Synthetic Studies of the Flavone Derivatives. I. Syntheses of Some 3-Methoxy-6, 7-methylenedioxyflavones

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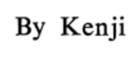
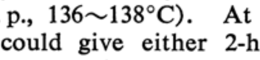
There have been only a few investigations of flavones which possess a methylenedioxy group in the chromone nucleus. Meliternatin (3, 5-dimethoxy-6, 7; 3′, 4′-bismethylenedioxy-flavone) (I) and wharangin have been isolated from the bark of *Melicope ternata*[1] and *M. mantelli*[2]. 3, 4′-Dihydroxy-5-methoxy-6, 7-methylenedioxyflavone have been obtained from naturally occurring vogoletin (3, 6, 7, 4′-tetrahydroxy-5-methoxyflavone) (II)[3]. 7, 8-Methylenedioxyflavone, 6, 7-methylenedioxyflavone and 3′, 4′-dimethoxy-6,7-methylenedioxyflavone have been synthesized[4-5]. However, 3-methoxy-6, 7-methylenedioxyflavone derivatives and 3, 5-dimethoxy-6, 7-methylenedioxyflavone derivatives have not yet been synthesized.



(I)



(II)

In the present paper, the syntheses of 3-methoxy-6, 7-methylenedioxyflavone (VIII) and its analogues are described. The Hoesch reaction of sesamol (3, 4-methylenedioxyphenol) and methoxyacetonitrile yielded a ketone, $C_{10}H_{10}O_5$ (m. p., 136∼138°C). At this stage, the reaction could give either 2-hydroxy-4, 5-methylenedioxy-ω-methoxyacetophenone (III) or 2-hydroxy-5, 6-methylenedioxy-ω-methoxyacetophenone (VI). The oxidation of the ω-methoxyacetophenone to a benzoic acid derivative was used to settle this question. The ketone was methylated to monomethyl ether (m. p., 99∼100°C), which was then converted into 2-methoxy-4, 5-methylenedioxybenzoic acid (VII)[6-7] by potassium permanganate oxidation. The acid VII was identified by direct comparison with an authentic sample. From this fact, the structure of 2-hydroxy-4, 5-methylenedioxy-ω-methoxyacetophenone (III) was established for the ketone.

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1) L. H. Briggs and R. H. Locker, *J. Chem. Soc.*, **1949**, 2157; **1951**, 3131.

2) R. C. Cambie, ibid., **1960**, 2376.

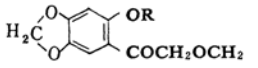
3) S. Rangaswami and K. H. Rao, *Proc. Indian Acad. Sci.*, **49A**, 241 (1959).

4) K. Viswesware Rao and N. Viswanadham, ibid., **29A**, 218 (1949).

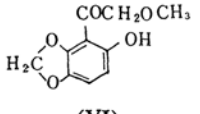
5) A. Romeo and G. Bargellini, *Ann. Chim.* (*Rome*), **42**, 361 (1952): *Chem. Abstr.*, **47**, 10529e (1953).

6) R. T. Arnold and N. Bortnick, *J. Am. Chem. Soc.*, **67**, 1798 (1945).

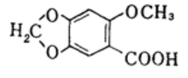
7) K. N. Campbell, P. F. Hopper and B. K. Campbell, *J. Org. Chem.*, **16**, 1741 (1951).



(III) R=H (IV) R=Ac
(V) R=CH_3



(VI)



(VII)

According to Allan and Robinson's flavone synthesis[8], the condensation of the ketone III with benzoic anhydride in the presence of potassium benzoate, followed by treatment with alcoholic potassium hydroxide, afforded 3-methoxy-6, 7-methylenedioxyflavone (VIII) (m. p., 180.5~182.5°C). By a similar reaction, 3, 4'-dimethoxy-6, 7-methylenedioxyflavone (IX) (m. p., 238.5~239°C), 3, 3', 4'-trimethoxy-6, 7-methylenedioxyflavone (X) (m. p., 171~172°C), 3-methoxy-6, 7 ; 3', 4'-bismethylenedioxyflavone (XI) (m. p., 247~248°C), 3, 3', 4', 5'-tetramethoxy-6,7-methylenedioxyflavone (XII) (m. p., 224~225°C) and 3-methoxy-3', 4'-dibenzyloxy-6, 7-methylenedioxyflavone (XIII) (m. p., 123.5~125°C) were obtained. These compounds gave a negative ferric reaction and were soluble in concentrated sulfuric acid to a yellow solution. The debenzylation of XIII with hydrogen afforded 3-methoxy-3', 4'-dihydroxy-6, 7-methylenedioxy-flavone (XIV) (m. p., 293~295°C) (decomp.), which was then converted into 3, 3', 4'-trimethoxy-6, 7-methylenedioxyflavone (X) by methylation. The ultraviolet spectra of these compounds are shown in Figs. 1 and 2. In most cases there are two peaks, ca. 245 and ca. 335 mμ, but the absorption maxima of VIII and IX is observed ca. 255 mμ in addition to these two peaks.

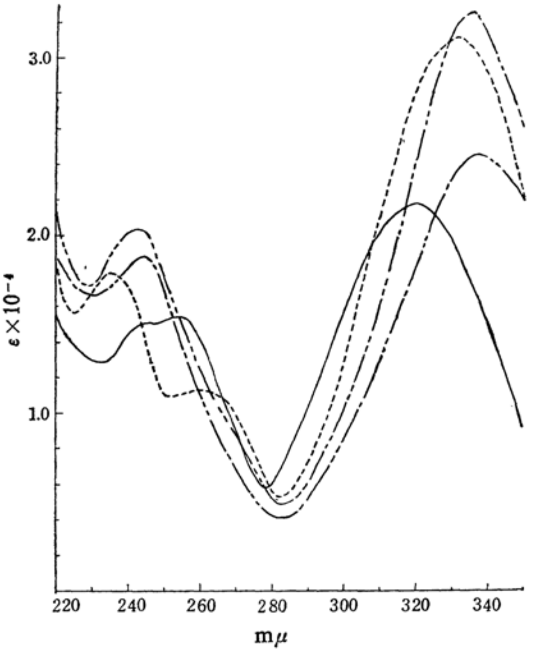


Fig. 1. Ultraviolet spectra of VIII (——), IX (----), X (–––) and XI (–·–·–) in ethanol.

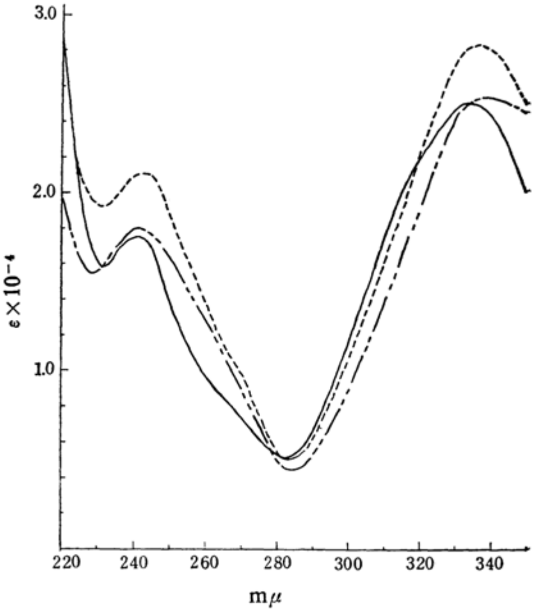
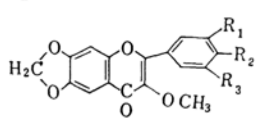


Fig. 2. Ultraviolet spectra of XII (——), XIII (----) and XIV (–––) in ethanol.



(VIII) $R_1=R_2=R_3=H$
(IX) $R_1=R_3=H$ $R_2=OCH_3$
(X) $R_1=R_2=OCH_3$ $R_3=H$
(XI) R_1, R_2=O-CH_2-O $R_3=H$
(XII) $R_1=R_2=R_3=OCH_3$
(XIII) $R_1=R_2=OCH_2C_6H_5$ $R_3=H$
(XIV) $R_1=R_2=OH$ $R_3=H$

Experimental*

2-Hydroxy-4, 5-methylenedioxy-ω-methoxyacetophenone (III).—A mixture of sesamol (3.1 g.),

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

* All melting points were uncorrected. The ultraviolet spectra were determined with a Shimadzu model SV-50A spectrophotometer, while the infrared spectra were determined with a Hilger model 800 spectrophotometer.

which had been obtained from piperonal by Baeyer-Villiger oxidation[9], methoxyacetonitrile (1.9 g.) and anhydrous zinc chloride (0.6 g.) in anhydrous ether (20 ml.) was saturated with dried hydrogen chloride in an ice-bath and allowed to stand overnight. The ether solution was decanted from the ketimine hydrochloride-zinc chloride complex which had separated. The residue was washed twice with dry ether and then heated on a steam bath with water (20 ml.) for 30 min. After this had cooled and stood, the precipitated ketone was collected. Recrystallization from ethanol gave colorless needles (m. p., 136∼138°C) which gave a dark blue color with ferric chloride; yield, 1.2 g. (26%). IR 1636 (C=O), 1025 (=C-O-C), 915 cm^{-1} (O-CH$_2$-O) (Nujol).

Found: C, 57.17; H, 4.84. Calcd. for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80%.

III was acetylated with acetic anhydride and pyridine. The acetate IV formed colorless needles from aqueous methanol (m. p., 87∼89°C) which gave a negative ferric reaction. IR 1753, 1675 (C=O), 1028 (=C-O-C), 925 cm^{-1} (O-CH$_2$-O) (Nujol).

Found: C, 57.08; H, 4.79. Calcd. for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80%.

2-Methoxy-4, 5-methylenedioxy-ω-methoxyacetophenone (V).—The ketone III (1.0 g.), dissolved in acetone (40 ml.), was heated under reflux with methyl iodide (1.0 g.) and anhydrous potassium carbonate (3.0 g.) for 6 hr. on a steam bath. The solution was then filtered and evaporated to dryness. The residue was collected, washed with a dilute alkaline solution and recrystallized from aqueous ethanol to give colorless needles (m. p., 99∼100°C) which gave a negative ferric reaction; yield, 0.45 g. (42%). IR 1663 (C=O), 1030 (=C-O-C), 915 cm^{-1} (O-CH$_2$-O) (Nujol).

Found: C, 58.65; H, 5.36. Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40%.

2-Methoxy-4,5-methylenedioxybenzoic Acid (VII).—A suspension of 2-methoxy-4,5-methylenedioxy-ω-methoxyacetophenone (V) (0.4 g.) in water (15 ml.) was treated under reflux with small portions of a 2% potassium permanganate solution until the consumption of the oxidant subsided. After the excess permanganate had been reduced with sodium bisulfite, the precipitate was separated by filtration and washed with hot water. The combined filtrates were acidified with dilute sulfuric acid and extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was recrystallized from aqueous methanol to give pale yellow needles (m. p., 150∼151°C) (reported 148∼149°C[6] and 147∼147.5°C[7]); yield, 0.1 g. Its identity with an authentic sample of 2-methoxy-4,5-methylenedioxybenzoic acid (VII) was established by mixed melting point determination and infrared spectral comparison. IR 1710, 1625 (C=O), 1026 (=C-O-C), 920 cm^{-1} (O-CH$_2$-O) (Nujol).

Found: C, 55.31; H, 4.10. Calcd. for $C_9H_8O_5$: C, 55.10; H, 4.11%.

3-Methoxy-6, 7-methylenedioxyflavone (VIII).—The ketone III (0.7 g.), benzoic anhydride (1.5 g.) and potassium benzoate (0.8 g.) were ground together and heated at 170∼180°C under reduced pressure for 3 hr. The reaction mixture was ground and boiled with 8% aqueous alcoholic (1 : 4) potassium hydroxide (25 ml.) for 15 min. After the removal of the solvent in vacuo, water (60 ml.) was added to the pasty mass. The precipitated solid was collected, washed with water and recrystallized from ethanol to give colorless needles m. p., 180.5∼182.5°C) which gave a negative ferric reaction and a yellow colored solution with concentrated sulfuric acid; yield, 0.35 g. (35%). IR 1618 (C=O), 1023 (=C-O-C), 928 cm^{-1} (O-CH$_2$-O) (Nujol). UV λ_{max}^{EtOH} mμ ($\varepsilon\times10^{-4}$); 247** (1.51), 254 (1.55), 320 (2.18).

Found: C, 68.95; H, 4.07. Calcd. for $C_{17}H_{12}O_5$: C, 68.91; H, 4.08%.

3, 4′-Dimethoxy-6, 7-methylenedioxyflavone (IX).—A mixture of the ketone III (1.0 g.), anisic anhydride (2.8 g.) and potassium anisate (1.4 g.) was treated in a way similar to that used for VIII. Yield, 0.8 g. of colorless needles (m. p., 238.5∼239°C) from acetic acid and then from ethyl acetate. This substance gave a negative ferric reaction and a yellow colored solution with concentrated sulfuric acid. IR 1629 (C=O), 1025 (=C-O-C), 928 cm^{-1} (O-CH$_2$-O) (Nujol). UV λ_{max}^{EtOH} mμ ($\varepsilon\times10^{-4}$); 235 (1.80), 260 (1.14), 332 (3.12).

Found: C, 66.04; H, 4.15. Calcd. for $C_{18}H_{14}O_6$: C, 66.25; H, 4.32%.

3, 3′, 4′-Trimethoxy-6, 7-methylenedioxyflavone (X).—From the ketone III (0.5 g.), veratric anhydride (1.7 g.) and potassium veratrate (0.8 g.), synthesis was carried out by a method similar to that used for VIII. Yield, 0.35 g. of pale yellow needles (m. p., 171∼172°C) from ethanol. This substance gave a negative ferric reaction and showed a yellow color in a concentrated sulfuric acid solution. IR 1630 (C=O), 1020 (=C-O-C), 923 cm^{-1} (O-CH$_2$-O) (Nujol). UV λ_{max}^{EtOH} mμ ($\varepsilon\times10^{-4}$); 243 (2.05), 336 (3.27).

Found: C, 64.31; H, 4.69. Calcd. for $C_{19}H_{16}O_7$: C, 64.04; H, 4.53%.

3-Methoxy-6, 7; 3′, 4′-bismethylenedioxyflavone (XI).—From the ketone III (1.0 g.), piperonylic anhydride (3.9 g.) and potassium piperonylate (1.5 g.), synthesis was carried out by a method similar to that used for VIII. Yield, 0.56 g. of colorless needles (m. p., 247∼248°C) from acetic acid. This substance gave a negative ferric reaction and showed a yellow color in a concentrated sulfuric acid solution. IR 1635 (C=O), 1025 (=C-O-C), 925 cm^{-1} (O-CH$_2$-O) (Nujol). UV λ_{max}^{EtOH} mμ ($\varepsilon\times10^{-4}$); 244.5 (1.89), 337 (2.46).

Found: C, 63.54; H, 3.67. Calcd. for $C_{18}H_{12}O_7$: C, 63.53; H, 3.55%.

3, 3′, 4′, 5′-Tetramethoxy-6, 7-methylenedioxyflavone (XII).—From the ketone (III) (1.0 g.), trimethylgallic anhydride[10] (4.0 g.) and potassium trimethylgallate (1.9 g.), synthesis was carried out by a method similar to that used for VIII. Yield,

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[9] J. Böesken, W. D. Coden and C. J. Kip, *Rec. trav. Chim.*, **55**, 815 (1936): *Chem. Abstr.*, **31**, 1017 (1937).

** Inflexion point.

[10] J. Kalff and R. Robinson, *J. Chem Soc.*, **1925**, 182.

[11] M. Shimizu and G. Ohta, *J. Pharm. Soc. Japan*, **71**, 1485 (1951).

0.8 g. of pale yellow needles (m. p., 224~225°C) from acetone. This substance gave a negative ferric reaction and showed a yellow color in a concentrated sulfuric acid solution. IR 1628 (C=O), 1023 (=C-O-C), 930 cm^{-1} (O-CH$_2$-O) (Nujol). UV λ_{max}^{EtOH} mμ ($\varepsilon\times10^{-4}$) ; 242 (1.76), 335 (2.50).

Found : C, 61.98 ; H, 4.61. Calcd. for $C_{20}H_{18}O_8$; C, 62.17 ; H, 4.70%.

3-Methoxy-3′, 4′-dibenzyloxy-6,7-methylenedioxyflavone (**XIII**). — From the ketone III (1.0 g.), 3, 4-dibenzyloxybenzoic anhydride[11] (6.5 g.) and potassium 3, 4-dibenzyloxybenzoate (2.8 g.), synthesis was carried out by a method similar to that used for VIII. Yield, 1.0 g. of pale yellow needles (m. p., 123.5~125°C) from aqueous acetone and then from ethanol. This substance gave a negative ferric reaction and showed a yellow color in a concentrated sulfuric acid solution. IR 1610 (C=O), 1035 (=C-O-C), 943 cm^{-1} (O-CH$_2$-O) (Nujol). UV λ_{max}^{EtOH} mμ ($\varepsilon\times10^{-4}$) ; 243 (2.11), 337 (2.83).

Found : C, 73.16 ; H, 4.83. Calcd. for $C_{31}H_{24}O_7$: C, 73.22 ; H, 4.76%.

3 - Methoxy-3′, 4′-dihydroxy-6, 7-methylenedioxyflavone (**XIV**). — A solution of 3-methoxy-3′, 4′-dibenzyloxy-6, 7-methylenedioxyflavone (XIII) (600 mg.) in acetic acid (30 ml.) was submitted to catalytic reduction in the presence of a 10% Pd-C catalyst (1.0 g.) at room temperature. The precipitate was collected and extracted with dilute aqueous sodium hydroxide. After the alkaline extract had been acidified with dilute sulfuric acid, the precipitate was collected, washed with water and recrystallized from ethanol to give yellow needles (m. p., 293~295°C) (decomp.) which gave a green color with ferric chloride ; yield, 170 mg. IR 1630 (C=O), 1028 (=C-O-C), 928 cm^{-1} (O-CH$_2$-O) (Nujol). UV λ_{max}^{EtOH} mμ ($\varepsilon\times10^{-4}$) ; 242 (1.80), 338 (2.53).

Found : C, 61.99 ; H, 3.85. Calcd. for $C_{17}H_{12}O_7$: C, 62.20 ; H, 3.68%.

A solution of 3-methoxy-3′, 4′-dihydroxy-6, 7-methylenedioxyflavone (XIV) (100 mg.) in acetone (50 ml.) was heated under reflux with methyl iodide (0.3 g.) and anhydrous potassium carbonate (0.5 g.) for 5 hr. The acetone solution was filtered and evaporated to dryness. The residue was washed with water and recrystallized from ethanol to give colorless needles (m. p., 171~172°C, undepressed on admixture with X).

Found : C, 64.00 ; H, 4.53. Calcd. for $C_{19}H_{16}O_7$: C, 64.04 ; H, 4.53%.

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