486. *Chemistry of New Zealand* Melicope *Species. Part IV.* Constituents of the Bark of* Melicope simplex.

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

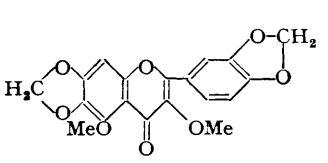
The dimethylchromens, evodionol and *allo*evodionol 7-methyl ether, the flavonols, meliternatin and ternatin, and two new flavonols, melisimplexin, $C_{20}H_{18}O_8$, and melisimplin, $C_{19}H_{16}O_8$, have been isolated from the bark of *Melicope simplex*. Degradative experiments show that the last two compounds are 3 : 5 : 6 : 7-tetramethoxy-3′ : 4′-methylenedioxyflavone and 5-hydroxy-3 : 6 : 7-trimethoxy-3′ : 4′-methylenedioxyflavone respectively.

Melicope simplex (genus *Melicope*, order *Rutaceae*, Maori name " Poataniwha ") is a small tree 3—12 feet high, endemic to, and distributed through, both Islands of New Zealand. As with *Melicope ternata*, the inner bark is yellow, aromatic, and bitter.

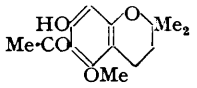
The resin, which separated during the extraction of the dried bark with light petroleum, was separated by fractional crystallisation into meliternatin, whose constitution has now been revised from that described in Part I (*J.*, 1949, 2157) to (I) (forthcoming communication) and two new flavonols, $C_{19}H_{16}O_8$ and $C_{20}H_{18}O_8$, for which the names melisimplin and melisimplexin respectively are proposed. The residual light-petroleum extract afforded (*a*) evodionol (II), a dimethylchromen derivative occurring in *Evodia littoralis* (Lahey and Jones, *Univ. Queensland Papers, Dept. Chem.*, 1939, **1**, No. 13; cf. Lahey, *ibid.*, 1940, **1**, No. 17; 1942, **1**, Nos. 20, 21), and (*b*) a further dimethylchromen derivative, *allo*evodionyl 7-methyl ether (III), first isolated by Jones and Wright (*Univ. Queensland Papers, Dept. Chem.*, 1946, **1**, No. 27) from the essential oil of a physiological form of *E. elleryana* and later by Sutherland (*ibid.*, 1949, **1**, No. 35) from the essential oil of *Medicosma cunninghamii*.

* Parts I—III of this series were published under the title " Flavonols from the Bark of *Melicope Ternata*."

In a separate experiment, the bark was extracted with acetone; and the extract afforded a minute amount of ternatin (IV) (cf. Parts I and III, *J.*, 1950, 864).



(I.)



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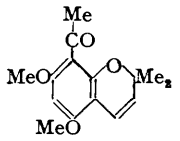

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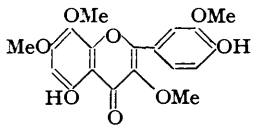


(IV.)

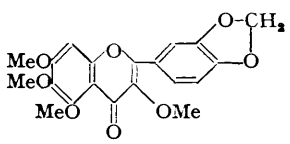
Melisimplexin, $C_{20}H_{18}O_8$.—Melisimplexin contains four methoxyl groups and gives a positive methylenedioxy-test. Reduction with magnesium in acid solution or sodium amalgam followed by acidification gave orange-red colours, indicative of a flavone with a methoxyl group at $C_{(3)}$. Its insolubility in alkalis, its negative ferric chloride reaction, and its solubility in concentrated hydrochloric acid with an intense yellow colour show that melisimplexin is a fully alkylated flavonol. It is therefore a tetramethoxymethylenedioxyflavone isomeric with meliternin, which it resembles very closely.

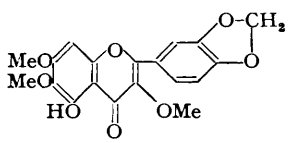
Hydrolysis with alcoholic potassium hydroxide gave quercetagetol tetramethyl ether and piperonylic acid. Melisimplexin must therefore be 3 : 5 : 6 : 7-tetramethoxy-3′ : 4′-methylenedioxyflavone (V), a derivative of quercetagetin.

Melisimplin, $C_{19}H_{16}O_8$.—Melisimplin contains three methoxyl groups and gives a positive test for the methylenedioxy-group. Reduction under the acid and the alkaline conditions previously mentioned indicated a flavonol methylated on $C_{(3)}$. Although insoluble in alkalis and concentrated hydrochloric acid it gave a green colour with ferric chloride characteristic of a 5-hydroxyflavonol with the remaining phenolic groups methylated (details of these observations will be submitted later). The presence of one free hydroxyl group was confirmed by the preparation of the monoacetate, $C_{21}H_{18}O_9$. Melisimplin must therefore be a 5-hydroxytrimethoxymethylenedioxyflavone. Methylation yielded melisimplexin, so that melisimplin must be 5-hydroxy-3 : 6 : 7-trimethoxy-3′ : 4′-methylenedioxyflavone (VI). The constitution of both melisimplexin and melisimplin has been confirmed by synthesis (succeeding paper).

For the small quantities of compounds isolated in these investigations we have found it expedient at times to purify the compounds as their acetyl derivatives, best prepared by acetic anhydride and a drop of 60% perchloric acid at room temperature (cf. Conant and Bramann,

(V.)





(VI.)

J. Amer. Chem. Soc., 1928, **50**, 2305). The flavonols do not dissolve in the acetic anhydride but do so immediately on the addition of the catalyst with the evolution of heat and production of a red colour. In some cases yellow crystals separate which decompose in water to give the colourless acetate. It appears that the initial product is the perchlorate of the acetate. Complete and immediate hydrolysis occurred when the flavonol acetates were dissolved in cold concentrated sulphuric acid. Dilution of the acid deposited the pure flavonol. Equal success has been attained in the hydroxyanthraquinone series.

Experimental.

(M. p.s are corr.)

Isolation of Constituents.—The bark was collected in August from mature trees of *Melicope simplex* growing in the northern Waitakere Ranges. The dark outer layer was scraped off and the yellow inner bark dried in air and finely powdered.

In a pilot experiment the bark (66 g.) was extracted with light petroleum (b. p. 50—60°) for 3 hours in a Soxhlet extractor. The extract was cooled and the clear yellow solution decanted from the residual brown resin which was dissolved in acetone. On concentration and cooling of the filtered acetone solution, an amorphous material separated which crystallised from alcohol in needles, m. p. 185—186° (76 mg.). Further recrystallisation from ethyl acetate gave two crops, (i) cream-coloured needles, m. p. 223—225° (20 mg.), of *melisimplin* (see below) and (ii) an amorphous solid, m. p. 197—197·5° (23 mg.). The latter, on crystallision twice from alcohol, formed small colourless needles, m. p. and mixed m. p. with meliternatin, 198—199°.

The main quantity of bark (420 g.) was extracted with light petroleum (b. p. 50—60°) for 24 hours. After cooling, the liquid was decanted and the solid residue dissolved in acetone. The filtered acetone solution was concentrated to *ca.* 100 c.c. and set aside. The crystalline material which separated, after repeated crystallisation from ethyl acetate and finally from acetone, formed light yellow needles of melisimplin, m. p. 233·5—234·5° (236 mg.).

The original acetone solution was further concentrated and set aside. The pale cream-coloured solid separating was purified by being dissolved in the first ethyl acetate mother-liquor from the purification of melisimplin and set aside. Slender cream-coloured needles were separated mechanically from colourless amorphous material and crystallised twice from alcohol and finally from acetone. The *melisimplexin* (37 mg.) so obtained had m. p. 182·5—183·5°.

The amorphous material crystallised from alcohol in small colourless needles, m. p. 186—189° (252 mg.). The m. p. was not depressed by meliternatin but attempts to raise it by further recrystallisation were unsuccessful. Better, but not complete, separation was achieved by chromatography. The material was absorbed on freshly activated alumina from a chloroform solution, developed with dry chloroform, and eluted in eight 30-c.c. fractions with acetone. The material from the second fraction gave on evaporation a colourless crystalline residue (220 mg.), m. p. 161—165°, raised to 183·5—184·5°, that of melisimplexin, on recrystallisation from alcohol and twice from acetone (total yield of melisimplexin, *ca.* 70 mg.).

The residues from the third—sixth fractions were combined and after crystallisation from alcohol and dioxan–water formed colourless needles of meliternatin, m. p. 198—198·5°.

The light-petroleum solution from the original extraction was shaken successively with saturated sodium hydrogen carbonate, sodium carbonate, and 10% sodium hydroxide solution. The first two fractions were only slightly coloured and were not investigated. The sodium hydroxide extracts, however, were bright yellow and on acidification yielded evodionol as a dark yellow solid, crystallising from alcohol in rhombic prisms, m. p. 86—86·5° (287 mg.).

The light-petroleum fraction was then shaken with 5% hydrochloric acid. Alkaloids were not present in appreciable quantity, as shown by the very slight precipitates when the acid extracts were treated with Mayer's and Dragendorff's reagents.

Finally, the light petroleum extract was concentrated and set aside. Yellow crystals separated with resinous material but, after repeated crystallisation from alcohol, colourless rhombic plates of *allo*evodionyl 7-methyl ether, m. p. 105·5—106° (534 mg.), were obtained.

In a further experiment, a sample of bark was extracted with acetone and the solid extract dissolved in chloroform. This solution was washed successively with sodium hydrogen carbonate, carbonate, and hydroxide solutions. The material obtained by acidifying the last extract crystallised in slender yellow needles (*ca.* 3 mg.), m. p. and mixed m. p. with ternatin, 210—212°.

Melisimplexin.—Melisimplexin crystallises from acetone in colourless flattened needles, m. p. 183·5—184·5°, with an unusually high solubility in hot alcohol (Found : C, 62·0; H, 4·8; OMe, 31·4. $C_{20}H_{18}O_8$ requires C, 62·2; H, 4·7; 4OMe, 32·1%). It gave a green colour within 10 minutes in the methylenedioxy-test with concentrated sulphuric acid and gallic acid.

Hydrolysis. A solution of melisimplexin (99 mg.) in alcohol (2 c.c. of 80%) and potassium hydroxide (200 mg.) was heated under reflux for 5 hours, concentrated to half volume, and diluted with water (2 c.c.). Most of the remaining alcohol was boiled off and more water (3 c.c.) added. The filtered solution was saturated with carbon dioxide, precipitating slender colourless needles (fraction I). After removal of the crystalline material, the residue was extracted with ether, yielding a greasy residue (fraction II). Acidification of the aqueous layer with hydrochloric acid precipitated a colourless solid (fraction III).

Fraction I (38 mg.) was a potassium salt. When acidified with dilute hydrochloric acid it yielded, through extraction by ether, a colourless solid which, after 3 crystallisations from water, formed needles, m. p. and mixed m. p. with a specimen of quercetagetol tetramethyl ether prepared synthetically (succeeding paper), 71°. Also in agreement with this identification were its insolubility in sodium carbonate solution, its ready solubility in 10% sodium hydroxide solution, and its brown colour with ferric chloride. Fraction II afforded a further 11 mg. of the same compound by similar treatment.

Fraction III (32 mg.) recrystallised from alcohol in colourless prisms, m. p. and mixed m. p. with piperonylic acid, 233°.

Melisimplin.—Melisimplin crystallises from ethyl acetate or acetone in light yellow needles, m. p. 234—235° (Found : C, 60·8; H, 4·5; OMe, 21·8, 23·0. $C_{19}H_{16}O_8$ requires C, 61·3; H, 4·3; 3OMe, 25·0%). It forms a bright yellow solution with concentrated sulphuric acid and with gallic acid this changes to a clear green within ½ hour. A pink colour is produced on reduction with magnesium and hydrochloric acid or with sodium amalgam followed by acidification.

Melisimplin (25 mg.) was treated with acetic anhydride (0·5 c.c.) and 60% perchloric acid (1 drop) in the cold. Yellow crystals formed when the orange solution was stirred. After addition of water, however, a colourless *acetate* formed which crystallised from alcohol in colourless needles, m. p. 201·5—202° (Found : C, 60·7; H, 4·4. $C_{21}H_{18}O_9$ requires C, 60·9; H, 4·3%).

Methylation of melisimplin to melisimplexin. Melisimplin (50 mg.), in dry acetone (8 c.c.), was refluxed for 5 hours with methyl sulphate (0·04 c.c., 3 mols.) and anhydrous potassium carbonate (0·5 g.). The acetone portion and washings of the solid material, on concentration, afforded colourless needles which, after recrystallisation from alcohol, had m. p. and mixed m. p. with melisimplexin, 181·5—182·5°.

Dealkylation of melisimplin. Melisimplin (40 mg.) was heated for 1 hour at 140° with hydriodic acid (3 c.c.; *d* 1·7) in an atmosphere of carbon dioxide. The brown solid (34 mg.) formed when the mixture

was poured into water was acetylated with acetic anhydride and a trace of 60% perchloric acid, and the process repeated to ensure complete acetylation. The product could not be crystallised but sublimed at 220°/0·01 mm. The sublimate, after two crystallisations from alcohol, formed colourless needles with m. p. 201—202°, still lower than that of quercetagetin hexa-acetate (m. p. 212—213°; cf. Part I) but the mixed m. p. was 204·5—205°. There was insufficient material for further purification.

Evodionol.—This compound crystallised from alcohol in yellow prisms, m. p. and mixed m. p. with evodionol, 86—86·5° [Found: C, 67·9; H, 6·5%; *M* (ebullioscopic in benzene), 233. Calc. for $C_{14}H_{16}O_4$: C, 67·8; H, 6·4%; *M*, 248]. It dissolved in sodium hydroxide solution and concentrated sulphuric acid yielding faintly and intensely yellow solutions respectively, and the ferric chloride reaction was green. These reactions are all given by the authentic compound.

Confirmation was provided by the preparation of the methyl ethers as described above for melisimplin. The methyl ether crystallised from alcohol in colourless rhombic prisms, m. p. 79·5—80°, identical, by mixed m. p., with a sample of the same m. p. prepared from authentic evodionol.

allo*Evodionyl 7-Methyl Ether.*—This constituent crystallised from alcohol in rhombic plates, m. p. and mixed m. p. with *allo*evodionyl 7-methyl ether, 105·5—106° (Found: C, 69·0; H, 7·1. Calc. for $C_{15}H_{18}O_4$: C, 68·7; H, 6·9%). It was slightly soluble in concentrated hydrochloric acid and freely soluble in concentrated sulphuric acid with an intensely yellow colour. The benzylidene derivative, prepared according to Sutherland (*loc. cit.*), crystallised from methyl alcohol in yellow prisms, m. p. and mixed m. p. with benzylidene *allo*evodionyl 7-methyl ether, 165·5—166·5°.

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 for a Research Scholarship to one of us (R. H. L.), and to Messrs. M. D. Sutherland and S. E. Wright for samples of evodionol and *allo*evodionyl methyl ether.

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