} at least, more especially in view of the fact that when allowance is made for unchanged material, the yield of octahydrorottlerone, as far as can be judged in a reaction of this type, is almost quantitative. Nevertheless the molecular-weight determinations on rottlerin and tetrahydrorottlerin and their ethers (Brockmann and Maier, *loc. cit.*, and present work) appear definitely to exclude this possibility, and therefore, on the available evidence, structures of the type (X or Xa, where Cr indicates the keto-chroman and P the C-methylphloracetophenone unit) need not be discussed at present. Consequently, taking into consideration the orientation of the 5 : 7-dihydroxy-8-β-phenylpropionyl-2 : 2-dimethylchroman residue now established in octahydrorottlerone (II, R = H), we consider that tetrahydrorottlerin is represented by the expression (VII, R = H) and the penta-acetate and pentamethyl ether by (VII, R = Ac) and (VII, R = Me) respectively. On this view rottlerin is represented by formula (VI, R = H) and not by the alternative orientation preferred in Part II (*loc. cit.*). Further, it would appear that the formation of (I, R = H) and (II, R = H) by the acetic acid method arises by a disproportionation of the molecule initiated by scission alternately at the dotted lines of formula (VII, R = H) according to the scheme 2(R·CH$_2$·R') → CH$_2$R$_2$ + CH$_2$R'$_2$. A similar type of reaction presumably takes place when rottlerin and tetrahydrorottlerin are warmed with alkali, but in this case, since the characteristically insoluble hydroxy-diphenylmethane (I, R = H) has never been encountered in detectable quantities, the conditions would not appear to be favourable to the union of the two unsymmetrical precursors of (I, R = H). In connection with the suggested explanation of the rottlerone change it may be noted that from the work of Boehm (*loc. cit.*) on the alkaline fission of polyhydroxydiphenylmethanes derived from phloroglucinol and its derivatives the methylene linking in (VI, R = H) and (VII, R = H) is clearly unstable, owing in all

probability to the exceptional reactivity of the phloroglucinol nucleus and its ability to react in tautomeric forms.

With regard to the structure of rottlerin, Ray and his co-workers (*loc. cit.*) maintain that this compound contains a lactone group and also state that in the conversion of tetra-hydrorottlerin into octahydrorottlerone by hot alcoholic hydrochloric acid an acidic substance is formed which apparently is an intermediate product in the rottlerone change. We have repeated the experiments described by the Indian workers and, though our examination of the complex mixture of by-products formed along with octahydrorottlerone is not yet complete, it may be stated that, if the experiment is stopped after 8 hours, as these authors describe, the insoluble product appears to consist only of octahydrorottlerone along with unchanged tetrahydrorottlerin, which in a finely divided or gelatinous state we have observed to be soluble in aqueous sodium bicarbonate, *e.g.*, if tetrahydrorottlerin is thrown down as a voluminous colloidal precipitate by the addition of much water to an alcoholic solution, this precipitate readily dissolves in aqueous sodium bicarbonate; the keto-chroman (III) behaves in the same manner. The presence of a lactone group in rottlerin and its derivatives is also excluded by the stability of the pentamethyl ethers of rottlerin and of tetrahydrorottlerin in boiling alcoholic sodium hydroxide. In this con-nexion it may be noted that the pentamethylrottlerin (VI, R = Me), m. p. 142°, which has been obtained by Brockmann and Maier (*loc. cit.*) and by us and is insoluble in aqueous sodium hydroxide, does not appear to be identical with the material described by Ray and his co-workers (J., 1937, 1864). Like the dimethyl ethers of rottlerin and tetra-hydrorottlerin the product, m. p. 144°, described by the latter authors seems to be soluble in 8% aqueous sodium hydroxide, because they describe its oxidation in solution in this medium (1 g. in 20 c.c. of 8% aqueous sodium hydroxide).

Though our investigations on perhydrorottlerin and perhydrorottlerone are not yet completed, it may be stated that we now regard these compounds as having structures analogous to tetrahydrorottlerin (VII, R = H) and octahydrorottlerone (II, R = H) respectively, in which the phenyl group of the β-phenylpropionyl residue is replaced by a *cyclo*hexyl radical.

EXPERIMENTAL.

Rottlerin Methyl Ethers.—Prepared from Kamala according to the procedure described in Part I (*loc. cit.*), rottlerin has been found invariably to have m. p. 212° (uncorrected), remaining unchanged after having been kept for 4 years, and gave the penta-acetate (VI, R = Ac), m. p. 213° [Found : C, 66·1; H, 5·3; $CH_3 \cdot CO$, 34·7. Calc. for $C_{30}H_{23}O_8(CH_3 \cdot CO)_5$: C, 66·1; H, 5·2; $CH_3 \cdot CO$, 29·6%] (Brockmann and Maier, and Ray and his co-workers respectively give m. p. 202° and 209° for rottlerin).

Methylation of rottlerin (2·5 g.) with methyl sulphate (10 c.c.) and potassium carbonate (20 g.) in boiling acetone (100 c.c.) was complete in 2½—3 hours and after the addition of water (300 c.c.) the mixture was kept for 24 hours. The yellow resinous product was washed with a little methyl alcohol, and crystallised twice from light petroleum (b. p. 60—80°), then from aqueous methyl alcohol, and finally from light petroleum, giving *O*-pentamethylrottlerin (VI, R = Me) in colourless prisms, (1 g.), m. p. 142°, having a negative ferric reaction [Found : C, 71·7; H, 6·5; OMe, 26·1; *M* (Rast), 553. Calc. for $C_{30}H_{23}O_3(OMe)_5$: C, 71·7; H, 6·5; OMe, 26·5%; *M*, 586]. This compound is precipitated from a hot alcoholic solution by the addition of excess of warm aqueous sodium hydroxide and, after having been boiled with 10% aqueous alcoholic sodium hydroxide for 5 hours, is recovered as an alkali-insoluble brown solid which on purification from light petroleum forms prisms, m. p. 142°.

A slight excess of ethereal diazomethane was slowly added to pure rottlerin (1 g.) suspended in dry acetone (10 c.c.) (agitate), and the mixture kept at 0° until a pale red solution was obtained. The dimethyl ether, which quickly began to separate, was collected 24 hours later and repeatedly crystallised from chloroform–methyl alcohol, forming pale yellow, rectangular prisms, m. p. 254° [Found : C, 70·5; H, 6·0; OMe, 10·7. Calc. for $C_{30}H_{26}O_6(OMe)_2$: C, 70·6; H, 5·9; OMe, 11·4%] (compare Brockmann and Maier, who give m. p. 245—246°).

Tetrahydrorottlerin.—Prepared by the method described in Part I, this substance invariably had m. p. 215° (Found : C, 69·2, 69·2; H, 6·3, 6·4. Calc. for $C_{30}H_{32}O_8$: C, 69·2; H, 6·2%) (Brockmann and Maier and Ray and co-workers give m. p. 211° and 212° respectively) and gave

the penta-acetate (VII, R = Ac), m. p. 188° (Found : C, 65·5; H, 5·7. Calc. for $C_{40}H_{48}O_{13}$: C, 65·7; H, 5·8%).

Methylation of tetrahydrorottlerin (2·5 g.) with methyl sulphate by the procedure employed for rottlerin gave a semi-solid, which was washed, dried, and extracted with boiling light petroleum (b. p. 40—60°). On cooling, the concentrated extract deposited the pentamethyl ether (VII, R = Me) in colourless short stout prisms (2 g.), m. p. 109° after repeated crystallisation from the same solvent [Found : C, 71·5, 71·5; H, 7·1, 7·2; OMe, 26·1. Calc. for $C_{30}H_{27}O_3(OMe)_5$: C, 71·2; H, 7·1; OMe, 26·3%]. Alternatively, the crude product was washed with the minimum amount of carbon tetrachloride, and the residual ether then purified from light petroleum. The behaviour of this compound towards ferric chloride and hot alkalis is identical with that of *O*-pentamethylrottlerin. An almost theoretical yield of the same ether was obtained by the hydrogenation of *O*-pentamethylrottlerin (5 g.), dissolved in absolute ethyl acetate, with a palladium–charcoal catalyst (from 0·2 g. of palladium chloride and 2 g. of charcoal) with hydrogen at 30 lb./sq. in.; m. p. 109° after purification from aqueous alcohol and then light petroleum (Found : C, 71·3, 71·3; H, 7·2, 7·1; OMe, 26·3, 26·1%).

Methylation of tetrahydrorottlerin (1 g.), suspended in acetone (10 c.c.), was effected with a slight excess of ethereal diazomethane at 0° and then at room temperature for 18 hours, and the solvent allowed to evaporate spontaneously. Crystallisation of the residual product (wash with a little cold methyl alcohol) from acetone–methyl alcohol gave a mixture, m. p. 147°, consisting of pale yellow and pale greenish crystals, which, as they appeared to have similar solubilities, were separated manually. Purification of the pale yellow material from acetone–methyl alcohol, benzene, and finally alcohol gave *O*-dimethyltetrahydrorottlerin in pale greenish-yellow prisms, m. p. 192°, having a greenish-brown ferric reaction [Found : C, 70·1; H, 6·6; OMe, 10·8. Calc. for $C_{30}H_{30}O_6(OMe)_2$: C, 70·0; H, 6·6; OMe, 11·3%]. Crystallisation of the pale green material from acetone–methyl alcohol and then alcohol gave a compound in bright yellow prisms, m. p. 153°, which appears to be a *trimethyl* ether of tetrahydrorottlerin [Found : C, 70·3; H, 6·9; OMe, 17·5. $C_{30}H_{29}O_5(OMe)_3$ requires C, 70·5; H, 6·7; OMe, 16·6%]. This derivative is readily soluble in acetone or aqueous sodium hydroxide and gives a green ferric reaction. A mixture of the two compounds melted at about 147° (compare Brockmann and Maier, *loc. cit.*, who obtained only the dimethyl ether).

Hydrogenation of *O*-dimethylrottlerin (2 g.), suspended in absolute acetone (150 c.c.), was effected with hydrogen at 10 lb./sq. in. and a palladium–charcoal catalyst (from 1 g. of charcoal and 0·2 g. of palladium chloride) during 3 hours, giving a good yield of tetrahydrorottlerin dimethyl ether, m. p. and mixed m. p. 192° after purification from acetone–methyl alcohol and then benzene.

When a hot solution of pure diazoaminobenzene (1 g.), m. p. 98·5°, in alcohol (10 c.c.) was added to a suspension of tetrahydrorottlerin (1 g.) in boiling alcohol (40 c.c.), and the mixture refluxed for 5 minutes, a deep crimson-red solution was obtained which on cooling deposited dark red crystals in about 1 hour. Recrystallisation of the latter from acetic acid and then alcohol gave 2 : 4 : 6-trihydroxy-5-acetyl-3-methylazobenzene (IX) in red plates (0·3 g.), m. p. 202°, unchanged on repeated crystallisation from ethyl acetate and identical in every way with an authentic specimen, m. p. 202°, prepared from *C*-methylphloracetophenone (Found : N, 9·8. Calc. for $C_{15}H_{14}O_4N_2$: N, 9·8%) (Brockmann and Maier, *loc. cit.*, give m. p. 206°). The same azo-compound was prepared from rottlerin by the method of Brockmann and Maier and by the following modification : Boiling solutions of rottlerin (2 g.) and diazoaminobenzene (2 g.) in 200 c.c. and 50 c.c. of alcohol respectively were mixed and, on allowing part of the alcohol to evaporate spontaneously, dark red crystals (0·9 g.) of impure product separated. Recrystallisation of this material from acetic acid, light petroleum (b. p. 60—80°), and finally alcohol gave the compound in red plates, m. p. 202°, unchanged on recrystallisation from ethyl acetate (Found : N, 9·6%).

O-*Tetramethylrottlerone* (VIII, R = Me).—Rottlerone (5 g.) (Part II, *loc. cit.*) was methylated with methyl sulphate (20 c.c.) and potassium carbonate (40 g.) in boiling acetone during 1½ hours, and the mixture treated with excess of water; 24 hours later the resinous product was collected, dried, washed with a little carbon tetrachloride, and crystallised from light petroleum (b. p. 60—80°) and then aqueous alcohol, giving the *ether* in faintly yellow, squat prisms (1·4 g.), m. p. 136° [Found : C, 75·8; H, 6·2; OMe, 17·3. $C_{41}H_{32}O_4(OMe)_4$ requires C, 75·8; H, 6·2; OMe, 17·4%]. This compound is insoluble in aqueous sodium hydroxide and has a negative ferric reaction. On hydrogenation it gave *O*-tetramethyloctahydrorottlerone, m. p. 100°, undepressed on admixture with an authentic sample.

Octahydrorottlerone (II, R = H).—Prepared according to Part I (*loc. cit.*), this compound

had m. p. 173° [Found (mean of eight analyses) : C, 73·9; H, 6·5. Calc. for $C_{41}H_{44}O_8$: C, 74·1; H, 6·6%]. Acetylation of octahydrorottlerone by the pyridine method gave the tetra-acetate, which had m. p. 215° after having been crystallised from acetic acid–alcohol and then acetone–alcohol (Found : C, 70·7; H, 6·4. Calc. for $C_{49}H_{52}O_{12}$: C, 70·7; H, 6·3%).

Methylation of octahydrorottlerone (1 g.) with methyl sulphate (5 c.c.) and potassium carbonate (10 g.) in boiling acetone (50 c.c.), with the addition of more sulphate (2·5 c.c.) and more carbonate (5 g.) after 2 hours, was complete in about 4 hours; on isolation the tetramethyl ether (II, R = Me) was purified by repeated crystallisation from aqueous alcohol and from light petroleum, forming colourless prisms (0·9 g.), m. p. 102° [Found : C, 75·0; H, 7·3; OMe, 17·3, 17·4; M (Rast), 604. Calc. for $C_{41}H_{40}O_4(OMe)_4$: C, 75·0; H, 7·2; OMe, 17·2%; M, 720]. The product of oximation, m. p. 204—205°, is the dioxime (Found : C, 72·1; H, 7·3; N, 4·0. Calc. for $C_{45}H_{54}O_8N_2$: C, 72·0; H, 7·2; N, 3·7%. Calc. for $C_{45}H_{53}O_8N$: C, 73·5; H, 7·2; N, 1·9%).

Action of Boiling Acetic Acid on Tetrahydrorottlerin.—A solution of tetrahydrorottlerin (2 g.) in acetic acid (90 c.c.) and water (10 c.c.) was refluxed for 12 hours, during which a small amount of a light yellow solid gradually separated; this was removed from the hot solution, extracted with boiling acetone (20 c.c.), and crystallised from dioxan, giving 2 : 4 : 6 : 2′ : 4′ : 6′-*hexahydroxy*-5 : 5′-*diacetyl*-3 : 3′-*dimethyldiphenylmethane* (I, R = H) in light yellow microscopic prisms, m. p. 291° (decomp.), very sparingly soluble in all the usual organic solvents except hot dioxan (moderately soluble) and hot acetone (sparingly soluble), soluble in aqueous sodium hydroxide and insoluble in aqueous sodium bicarbonate; it gave a red-brown coloration with alcoholic ferric chloride [Found (mean of four analyses) : C, 60·5; H, 5·4. $C_{19}H_{20}O_8$ requires C, 60·6; H, 5·3. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·0%].

On being kept for 48 hours, the acetic acid liquor left on separation of the foregoing compound gradually deposited octahydrorottlerone, which formed yellow plates, m. p. 173°, from alcohol, identical in every way with an authentic specimen. Evaporation of the acetic acid filtrate from the crude octahydrorottlerone in a vacuum left a brownish resinous mass, which was treated with cold methyl alcohol (15—20 c.c.). Next day the undissolved solid, consisting of moderately pure, unchanged tetrahydrorottlerin, was collected, m. p. 215° after crystallisation from hot alcohol, identified by comparison with an authentic specimen. When the material left on evaporation of the methyl-alcoholic washings was treated with a little benzene, a further small amount of tetrahydrorottlerin was left undissolved, but crystalline material could not be obtained from the benzene-soluble residue. This degradation was repeated a considerable number of times and the yields from 2 g. of tetrahydrorottlerin in a typical experiment were diphenylmethane derivative (I, R = H), 0·2 g.; octahydrorottlerone (II, R = H), 0·7 g.; unchanged tetrahydrorottlerin, 0·7 g.; amorphous material, 0·3 g. Allowing for 0·7 g. of unchanged material, the theoretical yields of (I, R = H) and (II, R = H) respectively are 0·47 g. and 0·83 g. Approximately the same results were obtained when absolute acetic acid was used as the solvent.

On being heated with methyl sulphate (3·5 c.c.), potassium carbonate (10 g.), and acetone (50 c.c.) on the steam-bath, the hydroxydiphenylmethane derivative (I, R = H) (0·7 g.), m. p. 291°, slowly dissolved and after 2 hours water (200 c.c.) was added. 48 Hours later the precipitate was isolated with ether and dissolved in excess of warm light petroleum (b. p. 40—60°). On spontaneous evaporation of the solvent the solution slowly deposited the *hexamethyl* ether (I, R = Me) in colourless prisms, m. p. 103° after having been recrystallised from light petroleum, aqueous alcohol, and finally light petroleum [Found : C, 65·3; H, 7·1; OMe, 41·1; M (Rast), 433, 464. $C_{19}H_{14}O_2(OMe)_6$ requires C, 65·2; H, 7·0; OMe, 40·3%; M, 460. $C_{14}H_9O(OMe)_5$ requires C, 65·5; H, 6·9; OMe, 44·3%; M, 350]. This compound, which has a negative ferric reaction, is readily soluble in benzene, acetone, or alcohol and insoluble in aqueous sodium hydroxide.

When diazoaminobenzene (0·3 g.) was added to boiling alcohol (20 c.c.) containing a suspension of the hydroxydiphenylmethane compound (0·3 g.), the solid dissolved and the solution rapidly became dark red. On cooling, 2 : 4 : 6-trihydroxy-5-acetyl-3-methylazobenzene (IX) gradually separated in dark red prisms, which on recrystallisation from alcohol and then ethyl acetate formed red plates, m. p. 202°, undepressed by admixture with an authentic specimen (Found : N, 9·5%).

Hydrolytic Fission of Octahydrorottlerone.—A mixture of this compound (1 g.), 20% aqueous sodium hydroxide (10 c.c.), alcohol (10 c.c.), and zinc dust (1 g.) was heated in nitrogen on the water-bath for 3 hours and after the removal of the zinc (wash with a little alcohol) the filtrate and washings were combined and diluted with water (200 c.c.). No precipitate appeared at

this stage, but in experiments where more dilute alkali was employed or the period of refluxing was considerably reduced a precipitate of unchanged octahydrorottlerone generally separated on the addition of water. The aqueous alcoholic liquors were saturated with carbon dioxide and 24 hours later the resulting precipitate was collected, washed, dried, and extracted with boiling light petroleum (b. p. 40—60°) (6 × 200 c.c.), leaving a small amount of brown resin. The volume of the combined extracts was reduced to about 200 c.c. by distillation and on being kept the residue slowly deposited a pale yellow solid (0·1 g.), m. p. 162°, which on recrystallisation from benzene–light petroleum (b. p. 40—60°), aqueous methyl alcohol, and finally aqueous alcohol gave 5 : 7-dihydroxy-8-β-phenylpropionyl-2 : 2-dimethylchroman (III), m. p. 171°, identical in every way with a synthetical specimen (Part III, *loc. cit.*) (Found : C, 73·8; H, 6·9. Calc. for $C_{20}H_{22}O_4$: C, 73·6; H, 6·8%). Concentration of the light petroleum filtrate from the crude ketone by spontaneous evaporation gave a small amount of this substance accompanied by much light brown resinous material.

The aqueous liquors left on separation of the foregoing crude solid were acidified with hydrochloric acid and extracted with ether in a continuous extractor for 4 days, and the extract separated into an acidic and a neutral fraction by means of aqueous sodium bicarbonate. From the acidic fraction β-phenylpropionic acid was isolated by distillation in a vacuum and characterised by conversion into the anilide according to the method of Hardy (J., 1936, 398). On cooling, a solution of the resulting crude oily product in warm light petroleum (b. p. 60—80°) deposited the anilide, m. p. 99·5°, undepressed on admixture with an authentic specimen (Found : N, 5·8. Calc. for $C_{15}H_{15}ON$: N, 6·2%).

The neutral fraction was invariably obtained as a light brown oil, from which 5 : 7-dihydroxy-2 : 2-dimethylchroman was separated by sublimation in a vacuum, leaving a dark brown residue. On purification this compound had m. p. 162° and was identified by comparison with an authentic specimen (J., 1937, 279). In another experiment the neutral oil was extracted five times with boiling light petroleum (b. p. 60—80°), the extract evaporated, the residue treated with an excess of diazoaminobenzene dissolved in a little hot alcohol, and the mixture boiled for 1 minute. On cooling, the dark red mixture slowly deposited the *bis-phenylazo*-derivative of 5 : 7-dihydroxy-2 : 2-dimethylchroman, which separated from warm methyl alcohol containing a little acetic acid in bright red needles, m. p. 256° (decomp.), identical with an authentic specimen (Found : N, 14·2. $C_{23}H_{22}O_3N_2$ requires N, 13·9%). An authentic specimen of this substance was prepared in the same manner from synthetic chroman and on crystallisation from benzene–ethyl acetate and then acetic acid and alcohol had m. p. and mixed m. p. 256° (decomp.) (Found : C, 68·6; H, 5·5; N, 14·0. $C_{23}H_{22}O_3N_4$ requires C, 68·7; H, 5·5; N, 13·9%).

When the hydrolysis was effected in the absence of zinc dust, the same products were obtained, but the resulting 5 : 7-dihydroxy-8-β-phenylpropionyl-2 : 2-dimethylchroman was much more difficult to purify.

The Synthesis of Hydroxydiphenylmethane Derivatives.—(a) 5 : 7 : 5′ : 7′-*Tetrahydroxy-8 : 8′-diacetyl-2 : 2 : 2′ : 2′-tetramethyl-6 : 6′-dichromanylmethane.* When 40% aqueous formaldehyde (0·5 c.c.) was added to a solution of 5 : 7-dihydroxy-8-acetyl-2 : 2-dimethylchroman (Part III, *loc. cit.*) (0·1 g.) in alcohol (10 c.c.), followed by 6 drops of concentrated sulphuric acid, a light yellow precipitate began to separate almost immediately. Next day the product (0·1 g.), m. p. 230°, was collected, washed with water, and crystallised from alcohol, forming yellow rectangular prisms, m. p. 240°, which gave an intense, rich purple ferric reaction in alcohol and were readily soluble in acetone (Found : C, 67·0; H, 6·5. $C_{27}H_{32}O_8$ requires C, 67·0; H, 6·6%). This *compound*, which slowly dissolved in 8% aqueous sodium hydroxide, was also obtained when the sulphuric acid was replaced by 12 drops of concentrated hydrochloric acid in the reaction mixture.

Acetylation of this compound (0·2 g.) with acetic anhydride (5 c.c.) and pyridine (2·5 c.c.) at room temperature for 24 hours and then on the steam-bath for 1 hour gave the tetra-acetate, m. p. 206°, which formed colourless plates, m. p. 213°, from aqueous alcohol.

(b) *Octahydrorottlerone.* On addition of concentrated sulphuric acid (1 c.c.) to a solution of 5 : 7-dihydroxy-8-β-phenylpropionyl-2 : 2-dimethylchroman (0·7 g.) in alcohol (20 c.c.) and 40% aqueous formaldehyde (5 c.c.) a crystalline precipitate of octahydrorottlerone began to separate immediately. Next day the solid (0·5 g., m. p. 171°) was isolated and on purification from warm alcohol formed yellow plates, m. p. 173°, undepressed by admixture with a natural specimen (Found : C, 74·1; H, 6·6. Calc. for $C_{41}H_{44}O_8$: C, 74·1; H, 6·6%). The solubilities and ferric reaction of the synthetical and the natural material were identical. Prepared by the pyridine method, the tetra-acetate separated from acetone–alcohol in colourless slender prisms, m. p. 215°, identical with the natural derivative.

(c) 2 : 4 : 6 : 2′ : 4′ : 6′-*Hexahydroxy*-5 : 5′-*diacetyl*-3 : 3′-*dimethyldiphenylmethane* quickly separated from a mixture of C-methylphloracetophenone (0·12 g.), 40% aqueous formaldehyde (2 c.c.), and 8 drops of concentrated sulphuric acid and on purification from aqueous dioxan and then dioxan formed microscopic light prisms, m. p. 291°, identical with a natural specimen (Found : C, 60·4; H, 5·5%).

(With ALFRED B. PERCIVAL.) *Perhydrorottlerin.*—In a detailed investigation on the preparation of this compound from rottlerin and from tetrahydrorottlerin by hydrogenation with a platinum catalyst (Part II, *loc. cit.*) it was found that the use of acetone, acetic acid, or ethyl acetate as solvents gave unsatisfactory results. Contrary to earlier observations (Part II, *loc. cit.*) we have found in the course of numerous successful experiments where alcohol is used as the solvent that the variety of perhydrorottlerin, m. p. 188°, occurs much less frequently than the variety, m. p. 182° (m. p. 181—182° in Part II, *loc. cit.*) (Found in material dried in a high vacuum at 100° : C, 68·3, 68·3; H, 7·2, 7·3. Calc. for $C_{30}H_{38}O_8$: C, 68·4; H, 7·2%). On treatment with warm alcoholic diazoaminobenzene by the method employed in the case of tetrahydrorottlerin both varieties (m. p. 182° and m. p. 188°) gave rise to 2 : 4 : 6-trihydroxy-5-acetyl-3-methylazobenzene, which had m. p. 202° after purification from acetic acid and then alcohol, identical with an authentic specimen.

From the products, m. p. 182° and 188°, the same perhydrorottlerone was obtained by the alkali method (Part II, *loc. cit.*), forming pale yellow prisms or plates, m. p. 147°, from alcohol (Found : C, 73·3, 73·2; H, 8·0, 8·0. Calc. for $C_{41}H_{56}O_8$: C, 72·8; H, 8·3%). In the course of the purification of this compound from alcohol or ethyl acetate a labile form, m. p. 159—160°, was occasionally obtained which on recrystallisation reverted to the stable form.