

62. *Rottlerin. Part II.*

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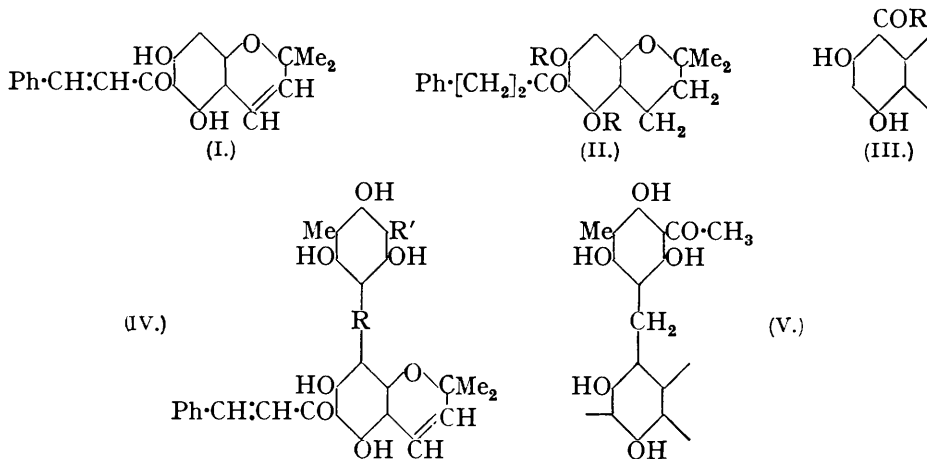
As the result of the re-examination of tetrahydrorottlerone and its derivatives, it has been shown that this compound and rottlerone have the empirical formulæ  $C_{20}H_{22}O_4$  and  $C_{20}H_{18}O_4$  respectively. Structural formulæ for rottlerone and its derivatives are deduced and a partial structure for rottlerin is tentatively suggested.

The formation of perhydrorottlerone by two methods has been re-investigated.

FROM the analytical results obtained for rottlerone and a number of its derivatives (Part I, J., 1937, 748), it appeared likely that this compound had the empirical formula  $C_{20}H_{18}O_4$  or  $C_{26}H_{24}O_5$  and since, on the basis of the formulæ\* proposed for rottlerin heretofore, the rottlerone residue clearly constitutes the greater part of the rottlerin molecule, it seemed highly desirable to establish the structure of this important degradation product. Because of the difficulty of obtaining quantities of rottlerone, despite repeated attempts to improve the yield, we have concentrated our attention on the tetrahydro-derivative. As the result of the analysis of further specimens of this compound and of its dimethyl ether, in conjunction with the molecular weight determined by the X-ray method, it appears to be conclusively established that tetrahydrorottlerone has the empirical formula  $C_{20}H_{22}O_4$  and that its acetyl and methyl derivatives are the diacetate  $C_{20}H_{20}O_4(CO \cdot CH_3)_2$  and the dimethyl ether  $C_{20}H_{20}O_2(OMe)_2$  respectively. This conclusion is in agreement with the fact that, in spite of a careful search, the only products obtained by the alkaline fission of tetrahydrorottlerone are 5 : 7-dihydroxy-2 : 2-dimethylchroman and  $\beta$ -phenylpropionic acid (compare Part I, *loc. cit.*). Consequently, rottlerone

\* Perkin (J., 1895, 67, 230), Hoffmann and Fari (*Arch. Pharm.*, 1933, 271, 97), and Ray and co-workers (J., 1937, 1862) respectively have suggested the empirical formulæ  $C_{33}H_{30}O_9$ ,  $C_{31}H_{30}O_8$ , and  $C_{27}H_{26}O_7$ . It may be noted here that the analytical data given in Part I (*loc. cit.*) are in close agreement with the formula  $C_{30}H_{28}O_8$ .

has the formula  $C_{20}H_{18}O_4$ , with which the analytical results stated in Part I (*loc. cit.*) are in good agreement, and further, in accordance with the arguments previously outlined (Part I), this compound, tetrahydrorottlerone, and *O*-dimethyltetrahydrorottlerone may be represented by formula type (I), (II, R = H), and (II, R = Me) respectively. In



this connexion, it may be noted that, since both rottlerone and its tetrahydro-derivative give strong ferric reactions in alcoholic solution, the acyl groups in these compounds are undoubtedly attached at either the 6- or the 8- position. Although direct experimental evidence on this point is lacking, the latter position appears to be excluded because compounds of the type (III) would be expected to dissolve readily in dilute aqueous sodium hydroxide, whereas both rottlerone and tetrahydrorottlerone are sparingly soluble in this reagent. In support of this conclusion, it may be recorded that 5 : 7-dihydroxy-8-acetyl-2 : 2-dimethylchroman is readily soluble in 4% aqueous sodium hydroxide (private communication from Mr. T. Backhouse of this laboratory).

In the formation of rottlerone and its hydrogenation products by means of alkalis, we have found that small amounts of *C*-methylphloroglucinol are simultaneously produced (compare Part I) and, in agreement with this observation, Brockmann and Maier (*Naturwiss.*, 1937, 25, 460) have recorded the formation of a derivative of *C*-methylphloracetophenone from rottlerin. It may, therefore, be tentatively suggested that the rottlerin molecule is composed essentially of a rottlerone unit linked to a *C*-methylphloroglucinol residue, as in the structure type (IV) in which the nature of the radicals  $\text{R}$  and  $\text{R}'$  cannot at present be clearly defined. Though the mode of union of the rottlerone and the *C*-methylphloroglucinol units is not yet clear, it would appear from the comparative stability of rottlerin methyl ether towards alkalis (unpublished work) that this linking is not of the ester or depside type (compare Part I). It may well be that  $\text{R}$  is the radical  $-\text{CH}_2-$ , a view which would account for the production of *C*-dimethylphloroglucinol from rottlerin by means of zinc dust and boiling aqueous sodium hydroxide; the possibility of an oxide link in addition to the carbon to carbon union of the *C*-methylphloroglucinol and rottlerone residues is also envisaged. Further, on the basis of a  $\text{C}_{30}$  formula for rottlerin in conjunction with the findings of Brockmann and Maier (*loc. cit.*), the radical  $\text{R}'$  may be  $\text{CH}_3\cdot\text{CO}$  and hence rottlerin would have the structure type (V).

The preparation of perhydrorottlerone from rottlerin and from tetrahydrorottlerone has been reinvestigated and the compound has now been found to melt at  $147^\circ$  and not at  $178^\circ$  as stated in Part I (*loc. cit.*).

#### EXPERIMENTAL.

Rottlerone has been prepared by the following modification of the procedure employed in Part I (*loc. cit.*). Saturated aqueous barium hydroxide (500 c.c.) was added to a solution of rottlerin (20 g.) in pyridine (50 c.c.), and the well-stirred mixture heated at  $75^\circ$  for 5 minutes

and rapidly cooled. The crimson solid which separated in the course of 24 hours was triturated with dilute acetic acid, and the friable product extracted with boiling ethyl acetate. On repeated crystallisation from methyl alcohol and then alcohol-chloroform, the residue gave rottlerone in characteristic garnet-red, pointed prisms (1 g.), m. p. 236°.

*Tetrahydrorottlerone.*—This compound has been prepared by the following improved method (compare Part I, *loc. cit.*). On being warmed, a solution of tetrahydrorottlerin (20 g.) in 8% aqueous sodium hydroxide (360 c.c.) became opaque at 63° and the mixture was then maintained at 63—70° for 20 minutes. The product, which separated on cooling, was collected and crystallised from acetone containing a little acetic acid and then from ethyl acetate, forming yellow prisms (5—6 g.), m. p. 172—173°, which gave a violet-green coloration with alcoholic ferric chloride (Found: C, 73.8; H, 6.7. Calc. for  $C_{20}H_{22}O_4$ : C, 73.6; H, 6.7%).

The buff precipitate obtained by acidification of the alkaline filtrate left on separation of the crude tetrahydrorottlerone was collected and triturated with aqueous sodium bicarbonate, aqueous sodium carbonate, water, and finally several times with cold methyl alcohol. On being kept, a solution of the resulting yellow resin in alcohol gradually deposited a further quantity of tetrahydrorottlerone, m. p. 172—173° after purification. Evaporation of the alcoholic washings and residues finally left much resinous material, from which crystalline material has not been obtained.

Extraction of the acidic filtrate from the buff precipitate with ether gave a small amount of a mixture of *C*-methylphloroglucinol and an unidentified phenol, m. p. 164°, which were separated by fractional sublimation in a high vacuum.

*O-Dimethyltetrahydrorottlerone.*—This has now been obtained more conveniently by the procedure first employed for the methylation of dehydrodihydrotoxicarol (J., 1937, 1535). A mixture of tetrahydrorottlerone (1 g.), methyl sulphate (5 c.c.), potassium carbonate (10 g.), and acetone (75 c.c.) was refluxed on the steam-bath for 2½ hours; after 2 hours, more sulphate (2.5 c.c.) and more carbonate (5 g.) were added. The reaction mixture was poured into water (200 c.c.) and the product, which solidified in the course of 2 hours, was collected next day and recrystallised from light petroleum (b. p. 60—80°), then aqueous alcohol, and finally methyl alcohol, forming colourless prisms, m. p. 101—102° [Found: C, 75.0; H, 7.4; OMe, 17.3, 17.4. Calc. for  $C_{20}H_{20}O_2(OMe)_2$ : C, 74.6; H, 7.4; OMe, 17.5%]. Oximation of this ether gave the oxime (Part I, *loc. cit.*), but attempts to obtain a 2:4-dinitrophenylhydrazone have been unsuccessful.

*Perhydrorottlerone.*—(A) Hydrogenation of tetrahydrorottlerin (1 g.) was effected in absolute alcohol (300 c.c.) in the presence of a platinum catalyst (0.15 g.) with hydrogen at 40 lb./sq. in. during 48 hours, and after the separation of the catalyst water was added until the solution became opalescent. The mixture was heated to 80° and on cooling deposited perhydrorottlerin in pale yellow needles, m. p. 185—187°, which, on repeated purification from ethyl acetate, aqueous alcohol, and finally benzene, had m. p. 188° and gave a purple-violet coloration with alcoholic ferric chloride (Found: C, 68.6; H, 7.2%). In the course of numerous experiments, a product was occasionally obtained which had m. p. 181—182°, unchanged on repeated purification. The direct hydrogenation of rottlerin with a platinum catalyst gave similar results. For the hydrogenation of rottlerin and its tetrahydro-derivatives with a platinum catalyst, ethyl acetate and acetone (compare Part I, *loc. cit.*) were found to be unsuitable as solvents, giving rise to impure products, and, when acetic acid was used, crystalline material could not be isolated from the product.

On being slowly heated, a solution of perhydrorottlerin (m. p. 188°) (2 g.) in 8% aqueous sodium hydroxide (40 c.c.) became opalescent at about 72—73°. The reaction mixture was kept at this temperature for 5 minutes and then rapidly cooled. Repeated crystallisation of the well-washed precipitate from alcohol or aqueous alcohol gave perhydrorottlerone in pale yellow prisms or plates (0.5 g.), m. p. 147°, which gave a violet coloration with alcoholic ferric chloride (Found: C, 73.2; H, 8.0%. Found for a specimen dried in a high vacuum at 80°: C, 73.0; H, 7.7%). A similar yield of the same product, m. p. 147°, was obtained from specimens of perhydrorottlerin, m. p. 181—182°.

Acetylation of perhydrorottlerone (0.5 g.) with acetic anhydride (12 c.c.) and pyridine (6 c.c.) on the water-bath for 15 minutes and then at room temperature for 14 days gave the *acetyl* derivative, which separated from acetone-alcohol in tiny colourless prisms, m. p. 206—207° (Found: C, 70.0; H, 7.0%).

In the course of many experiments on the preparation of perhydrorottlerin by the hydrogenation of rottlerin or tetrahydrorottlerin, we have observed that the melting point does not appear to be a safe criterion of the homogeneity of the product. The latter, however,

appears to be best tested by converting the material into perhydrorottlerone, m. p. 147°. Impure specimens of perhydrorottlerin, *e.g.*, m. p. 179°, arising from the use of an inefficient catalyst or an unsuitable solvent, furnished a mixed product from which, on several occasions, perhydrorottlerone, m. p. 147°, and tetrahydrorottlerone, m. p. 167°, could be isolated by a tedious fractional crystallisation.

(B) Hydrogenation of tetrahydrorottlerone (1 g.), dissolved in acetone (300 c.c.), with hydrogen at 40 lb./sq. in. and a platinum catalyst (0.1 g.) in the course of 44 hours gave rise to perhydrorottlerone (0.5 g.), m. p. 147° after recrystallisation from ethyl acetate, acetone, and finally alcohol. In the course of the purification of quantities of this compound from alcohol or ethyl acetate, a second form, pale yellow needles, m. p. 159—160°, was sometimes obtained. On further crystallisation from the same solvents, this material reverted to the form, m. p. 147°.

In several hydrogenation experiments the product appeared to be a mixture of perhydrorottlerone and unchanged material.

On account of the fact that tetrahydrorottlerone is sparingly soluble in cold acetic acid or alcohol, neither of these solvents was used as a medium for hydrogenation.

We are indebted to Dr. R. W. Roberts of the Department of Physics for the following summary of the data on tetrahydrorottlerone submitted by Mr. W. D. Goodman: The crystals of tetrahydrorottlerone are transparent yellow pinakoids belonging to the triclinic pinakoidal class;  $\alpha = 153^\circ 12'$ ,  $\beta = 109^\circ 6'$ ,  $\gamma = 68^\circ 48'$ .

*X-Ray data*:  $a = 11.01$  A.,  $b = 17.02$  A.,  $c = 21.69$  A. Space group  $C_1^1$ . Density 1.263 g. per c.c. With  $M = 326.2$ , the number of molecules in the unit cell is 4.03, *i.e.*, the unit cell must contain two non-equivalent sets of two asymmetric chemical molecules.

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