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# Nobusuke Kawano, Hiroshi Miura, and Eiko Matsuishi: The Partial Demethylation of Flavones. I. Preparation of Genkwanin.

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It has been reported[1] that the 7-methoxyl group in isoflavones is fairly resistan to demethylation because the basicity of the oxygen atom in the 7-position is reduce in the conjugate acid as it is para to the carbonyl group and that chrysin dimethy ether treated similarly is completely demethylated to chrysin, illustrating the marke difference in stability of the 7-methoxyl group in flavones and isoflavones.[1a] In ou experiments on bisflavones we have encountered a fact that the 7-methoxyl group i these compounds is also considerably resistant to demethylation with hydrogen iodide.[*] As these bisflavones have no isoflavone nucleus the 7-position in flavones should b resistant to demethylation as well as in isoflavones. We report now the preparatio of genkwanin (I) by partial demethylation of apigenin trimethyl ether (II).

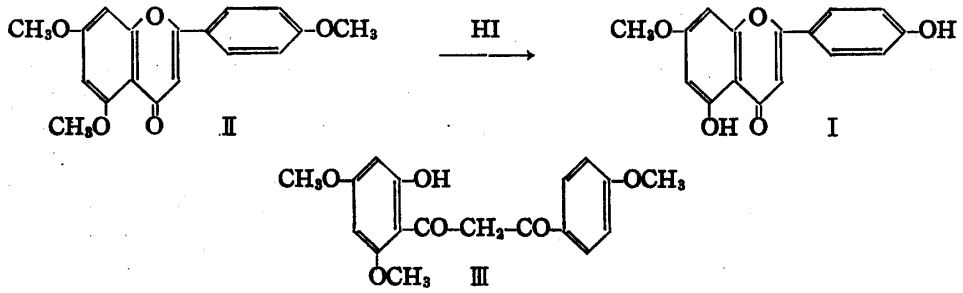


Table I. Reaction Conditions and Results of Demethylation[a]

| Experimental No. | | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Oil bath temp. (℃) | | 140 | 120 | 120 | 120 | 120 |
| Reaction time (hr.) | | 2 | 1 | 0.5 | 0.5 | 1 |
| $Ac_2O$ added (ml.) | | 1 | 1 | 1 | 2.5 | 2.5 |
| Phenol added (ml.) | | 1 | 1 | 1 | 0 | 0 |
| First crop[b] | (mg.) | 100 | 370 | 340 | 80 | 300 |
| | (m.p.) | 275~277° | 273~275° | 260~274° | 260~275° | 260~275° |
| Second crop[c] | A (mg.) | 550 | 380 | | | |
| | (m.p.) | 240~320° | 240~312° | | | |
| | B (mg.) | | | 190 | 140 | 150 |
| | (m.p.) | | | 230~260° | 245~265° | 240~270° |

*a*) 1 g. of apigenin trimethyl ether was demethylated with hydrogen iodide (15 ml.) in an oil bath. Melting points were uncorrected.
*b*) It was obtained from raw product by two time recrystallizations from ethanol and almost pure genkwanin by TLC but in No. 3, 4, and 5 contaminated with apigenin dimethyl ether.
*c*) It was obtained from the mother liquor separated from the first crop; A: a mixture of apigenin and genkwanin, apigenin is predominant, B: a mixture of genkwanin and apigenin dimethyl ether.

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*2 It will be reported later in detail but we obtained amentoflavone monomethyl ether from sciadopitysi (N. Kawano: This Bulletin, 7, 821 (1959)) and hinokiflavone monomethyl ether from hinokiflavon dimethyl ether (N. Kawano, H. Miura, A.C. Waiss, Jr.: Chem. & Ind.(London), 1964, 2020).

1) *a*) K. Aghoramurthy, N. Narasimhachari, T.R. Seshadri: Proc. Indian Acad. Sci., 33A, 257 (1951 *b*) N. Narasimhachari, T.R. Seshadri, S. Sethuraman: *Ibid.*, 36A, 194 (1952). *c*) N. Narasimhachar T.R. Seshadri: *Ibid.*, 37A, 531 (1953). *d*) W.D. Ollis: "The Chemistry of Flavonoid Compounds, edited by T.A. Geissman, 383 (1962). Pergamon Press, London.

Nakazawa noted[2] the formation of genkwanin as an intermediate in his synthesis of apigenin from the compound (Ⅲ) without the isolation of Ⅱ. This finding actually means the partial demethylation in flavones with hydrogen iodide but he did not realize it in any further studies. We treated apigenin trimethyl ether with hydrogen iodide under controlled conditions and obtained results shown in Table I. Reaction products were examined by thin-layer chromatography (TLC) as described in experimental part.

Genkwanin has been synthesized from apigenin 4′-benzyl ether[3] or apigenin 5,7-dimethyl ether[4] because of the difficulty of the partial methylation in the 7-position of apigenin. However, we are now able to get 7-methoxyl compound by partial demethylation. According to the results of Table I one hour heating at 120° seems to be the best condition to prepare genkwanin from apigenin trimethyl ether and to add phenol is recommended in this reaction. This reaction condition is almost similar to that in the case of isoflavones[1] but the yield is somewhat less than that in isoflavones.

## Experimental*3

**Genkwanin (I)**——A mixture of apigenin trimethyl ether (m.p. 153~155°, 1 g.), $Ac_2O$ (1 ml.), phenol (1 g.), and HI ($d$=1.7, 15 ml.) was heated for 1 hr. in an oil bath at 120°, then poured into water (200 ml.) containing $NaHSO_3$ (ca. 0.5 g. for decolorizing) to give yellow crystals, which was filtered, washed with water, and recrystallized twice from EtOH to get faint yellow crystals (370 mg.) of m.p. 273~275°. *Anal.* Calcd. for $C_{16}H_{12}O_5$ : C, 67.60; H, 4.26. Found : C, 67.51; H, 4.18. The combined mother liquor and washings separated from the crystals was condensed to get the second crop (380 mg.), m.p. 240~312°, giving two spots by TLC (Kieselgel G nach Stahl (Merck) and toluene-ethyl formate-formic acid, 5:4:1 were used) characteristic to apigenin (Rf 0.48) and genkwanin (Rf 0.57). Apigenin is predominant but pure apigenin is hardly obtainable by further recrystallizations because genkwanin is less soluble than apigenin in EtOH. The mother liquor separated from the second crop gave four spots characteristic to apigenin, genkwanin, apigenin dimethyl ether (Rf 0.93), and trimethyl ether (Rf 0.56, blue fluorescence).

No. 2 experiment in Table I was described above and the other demethylations were performed similarly to give the results shown in the table.

## Summary

Genkwanin (I) was prepared from apigenin trimethyl ether (Ⅱ) by partial demethylation with hydrogen iodide.

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*3 Melting points are uncorrected.

2) K. Nakazawa : "Yukikagobutsu Goseiho," edited by Yukigosei Kagaku Kyokai, **13**, 111 (1961). Gihodo, Tokyo.
3) K.F. Tseng : J. Pharm. Soc. Japan, **55**, 132 (1935).
4) H.S. Mahal, K. Venkataraman : J. Chem. Soc., **1936**, 569.