Synthetic Studies of the Flavone Derivatives. II[1]*. The Synthesis of Meliternatin and Some 3,5-Dimethoxy-6,7-methylenedioxyflavones*[*1]

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Meliternatin was first isolated from the bark of *Melicope ternata* by Briggs and Locker[2], together with wharangin, meliternin and ternatin, in 1949; it has also been recently isolated from the bark of *M. mantelli* by Cambie[3]. It has been shown to contain two methoxy groups and two methylenedioxy groups; up to now it has been only known naturally-occurring 3-methoxyflavone containing two methylenedioxy groups. From degradative experiments, Briggs and Locker first identified

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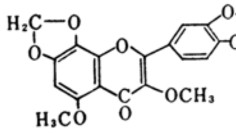
[*1] Presented at the Ube Local Meeting of the Chemical Society of Japan, November, 1962.

[1] Part I: K. Fukui and T. Matsumoto, This Bulletin, 35, 1931 (1962).

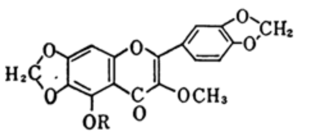
[2] L. H. Briggs and R. H. Locker, *J. Chem. Soc.*, **1949**, 2157.

[3] R. C. Cambie, ibid., **1960**, 2376.

it as 3, 5-dimethoxy-7, 8 ; 3′, 4′-bismethylenedioxyflavone (I)[2]. On the basis of further experiments[4], however, they proposed the revised formula of 3, 5-dimethoxy-6, 7 ; 3′, 4′-bismethylenedioxyflavone (II). It would be interesting to confirm the structure of meliternatin by synthesis.

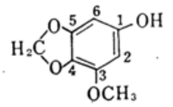


(I)

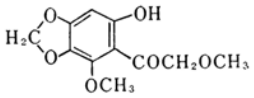


(II) R=CH_3
(VIII) R=H
(IX) R=$COCH_3$

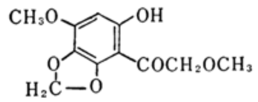
The present report describes the synthesis of meliternatin and some related compounds. The Hoesch condensation of 3-methoxy-4, 5-methylenedioxyphenol (III)[5] and methoxyacetonitrile yielded a ketone, $C_{11}H_{12}O_6$. Two structures (IV and V) were expected for this ketone. Since Folkers et al.[6] have demonstrated that III is condensed with *o*-acetoxybenzylcyanide to given 2′-(6-hydroxy-2-methoxy-3, 4-methylenedioxyphenyl)-benzofuran (VI), it seems probable that III is substituted not at the 6-position but at the 2-position in the Hoesch condensation. Therefore, IV was formed from the reaction with methoxyacetonitrile. In order to elucidate the structure of the ketone, a flavone was prepared with piperonylic anhydride from the ketone. This product did not agree in its properties with 3, 7-dimethoxy-5, 6 ; 3′, 4′-bismethylenedioxyflavone (VII) (cf. our succeeding paper). On the basis of this evidence, IV, 6-hydroxy-2, ω-dimethoxy-3, 4-methylenedioxyacetophenone is postulated as the structure for the ketone. Judging from its physical and chemical properties, IV was identical with the ketone which was obtained as the main phenolic product[2] of the action of alcoholic potassium hydroxide on meliternatin. According to Allan and Robinson's flavone synthesis[7], the condensation of IV with piperonylic anhydride in the presence of potassium piperonylate, followed by treatment with alcoholic potassium hydroxide, afforded the desired flavone II, whose identity with natural meliternatin was confirmed by mixed melting point, infrared and ultraviolet spectral comparison (Table I, Fig. 1 and Fig. 2). Synthetic meliternatin was also characterized as 5-demethyl compound VIII and its acetate IX (Table I).



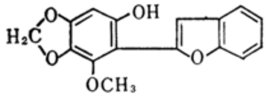
(III)



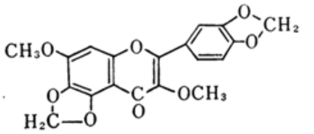
(IV)



(V)



(VI)



(VII)

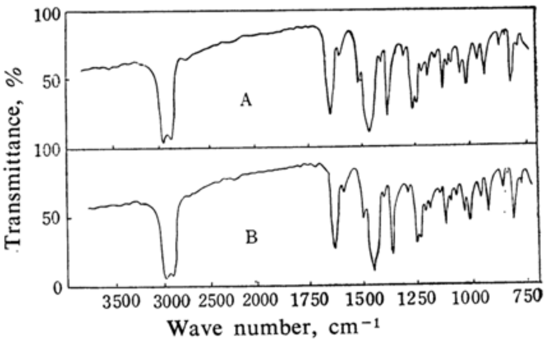


Fig. 1. IR spectra of synthetic (A) and natural meliternatin (B) in Nujol.

By a similar method, the condensation of the ketone IV with acid anhydrides (benzoic anhydride, anisic anhydride, veratric anhydride and trimethylgallic anhydride) in the presence of the potassium salt of the corresponding acids gave 3, 5-dimethoxy-6, 7-methylenedioxyflavone (X), 3, 5, 4′-trimethoxy-6, 7-methylenedioxyflavone (XI), 3, 5, 3′, 4′-tetramethoxy-6, 7-methylenedioxyflavone (XII) and 3, 5, 3′, 4′, 5′-pentamethoxy-6, 7-methylenedioxyflavone(XIII) respectively. These flavones gave a negative ferric chloride reaction and were soluble in concentrated sulfuric acid to a yellow solution.

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[4] L. H. Briggs and R. H. Locker, ibid., **1951**, 3131.

[5] A. F. Wagner, E. Walton, A. N. Wilson, J. O. Rodin and F. W. Holly, *J. Am. Chem. Soc.*, **81**, 4983 (1959).

[6] A. F. Wagner, A. N. Wilson and K. Folkers, ibid., **81**, 5441 (1959).

[7] J. Allan and R. Robinson, *J. Chem. Soc.*, **1924**, 2192.

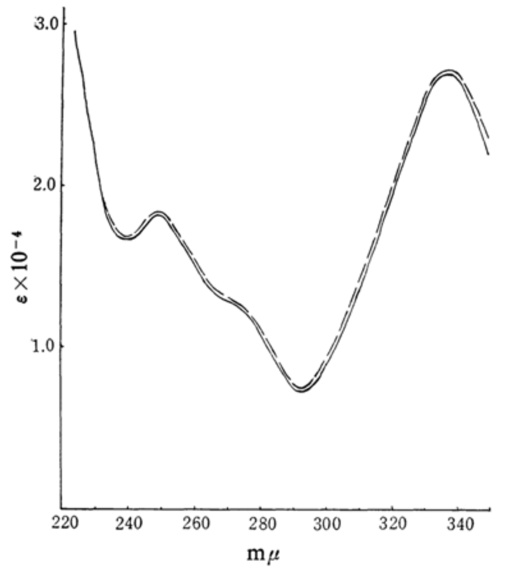
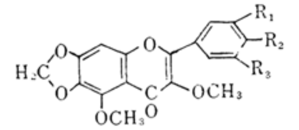


Fig. 2. UV spectra of natural (——) and synthetic meliternatin (----) in ethanol.

TABLE I. THE MELTING POINTS OF MELITERNATIN AND ITS DERIVATIVES (°C)

	Synthetic compound	Natural compound2,4)*
Meliternatin (II)	196～197	198～198.5
5-Demethylmeliternatin (VIII)	256～257	258～258.5
Acetate (IX) of VIII	205～206	208.5～210

* Melting points are corrected.



(X) $R_1=R_2=R_3=H$
(XI) $R_1=R_3=H, \quad R_2=OCH_3$
(XII) $R_1=R_2=OCH_3, R_3=H$
(XIII) $R_1=R_2=R_3=OCH_3$

Experimental*2

6-Hydroxy-2, ω-dimethoxy-3, 4-methylenedioxyacetophenone (IV).—A mixture of 3-methoxy-4, 5-methylenedioxyphenol (III) (790 mg.)5), methoxyacetonitrile (0.4 g.) and anhydrous zinc chloride (0.7 g.) in anhydrous ether (40 ml.) was saturated with dried hydrogen chloride at 0°C and allowed to stand overnight. The ethereal solution was decanted from the oily layer of ketimine hydrochloride, which had separated. The oily layer was washed twice with dry ether and heated on a steam bath with water (40 ml.) for 30 min. After cooling and standing, the product was collected and recrystallized from ethanol giving IV (m. p., 140～142°C) (reported m. p., 142～144°C2)) (golden yellow prisms), which showed a dark green ferric chloride reaction in ethanol; yield, 460 mg.

IR 1640～1606 (broad) (C=O), 1046 (=C-O-C), 930 (O-CH_2-O) cm^{-1}.

Found: C, 55.15; H, 5.13. Calcd. for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04%.

Meliternatin (3,5-Dimethoxy-6,7;3′,4′-bismethylenedioxyflavone) (II).—Ketone IV (240 mg.), piperonylic anhydride (780 mg.) and potassium piperonylate (300 mg.) were ground together and heated at 170～180°C under reduced pressure for 3.5 hr. The reaction mixture was then ground and boiled with 10% aqueous alcoholic (1:9) potassium hydroxide (20 ml.) for 7 min. After the removal of the solvent in vacuo, water (10 ml.) was added to the pasty mass. The precipitated solid was collected, washed with water, and recrystallized from ethanol, giving II (m. p., 196～197°C) (colorless needles), which gave a negative ferric chloride reaction in ethanol; yield, 120 mg. The melting point was undepressed on admixture with natural meliternatin kindly supplied by Dr. Cebalo.

IR 1640 (C=O), 1033 (=C-O-C), 921 (O-CH_2-O) cm^{-1}. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ ($\varepsilon \times 10^{-4}$); 248 (1.86), 270*3 (1.31), 337 (2.73).

Found: C, 61.98; H, 3.90. Calcd. for $C_{19}H_{14}O_8$: C, 61.62; H, 3.81%.

According to the method of Briggs and Locker4), II was demethylated with aluminum chloride to the 5-demethyl derivative VIII (m. p., 256～257°C) (reported m. p., 258～258.5°C3)) (slender yellow needles). IR 1678 (C=O), 1026 (=C-O-C), 929 919 (O-CH_2-O) cm^{-1}.

Found: C, 60.42; H, 3.50. Calcd. for $C_{18}H_{12}O_8$: C, 60.68; H, 3.40%.

With acetic anhydride and pyridine, VIII gave the acetate IX (m. p., 205～206°C) (reported m. p., 208.5～210°C4)) (pale yellow needles).

Found: C, 60.33; H, 3.76. Calcd. for $C_{20}H_{14}O_9$: C, 60.30; H, 3.56%.

3, 5-Dimethoxy-6, 7-methylenedioxyflavone (X).—From ketone IV (360 mg.), benzoic anhydride (700 mg.) and potassium benzoate (400 mg.), synthesis was carried out by a method similar to that used for II. Recrystallization from ethanol gave X (m. p. 192.5～193.5°C) (colorless needles); yield, 180 mg. IR 1624 (C=O), 1013 (=C-O-C), 920 (O-CH_2O) cm^{-1}. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ ($\varepsilon \times 10^{-4}$); 251*3 (1.63), 268.5 (1.99), 314 (1.98).

Found: C, 66.06; H, 4.36. Calcd. for $C_{18}H_{14}O_6$: C, 66.25; H, 4.32%.

3, 5, 4′ - Trimethoxy - 6, 7 - methylenedioxyflavone (XI).—Ketone IV (360 mg.), anisic anhydride (860 mg.) and potassium anisate (430 mg.) were treated with the same procedure as has been described for II. Recrystallization from ethanol gave XI (m. p., 184～185°C) (colorless needles); yield, 150 mg. IR 1638 (C=O), 1034 (=C-O-C), 925 (O-CH_2-O) cm^{-1}. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ ($\varepsilon \times 10^{-4}$); 272 (1.70), 328 (2.85).

Found: C, 64.04; H, 4.57. Calcd. for $C_{19}H_{16}O_7$: C, 64.04; H, 4.53%.

[*2] All melting points are uncocrrected; the infrared spectra were measured in Nujol.

[*3] Inflection point.

3, 5, 3′, 4′ - Tetramethoxy - 6, 7 - methylenedioxyflavone (XII). — Ketone IV (360 mg.), veratric anhydride (1.00 g.) and potassium veratrate (500 mg.) were treated with the above method. Recrystallization from ethanol gave XII (m. p.. 172~173°C (dried at 100°C)) (pale yellow needles); yield, 110 mg. IR 1621 (C=O), 1016 (=C-O-C), 930 cm^{-1} (O-CH$_2$-O). UV λ_{max}^{EtOH} mμ ($\varepsilon \times 10^{-4}$); 247 (1.87), 269*3 (1.48), 335 (2.69).

Found: C, 62.03; H, 4.69. Calcd. for $C_{20}H_{18}O_8$: C, 62.17; H, 4.70%.

3, 5, 3′, 4′, 5′-Pentamethoxy - 6, 7-methylenedioxyflavone (XIII).—Ketone IV (360 mg.) trimethylgallic anhydride (1.20 g.) and potassium trimethylgallate (600 mg.) were treated with the above method. Recrystallization from acetone gave XIII (m. p., 226~227°C) (colorless needles); yield, 150 mg. IR 1635 (C=O), 1018 (=C-O-C), 925 (O-CH$_2$-O) cm^{-1}. UV λ_{max}^{EtOH} mμ ($\varepsilon \times 10^{-4}$); 244 (1.57), 275 (1.37).

Found: C, 60.42; H, 4.95. Calcd. for $C_{21}H_{20}O_9$: C, 60.57; H, 4.84%.

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