A New Optically Active Flavanone from the Leaves of Rhododendron farrerae, *Tate.*

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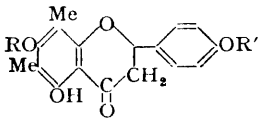
A new optically active flavanone, for which the name farrerol is proposed, has been isolated from the leaves of *Rhododendron farrerae*. It has been shown to be 5 : 7 : 4′-trihydroxy-6 : 8-dimethylflavanone (4′-demethylmatteucinol) and so it has, in common with two of the other known optically active naturally occurring flavanones, methyl groups in the 6- and 8-positions.

ARTHUR and HUI (*J.*, 1954, 4683) reported that the leaves of the *Rhododendrons* of Hong Kong contain the triterpene acid, ursolic acid; they also showed (*ibid.*, p. 2782) that the leaves of *R. simsii* contain in addition the flavanone, matteucinol. Examination of the leaves of the other *Rhododendrons* of Hong Kong in the manner adopted for *R. simsii* (*loc cit.*) reveals the presence of a new flavanone (hereafter called " farrerol ") in *R. farrerae*, but flavonoid compounds were not obtained from *R. championae*, *R. westlandii*, or *R. simiarum*. It is noteworthy that the two *Rhododendrons* which yield flavanones are alone in that they possess small leaves, and further, that their leaves possess a soft brown pubescence. The behaviour of farrerol indicated that it occurs in the plant in an optically active form and that it partly racemised during extraction and purification. From (±)-farrerol triacetate, (±)-farrerol was prepared and characterised as the dimethyl ether, the oxime, and the corresponding chalkone.

Since optically active flavanones which have previously been isolated include matteucinol and demethoxymatteucinol [Fujise, *Sci. Papers Inst. Phys. Chem. Res.* (*Tokyo*), 1929, **11**, 111] and since Arthur and Hui (*J.*, 1954, 2782) showed that matteucinol is present in the leaves of *Rhododendron simsii*, it was considered that farrerol (I) may have been related to matteucinol (II). This relationship was established when (±)-farrerol yielded



(I; R = R′ = H)
(II; R = H, R′ = Me)
(III; R = R′ = Me)

(±)-matteucinol monomethyl ether (III) on methylation with diazomethane. (±)-Farrerol was shown, finally, to be 5 : 7 : 4′-trihydroxy-6 : 8-dimethylflavanone, since it is identical with the demethylation product of (±)-matteucinol.

Attempts to resolve (±)-farrerol by the use of (−)-menthoxyacetyl chloride failed. An attempt was also made to obtain (−)-farrerol from the plant by a method which avoided the use of alkali. This gave a product richer in (−)-farrerol than that which had previously been obtained, but still not optically pure.

The structural regularity (methyl groups at the 6- and the 8-position) of farrerol and the two naturally occurring optically active flavanones matteucinol and demethoxymatteucinol is noted. Hillis (*Austral. J. Sci. Res.*, 1952, *A*, **5**, 379) reports that 3 : 5 : 7 : 4′-tetrahydroxyflavanone (dihydrokaempferol) obtained from the kinos of *Eucalyptus calophylla* and *E. corymbosa* is optically active.

Experimental

M. p.s are corrected. Analyses are by Dr. Zimmermann, Melbourne. Rotations are in acetone.

Isolation of the Flavanone.—Leaves (4 kg.) were extracted with ether (10 l.) and the ethereal extract was worked up as stated for that of *Rhododendron simsii* (*J.*, 1954, 2783). The crude yellow flavanone (34 g., 0·85%) was recrystallised from aqueous dioxan. Buff-coloured fern-like crystals (20 g., 0·5%) of a mixture of (−)-farrerol and (±)-farrerol separated. This mixture which gave the usual colour reactions for flavanones had m. p. 207—218°, $[\alpha]_D$ −16°, and further recrystallisations from aqueous dioxan or from other solvents did not improve the m. p.

(±)-*Farrerol Triacetate.*—Acetylation by acetic anhydride and sodium acetate gave a complex mixture which contained the chalkone acetate. The flavanone was therefore acetylated by Bannerjee and Seshadri's method (*Proc. Indian Acad. Sci.*, 1952, **36**, *A*, 138). To an ice-cooled solution of the farrerol mixture ($[\alpha]_D$ −16°) (2·5 g.) in pyridine (10 ml.), acetyl chloride (6·0 ml.) was added dropwise during 1 hr. Next morning the product ($[\alpha]_D$ +10°) (2·2 g.), isolated as usual, was recrystallised 7 times from methanol, then once from ethanol. The (±)-*triacetate* (1·1 g.), which separated in rectangular plates, m. p. 192°, $[\alpha]_D$ 0·02° (*c*, 0·81) (Found: C, 64·5; H, 5·2; Ac, 30·1%; *M*, 378. $C_{23}H_{22}O_8$ requires C, 64·8; H, 5·2; 3Ac, 30·3%; *M*, 426), was unchanged after chromatography (acetone solution over alumina). It gave no colour with ferric chloride solution and a magenta colour with hydrochloric acid and magnesium in methanol; it was insoluble in dilute sodium hydroxide solution.

(±)-*Farrerol.*—(a) *By deacetylation of* (±)-*farrerol triacetate.* The triacetate (0·5 g.) was deacetylated with dilute ethanolic sulphuric acid (40 ml.). The crude product which was recrystallised from aqueous dioxan separated as buff-coloured needles of (±)-*farrerol*, m. p. 223—224° (Found: C, 67·9; H, 5·4. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%). This compound was very soluble in methanol, soluble in dioxan, and sparingly soluble in water and light petroleum. It gave a green colour with ferric chloride solution in ethanol, a bright red colour with magnesium and hydrochloric acid in methanol, and an intense vermillion-red solution with aqueous sodium hydroxide.

(b) *By fractional recrystallisation of the farrerol mixture from the plant.* The mixture, m. p. 206—218° (10 g.), was dissolved in methanol (25 ml.). The first crop (0·5 g.) obtained as solvent evaporated had m. p. 223° and $[\alpha]_D$ −1·1°, and on recrystallisation yielded almost inactive farrerol, m. p. 223—224° [not depressed by the product from (a)], $[\alpha]_D$ −0·8°.

(c) *By racemisation of the farrerol mixture.* The mixture, m. p. 206—218° (0·5 g.), was dissolved in 0·2N-aqueous alcoholic potassium hydroxide solution (30 ml.) and the solution was left for 2 days. The precipitate was removed, and then the filtrate on acidification yielded (±)-farrerol, m. p. 223° after one recrystallisation from dioxan.

(d) *By demethylation of* (−)*matteucinol.* (i) (−)-Matteucinol (2·0 g.) was demethylated in a mixture of acetic anhydride (10 ml.) and 55% hydriodic acid (10 ml.). The product, on recrystallisation from aqueous ethanol, yielded almost colourless needles (1·1 g.) of (±)-farrerol, m. p. 223° alone or on admixture with the product from (a). Longer heating or increased temperature produced quantities of a bright red compound.

(ii) (−)-Matteucinol (1·0 g.) was demethylated with dry benzene and freshly powdered anhydrous aluminium chloride (6 g.). The product, isolated in the usual manner, on recrystallisation from aqueous methanol gave (±)-farrerol, m. p. 223°. An intensely red and fluorescent by-product, which was not further investigated, was also obtained.

These samples of (±)-farrerol [from d(i) and d(ii)] were further identified by conversion into 2′ : 4′ : 6′ : 4-tetra-acetoxy-3′ : 5′-dimethylchalkone (see below).

(±)-*Farrerol 7 : 4′-Dimethyl Ether.*—This was prepared from (±)-farrerol with diazomethane in ether. Recrystallisation from methanol gave pale yellow needles, m. p. 102° alone or in admixture with (±)-matteucinol monomethyl ether (Found: C, 69·1; H, 6·3; OMe, 18·7. Calc. for $C_{19}H_{20}O_5$: C, 69·5; H, 6·1; 2OMe, 18·9%).

(±)-*Farrerol Oxime.*—(±)-Farrerol (0·4 g.) was heated in aqueous ethanol with sodium acetate (0·5 g.) and hydroxylamine hydrochloride (0·5 g.) for 17·5 hr. The product on recrystallisation from aqueous methanol yielded colourless needles, m. p. 253—255°, of the *oxime* (Found: C, 65·4; H, 5·6; N, 4·3. $C_{17}H_{17}O_5N$ requires C, 64·8; H, 5·4; N, 4·4%), which became bright yellow on exposure to air and light; it gave a magenta-coloured solution with magnesium and hydrochloric acid in methanol.

2′ : 4′ : 6′ : 4-*Tetra-acetoxy*-3′ : 5′-*dimethylchalkone.*—A solution of (±)-farrerol triacetate (0·5 g.) in acetic anhydride (15 ml.) was boiled under reflux for 9 hr., and then poured into water.

The product which separated was recrystallised 4 times from methanol. The *chalkone* was obtained as colourless needles, m. p. 158—159° (Found : C, 64·2; H, 5·2; Ac, 35·7. $C_{25}H_{24}O_9$ requires C, 64·1; H, 5·1; 2 Ac, 36·7%).

Attempted Isolation of (−)-*Farrerol.*—Leaves (2 kg.) were extracted with cold light petroleum (b. p. 60—80°; 10 l.), then with ether (10 l.). The ethereal extract was evaporated to dryness and the greenish-black residue which remained was extracted with quantities of warm methanol until the extract showed a negative reaction for flavonoid compounds with magnesium and hydrochloric acid. The combined methanol extracts were treated with charcoal and then concentrated in stages (crops of triterpenoid material being removed after each concentration) until the extract failed to deposit triterpenoid material. The methanol extract was then evaporated almost to dryness. The greenish-black crop of crude flavanone was collected from the black filtrate. The crude flavanone was recrystallised several times from dioxan and aqueous dioxan (charcoal). Cream-coloured needles (0·2%) of a mixture of (−)-farrerol and (±)-farrerol, m. p. 213—217°, $[\alpha]_D$ −18·7° (*c*, 0·66) were obtained (Found : C, 68·4; H, 5·5. Calc. for $C_{17}H_{16}O_5$: C, 68·0; H, 5·3%). Acetylation of this material yielded an optically active acetate, m. p. 176—179° (after 8 recrystallisations from methanol), mixed m. p. with (±)-farrerol triacetate, 188—190° after contraction at 180°. This was considered to be very rich in (+)-farrerol triacetate, but, from the way in which it separated from organic solvents and from its m. p. range, was not considered to be pure.

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