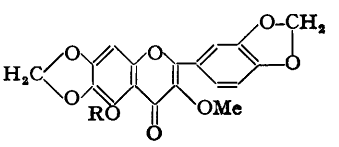
693. Chemistry of New Zealand Melicope Species. Part VI.* A Revised Constitution for Meliternatin, and the Identification of Xanthoxyletin from the Bark of Melicope ternata.

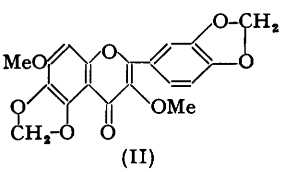
By Lindsay H. Briggs and R. H. Locker.

Further evidence has been adduced for the revised formulation of meliternatin as 3 : 5-dimethoxy-6 : 7-3′ : 4′-bismethylenedioxyflavone. " Compound E," the non-flavone substance isolated from *Melicope ternata*, has been identified as xanthoxyletin.

In Part I of this series (*J.*, 1949, 2157) a fully alkylated flavonol, meliternatin, from the bark of *Melicope ternata*, was shown to contain two methoxyl groups (one at $C_{(3)}$), and two methylenedioxy-groups. Hydrolysis with alcoholic potassium hydroxide yielded three phenolic substances and piperonylic acid, this acid establishing the nature of the side phenyl group. Three formulæ (I; R = Me), (II), and (III) were considered on this basis.



(I)



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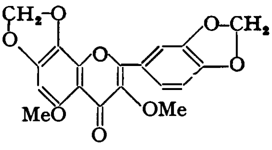

(III)

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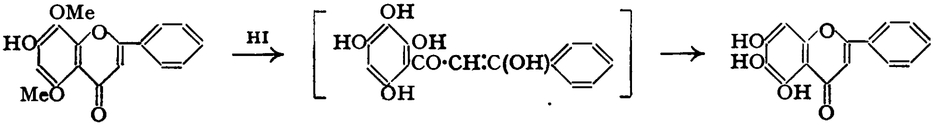
* Part V, *J.*, 1950, 2379.

Dealkylation with hydriodic acid afforded quercetagetin (3 : 5 : 6 : 7 : 3′ : 4′-hexahydroxyflavone), supporting a structure (I; R = Me) or (II) for meliternatin. However, by an apparent process of ring opening and closing, certain 5 : 8-dimethoxyflavones on demethylation form 5 : 6-dihydroxy-derivatives although, so far, the reverse transformation has not been observed (for a summary see Shah, Mehta, and Wheeler, *J.*, 1938, 1555; cf. also Baker,



J., 1939, 956; Baker and Simmonds, *J.*, 1940, 1370; Sastri and Seshadri, *Proc. Indian Acad. Sci.*, 1946, **24**, 243). For this reason a formula (III) could not be excluded for meliternatin.

The main phenol arising from the hydrolysis had the expected properties of a 2-hydroxy-*x* : ω-dimethoxy-methylenedioxyacetophenone. It gave a positive test with 2 : 6-dibromoquinonechloroimide (Gibbs, *J. Biol. Chem.*, 1927, **72**, 649), indicating a free position *para* to the phenolic group. This supported a structure (IV) for the phenol and (III) for meliternatin.

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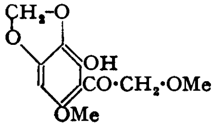
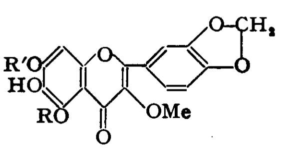


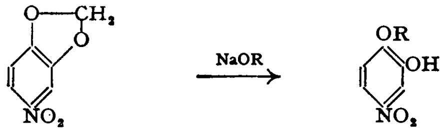


(V)

Further evidence, however, now definitely precludes formula (III) and supports (I; R = Me) rather than (II) for meliternatin.

In the alkaline hydrolysis of meliternatin with alcoholic potassium hydroxide, a second phenolic compound, m. p. 194—195°, was isolated in small yield for which a tentative formula, $C_{10}H_{10}O_4$, was given, with the observation that its composition did not correspond with that of any of the expected products. In making a survey of the absorption spectra of flavonols related to this series of investigations (succeeding paper), we measured that of the above phenolic compound and found that it was practically indistinguishable from that of 6-hydroxy-3 : 5 : 7-trimethoxy-3′ : 4′-methylenedioxyflavone (V; R = R′ = Me) obtained synthetically (Part V, *J.*, 1950, 2379). The phenolic compound gives the reduction tests for a flavonol methylated at $C_{(3)}$, but the analytical figures now equally fit the empirical formula, $C_{20}H_{18}O_8$, with two methoxyl groups. This compound was formed, we considered, by fission of the methylenedioxy-group in the benzo-nucleus under the activating influence of the carbonyl group at $C_{(4)}$. Robinson and Robinson (*J.*, 1917, **111**, 109, 929) have shown that a solution of a sodium alkoxide in the corresponding alcohol readily converted 4-nitrocatechol methylene ether (VI) into the 4-nitrocatechol 1-alkyl ether (VII), and Parijs (*Rec. Trav. chim.*, 1930, **49**, 41) obtained a similar result with the 4 : 5-dinitro-derivative. A much closer parallel to the present case is the fission of the methylenedioxy-group of melicopine and melicopidine (VIII) with alcoholic potassium hydroxide (Crow and Price, *Australian J. Sci. Res.*, 1949, **2**, *A*, 255, 282; cf. also evoxanthine, Hughes and Neill, *ibid.*, p. 429). That this view of the mechanism was correct was shown by the fact that the action of sodium methoxide on

(VI)



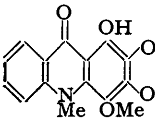
(VII)

(VIII)

meliternatin afforded 6-hydroxy-3 : 5 : 7-trimethoxy-3′ : 4′-methylenedioxyflavone (V; R = R′ = Me), identified by mixed melting points of the free compounds and their acetates. Since this reaction does not affect the position of the oxygen atoms meliternatin must therefore be a 5 : 6 : 7-derivative and not a 5 : 7 : 8-derivative. This excludes formula (III), and meliternatin must then be either (I; R = Me) or (II). The above reactions with alcoholic alkali do not enable a distinction to be made between (I; R = Me) and (II). Positions 5 and 7 are both activated by the carbonyl group at $C_{(4)}$ and the action of alcoholic potassium hydroxide on (I; R = Me) and (II) would give (V; R = Me, R′ = Et) and (V; R = Et, R′ = Me) respectively, probably indistinguishable in their absorption spectra from their methyl analogues. The same product (V; R = R′ = Me) would be obtained from both (I; R = Me) and (II) by the action of sodium methoxide.

In Part I (*loc. cit.*) we reported that the action of aluminium chloride on meliternatin in nitrobenzene at 100° formed an aluminium lake from which the metal could not be removed. Under milder conditions, with an excess of aluminium chloride in boiling ether, meliternatin was smoothly demethylated to a yellow, monohydric flavonol, $C_{18}H_{12}O_8$, forming a monoacetate and still containing one methoxyl group and giving a positive methylenedioxy-test. Although an absolute proof cannot be given for this substance the following accumulated evidence supports the formula (I; R = H), and hence (I; R = Me) rather than (II) for meliternatin.

Baker (*J.*, 1939, 961; Baker, Brown, and Scott, *ibid.*, p. 1922; Baker and Simmonds, *J.*, 1940, 1373) has shown that 5-methoxyflavones undergo demethylation with aluminium chloride in boiling ether, and Shah, Virkar, and Venkataraman (*J. Indian Chem. Soc.*, 1942, **19**, 135) have reported that 3-methoxyflavone is not demethylated by aluminium chloride at room temperature but is at 100°. In Part V (*loc. cit.*) we have shown that aluminium chloride in boiling ether demethylates melisimplexin (3 : 5 : 6 : 7-tetramethoxy-3′ : 4′-methylenedioxyflavone) to melisimplin. While no definite proof can be given for the constitution of the latter its colour reactions favour a 5-hydroxy-3 : 6 : 7-trimethyl-3′ : 4′-methylenedioxyflavone structure. This is supported on the phytochemical grounds that no naturally occurring 3 : 5-dihydroxyflavone exists which is methylated at $C_{(5)}$ but not at $C_{(3)}$. Our experiment, we believed therefore, supported those of Baker in that aluminium chloride in boiling ether was apparently a specific reagent for the demethylation of flavones methoxylated at $C_{(5)}$. We have now shown, however, that quercetin pentamethyl ether is demethylated by aluminium chloride in boiling ether to quercetin 5 : 7 : 3′ : 4′-tetramethyl ether, *i.e.*, demethylation has occurred at $C_{(3)}$. The reaction is therefore not specific for the $C_{(5)}$ position but may occur at $C_{(3)}$ or $C_{(5)}$ according to factors still unknown. Quercetin pentamethyl ether may, however, be demethylated at $C_{(5)}$ by using the technique of Crow and Price. They have shown (*Australian J. Sci. Res.*, 1949, **2**, *A*, 260) that acridone alkaloids methoxylated at $C_{(4)}$ are demethylated specifically at this point when they are heated with alcoholic hydrochloric acid or when their hydrochlorides are heated above their melting points, *e.g.*, the conversion of melicopidine (VIII) into normelicopidine (IX).



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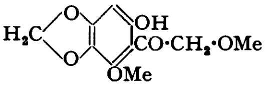
There are formal similarities between these alkaloids and fully alkylated flavonols which are reflected in their properties [cf. the basic properties of meliternatin recorded in Part I (*loc. cit.*) and the discussion in the succeeding paper]. Quercetin pentamethyl ether is also basic, readily forming coloured salts such as the hydrochloride (Watson, *J.*, 1914, **105**, 338). The pentamethyl ether may be recovered unchanged after treatment with alcoholic hydrochloric acid but when the hydrochloride is heated above its melting point it is smoothly converted into quercetin 3 : 7 : 3′ : 4′-tetramethyl ether. The specificity of these demethylating methods is worth further study.

On the above evidence, the demethylated meliternatin could have its free hydroxyl group at $C_{(3)}$ or $C_{(5)}$ if derived from (I; R = Me), or only at $C_{(3)}$ if derived from (II). The following properties of the compound definitely favour a free hydroxyl at $C_{(5)}$ rather than at $C_{(3)}$. Acid or alkaline reduction of the demethylated product gives a pink colour showing that the remaining methoxyl group is at $C_{(3)}$ (cf. Part I, *loc. cit.*). It gives a green colour with ferric chloride in alcohol. Both 5- and 3-hydroxyflavones give intense ferric chloride colours but the colours given by the 5-hydroxy-compounds are almost invariably green (cf. Seshadri and his co-workers, *Proc. Indian Acad. Sci.*, 1941, **14**, 290; 1945, **22**, 385; 1946, **23**, 299; 1946, **24**, 377, 457; 1947, **25**, 339, 402; 1947, **26**, 15, 19, 75, 214, 235; 1950, **31**, 33) and occasionally brown (Row and Seshadri, *ibid.*, 1945, **22**, 220) or purple (Rajagopalan, Rao, and Seshadri, *ibid.*, 1947, **25**, 436) while the colour given by 3-hydroxyflavones is, to our knowledge, invariably brown (cf. Seshadri and his co-workers, *ibid.*, 1945, **21**, 131; 1946, **23**, 99; 1946, **24**, 377, 457;

1947, **26**, 192; 1949, **30**, 216). The demethylated product shows no fluorescence in organic solvents. Fluorescence is a characteristic of 3-hydroxyflavones but not of 5-hydroxyflavones (Seshadri and Venkateswarlu, *ibid.*, 1947, **26**, 190; Seshadri and his co-workers, *ibid.*, 1945, **21**, 131; 1946, **23**, 99; 1949, **30**, 216). The demethylated product is insoluble in sodium hydroxide solution. The 5-hydroxyflavones quoted above are all recorded as insoluble or sparingly soluble in sodium hydroxide solution while the 3-hydroxyflavones quoted are recorded as soluble or sparingly soluble, not one example being noted as insoluble. The solubility of the demethylated product in concentrated hydrochloric acid is in agreement with its formulation as a 5-hydroxyflavone (cf. the succeeding paper) but there is insufficient evidence of the behaviour of 3-hydroxyflavones for this test to be of much value. Mordanted wool is dyed by the demethylated product but this is explicable by the presence of a hydroxyl group at either $C_{(5)}$ or $C_{(3)}$.

The accumulated evidence above supports the presence of a free hydroxyl group at $C_{(5)}$ for the demethylated product, *i.e.*, formula (I; R = H), and thus formula (I; R = Me) for meliternatin. Consequent on this, the product of the action of alcoholic potassium hydroxide on meliternatin has the formula (V; R = Me, R′ = Et) and the main phenol, m. p. 142—144°, arising from the hydrolysis of meliternatin, is most probably 6-hydroxy-2 : ω-dimethoxy-3 : 4-methylenedioxyacetophenone (X). The positive test given with 2 : 6-dibromoquinonechloroimide may be due to an impurity (the test is very sensitive, detecting phenol itself at a concentration of 1 in 2 × 10^7). In contrast, it is surprising that 2 : 4 : 6-trihydroxy-ω-methoxyacetophenone and 2-hydroxy-4 : 6 : ω-trimethoxyacetophenone, both of which have free positions *para* to phenolic groups, do not give positive tests with this reagent.

(X)



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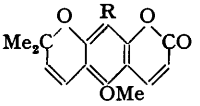


In Part I (*loc. cit.*) a tentative structure, 5 : 3′ : 4′-trihydroxy-3-methoxy-7 : 8-methylenedioxyflavone, was proposed for wharangin. This was based solely on colour reactions and on the phytochemical grounds that the other three flavonols accompanying it, *viz.*, meliternatin, meliternin, and ternatin, were all 5 : 7 : 8-derivatives. The revised formulation for meliternatin as a 5 : 6 : 7-derivative now removes these phytochemical grounds and allows for further possible structures for wharangin.

Accompanying the four flavonols in the bark of *Melicope ternata* (Part I, *loc. cit.*) was a colourless compound, " Compound E," m. p. 133·5—134°, which was not a flavone derivative. A tentative formula, $C_{16}H_{16}O_4$, was proposed for this substance which did not react with ferric chloride, but gave a positive methylenedioxy-test overnight. Apart from the latter reaction, the properties of this compound corresponded with those of xanthoxyletin (XI; R = H), $C_{15}H_{14}O_4$, from the related species of *Rutaceæ*, *Xanthoxylum americanum* (prickly ash). This was first isolated by Staples (*Amer. J. Pharm.*, 1829, 163), and its constitution has been elucidated by Robertson and his co-workers (*J.*, 1936, 627; 1937, 286). The combustion figures of our compound agreed equally well with those for $C_{15}H_{14}O_4$ and a direct comparison, by mixed melting point with an authentic sample of xanthoxyletin, kindly provided by Professor A. Robertson, showed that they were identical. The positive methylenedioxy-test is probably due to a trace of impurity (the test is only given overnight whereas the colour from methylenedioxy-compounds normally appears within half an hour) and the following bromo-derivative did not give it.

Gordin (*J. Amer. Chem. Soc.*, 1906, **28**, 1649) brominated xanthoxyletin in acetic acid to a dibromide monohydrate, crystallising from acetone–alcohol in colourless " warts," m. p. 171°. In seeking to confirm the identification of our compound with xanthoxyletin we brominated both compounds in chloroform. The products were identical (mixed melting point), but they were different (m. p. 157·5—158·5°) from that obtained by Gordin and corresponded to a monosubstituted derivative which we consider is (XI; R = Br) although it gives an inexplicably high analytical value for hydrogen. The monobromo-derivative gives an unusual colour reaction with concentrated sulphuric acid, the crystals becoming blue, then green, before dissolving to a yellow solution.

Xanthoxyletin exhibits absorption peaks (log ε in parentheses) at 227 (4·28), 269 (4·32), 322 (3·99) and 347 (4·05) when measured in *ca.* M/20,000 alcoholic solution.

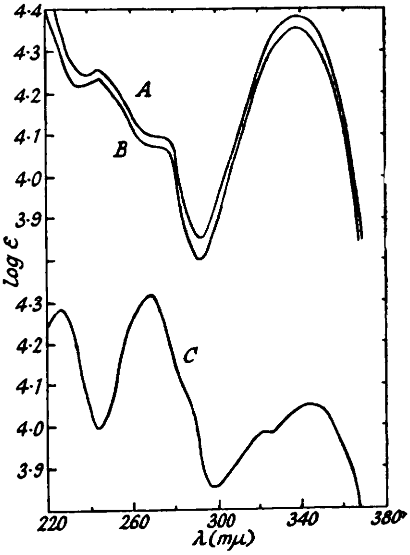
EXPERIMENTAL.

(M. p.s are corrected.)

The analyses are by Drs. Weiler and Strauss, Oxford, and Dr. T. S. Ma, Microchemical Laboratory, University of Otago, Dunedin.

Demethylation of Meliternatin with Aluminium Chloride.—Meliternatin (300 mg.) was refluxed with a solution of freshly prepared aluminium chloride (4 g.) in dry ether (16 c.c.) for 10 hours. The yellow precipitate formed when the mixture was poured into water was boiled for 20 minutes with acetic acid (20 c.c.) and concentrated hydrochloric acid (10 c.c.). The precipitate which formed on dilution of the mixture with water (150 c.c.) crystallised from acetone in light mustard-coloured needles, m. p. 253—255° (147 mg.). Two further crystallisations raised the m. p. to 258—258·5° (Found : C, 60·9; H, 3·4; OMe, 6·2. $C_{18}H_{12}O_8$ requires C, 60·7; H, 3·3; 1OMe, 8·7%). The *substance* is insoluble in 10% sodium hydroxide solution and concentrated hydrochloric acid but soluble in concentrated sulphuric acid with a bright yellow colour, becoming green on addition of gallic acid. Ferric chloride solution produces a light green colour and acid or alkaline reduction a pink colour.

The demethylated product (22 mg.) was acetylated, for ½ hour, with an excess of acetic anhydride containing one drop of 60% perchloric acid. After addition of water, the precipitated solid *acetate* formed slightly yellow needles, m. p. 208·5—210° (15 mg.) when crystallised twice from alcohol (Found : C, 60·4; H, 3·8. $C_{20}H_{14}O_9$ requires C, 60·3; H, 3·5%).



A, Flavonol (VI). *B, Flavonol* (V). *C, Xanthoxyletin.*

A sample of wool mordanted with potassium dichromate and tannic acid was dyed by immersing it in a boiling aqueous suspension of the demethylated product for an hour. The wool was dyed a pale yellow colour, unchanged after 20 minutes' boiling with fresh water; the colour was identical with that produced by melisimplin, of similar constitution [cf. Parts IV (*J.*, 1950, 2376) and V (*loc. cit.*)], under similar conditions.

Hydrolysis Product from Meliternatin.—The compound, m. p. 194—195°, described in Part I (*loc. cit.*) as one of the hydrolytic products of meliternatin, and now recognised as 6-hydroxy-3 : 5 : 7-trimethoxy-3′ : 4′-methylenedioxyflavone, has been re-analysed (Found : C, 61·9; H, 4·7; OMe, 11·6. Calc. for $C_{20}H_{18}O_8$: C, 62·2; H, 4·7; 1OMe, 12·5%). Reduction with magnesium and hydrochloric acid gave an orange-red colour; sodium amalgam gave a yellow solution which became pink on acidification.

Action of Sodium Methoxide on Meliternatin.—A solution of meliternatin (200 mg.) in absolute methyl alcohol (40 c.c.) was heated under reflux for 2 hours with sodium methoxide solution [2·4 c.c. of a solution obtained by dissolving sodium (3 g.) in absolute methyl alcohol (30 c.c.)]. On cooling, large amounts of meliternatin crystallised out. The remainder of the sodium methoxide was added (making a 13% solution) and the heating continued for 6 hours. On cooling, nothing separated from the bright yellow solution which was then made slightly acid with hydrochloric acid and taken almost to dryness on the water-bath. Part of the colourless residue was soluble in hot 2% sodium hydroxide solution (40 c.c.) with a yellow colour. The hot alkaline solution was filtered, cooled and saturated with carbon dioxide, whereupon a colourless, partly crystalline material, m. p. 235—237°, was precipitated (yield, 92 mg.). Ether-extraction of the filtrate gave no further product, and acidification with hydrochloric acid produced no precipitate.

The material insoluble in sodium hydroxide solution was boiled successively with water (30 c.c. and 100 c.c.), containing a few drops of 10% sodium hydroxide solution, and filtered. The yellow residue (44 mg.) became colourless on acidification and, after crystallisation from aqueous dioxan, afforded meliternatin. The yellow alkaline solutions were combined and saturated with carbon dioxide. The colourless crystalline precipitate (50 mg.; m. p. 233—235°) was combined with the first product and, after three crystallisations from alcohol, the first with charcoal, colourless, hexagonal plates were obtained, having m. p. 243—244·5°, undepressed by a synthetic sample of 6-hydroxy-3 : 5 : 7-trimethoxy-3′ : 4′-methylenedioxyflavone (Part V, *loc. cit.*) of the same crystalline form and of m. p. 244·5—246°.

The acetate, prepared as for the synthetic specimen (Part V), crystallised from dioxan in colourless, rhombic plates, m. p. and mixed m. p. with the synthetic acetate, 246—247°.

Demethylation of Quercetin Pentamethyl Ether.—(a) *With aluminium chloride.* Quercetin pentamethyl ether, treated similarly to meliternatin, afforded a product crystallising from alcohol in long, pale-yellow, flat needles, m. p. 197—198°, showing a strong fluorescence in concentrated sulphuric acid and giving a brown colour with ferric chloride solution. Kostanecki, Lampe, and Tambor (*Ber.*, 1904, **37**, 1404) record m. p. 197—198° for quercetin 5 : 7 : 3′ : 4′-tetramethyl ether.

(b) *By heating the hydrochloride.* The hydrochloride of quercetin pentamethyl ether was formed by dissolving the ether (100 mg.) in boiling hydrochloric acid (4 c.c.) and acetic acid (1 c.c.) and crystallisation. The yellow needles, which separated in sheaf-like aggregates, were filtered on a sintered-glass funnel and washed with concentrated hydrochloric acid. This material, while being stirred in an open tube, was heated in an oil-bath up to 160°. Gas was liberated at *ca.* 110—120° and reaction was complete at 160°. The product partly crystallised on cooling, and completely from hot alcoholic solution in fine, pale yellow needles, m. p. and mixed m. p. with quercetin 3 : 7 : 3′ : 4′-tetramethyl ether, 159°. In alcoholic solution it gives a brown colour with ferric chloride solution.

Identification of "Compound E" with Xanthoxyletin.—"Compound E" (Part I, *loc. cit.*), m. p. 133·5—134°, was undepressed in m. p. on admixture with a sample of xanthoxyletin, m. p. 131·5—135·5°, of the same crystalline form. The absorption spectrum measured in *ca.* M/20,000 alcoholic solution, is shown in the figure.

Bromoxanthoxyletin.—Bromine (18·6 mg., 1 mol.) in chloroform solution (1·5 c.c.) was added dropwise to a solution of xanthoxyletin (30 mg. *ex Melicope ternata*) in the same solvent. Absorption of the bromine was at first instantaneous but decolorisation of the last few drops required some seconds. The yellow resin obtained after removal of the chloroform (the last portion in a vacuum) formed, after two crystallisations from slightly diluted alcohol, colourless, hexagonal plates, m. p. 157·5—158·5° (25 mg.), undepressed by a *bromo*-compound of the same m. p. prepared from authentic xanthoxyletin (Found: C, 53·5; H, 5·3; Br, 21·3. $C_{15}H_{13}O_4Br$ requires C, 53·4; H, 3·9; Br, 23·7%).

We are indebted to the Chemical Society, the Australian and New Zeaand Association for the Advancement of Science, the Royal Society of New Zealand, and the Research Grants Committee of the University of New Zealand for continued grants, and one of us (R. H. L.) for a Research Scholarship.

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[*Received, August 24th*, 1950.]