

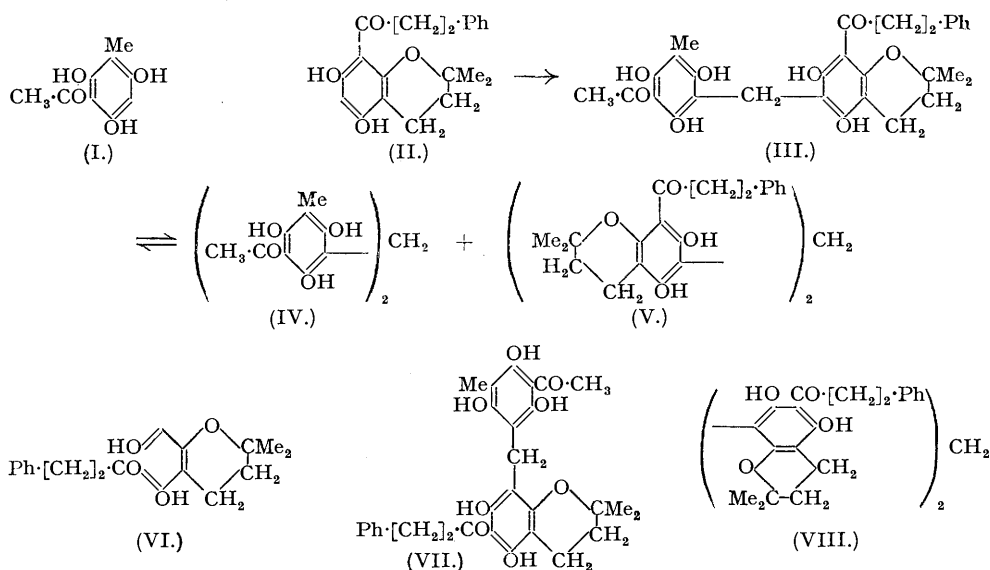
## 28. Rottlerin. Part VII. The Synthesis of Tetrahydrorottlerin and of Tetrahydroallorottlerin and the Reversibility of the Rottlerone Change.

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Interaction of a mixture of (I), (II), and formaldehyde in alcoholic sulphuric acid gave rise to tetrahydrorottlerin (III) in addition to (IV) and (V). Similarly tetrahydroallorottlerin was obtained along with (IV) and (VIII) when the keto-chroman (II) was replaced by the isomeride (VI).

The conversion of tetrahydrorottlerin (III) into (IV) and (V) and of tetrahydroallorottlerin (VII) into (IV) and (VIII) have been shown to be reversible reactions.

In Parts IV (*J.*, 1939, 1579) and V (*ibid.*, p. 1587) it was shown that the condensation of a molecule of formaldehyde with two molecules of 5:7-dihydroxy-8- $\beta$ -phenylpropionyl-2:2-dimethylchroman (II) in alcoholic sulphuric acid gave rise to octahydrorottlerone (V), and similarly that *C*-methylphloracetophenone yielded the hexahydroxydiphenylmethane (IV); it therefore seemed reasonably certain that the interaction of formaldehyde with a mixture of (I) and (II) would furnish synthetic tetrahydrorottlerin (III) in addition to (IV) and (V). This objective has now been achieved and the synthetical tetrahydro-derivative (III) thus formed is identical in every way with a specimen obtained by the hydrogenation of rottlerin. In a similar manner when the keto-chroman (II) is replaced by the isomeride, 5:7-dihydroxy-6- $\beta$ -phenylpropionyl-2:2-dimethylchroman (VI), tetrahydroallorottlerin (VII) is formed along with (IV) and octahydroallorottlerone (VIII).



In Part I (*J.*, 1937, 748) it was shown that in the presence of dilute alkalis tetrahydrorottlerin like rottlerin undergoes the rottlerone change, thus showing that this reaction is entirely independent of the presence of the double bonds in the rottlerin molecule. Under these conditions, the greater part of the product consists of intractable material, presumably formed by side reactions arising on account of the reactivity of the phloroglucinol nucleus in alkaline media, and a detailed investigation of the reaction was impossible. The nature of the rottlerone change, however, was further clarified when it was subsequently discovered that the reaction can be effected in the case of tetrahydrorottlerin by means of boiling acetic acid with the formation of only small amounts of amorphous material, and that the resulting octahydrorottlerone (V) is accompanied by the hexahydroxydiphenylmethane (IV), thus accounting for the "second half" of the rottlerin molecule (Part IV, *loc. cit.*). Further, in the course of numerous experiments on the conversion of tetrahydrorottlerin into (IV) and (V) by the acetic acid method it has been observed that a proportion of the initial material was invariably recovered unchanged and hence it seemed probable that the change was a reversible

one, *i.e.*,  $2(\text{R}\cdot\text{CH}_2\cdot\text{R}') \rightleftharpoons \text{CH}_2\text{R}_2 + \text{CH}_2\text{R}_2'$ . This view has been conclusively established since it has been found that on being heated with acetic acid a mixture of synthetic (or natural) specimens of (IV) and (V) is partly converted into tetrahydrorottlerin (III). Similarly the conversion of tetrahydroallorottlerin (VII) into octahydroallorottlerone (VIII) and (IV) is also a reversible reaction because when a mixture of synthetic specimens of (IV) and (VIII) is heated in acetic acid tetrahydroallorottlerin (VII) is regenerated. It may be noted that in general it has been found (unpublished results) that polyhydroxydiphenylmethane compounds undergo the same disproportionation.

These results serve to confirm the final conclusions regarding the structures of rottlerin (Part IV, *loc. cit.*), allorottlerin (Part V, *loc. cit.*), and their respective derivatives, thus, *inter alia*, affording conclusive evidence of the complex nature of the reaction involved in the formation of isoallorottlerin\* (previously named isorottlerin). Further it may be noted here that the original formula for rottlerin, first proposed by workers in this laboratory (Part II, *J.*, 1938, 309), contained all the essential features but is now known to have the orientation of allorottlerin. Subsequently Brockmann and Maier (*Annalen*, 1938, 535, 149; 1939, 541, 53) employed this original structure for rottlerin, and as far as we are aware these authors have not modified their formulæ for the degradation and transformation products to conform with the final orientations established in Parts IV and V (*loc. cit.*). Moreover, these authors failed to interpret the complex nature of the changes obtaining in the conversion of rottlerin into isoallorottlerin (cf. Mayer, "Natural Organic Colouring Matters", translated by Cook, 1943, p. 204). The compound named  $\psi$ -rottlerin by Brockmann and Maier is clearly allorottlerin (formula III, Part V, *loc. cit.*), and dihydro- $\psi$ -rottlerin is dihydroisoallorottlerin, having formula type VII (Part V), both of which on hydrogenation under appropriate conditions have been found to yield tetrahydroallorottlerin, m. p. 241° (not 225—226° as given by the German authors). Similarly tetrahydro- $\psi$ -rottlerone is tetrahydroallorottlerone.

#### EXPERIMENTAL.

*C*-Methylphloroglucinol required for the preparation of *C*-methylphloracetophenone was prepared by an improved modified method (cf. Weidel, *Monatsh.*, 1898, 19, 224; Hein and Wagner, *Ber.*, 1935, 68, 856). 2 : 4 : 6-Trinitrotoluene (5 g.) dissolved in absolute alcohol (250 c.c.) was reduced with hydrogen at 40 lb./sq. in. and a palladium-charcoal catalyst (from 0.2 g. of palladium chloride and 2 g. of charcoal) in the course of 3 hours, and the triamine converted into the phenol by the following procedure in which all the operations were carried out in an atmosphere of oxygen-free carbon dioxide. After addition of concentrated hydrochloric acid (8 c.c.) the catalyst was removed by filtration, the solution evaporated in a vacuum, and the residue dissolved in oxygen-free water (250 c.c.) and concentrated hydrochloric acid (4 c.c.), the mixture refluxed for 30 hours, and the resulting *C*-methylphloroglucinol isolated with ether. Purified by being twice sublimed in a high vacuum and then crystallised from benzene the phenol (1.3 g.) had m. p. 213—216°.

Treatment of a solution of 2 : 4 : 6-triaminotoluene in dilute hydrochloric acid with excess of acetic anhydride in an atmosphere of carbon dioxide gave the *triacetyl* derivative which separated from water in elongated rectangular prisms, m. p. 280° (Found : N, 15.7.  $\text{C}_{13}\text{H}_{17}\text{O}_3\text{N}$  requires N, 16.0%).

*Tetrahydrorottlerin*.—To a solution of 5 : 7-dihydroxy-8- $\beta$ -phenylpropionyl-2 : 2-dimethylchroman (Part III, *J.*, 1939, 1257) (0.41 g.) and *C*-methylphloracetophenone (Curd and Robertson, *J.*, 1933, 443) (0.25 g.) in alcohol (20 c.c.) maintained at room temperature, 40% aqueous formaldehyde (5 c.c.) was added followed by concentrated sulphuric acid (2 c.c., dropwise), and after a short time a microcrystalline yellow precipitate began to separate. Next day the product (0.56 g.) was collected, washed with water, dried, and extracted several times with cold acetone (total vol., 50 c.c.) leaving an insoluble residue which consisted of impure 2 : 4 : 6 : 2' : 4' : 6'-hexahydroxy-5 : 5'-diacetyl-3 : 3'-dimethyldiphenylmethane, m. p. about 265° (Part IV, *loc. cit.*). The solid left on evaporation of the acetone extracts was digested with boiling alcohol (20 c.c. in several portions), the insoluble material consisting of slightly impure octahydrorottlerone (0.1 g.), m. p. 168°, was collected, the alcoholic solution was evaporated to half its volume, and the product (0.04 g.), m. p. about 160°, which separated from the cooled residual liquor was removed. On further concentration the latter liquor then deposited tetrahydrorottlerin (0.12 g.), m. p. 211°, which on purification from alcohol formed pale yellow, elongated prisms, m. p. and mixed m. p., 214°, identical in every way with a natural specimen (Found : C, 69.3; H, 6.2. Calc. for  $\text{C}_{30}\text{H}_{32}\text{O}_8$  : C, 69.2; H, 6.2%). Acetylation of the synthetic product (0.05 g.) with acetic anhydride (0.3 c.c.) and pyridine (1 c.c.) at room temperature for 3 days gave the penta-acetate which formed colourless prisms, m. p. 188°, from methyl alcohol, identical with authentic *O*-penta-acetyltetrahydrorottlerin (Part I, *J.*, 1937, 753). When a solution of synthetic tetrahydrorottlerin (0.03 g.) in 4% aqueous sodium hydroxide (0.4 c.c.) was kept at 65—70° for 20 minutes a precipitate of octahydrorottlerone separated, and on isolation this product formed yellow prisms, m. p. 171°, from warm acetone containing a little acetic acid, identical with a specimen from natural sources.

*Tetrahydroallorottlerin*.—When concentrated sulphuric acid (0.5 c.c.) was added dropwise to a well-stirred solution of 5 : 7-dihydroxy-6- $\beta$ -phenylpropionyl-2 : 2-dimethylchroman (Part III, *loc. cit.*) (0.16 g.) and *C*-methylphloracetophenone (0.1 g.) in alcohol (6 c.c.), containing 40% aqueous formaldehyde

\* In view of the conclusive evidence now available regarding the chemistry of rottlerin and its derivatives and for the sake of clarity we have now adopted the nomenclature suggested in a footnote to Part V (*loc. cit.*).

(1 c.c.), a yellow precipitate began to separate. Next day the product (0.25 g.) was collected, washed with water, dried, and extracted with warm acetone (5 c.c.). On cooling, the extract deposited tetrahydroallorotlerin (0.1 g.), m. p. 235—240°, which on recrystallisation from alcohol formed long, slender, bright yellow prisms (0.05 g.), m. p. 241°, alone or mixed with a natural specimen with which it was identical in every way (Found: C, 69.3; H, 6.0. Calc. for  $C_{30}H_{32}O_8$ : C, 69.2; H, 6.2%). On being kept the acetone filtrate from the crude tetrahydroallorotlerin slowly deposited crystals of a further quantity (small) of this material mixed with octahydroallorotlerone which were separated manually. On purification from alcohol the latter compound had m. p. 174—175° and was identical with an authentic specimen.

Treatment of the synthetic tetrahydroallorotlerin with warm 4% aqueous sodium hydroxide as described in Part V (*loc. cit.*) gave rise to octahydroallorotlerone, m. p. and mixed m. p. 174—175°.

*Rotlerone Change.*—(a) A mixture of synthetic octahydrorotlerone (Part IV, *loc. cit.*) (1 g.), 2 : 4 : 6 : 2' : 4' : 6'-hexahydroxy-5 : 5'-diacetyl-3 : 3'-dimethyldiphenylmethane (*loc. cit.*) (0.7 g.), and acetic acid (140 c.c.) was refluxed (oil-bath at 140—145°) for 12 hours and, after having been filtered to remove the unchanged hexahydroxy-diphenylmethane, was treated with water (7 c.c.). Two days later the crystalline octahydrorotlerone (0.63 g.) which had separated was removed, the mixture was diluted with excess of water, and the resulting reddish precipitate (0.2 g.) was repeatedly crystallised from alcohol, giving tetrahydrorotlerin, m. p. 212°, identical in every way with an authentic specimen (Found: C, 69.4; H, 6.2%). The same result was obtained when a specimen of octahydrorotlerone from natural sources was used.

(b) Synthetic octahydroallorotlerone (Part V, *loc. cit.*) (0.1 g.) and 2 : 4 : 6 : 2' : 4' : 6'-hexahydroxy-5 : 5'-diacetyl-3 : 3'-dimethyldiphenylmethane (*loc. cit.*) (0.07 g.) were gently boiled with acetic acid (40 c.c.) for 12 hours and the hot mixture filtered to remove the unchanged hexahydroxydiphenylmethane. On being kept the solution gradually deposited a yellow solid consisting of tetrahydroallorotlerin and unchanged octahydroallorotlerone (0.065 g.). Extraction of the mixture with hot benzene removed octahydroallorotlerone, and then repeated crystallisation of the residue from alcohol gave tetrahydroallorotlerin (0.004 g.), m. p. 240—241°, alone or mixed, with a natural specimen with which it was identical in every way. When the acetic acid filtrate from the crude mixture of tetrahydroallorotlerin and octahydroallorotlerone was diluted with twice its volume of water a precipitate separated which consisted mainly of octahydroallorotlerone, m. p. 175°, after purification. The use of natural octahydroallorotlerone gave identical results.

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