487. *Chemistry of New Zealand* Melicope *Species. Part V. A Synthesis of 6-Hydroxy-3 : 5 : 7-trimethoxy-3′ : 4′-methylenedioxyflavone, Melisimplexin, and Melisimplin.*

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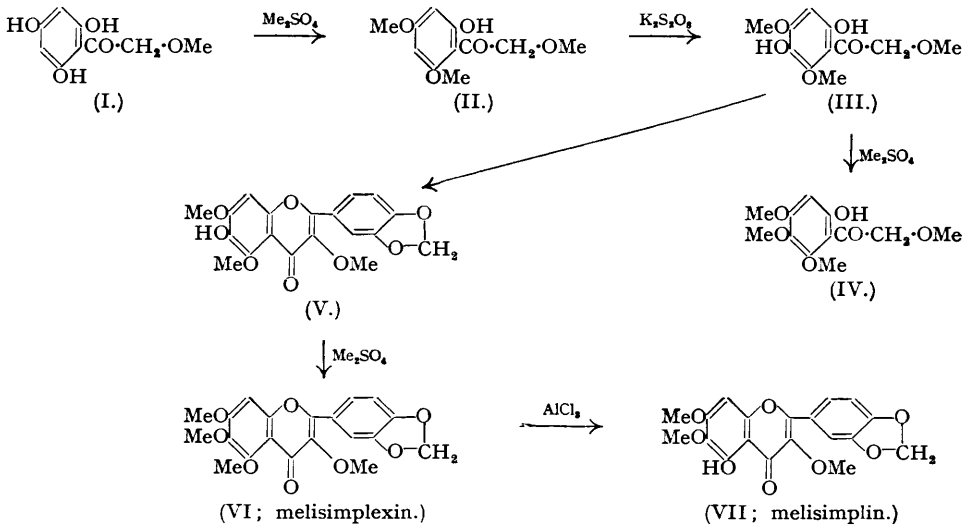
The above compounds have been synthesised by an application of the method of Row and Seshadri (*Proc. Indian Acad. Sci.*, 1946, **23**, *B*, 23) for the synthesis of 5 : 6 : 7-hydroxyflavonols.

Seshadri and his co-workers (cf. Balakrishna, Seshadri, and Viswanath, *Proc. Indian Acad. Sci.*, 1949, **30**, A, 120, and earlier papers) have introduced methods for the nuclear oxidation of flavones leading to 5 : 8-di- and 5 : 7 : 8-tri-hydroxy-derivatives. 5 : 6 : 7-Trihydroxy-derivatives cannot be thus prepared but Row and Seshadri (*ibid.*, 1946, **23**, *B*, 23) were successful by employing nuclear oxidation at the acetophenone stage before condensation to the flavone. By an application of the last method, 6-hydroxy-3 : 5 : 7-trimethoxy-3′ : 4′-methylenedioxyflavone, melisimplexin, and melisimplin, all 5 : 6 : 7-derivatives, have been synthesised according to the scheme shown on the next page.

Partial methylation of 2 : 4 : 6-trihydroxy-ω-methoxyacetophenone (I) with 2 moles of methyl sulphate afforded the 2 : 4-dimethyl ether (II), oxidised by potassium persulphate to 3 : 6-dihydroxy-2 : 4 : ω-trimethoxyacetophenone (III). Partial methylation of the last named compound yielded quercetagetol tetramethyl ether (IV) required for comparison with one of the hydrolytic products of melisimplexin (cf. Part IV, preceding paper). Condensation of (III) with piperonylic anhydride and potassium piperonylate followed by treatment with alcoholic potassium hydroxide afforded 6-hydroxy-3 : 5 : 7-trimethoxy-3′ : 4′-methylenedioxyflavone (V). Methylation gave melisimplexin (VI), identified by mixed melting point and its ultra-violet absorption spectrum. Partial demethylation of melisimplexin with aluminium chloride in boiling ethereal solution afforded melisimplin (VII). Methoxyl groups at $C_{(3)}$ are demethylated by aluminium chloride only at 100°, and not at room temperature (cf. Shah, Virkar, and Venkataraman, *J. Indian Chem. Soc.*, 1942, **19**, 135), whereas methoxyl groups at $C_{(5)}$ are demethylated under the above conditions (cf. Baker, *J.*, 1939, 961; Baker and Wilson, *J.*, 1940, 1370). This agrees with the converse properties of 3 : 5-dihydroxyflavones where the 3-hydroxyl is more readily methylated than the 5-hydroxyl group, and is in harmony with the naturally occurring partly methylated 3 : 5-dihydroxyflavones. No naturally occurring 3 : 5-dihydroxyflavone exists which is methylated at $C_{(5)}$ but not at $C_{(3)}$, whereas there are numerous examples of the inverse case. For these and other reasons (cf. Part IV) the free hydroxyl group of

melisimplin is placed at $C_{(5)}$, and the constitutions of melisimplexin and melisimplin based on degradative experiments (Part IV) are thus confirmed.



Experimental.

(M. p.s are corr.)

6-*Hydroxy*-3 : 5 : 7-*trimethoxy*-3′ : 4′-*methylenedioxyflavone*.—2 : 4 : 6-Trihydroxy-ω-methoxyacetophenone (Slater and Stephen, *J.*, 1920, 312) was partly methylated, and 2-hydroxy-4 : 6 : ω-trimethoxyacetophenone obtained as thin colourless plates, m. p. 98—100°, from alcohol–water (1 : 2). Row and Seshadri (*loc. cit.*) record colourless prisms, m. p. 103—104°. Persulphate oxidation of the product afforded 3 : 6-dihydroxy-2 : 4 : ω-trimethoxyacetophenone, crystallising from water in bright yellow, slender, flat needles, m. p. 139·5—141·5°. Addition of benzoyl peroxide did not improve the yield above that obtained by Row and Seshadri (*loc. cit.*), who obtained rhombohedral plates, m. p. 135—136°. Methylation of the last named product according to Row and Seshadri yielded quercetagetol tetramethyl ether, m. p. 71°, crystallising from water in colourless needles, undepressed in m. p. by a product of the same m. p. obtained by hydrolysis of melisimplexin (Part IV, *loc. cit.*). Row and Seshadri (*loc. cit.*) record long, rectangular plates, m. p. 77—78°.

3 : 6-Dihydroxy-2 : 4 : ω-trimethoxyacetophenone (680 mg., 1 mol.), piperonylic anhydride (2·2 g., 2·5 mols.; Rao and Seshadri, *Proc. Indian Acad. Sci.*, 1946, **23**, 148) and potassium piperonylate (920 mg., 1·5 mols.) were powdered together and heated at 170—175°/300 mm. for 2 hours. The fawn-coloured melt was powdered and boiled for a short time with alcohol (60 c.c.) and water (4 c.c.) containing potassium hydroxide (6 g.). The bulk of the alcohol was distilled off under reduced pressure and the volume made up to 50 c.c. with water. When carbon dioxide was bubbled into the solution, crystalline 6-*hydroxy*-3 : 5 : 7-*trimethoxy*-3′ : 4′-*methylenedioxyflavone* (440 mg.) separated, which, after 3 recrystallisations from alcohol, formed colourless, hexagonal plates, m. p. 244·5—246° (Found : C, 61·8; H, 4·6. $C_{19}H_{16}O_8$ requires C, 61·3; H, 4·3%). The flavonol is insoluble in sodium carbonate solution but soluble in sodium hydroxide solution forming a yellow solution from which the sodium salt soon separates as needles. It has a limited solubility in concentrated hydrochloric acid but dissolves freely in concentrated sulphuric acid with a bright yellow colour. Ferric chloride produces no colour, but acid or alkaline reduction gives strong red colours.

The *monoacetate*, prepared with acetic anhydride and perchloric acid, after crystallisation from alcohol and dioxan, formed colourless, rhombic plates, m. p. 246—247° (Found : C, 61·2; H, 4·4. $C_{21}H_{18}O_9$ requires C, 60·9; H, 4·3%).

Melisimplexin.—A solution of the foregoing flavonol (250 mg.) in dry acetone (10 c.c.) was heated under reflux with methyl sulphate (0·3 c.c.) and anhydrous potassium carbonate (1 g.) for 4 hours. Concentration of the acetone portion and washings yielded colourless, flat needles (217 mg.), which, after recrystallisation from acetone, had m. p. 185—185·5°, undepressed by an authentic sample of melisimplexin. The ultra-violet absorption spectra of the natural and synthetic specimens also corresponded (forthcoming communication).

Melisimplin.—A solution of melisimplexin (150 mg.) and aluminium chloride (1 g.) in dry ether (4 c.c.) was heated under reflux for 10 hours. After the solution had been poured into water and the whole kept for several hours, the precipitate was boiled with glacial acetic acid (5 c.c.) and concentrated hydrochloric acid (2·5 c.c.) for 20 minutes. The yellow solid which formed on dilution, after successive crystallisation from ethyl acetate and acetone, formed yellow needles (75 mg.), m. p. and mixed m. p. with melisimplin, 235—236°. The acetate (cf. Part IV), after crystallisation successively from ethyl and

methyl alcohol, was obtained as colourless needles, m. p. 199·5—200·5°, undepressed by a sample of the natural derivative, m. p. 201·5—202°.

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

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