175. *Flavonols from the Bark of* Melicope ternata. *Part III. A Synthesis of Quercetin* 3 : 3′-*Dimethyl Ether, Quercetin* 3 : 7 : 3′-*Trimethyl Ether, Quercetin* 3 : 5 : 7 : 3′-*Tetramethyl Ether, Ternatin, and Related Benzyl Ethers.*

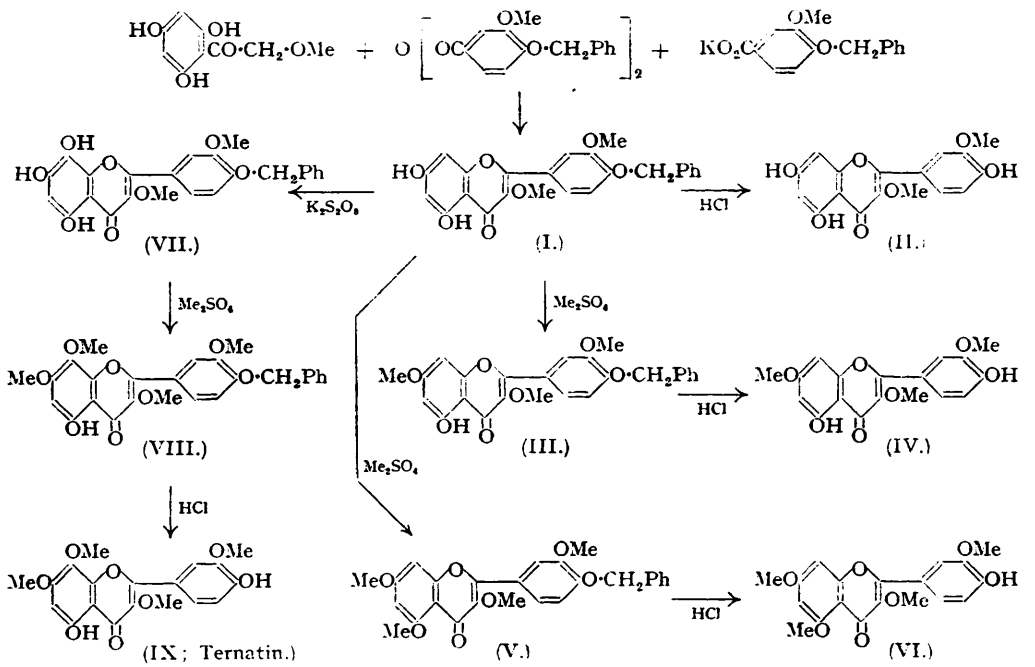
By Lindsay H. Briggs and R. H. Locker.

The above compounds have been synthesised by combining Allan and Robinson's flavonol synthesis (*J.*, 1924, **125**, 2192) and Seshadri's recent methods of nuclear oxidation (*Proc. Indian Acad. Sci.*, 1948, **28**, *A*, 1).

By combining the above flavonol synthesis, protection of appropriate free phenolic groups by formation of their benzyl ethers, and the nuclear oxidation with potassium persulphate (see Seshadri, *loc. cit.*, for summary), the 3 : 3′-*dimethyl*, 3 : 7 : 3′-trimethyl, and 3 : 5 : 7 : 3′-*tetramethyl ethers* of quercitin, and also ternatin (5 : 4′-dihydroxy-3 : 7 : 8 : 3′-tetramethoxyflavone; cf. Part I, *J.*, 1949, 2157), have been synthesised according to the following scheme.

Condensation of *O*-benzylvanillic anhydride with ω-methoxyphloracetophenone in the presence of potassium *O*-benzylvanillate at 160—170° afforded 5 : 7-*dihydroxy*-4′-*benzyloxy*-3 : 3′-*dimethoxyflavone* (I), hydrolysed by hydrochloric acid–acetic acid to quercetin 3 : 3′-dimethyl ether (II). Partial methylation of (I) gave 5-*hydroxy*-4′-*benzyloxy*-3 : 7 : 3′-*trimethoxyflavone* (III), hydrolysed as before to quercetin 3 : 7 : 3′-trimethyl ether (IV), described by Kuhn

and Low (*Ber.*, 1944, **77**, 202). Complete methylation of (I) produced 4′-*benzyloxy*-3 : 5 : 7 : 3′-*tetramethoxyflavone* (V), hydrolysed as previously to quercetin 3 : 5 : 7 : 3′-tetramethyl ether. Nuclear oxidation of (I) with potassium persulphate (cf. Seshadri, *loc. cit.*, and Baker and Brown, *J.*, 1948, 2303 for the mechanism of the reaction) introduced a phenolic group at $C_{(8)}$, forming 5 : 7 : 8-*trihydroxy*-4′-*benzyloxy*-3 : 3′-*dimethoxyflavone* (VII) in poor yield, which was partly methylated to 5-*hydroxy*-4′-*benzyloxy*-3 : 7 : 8 : 3′-*tetramethoxyflavone* (VIII). Hydrolysis of the last compound, as before, afforded 5 : 4′-dihydroxy-3 : 7 : 8 : 3′-tetramethoxyflavone (IX), identical in all respects with ternatin, the structure of which, suggested in Part I (*loc. cit.*), is thus confirmed.



Experimental.

(All m. p.s are corrected.)

Methyl O-Benzylvanillate.—Methyl vanillate, m. p. 62°, was prepared from vanillin *via* vanillic acid (Pearl, *J. Org. Chem.*, 1947, **12**, 86), esterification being by methyl alcohol and sulphuric acid (Matsmoto, *Ber.*, 1878, **11**, 128). Methyl vanillate (85 g., 1 mol.) and potassium hydroxide (27·5 g., 1 mol.) were dissolved separately in hot methyl alcohol (total, 125 c.c.). Benzyl chloride (60 g., 1 mol.) was added, and the mixture heated under reflux for 5 hours and filtered hot. The potassium chloride was washed with hot methyl alcohol, the combined filtrate concentrated and cooled, whereupon long colourless prisms (95·5 g.) separated, m. p. 86—86·5° (after recrystallisation from alcohol) (Found: C, 70·5; H, 5·9. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%). Alkaline hydrolysis afforded *O*-benzylvanillic acid, m. p. 173·5—175·5° (Lovecy, Robinson, and Sugasawa, *J.*, 1930, 821), converted into the anhydride, m. p. 137·5—193·5°, by treatment with thionyl chloride and pyridine (*idem. ibid.*). The potassium salt of *O*-benzylvanillate was formed by mixing equimolecular quantities of the acid and potassium hydroxide in hot alcohol, and concentration. The silky needles which formed were very soluble in alcohol and decomposed and carbonised above 250°.

5 : 7-*Dihydroxy*-4′-*benzyloxy*-3 : 3′-*dimethoxyflavone.*—*O*-Benzylvanillic anhydride (38 g., 2·5 mols.), potassium *O*-benzylvanillate (13·8 g., 1·5 mols.), and ω-methoxyphloracetophenone (6·1 g., 1 mol.; Slater and Stephen, *J.*, 1920, **117**, 312) were powdered together and heated at 160—170° for 2 hours. The powdered cake was dissolved in alcohol (300 c.c.) and water (20 c.c.) containing potassium hydroxide (30 g.), and the solution was boiled for 10 minutes before the alcohol was distilled off under reduced pressure almost to dryness. A yellow precipitate (7·7 g.) formed when carbon dioxide was passed into the solution of the yellow residue in water (300 c.c.). Pale yellow needles separated, having m. p. 258—259° when crystallised from acetone (Found: C, 68·2; H, 4·9. $C_{24}H_{20}O_7$ requires C, 68·6; H, 4·7%). The *flavone* is insoluble in sodium carbonate or concentrated hydrochloric acid but soluble in 10% sodium hydroxide solution or concentrated sulphuric acid with a yellow and an intense yellow colour, respectively. It gives a brown colour with alcoholic ferric chloride solution and a strong red colour when reduced with magnesium, hydrochloric acid, and alcohol and also with sodium amalgam and alcohol followed by acidification.

5 : 7 : 4′-*Trihydroxy*-3 : 3′-*dimethoxyflavone* (*Quercetin* 3 : 3′-*Dimethyl Ether*).—5 : 7-Dihydroxy-4′-benzyloxy-3 : 3′-dimethoxyflavone (100 mg.) was heated on the water-bath with glacial acetic acid (4 c.c.) and concentrated hydrochloric acid (2 c.c.) for an hour. The flocculent yellow precipitate, obtained by pouring the mixture into water, was coagulated by heating on the water-bath for ½ hour and crystallised 3 times from alcohol, yielding yellow plates, m. p. 257—258° (Found : C, 61·8; H, 4·2. $C_{17}H_{14}O_7$ requires C, 61·8; H, 4·2%). The *flavone* is slightly soluble in sodium hydrogen carbonate solution, readily soluble in sodium carbonate and hydroxide solution with a bright yellow colour. It is insoluble in concentrated hydrochloric acid but soluble in concentrated sulphuric acid with an intense yellow colour. In a buffer at pH 9·8, a stable yellow colour is formed. A brown colour is given with alcoholic ferric chloride solution, and a strong red colour when reduced both with magnesium in concentrated hydrochloric acid and alcohol and with sodium amalgam and alcohol followed by acidification. The *triacetate* of the flavone was produced by dissolving 23 mg. in acetic anhydride (0·5 c.c.) and one drop of 60% perchloric acid and ½ hour's keeping. The product, formed by pouring into water, separated from ethyl or methyl alcohol in colourless needles, m. p. 199—200° (Found : C, 60·7; H, 4·5. $C_{23}H_{20}O_{11}$ requires C, 60·5; H, 4·4%).

5-*Hydroxy*-4′-*benzyloxy*-3 : 7 : 3′-*trimethoxyflavone*.—5 : 7-Dihydroxy-4′-benzyloxy-3 : 3′-dimethoxyflavone (320 mg.) was partly methylated by dissolving it in dry acetone (18 c.c.) and heating the mixture under reflux for 6½ hours with methyl sulphate (0·08 c.c., 1·1 mols.) and anhydrous potassium carbonate (2 g.). The acetone solution, together with washings of the insoluble salts, was concentrated, yielding yellow prisms (68 mg.), m. p. *ca.* 154°. The yellow insoluble salts were dissolved in water, acidified, and warmed to coagulate the product, a light yellow solid, m. p. 153—154° (175 mg.). The combined product was crystallised 3 times from alcohol, forming light-yellow plates of constant m. p. 151—152° (Found : C, 68·8; H, 5·3. $C_{25}H_{22}O_7$ requires C, 69·1; H, 5·1%). The *flavone*, typical of many flavones with a free 5-hydroxy-position, is insoluble in 10% sodium hydroxide solution. It is insoluble in concentrated hydrochloric acid but soluble in concentrated sulphuric acid with an intense yellow colour. A brown colour is given with alcoholic ferric chloride solution, a scarlet colour with magnesium, hydrochloric acid, and alcohol, and a red colour with sodium amalgam and alcohol followed by acidification.

5 : 4′-*Dihydroxy*-3 : 7 : 3′-*trimethoxyflavone* (*Quercetin* 3 : 7 : 3′-*Trimethyl Ether*).—The preceding flavone (130 mg.) was hydrolysed for an hour at 100° with a mixture of glacial acetic acid (7 c.c.) and concentrated hydrochloric acid (3·5 c.c.). The product crystallised from alcohol in slender needles, m. p. 167—168·5°. Kuhn and Low (*loc. cit.*) record m. p. 169—170° for this compound. It is insoluble in sodium carbonate solution or concentrated hydrochloric acid, but soluble in 10% sodium hydroxide solution or concentrated sulphuric acid with a yellow coloration. A brown colour is given with alcoholic ferric chloride, and a scarlet colour both with magnesium, hydrochloric acid, and alcohol and with sodium amalgam and alcohol after acidification. The diacetate, prepared from 20 mg. as previously described, after successive crystallisation from ethyl and methyl alcohol, formed prismatic needles, m. p. 177·5—178° (Kuhn and Low, *loc. cit.*, record m. p. 174—175°).

4′-*Benzyloxy*-3 : 5 : 7 : 3′-*tetramethoxyflavone*.—5 : 7-Dihydroxy-4′-benzyloxy-3 : 3′-dimethoxyflavone (200 mg.) was completely methylated by heating in dry acetone solution (15 c.c.) with methyl sulphate (0·3 c.c., 6 mols.) and anhydrous potassium carbonate (1 g.) for 3 hours. The acetone solution and washings of the insoluble salts were concentrated and gave colourless crystals (170 mg.), which, after 2 crystallisations from alcohol, formed needles, m. p. 162—163° (Found : C, 69·5; H, 5·5. $C_{26}H_{24}O_7$ requires C, 69·6; H, 5·4%). The *flavone* is insoluble in 10% sodium hydroxide solution, slightly soluble in concentrated hydrochloric acid, and freely soluble in concentrated sulphuric acid with weak and intensely yellow colours, respectively. There is no colour with alcoholic ferric chloride solution, but a scarlet colour with magnesium, hydrochloric acid, and alcohol as well as with sodium amalgam and alcohol followed by acidification.

4′-*Hydroxy*-3 : 5 : 7 : 3′-*tetramethoxyflavone* (*Quercetin* 3 : 5 : 7 : 3′-*Tetramethyl Ether*).—The preceding flavone (110 mg.) was hydrolysed with glacial acetic acid (4 c.c.) and concentrated hydrochloric acid (2 c.c.) for an hour at 100°. After addition of boiling water (50 c.c.) and cooling, pale yellow slender needles separated, which, after recrystallisation from alcohol, yielded light yellow prisms, m. p. 202—203° (Found : C, 63·5; H, 5·2. Calc. for $C_{19}H_{18}O_7$: C, 63·7; H, 5·0%). Rao and Seshadri (*J.*, 1947, 771) record very pale yellow, rectangular plates and prisms, m. p. 200—201°, for this compound. The flavone is insoluble in sodium hydrogen carbonate solution, soluble in sodium carbonate and sodium hydroxide solutions with bright yellow colours, and readily soluble in concentrated hydrochloric or sulphuric acid with an intense yellow colour. No colour is given with alcoholic ferric chloride solution, but a red colour when reduced both with magnesium, hydrochloric acid, and alcohol and with sodium amalgam and alcohol after acidification. The acetate, prepared as previously from 30 mg., after repeated crystallisation from alcohol, formed colourless needles, m. p. 179·5° (Found : C, 63·4; H, 5·1. Calc. for $C_{21}H_{20}O_8$: C, 63·0; H, 5·0%). Rao and Seshadri (*loc. cit.*) record m. p. 178—180°.

5 : 7 : 8-*Trihydroxy*-4′-*benzyloxy*-3 : 3′-*dimethoxyflavone*.—5 : 7-Dihydroxy-4′-benzyloxy-3 : 3′-dimethoxyflavone (2·7 g., 1 mol.) was added to a solution of potassium hydroxide (2·7 g.) in water (450 c.c.). Complete dissolution did not occur owing to the limited solubility of this flavone in aqueous alkali. Potassium persulphate (3·5 g., 2 mols.), dissolved in water (100 c.c.), was added dropwise during 1 hour. It was found in a trial run that warming to complete dissolution after the addition of persulphate gave a better yield than did adding pyridine. The mixture was therefore heated to 53°, solution then being nearly complete, and set aside overnight. After removal of a yellow sediment (0·4 g.), the filtrate was acidified, filtered, and extracted with ether. The aqueous residue was then treated with sodium sulphite (6 g.) and concentrated hydrochloric acid (50 c.c.) on the water-bath for 1½ hours. A brown solid (0·4 g.) separated, which, after repeated crystallisation from alcohol (charcoal), formed deep yellow needles, m. p. 198—199° (Found : C, 66·0; H, 5·2. $C_{24}H_{20}O_8$ requires C, 66·1; H, 4·6%). No further product could be obtained from the residue by continuous extraction with ether. The *flavone* is insoluble in sodium carbonate solution but soluble in sodium hydroxide solution, giving a yellowish-brown colour which rapidly fades to a colourless solution with black insoluble particles, the solution finally changing

to a faint blue. In a buffer at pH 9·8 it gives a bright yellow solution which slowly fades. It is insoluble in concentrated hydrochloric acid but soluble in concentrated sulphuric acid with an intense yellow colour. A dark brown colour is given with alcoholic ferric chloride solution, and a reddish-brown colour on reduction with magnesium, hydrochloric acid, and alcohol. Only a weak yellow colour is produced by sodium amalgam and alcohol followed by acidification.

5-*Hydroxy*-4′-*benzyloxy*-3 : 7 : 8 : 3′-*tetramethoxyflavone*.—The preceding flavone (185 mg., 1 mol.), dissolved in dry acetone, was heated under reflux for 6 hours with methyl sulphate (0·09 c.c., 2·2 mols.) and anhydrous potassium carbonate. The acetone solution and washings of the insoluble salts were concentrated and acidified with one drop of concentrated hydrochloric acid. On cooling, yellow needles separated which, after recrystallisation from alcohol, had m. p. 170—171° (33 mg.) (Found : C, 67·1; H, 5·3. $C_{26}H_{24}O_8$ requires C, 67·2; H, 5·2%). The *flavone* is insoluble in 10% sodium hydroxide solution or concentrated hydrochloric acid, but soluble in concentrated sulphuric acid with an intense yellow colour. A green colour is given with alcoholic ferric chloride solution, and a strong pink colour with magnesium, hydrochloric acid, and alcohol; reduction with sodium amalgam and alcohol followed by acidification produces a violet colour.

5 : 4′-*Dihydroxy*-3 : 7 : 8 : 3′-*tetramethoxyflavone* (*Ternatin*).—The preceding flavone (25 mg.) was hydrolysed with glacial acetic acid (1 c.c.) and concentrated hydrochloric acid (0·5 c.c.) for one hour at 100°. On pouring the solution into boiling water (10 c.c.), pale yellow needles (18 mg.) separated on cooling, which, after recrystallisation from alcohol, had m. p. 210·5—212·5°, undepressed by a specimen of natural ternatin, m. p. 210—212°. The ultra-violet and visible spectra of the synthetic and the natural specimen were also identical (forthcoming communication). The synthetic product was also insoluble in sodium carbonate solution but soluble in sodium hydroxide solution, and gave a green colour with ferric chloride solution. The acetate, prepared as previously from 6 mg., on crystallisation from alcohol, formed colourless needles, m. p. 168—169°, which did not depress the m. p. of a sample prepared from natural sources. The synthetic acetate, like that from a natural sample, is photosensitive, becoming orange on exposure to light (Found, on a sample crystallised from both sources : C, 60·8; H, 4·8. Calc. for $C_{23}H_{22}O_{10}$: C, 60·3; H, 4·8%).

The analyses are by Drs. Weiler and Strauss, Oxford. We are indebted to the Chemical Society, the Australian and New Zealand Association for the Advancement of Science, the Royal Society of New Zealand, and the Research Grants Committee of the University of New Zealand for grants, and one of us (R. H. L.) for a Research Scholarship.

Auckland University College,
Auckland, New Zealand.

[*Received, December 28th,* 1949.]