394. *Rottlerin. Part I.*

By Kartar Singh Narang, Jnanendra Nath Ray, and Bharpur Singh Roy.

Determinations of the molecular weights of various derivatives indicate that rottlerin has the formula $C_{27}H_{26}O_7$. It forms a tetrahydro-derivative, a tetra-acetyl derivative and a *tetramethyl* ether. This ether is oxidised by alkaline hydrogen peroxide, a *substance* $C_{31}H_{36}O_8$ being formed which on catalytic reduction is converted into *tetrahydrorottlerin tetramethyl ether*, indicating that an oxygen atom attaches itself to a double bond during oxidation.

Rottlerin tetramethyl ether gives a *substance* $C_{19}H_{21}O_6N$ when treated with nitrous acid at 40°.

ROTTLERIN has often been investigated (for references, see McGookin, Reed, and Robertson, this vol., p. 748) and the formula in vogue at present is $C_{33}H_{30}O_9$, which was advocated by Perkin (J., 1895, **67**, 230), although Robertson admitted the possibility of a C_{34} formula.

Telle (*Arch. Pharm.*, 1906, **244**, 441) confirmed the empirical formula $C_{11}H_{10}O_3$, but found 496 for the molecular weight in naphthalene. Dutt (J., 1925, **127**, 2044) obtained the values 585, 615, and 598 in boiling toluene and 675 by the silver salt method. Since, however, rottlerin is a polyhydric phenol, the evidence of molecular weight cannot be accepted without reserve. We have isolated a *tetramethyl* ether which, unlike the ether described by Dutt (which we have been unable to obtain), does not form an acetyl derivative; therefore its molecular weight, which agrees with the formula $C_{27}H_{26}O_7$ for rottlerin, is unlikely to be influenced by association or dissociation.

Genuine kamala powder was procured from Raja Sir Daya Kishen Kaul and Sons, Lahore, and rottlerin isolated essentially as prescribed by Dutt; its m. p. was 209°. McGookin, Reed, and Robertson (*loc. cit.*) found that crystallisation of rottlerin from toluene as recommended by Dutt appeared to cause slight resinification. We have noticed no signs of resinification provided the substance is not heated too long during dissolution. Crystallisation from ethyl acetate did not change the m. p. and the crystals were homogeneous under the microscope. Tetrahydrorottlerin is formed in quantitative yield from rottlerin and we believe that degradation of the molecule does not take place during reduction. Robertson *et al.* acetylated rottlerin at room temperature for 5 days and isolated an acetyl derivative, m. p. 213°, which was also formed in a much shorter time by boiling rottlerin with acetic anhydride; we confirm their statement that in no circumstances is the acetyl derivative described by Dutt formed. Analysis of the acetyl derivative gives results in better agreement with the C_{27} than the C_{33} formula for rottlerin: the difference in the two carbon values is 1%. The molecular weight of the acetyl derivative of tetrahydrorottlerin also agrees with the C_{27} formula.

The methylation of rottlerin by all the usual methods gives uncrystallisable mixtures.

When rottlerin tetramethyl ether (the methoxyl content of which completely militates against a C_{33} structure for rottlerin) is oxidised by alkaline hydrogen peroxide, it is quantitatively converted into a *substance* $C_{31}H_{36}O_8$, m. p. 128° (decomp.), which on catalytic reduction is converted into *tetrahydrorottlerin tetramethyl ether*. Rottlerin tetramethyl ether, on treatment with sodium nitrite and acetic acid, gives a *substance* $C_{19}H_{21}O_6N$(?), which is catalytically reducible to a *dihydro*-derivative.

The hydrolysis of tetrahydrorottlerin with hydrochloric acid in alcohol furnished a substance $C_{20}H_{22}O_4$, m. p. 171°, which we think may be identical with the similar product isolated by Robertson *et al.* from tetrahydrorottlerin by hydrolysis with sodium hydroxide (*loc. cit.*, p. 753).

EXPERIMENTAL.

Rottlerin, isolated essentially as described by Dutt, washed with alcohol, and crystallised thrice from toluene (without prolonged heating), had m. p. 209° (Found: C, 69·83, 69·99; H, 5·63, 5·33. Calc. for $C_{27}H_{26}O_7$: C, 70·13; H, 5·63%. Calc. for $C_{33}H_{30}O_9$: C, 69·47; H, 5·26%).

A colouring matter was isolated from the benzene filtrate and obtained in pale yellow needles, m. p. 181° (acetyl derivative, m. p. 200°; methyl ether, m. p. 105°). It has not been described by other workers and its examination is reserved for the time being.

The acetyl derivative of rottlerin was formed when rottlerin (1·0 g.), acetic anhydride (5 c.c.), and pyridine (2 drops) were refluxed for 1½ hours. It crystallised from ethyl acetate (charcoal) in prisms and had m. p. 214° after recrystallisation from ethyl acetate or alcohol [Found: C, 66·8, 66·72; H, 5·3, 5·6; $CH_3{\cdot}CO$, 27·4. Calc. for $C_{27}H_{22}O_3(O{\cdot}CO{\cdot}CH_3)_4$: C, 66·6; H, 5·4; $CH_3{\cdot}CO$, 27·4%. Calc. for $C_{33}H_{24}O_3(O{\cdot}CO{\cdot}CH_3)_4$: C, 65·7; H, 5·1; $CH_3{\cdot}CO$, 31·4%. Often a high value for acetyl is obtained owing to decomposition of sulphuric acid by the substance, unless precautions are taken to prevent it].

Tetrahydrorottlerin.—Rottlerin (1 g.), dissolved in purified ethyl acetate (40 c.c.) and alcohol (6 c.c.), was completely reduced in 1½ hours in presence of 3 c.c. of 1% palladium chloride solution. The product, crystallised successively from benzene, toluene, and ethyl acetate, had m. p. 212°. In an experiment in which 3 g. of rottlerin were reduced, 370 c.c. of hydrogen were absorbed at 18°/748 mm., indicating the absorption of approximately 4H per molecule [Found: C, 69·30, 69·41, 69·59; H, 6·30, 6·57, 6·49; *M* (micro-Rast), 476. Calc. for $C_{27}H_{30}O_7$: C, 69·51; H, 6·44%; *M*, 466. Calc. for $C_{33}H_{34}O_9$: C, 68·99; H, 5·92%; *M*, 574].

Tetra-acetyl Tetrahydrorottlerin.—Tetrahydrorottlerin (3·5 g.), acetic anhydride (15 c.c.), and pyridine (1 c.c.) were refluxed together for 1½ hours and the mixture was cooled and poured into water (400 c.c.). The product (4·7 g.), crystallised from ethyl acetate and then from alcohol, had m. p. 178°. The same substance, m. p. and mixed m. p. 178°, was obtained when tetra-acetyl rottlerin (m. p. 214°) (0·8 g.) was dissolved in ethyl acetate (100 c.c.) and alcohol (20 c.c.) and reduced in presence of 10 c.c. of 1% palladium chloride solution. Robertson *et al.* give m. p. 188° [Found: C, 65·92, 65·92, 65·76; H, 5·69, 5·75, 6·19; *M* (micro-Rast), 642; *M* (cryoscopic in benzene), 630, 641. Calc. for $C_{27}H_{22}O_3(O{\cdot}CO{\cdot}CH_3)_4$: C, 66·24; H, 5·99%; *M*, 634].

Rottlerin Tetramethyl Ether.—A mixture of rottlerin (2 g.), dry potassium bicarbonate (16 g.), methyl sulphate (8 c.c.), and purified acetone (50 c.c.) was refluxed on the steam-bath for 4 hours. Anhydrous potassium carbonate (8 g.) was now introduced, and the heating continued. After 45 minutes, when the solution had become pale yellow, the acetone was distilled off, and the residue diluted with water (150 c.c.) and left for 12 hours. The pale yellow solid was collected and crystallised from 90% alcohol. The *tetramethyl* ether is very soluble in acetone, glacial acetic acid, benzene, and ethyl acetate and is crystallisable from light petroleum; m. p. 144° [Found: C, 71·71; H, 6·65; OMe, 24·13; *M* (micro-Rast), 524, 562. $C_{27}H_{22}O_3(OMe)_4$ requires C, 71·81; H, 6·56; OMe, 23·94%; *M*, 518. $C_{33}H_{24}O_3(OMe)_6$ requires C, 71·56; H, 6·42; OMe, 28·4%; *M*, 654].

Tetrahydrorottlerin Tetramethyl Ether.—Tetrahydrorottlerin (2·5 g.), pure methyl sulphate (10 c.c.), acetone (100 c.c.), and potassium carbonate (20 g.) were refluxed together for 4 hours. As soon as the bright yellow colour of the solution changed to pale yellow, acetone was distilled off and water (400 c.c.) was added to the residue. After 16 hours, the solid was collected, washed with water, and crystallised from 90% alcohol, forming colourless plates, m. p. 108°, readily soluble in acetone, ethyl acetate, and benzene and moderately soluble in hot ethyl and methyl alcohol [Found: C, 71·27, 71·32; H, 7·29, 7·41. $C_{27}H_{26}O_3(OMe)_4$ requires C, 71·26; H, 7·28%]. When rottlerin tetramethyl ether (1 g.) was reduced in ethyl acetate (40 c.c.) and alcohol (10 c.c.) in presence of 5 c.c. of 1% palladium chloride solution, the same *tetrahydrorottlerin tetramethyl ether* was formed (m. p. and mixed m. p.).

Action of Hydrochloric Acid in Alcohol on Tetrahydrorottlerin.—Tetrahydrorottlerin (2 g.), alcohol (60 c.c.), hydrochloric acid (*d* 1·16, 6 c.c.), and water (4 c.c.) were refluxed together for 32 hours. The liquid was filtered hot; on cooling, it deposited a brownish solid, which was collected and triturated with ether. This removed a crimson-red powder, m. p. 274—278°, which was soluble in sodium bicarbonate solution but could not be satisfactorily crystallised. The ether-insoluble portion crystallised from ethyl acetate in brownish plates, m. p. 171° (Found: C, 73·5, 73·7; H, 6·9, 7·1. Calc. for $C_{20}H_{22}O_4$: C, 73·6; H, 6·75%).

Oxidation of Rottlerin Tetramethyl Ether with Alkaline Hydrogen Peroxide.—The ether (1·0 g.) was dissolved in 8% sodium hydroxide solution (20 c.c.) and heated to 40°, and 30% hydrogen peroxide (8 c.c.) and 8% sodium hydroxide solution (5 c.c.) added alternately during ½ hour. After 1 hour the solution deposited a colourless crystalline *substance* (0·96 g.), which, recrystallised from not too hot methyl or ethyl alcohol, formed plates, m. p. 127—128° with evolution of benzaldehyde (Found: C, 70·06, 69·87; H, 7·19, 7·27; OMe, 23·49. $C_{31}H_{36}O_8$ requires C, 69·4; H, 6·7; OMe, 23·13%).

Tetrahydrorottlerin tetramethyl ether was not affected under the conditions of the above experiment. The foregoing substance (0·05 g.), m. p. 128°, was dissolved in ethyl alcohol (60 c.c.) and reduced with palladium and hydrogen; tetrahydrorottlerin tetramethyl ether (m. p. and mixed m. p. 108°) was formed, indicating that an oxygen atom had been added to one of the double bonds. The foregoing oxide (0·5 g.) was dissolved in acetic acid (10 c.c.) and refluxed with N/2-sulphuric acid (4 c.c.) for 1 hour; benzaldehyde was isolated by steam-distillation and identified as the phenylhydrazone (m. p. and mixed m. p. 155°).

Action of Nitrous Acid on Rottlerin Tetramethyl Ether.—The ether (1·3 g.) was dissolved in acetic acid (15 c.c.) by gentle warming, and sodium nitrite (10 g.) added gradually to the cooled solution during ½ hour. The solution was then warmed at 80° for 10 minutes and diluted with water. The golden-yellow solid obtained was washed with water, dried, and triturated with ether (60 c.c.). The insoluble portion (0·9 g.) crystallised from toluene in pale yellow plates, m. p. 208—209° (decomp.) (Found: C, 63·66; H, 6·2; N, 4·2, 4·17. $C_{17}H_{19}O_3N$ requires C, 64·35; H, 5·99; N, 4·41%. $C_{19}H_{21}O_6N$ requires C, 63·51; H, 5·85; N, 3·89%). This *substance*, when boiled with dilute alkali solution, gave benzaldehyde.

The foregoing substance (1 g.), dissolved in ethyl acetate (30 c.c.) and alcohol (15 c.c.), was reduced in presence of 3 c.c. of 1% palladous chloride solution. The *product*, isolated by the removal of the solvents in a vacuum, crystallised from alcohol in bunches of colourless needles, m. p. 162°. The same product was formed when the reduction was done with Adams's platinum oxide catalyst (Found: C, 63·44; H, 6·23; N, 3·85. $C_{19}H_{23}O_6N$ requires C, 63·2; H, 6·4; N, 3·8%).

UNIVERSITY CHEMICAL LABORATORIES, LAHORE (INDIA).

[*Received, August 9th*, 1937.]