198. *Chemistry of New Zealand* Melicope *Species. Part IX.*[1] *A Synthesis of Meliternatin.*

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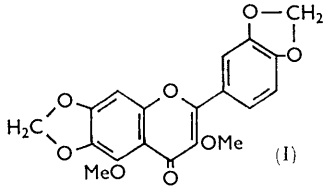
Meliternatin (I) has been synthesised by an Allan–Robinson condensation of piperonylic anhydride and potassium piperonylate with 6-hydroxy-2,ω-dimethoxy-3,4-methylenedioxyacetophenone (II) prepared by two different methods.

In Part VI,[2] formula (I) was adduced for meliternatin, a flavonoid from *Melicope ternata*.[3] Its synthesis, by way of 6-hydroxy-2,ω-dimethoxy-3,4-methylenedioxyacetophenone (II),[2] is now reported.*

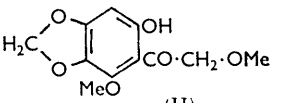
* Since this Paper was submitted, Fukui and Matsumoto (*Bull. Chem. Soc. Japan*, 1963, **36**, 806) have synthesised meliternatin from the same intermediate.

[1] Part VIII, *J.*, 1960, 2376.
[2] Briggs and Locker, *J.*, 1951, 3131.
[3] Briggs and Locker, *J.*, 1949, 2157.

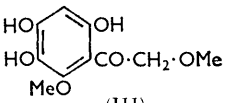
The ketone (II) has been prepared by two different methods. First, 2,4-dihydroxy-6,ω-dimethoxyacetophenone [4] was subjected to an Elbs persulphate oxidation.[5,6] The 3,4,6-trihydroxy-2,ω-dimethoxyacetophenone (III) obtained, reacted with methylene



(I)



(II)



(III)

iodide and potassium carbonate in anhydrous acetone [7] to give (II) in almost negligible yield.

In the second method, 3-methoxy-4,5-methylenedioxyphenol [7a,b] and methoxymethyl cyanide condensed in a Hoesch reaction to give the ketone (II) directly. Although there is a possibility of obtaining the isomer of (II) in which the methoxyacetyl group occupies the present 5-position, the formation of the desired isomer alone was predicted from the results of Salway [8,9] who showed that nitration of myristicinaldehyde and myristicinic acid gave single products, the 2-nitro-aldehyde and -acid, respectively. Wagner, Wilson, and Folkers [9a] have shown that this phenol is also substituted in the 2-position on reaction with *o*-acetoxyphenylacetonitrile. The only product obtained in the present investigation was identical with that obtained from the degradation of meliternatin.

3-Methoxy-4,5-methylenedioxyphenol for the above condensation was prepared by two methods. Reaction of isomyristicin [10] with one mol. of ozone, followed by catalytic reduction,[11] gave an oil from which myristicinaldehyde could not be isolated. However, reaction with three mol. of ozone gave the aldehyde directly in almost quantitative yield, no treatment of the ozonide with sodium hydrogen sulphite [12] being required. 3-Methoxy-4,5-methylenedioxynitrobenzene, prepared from myristicinaldehyde by Salway's method [9] was reduced to the amine with sodium hyposulphite [13] or with Raney nickel.[14] Conversion of this amine, by way of diazotisation, into 3-methoxy-4,5-methylenedioxyphenol took place in low yield. The preparations of the amine and phenol were carried out before the publication of Wagner *et al.*[7b] The direct conversion of myristicinaldehyde into this phenol was then attempted. In preliminary experiments, oxidation of 3,4-methylenedioxybenzaldehyde with peracetic acid by Böeseken's method [15] failed to give the related phenol in reasonable yields, much resinification taking place. If the reaction temperature was maintained at 5—10°, however, yields of 60% of the phenol could be obtained. By use of this modification myristicinaldehyde gave 3-methoxy-4,5-methylenedioxyphenol in reasonable yield.

Finally, by subjecting the ketone (II) to an Allan–Robinson condensation [16] with

[4] Kuhn and Löw, *Ber.*, 1944, **77**, *B*, 202.
[5] Baker and Brown, *J.*, 1948, 2303.
[6] Krishnamurti and Seshadri, *Proc. Indian Acad. Sci.*, 1952, **35**, *A*, 82.
[7] Trikojus and White, *J.*, 1949, 436; Rao, Seshadri, and Thiruvengadam, *Proc. Indian Acad. Sci.*, 1949, **30**, *A*, 114.
[7a] Crabbe, Leaming, and Djerassi, *J. Amer. Chem. Soc.*, 1958, **80**, 5258.
[7b] Wagner, Walton, Wilson, Rodin, Holly, Brink, and Folkers, *J. Amer. Chem. Soc.*, 1959, **81**, 4983.
[8] Salway, *J.*, 1909, **95**, 1155.
[9] Salway, *J.*, 1911, **99**, 266.
[9a] Wagner, Wilson, and Folkers, *J. Amer. Chem. Soc.*, 1959, **81**, 5441.
[10] Power and Salway, *J.*, 1907, **91**, 2037; Thoms, *Ber.*, 1903, **36**, 3446; Pickles, *J.*, 1912, **101**, 1433; Salway, *J.*, 1909, **95**, 1204.
[11] Challis and Clemo, *J.*, 1947, 1692.
[12] Nagai, *J. Chem. Ind. Tokyo*, 1922, **25**, 631.
[13] Prélog and Wiesner, *Helv. Chim. Acta*, 1948, **31**, 870; Hodgson and Ward, *J.*, 1947, 327.
[14] Drake, Harris, and Jaeger, *J. Amer. Chem. Soc.*, 1948, **70**, 168.
[15] Böeseken, Coden, and Kip, *Rec. Trav. chim.*, 1936, **55**, 815.
[16] Allan and Robinson, *J.*, 1924, 2192.

potassium 3,4-methylenedioxybenzoate and the corresponding anhydride, meliternatin (I) was obtained.

Experimental

Analyses were by Dr. A. D. Campbell and associates, University of Otago, New Zealand. Infrared spectra were measured for potassium bromide discs with a Beckman IR2 instrument. Light petroleum was of b. p. 40—60°.

Myristicinaldehyde (3-*Methoxy*-4,5-*methylenedioxybenzaldehyde*).—Isomyristicin (20 g.) was dissolved in glacial acetic acid (75 ml.) and light petroleum (150 ml.), cooled in an ice-bath, and treated with ozonised oxygen (13·4% of ozone) at 150 ml./min. for 6 hr. During the reaction two layers separated, followed by rapid separation of a white solid which was filtered off. The light petroleum layer was separated, and water was added to the residue to precipitate further product. The combined solids (16 g.) crystallised from hot water to give myristicinaldehyde, m. p. 131—132° (lit.,[17,18] 130°).

3-*Methoxy*-4,5-*methylenedioxyaniline*.—(*a*) To a refluxing solution of 3-methoxy-4,5-methylenedioxynitrobenzene [8,19] (400 mg.), ethanol (10 ml.), and 2N-sodium hydroxide (20 ml.), sodium dithionite (1·5 g.) was added portionwise, whereupon the reddish colour permanently disappeared. After 20 min. the solution was cooled, diluted, and extracted with ether. The ether yielded an oil which, on trituration with water, gave 3-methoxy-4,5-methylenedioxyaniline, hexagonal plates (80 mg.) (from hot water), m. p. 87—87·5° (lit.,[8] 85—86°).

(*b*) 3-Methoxy-4,5-methylenedioxynitrobenzene (1 g.) was dissolved in boiling ethanol (50 ml.), and reduced with hydrogen and Raney nickel W-6 (150 mg.) at 70—75°/100 atm. for 2½ hr. The cooled mixture was filtered, and the filtrate, after evaporation to half volume, was extracted with ether. Treatment of this extract with 2N-hydrochloric acid gave a precipitate of 3-methoxy-4,5-methylenedioxyaniline hydrochloride (430 mg.), while treatment of the aqueous filtrate with sodium carbonate afforded the free amine (370 mg.), m. p. 85—87° (from water). 3-Methoxy-4,5-methylenedioxyaniline hydrochloride crystallised from aqueous alcoholic hydrochloric acid as nacreous plates, m. p. 240—242° (decomp.) (Found: Cl, 17·2. Calc. for $C_8H_{10}ClNO_3$: Cl, 17·4%) [lit.,[8] m. p. 245° (decomp.)].

3-*Methoxy*-4,5-*methylenedioxyphenol*.—(*a*) 3-Methoxy-4,5-methylenedioxyaniline (170 mg.) was dissolved, with heating, in N-sulphuric acid (4 ml.), and the volume made up to 20 ml. Diazotisation at 0° with sodium nitrite (0·25N; 4 ml.), treatment of the aqueous solution with urea and copper sulphate, extraction with ether, and treatment of the ether solution with sodium hydroxide yielded a reddish oil (45 mg.) which sublimed at 15 mm./50° and had m. p. 89·5—90·5° (lit.,[7a,b] 89—91°, 88—89°).

(*b*) To myristicinaldehyde (1·8 g.) dissolved in glacial acetic acid (30 ml.) was added peracetic acid (17·5%; 4·8 g.), dropwise with vigorous stirring, the temperature being kept at 0—10°. The mixture was then kept at 15—18° for 1 hr., set aside at *ca.* 4° overnight, and poured into water (100 ml.). Neutralisation ($KHCO_3$) and extraction with ether yielded a solid which was boiled with potassium hydroxide (2 g.), water (15 ml.), and methanol (50 ml.) for 45 min. Removal of methanol, extraction with ether, acidification of the basic residue, and extraction with ether yielded an oil (600 mg.) which solidified as needles. Vacuum sublimation (15 mm./80°) gave 3-methoxy-4,5-methylenedioxyphenol, m. p. 87—89°. The ether extract of the material insoluble in alkali yielded starting material (800 mg.).

3,4,6-*Trihydroxy*-2,ω-*dimethoxyacetophenone* (III).—Aqueous potassium persulphate (8·4 g. in 80 ml.) was added dropwise with continuous stirring during 5 hr. to a solution of 2,4-dihydroxy-6,ω-dimethoxyacetophenone (1·8 g.) in aqueous sodium hydroxide (2·4 g. in 67 ml.), at 15—20° under nitrogen. The mixture was then stirred for 2 hr. and left at room temperature for a further 36 hr. Acidification to Congo Red with concentrated hydrochloric acid, and extraction with ether, yielded starting material (300 mg.). Sodium sulphite (4 g.) and concentrated hydrochloric acid (25 ml.) were added to the aqueous solution and the mixture heated at 100° for 30 min. After concentration of the aqueous solution to half volume, extraction with ether gave a dark solid which was chromatographed on Magnesol–Celite and eluted with ethyl acetate (500 ml.). Repeated crystallisation from benzene–acetone gave the *product* as stout pale yellow

[17] Pickles, *J.*, 1912, **101**, 1433.
[18] Semmler, *Ber.*, 1891, **24**, 3818.
[19] Baker, Montgomery, and Smith, *J.*, 1932, 1281.

prisms (215 mg.), m. p. 162—163° (Found: C, 52·1, 53·85, 53·35; H, 4·6, 4·8, 5·7. $C_{10}H_{12}O_6$ requires C, 52·65; H, 5·3%), $\nu_{max.}$ 3279 (OH) and 1650 cm.$^{-1}$ (C:O).

6-Hydroxy-2,ω-dimethoxy-3,4-methylenedioxyacetophenone (II).—A mixture of 3,4,6-trihydroxy-2,ω-dimethoxyacetophenone (200 mg.), anhydrous potassium carbonate (121 mg.), and methylene iodide (240 mg.) in dry acetone (100 ml.) was refluxed under nitrogen for 30 hr. and left at room temperature for a further 2½ days; the mixture darkened considerably during this time. After acidification with 2N-hydrochloric acid the solution was reduced to 10 ml. and water (70 ml.) added. Extraction with ether (3 × 40 ml.) yielded an orange gum which crystallised from light petroleum to give the ketone (II) (2 mg.) as yellow prisms, m. p. 131—134° (same infrared spectrum as product from alkaline degradation of meliternatin [2]).

(*b*) 3-Methoxy-4,5-methylenedioxyphenol (368 mg.), methoxymethyl cyanide (155 mg.), and freshly fused zinc chloride (400 mg.) were dissolved in anhydrous ether (20 ml.), cooled in an ice-bath, and saturated with hydrogen chloride. The mixture, after standing in the refrigerator for 65 hr., was poured into ether. The solid which separated was washed with ether, dissolved in water (75 ml.), and heated at 100° for 2 hr. On cooling, light brown plates (150 mg.) separated which crystallised from ethanol as pale yellow rods of the ketone (II), m. p. and mixed m. p. with product from degradation of meliternatin, 140—142°. The infrared spectra [$\nu_{max.}$ 3135(OH) and 1623 cm.$^{-1}$ (C:O)] were also identical.

Meliternatin (I).—6-Hydroxy-2,ω-dimethoxy-3,4-methylenedioxyacetophenone (II) (300 mg.) was ground intimately with 3,4-methylenedioxybenzoic anhydride [20] (985 mg.) and potassium 3,4-methylenedioxybenzoate (235 mg.) and the mixture heated for 2½ hr. at 170—175°/15—20 mm. Alkaline hydrolysis with boiling ethanolic potassium hydroxide, removal of the ethanol, and pouring into water yielded meliternatin (180 mg.) which, after repeated crystallisations from ethanol (charcoal), afforded needles, m. p. and mixed m. p. 199—200°. The infrared spectra [21] were also identical.

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Auckland, New Zealand. [*Received, August 14th*, 1963.]

[20] Rao and Seshadri, *Proc. Indian Acad. Sci.*, 1946, **23**, *A*, 148.
[21] Briggs and Colebrook, *Spectrochim. Acta*, 1962, **18**, 939.