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Synthetic Studies of the Flavone Derivatives. V.[1] The Use of DDQ in the Dehydrogenation of Flavanones. (I).[2]

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A novel procedure is described for the expedient preparation of flavone. Application of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in boiling dioxane as dehydrogenating agent to the several flavanones, *e.g.* 5,6,7-trimethoxy-, 4′,5,7-trimethoxy-, 4′,5,6,7-tetramethoxy-, 4′,5,6,7,8-pentamethoxy-, 4′-benzyloxy-5,6,7-trimethoxy-, 3′,4′,5,6,7-pentamethoxy-, 4′-benzyloxy-3′,5,6,7-tetramethoxy- and 3′,4′-dibenzyloxy-5,6,7-trimethoxy-flavanone, furnishes a convenient and appropriate method for the preparation of the corresponding flavones, in excellent yields or without any contamination of undesired products.

Keywords——dehydrogenation (oxidation); 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ); 5,6,7-trimethoxyflavone; 4′,5,7-trimethoxyflavone; 4′,5,6,7-tetramethoxyflavone; 4′,5,6,7,8-pentamethoxyflavone; 4′-fenzyloxy-5,6,7-trimethoxyflavone; 3′,4′,5,6,7-pentamethoxyflavone; 4′-benzyloxy-3′,5,6,7-tetramethoxyflavone; 3′4′-dibenzyloxy-5,6,7-trimethoxy-flavone.

Several procedures have been reported on the conversion of flavanone to flavone through dehydrogenation: One involves heating with selenium dioxide in amylalcohol to bring about the dehydrogenation,[4] another employs bromination at the C_3 of the flavanone, with bromine or N-bromosuccinimide), followed by dehydrobromination (with alcoholic potassium hydroxide or some organic bases),[5] or the alternative is the use of iodine in the presence of some weak bases.[6] Despite well-developed and versatile methodology for dehydrogenation, each of these procedures suffers some disadvantages, a troublesome of the reaction mixture, a prolonged reaction time, or a relatively moderate yield, and most efforts made for the improvement have remained as yet unexploited.

The novel procedure described in this paper for the conversion of flavanone to flavone, uses 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[7] in boiling dioxane to perform an expedient preparation of the several flavones in excellent yield, or without any contamination of undesired products. DDQ has been widely employed for the selective dehydrogenation in the area of 3-keto-steroids,[8] and application of this reagent for the dehydrogenation of some flavanones would be reasonably expected from an aspect of similarity between the partial structures of these compounds.

In fact, an attempted dehydrogenation of 5,6,7-trimethoxyflavanone (I),[9] using DDQ

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[4] S. Matsuura and T. Kunii, *Yakugaku Zasshi*, **94**, 645 (1974).

[5] K. Nakazawa and S. Matsuura, *Yakugaku Zasshi*, **75**, 467 (1955).

[6] N. Narasimhachari and T.R. Seshadri, *Proc. Indian Acad. Sci.*, **30A**, 151 (1949).

[7] J. Tiele and F. Gunther, *Ann.*, **349**, 45 (1906).

[8] M. Fieser and L. Fieser, "Reagents for Organic Synthesis," Vol. 1 John Wiley and Sons, Inc., New York, 1967, p. 216.

[9] A. Oliverio and G. Bargellini, *Gazz. Chim. ital.*, **78**, 372 (1948); V.D Nageswara Sastri and T.H. Seshadri, *Proc. Indian Acad. Sci.*, **23A**, 262 (1946).

in boiling benzene (a general experimental condition in the steroid chemistry), proceeded to convert the material completely to the corresponding flavone, but required a very prolonged reaction time (*ca.* 60 hours). Replacement of benzene with dioxane reduced the reaction time markedly (the dehydrogenation of I was completed within 12 hours), and an experimental condition, heating the flavanone (1 mol) with DDQ (1.3 mol) in dry dioxane (40 l), was set up for the conversion of flavone. Under the reaction condition, the other polysubstituted flavanones, such as 4′,5,7-trimethoxy-,[10] 4′,5,6,7-tetramethoxy-,[9] 4′,5,6,7,8-pentamethoxy-,[11] 4′-benzyloxy-5,6,7-trimethoxy-,[4] 3′,4′,5,6,7-pentamethoxy-,[9] 4′-benzyloxy-3′,5,6,7-tetramethoxy- and 3′,4′-dibenzyloxy-5,6,7-trimethoxy-flavanone, underwent smoothly the dehydrogenation to result in the formation of the corresponding flavones, with some advantages, excellence in quality and yield of the product, shortening the reaction time, or ease in the material treatment (Table I).

TABLE I. Oxidative Reaction Times of the Flavanones and mp of the Flavones

Flavanones		Reaction time (hr)	mp (°C) of flavones
5,6,7-OMe[9]	(I)	12	166[9]
4′,5,7-OMe[10]	(II)	5	157[10]
4′,5,6,7-OMe[9]	(III)	9	142[9]
4′,5,6,7,8-OMe[11]	(IV)	16	152[11]
4′-OBz-5,6,7-OMe[4]	(V)	5	154[4]
3′,4′,5,6,7-OMe[9]	(VI)	5	176[9]
4′-OBz-3′,5,6,7-OMe	(VII)	9	179[12]
3′,4′-OBz-5,6,7-OMe	(VIII)	6	122[12]

Bz=-CH$_2$-C$_6$H$_5$.

Experimental[13]

4′-Benzyloxy-3′,5,6,7-tetramethoxyflavanone (VII)——A mixture of 4-benzyloxy-2′-hydroxy-3,4′,5′,6′-tetramethoxychalcone[12] (1.35 g, 0.003 mol), 85% phosphoric acid (4 g) and ethanol (100 ml) was refluxed for 62 hr. After the mixture was allowed to stand overnight, precipitated orange needles (recovered chalcone) (0.52 g) were filtered off. The filtrate was concentrated *in vacuo*, poured into water (100 ml) and extracted with chloroform. The chloroform extract was concentrated and chromatographed on silica gel. At first, the starting material was recovered, 0.64 g (47.4%), mp 157° (from acetic acid). TLC: *Rf* 0.59 (n-C$_6$H$_{14}$: AcOEt=3: 2). Next, the flavanone (VII) was obtained as colorless, 0.67 g (50.0%), mp 125° (from benzene and n-hexane). Mg–HCl reaction: violet-red, TLC: *Rf* 0.36 (n-C$_6$H$_{14}$: AcOEt=3: 2). *Anal.* Calcd. for $C_{26}H_{26}O_7$: C, 69.32; H, 5.82. Found: C, 69.69; H, 5.83. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} 2920, 2810 (CH$_3$, CH$_2$), 1670 (C=O), 1602 (C=C), 1450 (C–H), 1260 (–C–O–C–). NMR (CDCl$_3$) δ: 2.83 (1H, d, J_{cis}=4.8 Hz, C$_3$–H), 2.91 (1H, d, J_{trans}=11.0 Hz, C$_3$–H), 3.85, 3.90 (3H each, s, OCH$_3$), 3.96 (6H, s, 2×OCH$_3$), 5.20 (2H, s, –OCH$_2$–Ar), 5.32 (1H, dd, J=11.0 Hz, 4.8 Hz, C$_2$–H), 6.38 (1H, s, C$_8$–H), 7.0 (1H, d, J=9.0 Hz, C$_5$′–H), 7.43 (2H, m, C$_2$′,$_6$′–H).

3′,4′-Dibenzyloxy-5,6,7-trimethoxyflavanone (VIII)——To a solution of 3,4-dibenzyloxy-2′-hydroxy-4′,5′,6′-trimethoxychalcone (1.83 g, 0.003 mol) in ethanol (100 ml) was added 85% phosphoric acid (8 g), and the mixture was refluxed for 60 hr. The reaction mixture was treated in the same way as above mentioned. At first, the starting material was recovered, 0.98 g (62.03%), mp 108° (from ethanol). TLC: *Rf* 0.25 (n-C$_6$H$_{14}$: AcOEt=3: 1). Next, the flavanone (VIII) was obtained as colorless needles, 0.47 g (29.4%), mp 126° (MeOH). TLC: *Rf* 0.25 (n-C$_6$H$_{14}$: AcOEt=3: 1). *Anal.* Calcd. for $C_{32}H_{30}O_7$: C, 72.99; H, 5.74. Found: C, 73.01; H, 5.69. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} 2930, 2850 (CH$_3$, CH$_2$), 1670 (C=O), 1602 (C=C), 1440 (C–H), 1264 (–C–O–C–).

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10) M. Berger and St. V. Kostanecki, *Chem. Ber.*, **38**, 931 (1905).

11) S. Matsuura, *Yakugaku Zasshi*, **77**, 328 (1957).

12) S. Matsuura, T. Kunii, and A. Matsuura, *Chem. Pharm. Bull.* (Tokyo), **21**, 2757 (1973).

13) All melting points were uncorrected. Melting points were determined with Buch Schmeltzpunkt Bestimmungsapparat. Infrared (IR) spectra were taken with a Nipponbunko IRA-1 Infrared Spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Hitachi Model R20B (tetramethylsilane as the internal standard, the chemical shifts are given in δ values). For analytical thin-layer chromatography (TLC) Silica gel G was used and spots were visualized spraying with 10% H$_2$SO$_4$ followed by heating. Column chromatography was carried out with the WAKOGEL C200.