Synthetic Studies of the Flavone Derivatives. III.[1] *The Synthesis of 3, 7-Dimethoxy-5, 6 ; 3′, 4′-bismethylenedioxyflavone, an Isomer of Meliternatin*

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In a previous paper,[1] meliternatin (I)' which had been isolated from the bark of *Melicope ternata* by Briggs and Locker,[2] was synthesized. In this case, I was obtained from a ketone which had been prepared with the Hoesch condensation of 3-methoxy-4, 5-methylenedioxyphenol and methoxyacetonitrile. The structure of the ketone was expected to be either 2-hydroxy-6, ω-dimethoxy-4, 5-methylenedioxyacetophenone (II) or 2-hydroxy-4, ω-dimethoxy-5, 6-methylenedioxyacetophenone (III). According to the Allan and Robinson method, a flavone was prepared with piperonylic anhydride from the ketone. If the structure of the ketone is II, the flavone must 3, 5-dimethoxy-6, 7 ; 3′, 4′-bismethylenedioxyflavone (I), which has been proposed by Briggs et al[3] as the structure of meliternatin. An unambiguous synthesis of 3, 7-dimethoxy-5, 6 ; 3′, 4′-bismethylenedioxyflavone (IV) must be made in order to settle this question. In the present paper, therefore, the synthesis of IV is described.

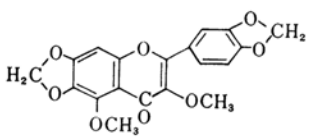
The treatment of 6-hydroxy-3, 5, 7-trimethoxy-3′, 4′-methylenedioxyflavone (V)[4] with anhydrous aluminum chloride afforded a demethyl compound, which gave a dark green color ferric

1) K. Fukui and T. Matsumoto, This Bulletin, **36**, 806 (1963).
2) L. H. Briggs and R. H. Locker, *J. Chem. Soc.*, **1949**, 2157.

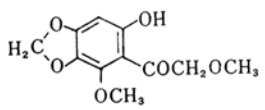
chloride reaction and a diacetate. It is well known that the demethylation of flavonols under the above-mentioned condition occurs at the 5-position[3-7] or occasionally at the 3-position.[3] Therefore, this demethyl compound should be either 5, 6-dihydroxy-3, 7-dimethoxy-3' 4'-methylenedioxyflavone (VI) or 3, 6-dihydroxy-5, 7-dimethoxy-3', 4'-methylenedioxyflavone (VII). As the compound was methylated with diazomethane to yield melisimplin (VIII; 5-hydroxy-3, 6, 7-trimethoxy-3', 4'-methylenedioxyflavone),[4,8,9] it is clear that the demethyl compound has one hydroxy group at the 5-position which is not methylated with diazomethane. On the basis of this result, VI is postulated as its structure.

VI has previously been prepared;[9] our product differs in melting point from that previously reported, but the color reaction with ferric chloride, the elementary analysis and the infrared spectrum (hydroxy bands, 3615 and 3483; carbonyl band, 1659; methylenedioxy band, 926 cm^{-1}) all confirm our assignment of structure to the material. Therefore, the preparation of VI from 2, 5-dihydroxy-4, ω-dimethoxyacetophenone (IX) via the intermediates, 6-hydroxy-3, 7-dimethoxy-3', 4'-methylenedioxyflavone (X) and 5-formyl-6-hydroxy-3, 7-dimethoxy-3', 4'-methylenedioxyflavone (XI), according to the published procedure,[9] was reexamined. The VI obtained was identified with the above demethyl compound by a mixed melting point determination and by an infrared spectral comparison. The melting points of some compounds (VI, X and XI) differed from those previously reported,[9] as is shown in the Experimental section.

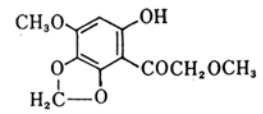
The methylenation of VI with methylene iodide afforded 3, 7-dimethoxy-5, 6; 3', 4'-bismethylenedioxyflavone (IV). IV did not agree



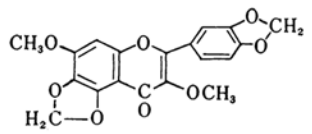
(I)



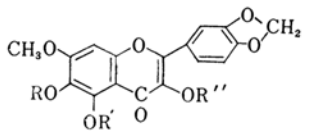
(II)



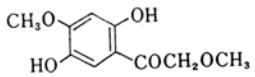
(III)



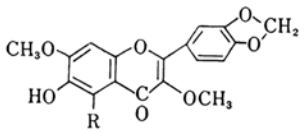
(IV)



(V) R=H R'=R''=CH_3
(VI) R=R'=H R''=CH_3
(VII) R=R''=H R'=CH_3
(VIII) R'=H R=R''=CH_3



(IX)



(X) R=H
(XI) R=CHO

with meliternatin in its properties. The structure of meliternatin has, therefore, been established as 3, 5-dimethoxy-6, 7; 3', 4'bismethylenedioxyflavone (I).[1,2]

Experimental*

2,5-Dihydroxy-4, ω-dimethoxyacetophenone (IX).—This ketone was prepared by a method reported in the literature;[10] m. p. 148~149°C (reported m. p. 145~146°C[10]).

6-Hydroxy-3, 7-dimethoxy-3', 4'-methylenedioxyflavone (X).—From the ketone IX, X was obtained in the form of colorless needles according to a procedure previously reported[9]; m. p. 253~254°C (reported m. p. 213~214°C[9]). X gave a negative ferric chloride reaction in ethanol. IR: 3384(OH), 1624(C=O), 1037(=C-O-C), 929 (O-CH_2-O) cm^{-1}.

Found: C, 62.94; H, 4.14. Calcd. for $C_{15}H_{14}O_7$: C, 63.16; H, 4.12%.

The acetylation of X gave the acetate (m. p. 201~202°C, reported m. p. 202°C[9]) in the form of colorless rectangular plates. IR: 1757(OAc), 1621 (C=O), 1037(=C-O-C), 934 (O-CH_2-O) cm^{-1}.

3) L. H. Briggs and R. H. Locker, ibid., **1951**, 3131.
4) L. H. Briggs and R. H. Locker, ibid., **1950**, 2379.
5) W. Baker, ibid., **1939**, 961.
6) W. Baker, N. C. Brown and J. A. Scott, ibid., **1939**, 1925.
7) W. Baker and W. H. C. Simmonds, ibid., **1940**, 1373.
8) L. H. Briggs and R. H. Locker, ibid., **1950**, 2376.
9) A. C. Jain, T. R. Seshadri and K. R. Sreenivasan, ibid., **1955**, 3908.

* All melting points are uncorrected; the infrared spectra were measured in Nujol.
10) L. R. Row and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **21A**, 155 (1945).

Found : C, 62.57 ; H, 4.26. Calcd. for $C_{20}H_{16}O_8$: C, 62.50 ; H, 4.20%.

5-Formyl-6-hydroxy-3, 7-dimethoxy-3', 4'-methylenedioxyflavone (XI).—From the flavone X, XI was obtained in the form of yellow needles according to a procedure previously reported ;[9] m. p. 262～263°C(decomp.) (reported m. p. 248～249°C[9]). XI gave a brown ferric chloride reaction in ethanol. IR : 1647, 1619(C=O), 1038(=C-O-C), 929 (O-CH_2-O) cm^{-1}.

Found : C, 61.39 ; H, 3.99. Calcd. for $C_{19}H_{14}O_8$: C, 61.62 ; H, 3.81%.

5, 6-Dihydroxy-3, 7-dimethoxy-3', 4'-methylenedioxyflavone (VI).—*a) From 6-Hydroxy-3, 5, 7-trimethoxy-3', 4'-methylenedioxyflavone (V).*—A solution of V[4] (1.0 g.) and anhydrous aluminum chloride (13.5 g.) in anhydrous ether (60 ml.) was refluxed for 10 hr. After the reaction mixture had been poured into ice-water and kept for several hours at room temperature, the precipitate was collected and refluxed with a solution of acetic acid (55 ml.) and concentrated hydrochloric acid (30 ml.) for 20 min. The resulting precipitate was collected and recrystallized from ethanol to give VI in the form of yellow needles (m. p. 187～188°C) (reported m. p. 218～219°C[9]), which gave a dark green ferric chloride reaction in ethanol ; yield, 0.4 g. IR : 3615, 3483(OH), 1659(C=O), 1035(=C-O-C), 926 (O-CH_2-O) cm^{-1}.

Found : C, 60.34 ; H, 4.03. Calcd. for $C_{18}H_{14}O_8$: C, 60.34 ; H, 3.94.

The acetylation of VI gave the acetate (m. p. 231～233°C) (reported m. p. 226～227°C[9]), which gave a negative ferric chloride reaction in ethanol. IR : 1771(OAc), 1631(C=O), 1032(=C-O-C), 925 (O-CH_2-O) cm^{-1}.

Found : C, 59.76 ; H, 4.16. Calcd. for $C_{22}H_{18}O_{10}$: C, 59.73 ; H, 4.10%.

b) From 5-Formyl-6-hydroxy-3, 7-dimethoxy-3', 4'-methylenedioxyflavone (XI).—From the aldehyde XI, VI was prepared in the form of yellow needles (m. p. 187～188°C) according to a procedure previously reported.[9] This substance was identified with a specimen, prepared by the above-mentioned method a), by a mixed melting point determination and by an infrared spectral comparison.

Milisimplin (VIII).—The treatment of VI (60 mg.) in acetone (20 ml.) with an ethereal solution of diazomethane gave VIII as yellow needles (m. p. 233～234°C) (reported m. p. 234～235°C[9] and 235～236°C[4,8]) from ethyl acetate ; yield, 20 mg. This substance gave a green ferric chloride reaction in ethanol. IR : 1667(C=O), 1037(=C-O-C), 925 (O-CH_2-O) cm^{-1}.

Found : C, 61.08 ; H, 4.36. Calcd. for $C_{19}H_{16}O_8$: C, 61.29 ; H, 4.33%.

3, 7-Dimethoxy-5, 6 ; 3', 4'-bismethylenedioxyflavone (IV).—A mixture of VI (350 mg.), methylene iodide (1.1 g.) and anhydrous potassium carbonate (4.0 g.) in anhydrous ethyl methyl ketone (50 ml.) was refluxed for 26 hr. on a steam bath. The reaction mixture was filtered from the precipitates, and ethyl acetate (70 ml.) was added to the filtrate. The solution was washed with a 5% aqueous sodium hydroxide solution and then with water. The solvent was distilled off, and the residue was recrystallized from acetone and then from aqueous acetic acid to give IV in the form of pale yellow needles (m. p. 233～234°C), which gave a negative ferric chloride reaction in ethanol : yield, 60 mg. IR : 1650～1643 (C=O), 1041 (=C-O-C), 930 (O-CH_2-O) cm^{-1}.

Found : C, 61.33 ; H, 3.99. Calcd. for $C_{19}H_{14}O_8$: C, 61.62 ; H, 3.81%.

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