

150. Rottlerin. Part I.

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THE main phenolic crystalline constituent of the Indian colouring matter and anthelmintic drug "kamala," which is obtained from the fruit glands of *Mallotus philippinensis* (Muell) (synonym *Rottlera tinctoria*, Roxb.), appears to have been isolated first in 1855 by Anderson (*Edin. New Phil. J.*, **1**, 296), who named the compound, $C_{11}H_{10}O_3$, rottlerin.* Although Leube (*Vierteljahrsschrift für prakt. Pharm.*, 1860, **9**, 319) and Oettingen (*Dissert.*, St. Petersburg, 1862) failed to obtain crystalline material from kamala, Anderson's results were amply confirmed by Perkin and Perkin (*Ber.*, 1886, **19**, 3109) and by Jawein (*ibid.*, 1887, **20**, 182), who gave m. p. 200° for rottlerin. The substance has been the subject of a number of investigations by several authors, but the results so far obtained have been somewhat contradictory [Perkin, J., 1893, **63**, 975; 1895, **67**, 230; 1899, **75**, 443, 829; Bartolotti, *Gazzetta*, 1894, **24**, (i), 1; (ii), 480; Telle, *Arch. Pharm.*, 1906, **244**, 441; Hermann, *ibid.*, 1907, **245**, 572; Dutt, J., 1925, **127**, 2044; Dutt and Goswani, *J. Indian Chem. Soc.*, 1928, **5**, 21; Hoffmann and Fari, *Arch. Pharm.*, 1933, **271**, 97] and accordingly a detailed summary of the work and conclusions of previous authors, which would not appear to be of special value at present, has been omitted from this memoir (see, however, Perkin and Everest, "Natural Organic Colouring Matters," London, 1918, p. 598, for a résumé of the results of Telle and earlier workers. It may be noted that the derivatives of phloroglucinol which Telle claims to have obtained from rottlerin were C-methyl compounds and not methyl ethers as quoted by Perkin and Everest, *loc. cit.*, and by Dutt, *loc. cit.*).

In the course of preliminary experiments it became evident that rottlerin is a highly reactive substance, difficult to obtain free from minute traces of accompanying impurities and unstable when heated with high-boiling solvents; *e.g.*, the use of toluene as a solvent for crystallisation purposes appears to cause slight resinification. Although an improved procedure for the preparation of the pure compound has been developed and the material has been obtained having a higher melting point, 212° , than that previously recorded, nevertheless in the case of rottlerin melting point alone cannot be regarded as an entirely satisfactory criterion of absolute purity. A considerable number of analyses of the com-

* The name mallotoxin suggested by Perkin and Perkin (*loc. cit.*) is more appropriate than rottlerin, but the latter has precedence and has been adopted in the literature.

pound have been carried out for us by Dr. A. Schoeller of Berlin and by Dr. Weiler of Oxford and though the results agree fairly well amongst themselves they do not permit us to make a final decision between the empirical formulæ $C_{33}H_{30}O_9$ and $C_{31}H_{30}O_8$ proposed by Perkin (*loc. cit.*) and by Hoffmann and Fari (*loc. cit.*) respectively. For the present we have employed Perkin's formula as a working hypothesis, since it appears to accord best with certain derivatives subsequently described, but further evidence from studies of the degradation products may well necessitate some modification of this formula.

Acetylation of rottlerin by the pyridine method at room temperature gave an acetyl derivative (hexa-acetate?), apparently identical with that described by Hoffmann and Fari (*loc. cit.*), and a small yield of the same product, accompanied by much amorphous material, was also obtained when rottlerin was boiled with acetic anhydride for 1 hour (compare Perkin and Dutt, *loc. cit.*). All efforts to isolate an acetyl derivative, m. p. 130—135° (Perkin) or m. p. 165° (Dutt), were unsuccessful. In this connexion it may be noted that prolonged treatment of rottlerin with hot formic acid, acetic acid, or acetic anhydride resulted in the formation of amorphous products from which crystalline material could not be obtained. Attempts to methylate rottlerin with methyl sulphate and aqueous sodium hydroxide under a variety of conditions invariably yielded resinous materials, a result which is readily explained by the instability of rottlerin to dilute aqueous sodium hydroxide. On this account also it is clear that the crystalline methylation product described by Dutt (*loc. cit.*) cannot be regarded as a methyl ether of unchanged rottlerin. Less drastic methylating reagents, diazomethane and methyl iodide-potassium carbonate, gave equally unsatisfactory results.

Treatment of rottlerin with phenylhydrazine led to the formation of an amorphous product as recorded by Bartolotti (*loc. cit.*), and similarly intractable products were obtained by the action of semicarbazide acetate and with hydroxylamine hydrochloride.

In the course of a considerable number of experiments on the hydrolytic fission of rottlerin it was found that the nature of the products depends to a large extent on the conditions employed. We have confirmed the formation of rottlerone* along with traces of benzaldehyde when rottlerin is warmed with aqueous sodium carbonate as described by Perkin (*loc. cit.*), but the yield of crystalline material was small and inconsistent. The same products were obtained by means of warm aqueous baryta and thus Telle's ψ -rottlerin (*loc. cit.*) is identical with rottlerone, for which Perkin did not give a melting point. Under both sets of conditions we have found that rottlerone is accompanied by *C*-methyl-phloroglucinol. On the other hand, with hot concentrated aqueous potassium hydroxide in the absence of zinc dust, rottlerin gave rise to phloroglucinol, acetic acid, benzoic acid, and cinnamic acid (compare Perkin, *loc. cit.*), and with boiling dilute aqueous sodium hydroxide and zinc dust *C*-methyl- and *C*-dimethyl-phloroglucinol together with β -phenylpropionic acid were produced in agreement with the findings of Hermann (*loc. cit.*) and of Telle (*loc. cit.*). Contrary to the results of Telle, however, all attempts to obtain *C*-trimethylphloroglucinol by means of boiling 2% aqueous sodium hydroxide and zinc dust were entirely unsuccessful. Under the latter conditions this author also obtained a small amount of a steam-volatile, camphor-like solid, m. p. 170—172°, but although the crude volatile product isolated by us had a strong camphoraceous odour, the pure solid, m. p. 175°, was odourless; the smell was observed to be due to traces of neutral oily material. For the solid, which reacts with 2 : 4-dinitrophenylhydrazine, the provisional formula $C_{18}H_{18}O$ is suggested, but the quantity of material obtained from several experiments was too small for a detailed investigation.

Oxidation of rottlerin with alkaline potassium permanganate and of rottlerin acetate with the neutral reagent furnished benzoic acid and acetic acid, but contrary to the statement of Dutt (*loc. cit.*) neither phthalic acid nor terephthalic acid could be detected. Similarly, the results obtained by the action of nitric acid on rottlerin were identical with those described by Perkin (*loc. cit.*), but all attempts to isolate nitro-derivatives of phthalic acid or of terephthalic acid by repetition of Dutt and Goswami's experiments (*loc. cit.*)

* It is clear that this compound is not simply an oxidation product of rottlerin as is implied by the name rottlerone, but there is evidence (present work) that the compound contains an active carbonyl group and therefore it is convenient to retain this designation for the present at least.

have so far been unsuccessful. From a series of quantitative oxidation experiments with alkaline potassium permanganate it has been found that for an empirical formula approximating to $C_{33}H_{30}O_9$ rottlerin yields slightly less than one molecular proportion of benzoic acid and therefore it is clear that rottlerin contains one cinnamyl residue and that in degradation experiments where both cinnamic acid and benzoic acid are formed the latter arises by oxidation of the cinnamyl residue and not as the result of the presence of a second phenyl radical in the molecule. In the ozonolysis of rottlerin the cinnamyl radical gives rise to benzaldehyde, which is accompanied by an intractable resin.

On hydrogenation with a palladium catalyst rottlerin gives rise to a tetrahydro-derivative, m. p. 215° , the analytical data for which agree remarkably well with the empirical formula $C_{33}H_{34}O_9$. When a platinum catalyst is employed, hydrogenation proceeds beyond the tetrahydro-stage and both rottlerin and tetrahydrorottlerin yield a product, m. p. 178° , which we have termed *perhydrorottlerin* ($C_{33}H_{40}O_9$?). Hoffmann and Fari (*loc. cit.*) describe a tetrahydro-derivative, m. p. 200 — 201° , which they consider to be $C_{31}H_{34}O_8$, but which is in all probability a slightly impure form of the product obtained in the present work, since the acetate, m. p. 188° , of the latter, also obtainable directly by the hydrogenation of rottlerin acetate, appears to be identical with the acetate, m. p. 183 — 185° , described by these authors. In consequence we consider that the evidence is insufficient to warrant the adoption of the empirical formula $C_{31}H_{30}O_8$ which they have deduced for rottlerin from that of their tetrahydro-derivative.

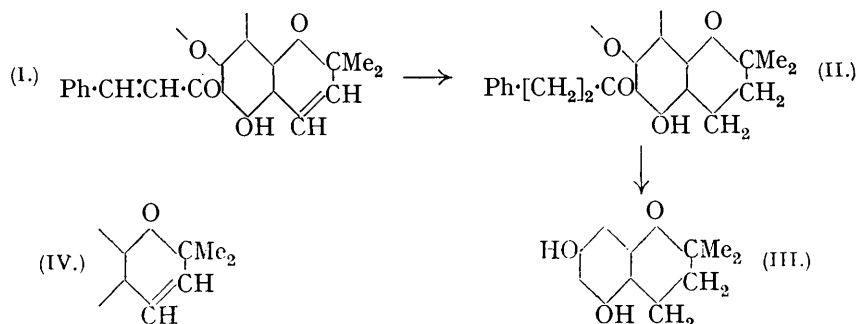
In experiments on the hydrolytic fission of tetrahydrorottlerin with warm dilute aqueous sodium or barium hydroxide a well-crystallised degradation product was formed, which was subsequently found to be identical with *tetrahydrorottlerone* obtained by the hydrogenation of rottlerone with a palladium catalyst. Fission of perhydrorottlerin under similar conditions gave rise to *perhydrorottlerone*, identical with the product formed by the hydrogenation of tetrahydrorottlerone with a platinum catalyst. In the hydrolysis of both tetra- and perhydrorottlerin the resulting rottlerone derivatives are accompanied by *C*-methylphloroglucinol and a considerable amount of amorphous acidic material.

On account of the extremely poor yields of rottlerone, the purification of which is somewhat difficult, a detailed investigation of this compound is reserved. Since the substance and its hydrogenation products are practically insoluble in aqueous sodium hydroxide but are soluble in an alcoholic solution of this reagent and all give ferric reactions, it is reasonably certain that they contain a phenolic hydroxyl group in the *o*-position to a carbonyl group. The analytical results obtained for rottlerone accord with the formula $C_{20}H_{18}O_4$ or $C_{26}H_{24}O_5$ and for tetrahydrorottlerone with the corresponding formula $C_{20}H_{22}O_4$ (A) or $C_{26}H_{28}O_5$ (B), of which (B) is in closer agreement with the molecular-weight determinations carried out on the tetrahydro-compound and its derivatives. Acetylation and methylation of tetrahydrorottlerone yield an *acetate* and a *methyl ether*, which are both devoid of ferric reactions and are respectively either a diacetate and a dimethyl ether of (A) or a triacetate and a trimethyl ether of (B). Attempts to determine the presence of an active carbonyl group in tetrahydrorottlerone by the usual reagents gave unsatisfactory results, but when the methyl ether was warmed with hydroxylamine hydrochloride in the presence of pyridine a nitrogen-containing product was obtained which appears to be the *oxime*, although the analytical results do not correspond with those required for a derivative of (A) or (B).

Hydrolytic fission of tetrahydrorottlerone with hot concentrated aqueous sodium hydroxide gave rise to β -phenylpropionic acid and a phenolic product which was shown to be 5 : 7-dihydroxy-2 : 2-dimethylchroman (III) by comparison with a synthetical specimen. On the basis of this result it is reasonably certain that tetrahydrorottlerone contains the β -phenylpropionylchroman residue, type (II), a conclusion which is supported by the insolubility of the compound in aqueous sodium hydroxide, its ferric reaction, and the formation of an oxime of its methyl ether.

Further, in view of the fact that the 2 : 2-dimethyl- Δ^3 -chromen unit, type (IV), has been shown to be present in the molecular structures of a number of natural compounds (Robertson and co-workers, J., 1933, 489; 1936, 627, 1828; this vol., pp. 279, 286) it is highly probable that rottlerone and rottlerin contain this unit, and, since the residue

appearing as the β -phenylpropionyl radical in the tetrahydro-derivatives has been shown by alkaline hydrolysis and by oxidation to be present as a cinnamyl group in the parent compounds, it is reasonable to suppose that rottlerinone and rottlerin contain the cinnamyl-



chromen unit, type (I). The presence of this unit affords a satisfactory explanation of the ease of formation of the tetrahydro-derivatives, because the chromen double bond, like that in the cinnamyl group, has been shown to be readily hydrogenated with a palladium catalyst, *e.g.*, formation of dihydroxanthyletin and dihydroxanthoxyletin (Robertson and co-workers, *loc. cit.*). Further, leaving aside the undetermined part of the molecule, the proved instability of the unit (IV) in toxicarol, xanthoxyletin, and xanthyletin in the presence of alkaline reagents would account to some extent at least for the behaviour of rottlerin on hydrolytic fission.

The conversion of rottlerin and its hydrogenation products into corresponding members of the rottlerone series by means of alkalis under comparatively mild conditions appears to be a complex reaction giving poor yields of crystallisable material, but in each case we have always observed the simultaneous formation of *C*-methylphloroglucinol. This compound is also obtained along with much resinous material when rottlerin is warmed with dilute hydrochloric acid. These reactions are suggestive that rottlerin may be a depside type of ester, but we have been unable to obtain decisive evidence on this point. The results of the present investigation, however, clearly disprove the structure proposed for rottlerin by Dutt and Goswani (*loc. cit.*).

EXPERIMENTAL.

Rottlerin.—Kamala (250 g.) was heated with boiling benzene (2 l.) for 8 hours, and on being kept for 12 hours the extract, which had been filtered from the yellow insoluble residue (118 g.), deposited part of the rottlerin (11 g.), m. p. 198°. After the isolation of the solid and the evaporation of the greater part of the solvent the residual solution (330 c.c.) gradually deposited more rottlerin (31 g.). As a rule further concentration failed to yield more crystalline material and the resinous residue has been saved for further investigation. The benzene-insoluble material was further extracted with fresh solvent, which was then employed for the extraction of fresh batches of kamala.

Thus obtained, the crude rottlerin was contaminated with considerable quantities of resinous material, and after numerous experiments the following procedure was found to be the most efficacious method of purification: The crude product (600 g.) was boiled with carbon tetrachloride (1.3 l.) for 4 hours, and the solid isolated and extracted with fresh solvent (700 c.c.). The resulting insoluble product (380 g.), m. p. 206°, consisting of fairly pure rottlerin, was purified by repeated crystallisation from ethyl acetate (about 100 g. of solid dissolved in 1.3 l. of solvent), being finally obtained in light reddish-brown plates or needles having a golden lustre (70 g.), m. p. 212°, unchanged by repeated crystallisation from acetone [Found (mean of six analyses): C, 69.69 (\pm 0.11); H, 5.57 (\pm 0.21). Calc. for C₃₃H₃₀O₉: C, 69.44; H, 5.30%. Calc. for C₃₁H₃₀O₈: C, 70.16; H, 5.7%. Calc. for C₃₄H₃₂O₉: C, 69.86; H, 5.48%] (Perkin, Dutt, and Hoffmann and Fari, *loc. cit.*, respectively give m. p. 191—191.5°, 206—207°, 206—207°). Rottlerin is readily soluble in pyridine or aniline, moderately soluble in hot acetone, ethyl acetate, benzene, toluene, chloroform or ether, and sparingly soluble in cold alcohol or acetic acid. It reduces Fehling's solution and gives a reddish-brown coloration with alcoholic ferric chloride.

The mixture obtained by the interaction of rottlerin (3 g.) with acetic anhydride (30 c.c.) and pyridine (15 c.c.) at room temperature for 5 days was poured into ice and acetic acid, and the granular precipitate collected 24 hours later, washed with dilute acetic acid, and recrystallised from acetone-alcohol, giving the acetyl derivative in stout colourless prisms, m. p. 213°, insoluble in aqueous sodium hydroxide and having a negative ferric reaction (Found: C, 66.1; H, 5.3; CH_3CO , 34.7, 35.8, 38.5%) (Hoffmann and Fari, *loc. cit.*, give m. p. 212°).

Acetylation of rottlerin according to the procedure of Dutt (*loc. cit.*) gave a small yield of the same acetate, m. p. and mixed m. p. 213°, when the reaction mixture was heated for 1 hour, but if the heating was continued for longer periods amorphous products were obtained.

Oxidation of Rottlerin with Alkaline Potassium Permanganate.—1% Aqueous potassium permanganate (approx. 2.5 l.) was slowly added to a solution of rottlerin (10 g., well powdered) in 2% aqueous sodium hydroxide (300 c.c.) until the solution retained a permanganate colour; precautions were taken to prevent the loss of traces of benzaldehyde formed in the early stages of the reaction. The manganese dioxide was removed (wash with hot water), the excess of permanganate destroyed with sulphur dioxide, the solution acidified with dilute sulphuric acid and repeatedly extracted with ether, and the combined dried extracts evaporated, leaving a pale yellow residue (2.2 g.) containing a little acetic acid. Crystallisation of the product, which had been dried in a vacuum at room temperature, from the minimum volume of hot water gave benzoic acid in colourless plates (1.8 g.), m. p. 121° (theoretical for one cinnamyl residue, 2.14 g.); approximately the same yield of benzoic acid was obtained in three experiments. In another experiment the acetic acid was isolated and identified by conversion into the anilide, m. p. 112°.

Action of Aqueous Sodium and Potassium Hydroxide on Rottlerin.—(A) Rottlerin (10 g.) was heated with 50% aqueous potassium hydroxide (50 g.) at 150–160° for $\frac{3}{4}$ hour in an atmosphere of nitrogen, and the cooled mixture dissolved in water (300 c.c.), acidified with hydrochloric acid, and repeatedly extracted with ether. After the removal of the acidic material from the combined extracts with aqueous sodium bicarbonate evaporation of the solvent left a brown semi-solid, which was extracted once with hot benzene (5 c.c.). A hot aqueous solution of the benzene-insoluble residue was treated with charcoal, filtered, and evaporated in a vacuum at room temperature and the resulting phloroglucinol, which gradually separated in colourless plates (0.1–0.2 g.), m. p. 214–215°, was identified by comparison with an authentic specimen and by conversion into the triacetate, m. p. and mixed m. p. 105–106° (Found: C, 57.2; H, 4.9. Calc. for $\text{C}_{12}\text{H}_{12}\text{O}_6$: C, 57.1; H, 4.8%).

Acidification of the sodium bicarbonate solution gave cinnamic acid (isolated with ether), m. p. and mixed m. p. 133°, after purification.

When a mixture of rottlerin (5 g.) and 50% aqueous potassium hydroxide (50 c.c.) was gradually heated to 250° and kept at this temperature for 10 minutes, cinnamic acid and acetic acid could be isolated in the usual manner.

(B) Well-powdered rottlerin (10 g.) was boiled with 15% aqueous sodium hydroxide (100 c.c.) containing zinc dust (20 g.) for 5 minutes, and the mixture cooled, diluted with water (300 c.c.), and filtered. The filtrate was acidified with sulphuric acid and next day the precipitated resinous solid was removed, the excess of acid neutralised with sodium bicarbonate, and the solution extracted with ether (200 c.c. \times 10); the red-brown viscous oil left on evaporation of the solvent was digested with water, and the aqueous soluble fraction isolated by means of ether and boiled with six successive portions of benzene (75 c.c.). In the course of 12 hours the first two benzene extracts deposited crystalline material and in the first case this was further purified by means of warm benzene. The two products, 0.1 g. and 0.15 g., m. p. 150–155°, were then combined and recrystallised from ethyl acetate-xylene, giving *C*-dimethylphloroglucinol in colourless needles, m. p. 162°, identical with an authentic specimen and giving the characteristic blue-violet ferric reaction (Found: C, 62.5; H, 6.5. Calc. for $\text{C}_8\text{H}_{10}\text{O}_3$: C, 62.3; H, 6.5%). On being kept, the remaining benzene extracts deposited resinous material only.

When the brown benzene-insoluble residue was heated in a high vacuum at about 160°, a small amount of sublimate, m. p. 200°, was obtained which on crystallisation from ethyl acetate-xylene gave *C*-methylphloroglucinol (characteristic blue ferric reaction), m. p. 212–213°, identical in every way with an authentic specimen.

(C) A solution of rottlerin (10 g.) in 2% aqueous sodium hydroxide (1.2 l.), containing zinc dust (100 g.), was distilled with the addition of water to keep the volume of the solution approximately constant; from the camphoraceous aqueous distillate, which was collected in the course of 8 hours, a small amount of a crystalline solid separated in colourless needles contaminated

with traces of oily material. Recrystallisation of this solid from light petroleum (b. p. 60—80°) gave colourless, odourless, diamond-shaped plates (25 mg.), m. p. 175°, which reacted with an aqueous-alcoholic solution of 2 : 4-dinitrophenylhydrazine hydrochloride (Found : C, 86.4; H, 7.0. $C_{18}H_{18}O$ requires C, 86.4; H, 7.2%).

A thorough investigation of the phenolic products in the aqueous alkaline liquors from a number of experiments failed to reveal the presence of *C*-trimethylphloroglucinol. The only phenolic compounds isolated were *C*-methyl- and *C*-dimethyl-phloroglucinol.

Tetrahydrorottlerin.—For the preparation of this compound in quantity rottlerin (10 g.), dissolved in ethyl acetate (250 c.c.), was hydrogenated with a palladium-charcoal catalyst (from 0.2 g. of palladium chloride and 2 g. of charcoal); the end of the reaction was indicated when the orange-red solution had become almost colourless. On isolation the product (yield, almost theoretical) separated from alcohol in pale yellow, elongated prisms, m. p. 215° (Found : C, 69.0, 69.0, 68.9; H, 6.0, 6.1, 6.1. Calc. for $C_{31}H_{30}O_8$: C, 69.7; H, 6.4%. Calc. for $C_{33}H_{34}O_9$: C, 69.0; H, 5.9%. Calc. for $C_{33}H_{38}O_9$: C, 69.2; H, 6.4%). The same compound was obtained by means of a palladium-barium sulphate catalyst in acetic acid, ethyl acetate, or acetone and in a series of quantitative experiments at atmospheric pressure it was found that 0.3 g. of rottlerin absorbed approximately 27.4 c.c. of hydrogen; the theoretical quantity for saturation of two double bonds in a compound having a formula approximately $C_{33}H_{30}O_9$ is 23 c.c. Tetrahydrorottlerin, which is slightly more soluble in organic solvents than rottlerin, forms a yellow solution with aqueous sodium hydroxide and gives an intense green-violet coloration with alcoholic ferric chloride. When a solution of tetrahydrorottlerin (2 g.) in 50% aqueous sodium hydroxide (50 c.c.) was gradually heated to 270°, then kept at this temperature for 15 minutes, cooled, and acidified, β -phenylpropionic acid, m. p. and mixed m. p. 47°, was isolated with ether.

Acetylation of tetrahydrorottlerin (1.5 g.) with acetic anhydride (7.5 c.c.) and pyridine (5 c.c.) at room temperature for 3 days gave the hexa-acetate (2 g.), which separated from methyl alcohol in colourless prisms or plates, m. p. 188°, insoluble in aqueous sodium hydroxide and having a negative ferric reaction [Found : C, 65.5; H, 5.6; $CH_3\cdot CO$, 37.34, 36.6. Calc. for $C_{33}H_{28}O_9(CH_3\cdot CO)_6$: C, 65.4; H, 5.6; $CH_3\cdot CO$, 31.2%]. Hydrogenation of rottlerin acetate (1.5 g.), dissolved in acetone (50 c.c.), with hydrogen (approx. 2.5 mols. absorbed) and a palladium catalyst gave rise to the same tetrahydro-derivative, m. p. and mixed m. p. 188°.

Rottlerone.—When a filtered solution of rottlerin (20 g.) in saturated aqueous barium hydroxide (750 c.c.) was boiled for 10 minutes, traces of benzaldehyde were evolved, much frothing occurred, and an orange product separated which after cooling was isolated, washed, dried, and extracted (Soxhlet) with ether. On being kept, a solution of the resulting deep red extract in chloroform-alcohol deposited garnet-red, pointed prisms (0.8 g.) of rottlerone, m. p. 236° after repeated crystallisation from the same solvent (Found : C, 74.6; H, 5.6. Calc. for $C_{20}H_{18}O_4$: C, 74.5; H, 5.6%. Calc. for $C_{22}H_{24}O_5$: C, 75.0; H, 5.8%). A similar yield of the compound can be obtained by Perkin's method (*loc. cit.*), but in this case the purification of the product is considerably more difficult and the yield is inconsistent. Rottlerone is soluble in warm chloroform, ethyl acetate, carbon tetrachloride, or pyridine, sparingly soluble in acetic acid or ether, and almost insoluble in alcohol, light petroleum, or aqueous sodium hydroxide. On the addition of ferric chloride to an alcoholic solution of the substance a brown coloration slowly develops.

The baryta liquors were acidified with hydrochloric acid, filtered to remove precipitated resinous material, treated with excess of sodium bicarbonate, and extracted with ether (300 c.c. \times 10). The product was digested with boiling benzene (50 c.c.) and *C*-methylphloroglucinol, m. p. 209—210°, was isolated from the insoluble residue by sublimation at about 160° in a high vacuum and recrystallised from ethyl acetate-xylene; m. p. and mixed m. p. 214° (Found : C, 60.1; H, 5.8. Calc. for $C_7H_8O_3$: C, 60.0; H, 5.7%). Perkin's method also gave rise to *C*-methylphloroglucinol.

Tetrahydrorottlerone.—(A) On being heated to its boiling point, the yellow solution of tetrahydrorottlerin (1 g.) in 8% aqueous sodium hydroxide (20 c.c.) darkened at about 88—90° and a yellow semi-solid (0.25 g.) separated, which was isolated from the cooled solution with ether and on crystallisation from acetone gave *tetrahydrorottlerone* in slender yellow prisms, m. p. 172—173°, having a violet-green ferric reaction in alcohol [Found (mean of five analyses) : C, 74.1; H, 6.7. $C_{20}H_{22}O_4$ requires C, 73.6; H, 6.7%. $C_{22}H_{28}O_5$ requires C, 74.3; H, 6.7%]. The compound is soluble in benzene or chloroform and almost insoluble in aqueous sodium hydroxide. When a solution of tetrahydrorottlerin (5 g.) in saturated aqueous barytra (200 c.c.) was boiled for 5 minutes, a somewhat inferior yield of tetrahydrorottlerone was obtained, m. p. 172—173° after purification.

Acidification of the alkaline liquors left on removal of the tetrahydrorottlerone gave rise to a product, which was isolated with ether and resolved into an amorphous acidic fraction and a small amount of *C*-methylphloroglucinol. The latter compound, m. p. 214°, was separated from accompanying resinous impurities and purified as previously described.

Acetylation of tetrahydrorottlerone (0.5 g.) with acetic anhydride (12 c.c.) and pyridine (5 c.c.) at room temperature for 12 hours and then at 100° for $\frac{3}{4}$ hour gave the *acetyl* derivative, which formed colourless slender prisms, m. p. 214—215°, from acetone-alcohol (ferric reaction negative) [Found: C, 70.6; H, 6.3; CH₃·CO, 25.3. C₂₀H₂₀O₄(CO·CH₃)₂ requires C, 70.2; H, 6.4; CH₃·CO, 21.0%. C₂₆H₂₅O₅(CO·CH₃)₃ requires C, 70.3; H, 6.2; CH₃·CO, 23.6%].

(B) Hydrogenation of rottlerone (0.2 g.), dissolved in ethyl acetate (50 c.c.), with a palladium-charcoal catalyst (from 0.1 g. of palladium chloride) was complete in about 3 hours and on isolation the product separated from acetone in yellow prisms, m. p. 172—173°, identical with a specimen obtained by method (A).

Methylation of Tetrahydrorottlerone.—This was effected with the substance (1 g.), methyl iodide (3 c.c.), and potassium carbonate (4 g.) in boiling acetone (100 c.c.) in the course of 8 hours; after 3 hours more iodide (3 c.c.) and carbonate (4 g.) were added. On isolation the *product*, which did not give a ferric reaction, solidified in contact with a little methyl alcohol and then formed colourless prisms, m. p. 102°, from light petroleum (b. p. 60—80°), easily soluble in alcohol or acetone and insoluble in aqueous sodium hydroxide [Found (mean of four analyses): C, 74.9; H, 7.5; OMe, 18.5; *M*, 497, 478. C₂₀H₂₀O₂(OMe)₂ requires C, 74.6; H, 7.3; OMe, 17.5%; *M*, 354. C₂₆H₂₅O₂(OMe)₃ requires C, 75.3; H, 7.4; OMe, 20.0%; *M*, 462]. This compound was recovered unchanged after being treated with warm acetic anhydride and pyridine.

Treatment of the ether (0.5 g.) with hydroxylamine hydrochloride (0.5 g.) and pyridine (5 c.c.) at 100° for 6—8 hours gave rise to a small yield of a *product*, m. p. 188°, which separated from aqueous alcohol in tiny prisms, m. p. 204—205° (Found: C, 72.1; H, 7.3; N, 4.0. C₂₂H₂₇O₄N requires C, 71.6; H, 7.3; N, 3.8%. C₂₉H₃₅O₅N requires C, 73.0; H, 7.3; N, 2.9%).

Perhydrorottlerin, obtained by hydrogenation of rottlerin (1 g.) in pure acetone (150 c.c.) with hydrogen at 40 lb./sq. in. and a platinum oxide (0.1 g.) catalyst during 48 hours, separated from alcohol in clusters of yellow needles, m. p. 178°. Hydrogenation of tetrahydrorottlerin by this procedure gave the same product, m. p. 178° after purification (Found: C, 68.4; H, 7.3. C₃₃H₄₀O₉ requires C, 68.2; H, 7.0%. C₃₄H₄₄O₉ requires C, 68.5; H, 7.4%). The properties of this compound are similar to those of tetrahydrorottlerin except that it is slightly more soluble in organic solvents. With alcoholic ferric chloride it gives a violet-green coloration.

Perhydrorottlerone was prepared from the foregoing substance (1 g.) by means of 8% aqueous sodium hydroxide (20 c.c.) according to the procedure used for the preparation of tetrahydrorottlerone; on crystallisation from acetone it formed yellow prisms, m. p. 166°, giving (slowly) a violet-green coloration with alcoholic ferric chloride (Found: C, 73.0; H, 8.3. C₂₆H₂₈O₄ requires C, 72.3; H, 8.4%. C₂₆H₃₄O₅ requires C, 73.2; H, 8.0%). The same compound, m. p. and mixed m. p. 166°, was obtained by hydrogenation of tetrahydrorottlerone with a platinum catalyst.

Hydrolytic Fission of Tetrahydrorottlerone.—Tetrahydrorottlerone is almost insoluble even at high temperatures in hot aqueous sodium or potassium hydroxide and it was found necessary to use an aqueous alcoholic solution of the reagent in order to obtain a homogeneous solution. The compound (0.6 g.) dissolved readily in a warm mixture of 75% aqueous potassium hydroxide (50 c.c.) and alcohol (25 c.c.) and the resulting pale yellow solution was maintained at 160—170° for $\frac{3}{4}$ hour in an atmosphere of nitrogen. After cooling, the reaction mixture was acidified with excess of hydrochloric acid, the excess of acid neutralised with sodium bicarbonate, and the solution extracted several times with ether. Sublimation of the residue left on evaporation of the extracts gave colourless prisms (0.23 g.) of 5 : 7-dihydroxy-2 : 2-dimethylchroman, which on recrystallisation from benzene had m. p. 162° and was identical in every way with a synthetic specimen (Bridge, Heyes, and Robertson, this vol., p. 279) (Found: C, 68.1; H, 7.1. Calc. for C₁₁H₁₄O₃: C, 68.0; H, 7.2%).

From the aqueous liquor left on removal of the chroman, which had been acidified with hydrochloric acid, only β-phenylpropionic acid, m. p. and mixed m. p. 47°, was isolated with ether.

C-Methylphloroglucinol.—This was prepared by the reduction of phloroglucinolaldehyde (1 g.), dissolved in acetic acid (25 c.c.), with hydrogen and a palladium-charcoal catalyst (from 1 g. of charcoal and 5 c.c. of 4% aqueous palladium chloride) in the course of 4 hours and on isolation was purified by sublimation in a high vacuum and then by crystallisation from ethyl

acetate-xylene, forming colourless needles (0.3 g.), m. p. 215—216°, identical with an authentic specimen (Curd and Robertson, J., 1933, 437) (Found : C, 60.1; H, 5.7%).

C-Dimethylphloroglucinol (0.25 g.) was obtained from C-methylphloroglucinolaldehyde (0.5 g.) (Herzig and co-workers, *Monatsh.*, 1903, 24, 876) by the same procedure, m. p. 163° after sublimation and recrystallisation from ethyl acetate-xylene (Found : C, 62.3; H, 6.6%).

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