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The Partial Demethylation of Flavones. IV.[1] Formation of New Bisflavones, Hinokiflavone-7,7″-dimethyl Ether and Neocryptomerin

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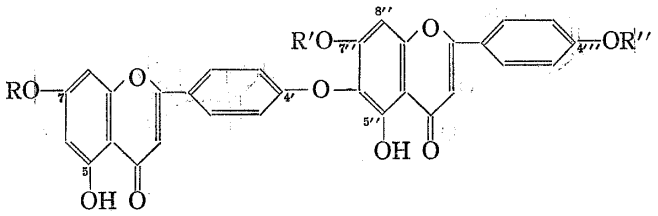
In this series of paper, it has been reported that 7-methoxyl group in flavones is fairly resistant to demethylation and that isocryptomerin (I)[3] is formed by partial demethylation of cryptomerin B (II).[4] This paper deals with the partial demethylation of hinokiflavone (III)[5] pentamethyl ether.

Since this pentamethyl ether has two methoxyl groups 7 and 7″ positions it is interesting to know which is more resistant to demethylation. When demethylated under a condition described in experimental part, hinokiflavone pentamethyl ether produced a mixture which consists of hinokiflavone and its monomethyl and dimethyl ethers detected by thin-layer chromatography (TLC). The mixture was subjected to countercurrent distribution followed by recrystallization.



	R	R′	R″
I :	H	Me	H
II :	H	Me	Me
III :	H	H	H
IV :	Me	Me	H
V :	Me	H	H
VI :	H	H	Me

The dimethyl ether should be hinokiflavone-7,7″-dimethyl ether (IV) because 4‴,[3a] 5-and 5″-methyl groups have been known to be demethylated easily. The ultraviolet (UV) spectrum of this compound exhibits no bathochromic shift of the low-wave length absorption band on addition of a little fused sodium acetate showing that it has no hydroxyl group in 7 and 7″ positions.[6] The monomethyl ether was crystallized from a mixture of pyridine and methanol to give isocryptomerin (I) which was identified by infrared (IR) spectrum. From the mother liquor separated from isocryptomerin, another monomethyl ether was obtained. The IR spectrum (Fig. 1) of this compound is not iden-

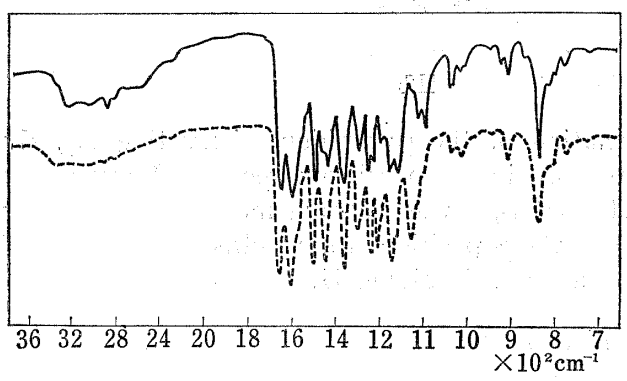


Fig. 1. Infrared Absorption Spectra of Neocryptomerin (V) and a Dimethyl Ether (IV)

—— neocryptomerin (V) ----- dimethyl ether (IV)

1) Part III: N. Kawano, H. Miura and E. Matsuishi, *Chem. Pharm. Bull.* (Tokyo), **15**, 711 (1967).
2) Location: *4–23 Bunkyo-machi, Nagasaki.*
3) *a*) H. Miura and N. Kawano, *Chem. Pharm. Bull.* (Tokyo), **15**, 232 (1967); *b*) H. Miura, *Yakugaku Zasshi*, **87**, 871 (1967).
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tical with that of isocryptomerin. The nuclear magnetic resonance (NMR) spectrum of its acetate listed in Table I in comparison of the chemical shifts of methyl protons with those of known derivatives[7] of hinokiflavone shows that the structure of the monomethyl ether is in accord with hinokiflavone–7–monomethyl ether (V), a new compound named neocryptomerin.

Thus, isocryptomerin (I), neocryptomerin (V), and hinokiflavone–7,7″–dimethyl ether (IV) are obtainable by partial demethylation of hinokiflavone pentamethyl ether. This may mean that the resistance of 7– and 7″– methoxyl groups to demethylation is not so different each other.

Table I. NMR Signals of Methyl Protons in Pyridine

Compounds	Assigned position				
	4‴	5	5″	7	7″
Dimethyl ether (IV) acetate	(2.24)	(2.41,	2.47)	3.75	3.83
Neocryptomerin (V) acetate	(2.24)	(2.35,	2.47)	3.77	(2.12)
Isocryptomerin (I) acetate	(2.25)	(2.41,	2.45)	(2.25)	3.86
Cryptomerin A (VI)[4] acetate	3.74	(2.35,	2.45)	(2.24)	(2.13)
Cryptomerin B (II) acetate	3.76	(2.42,	2.45)	(2.24)	3.85
Hinokiflavone (III) acetate	(2.24)	(2.35,	2.45)	(2.24)	(2.12)
Trimethyl ether acetate of III	3.74[a]	(2.41,	2.46)	3.77[a]	3.84
Pentamethyl ether of III	3.77[a]	3.81	4.08	3.79[a]	3.86

Figures in parentheses show the chemical shifts of acetyl protons.
Specrta were determined on a Hitachi H–60 instrument with tetramethylsilane as internal reference. Chemical shifts are given in δ values (ppm). *a*) Assignment is tentative.

Experimental[8]

Partial Demethylation of Hinokiflavone Pentamethyl Ether——A mixture of hinokiflavone pentamethyl ether (820 mg), PhOH (16 g), Ac_2O (8 ml), and HI (24 ml) was refluxed in an oil bath at 120° during 2 hr. The cooled reaction mixture was added to excess of dil. Na_2SO_3 solution. The solid was collected, washed with water, and recrystallized from MeOH–pyridine to give pale yellow prisms (626 mg), which gave three spots by TLC (*Rf*: 0.26, 0.37, 0.41).

Countercurrent distribution of Partially Demethylated Bisflavones——The partially demethylated bisflavone mixture (626 mg) described above was subjected to countercurrent distribution between ethyl methyl ketone (10 ml; equilibrated) and a borate buffer (pH 9.8, 10 ml). The mixture was dissolved in the first two tubes. After 130 transfers the following fractions were collected, acidified with HCl, and ethyl methyl ketone was distilled off to give pale yellow precipitates: fraction 1 (tubes 130—112); fraction 2 (tubes 92—40); fraction 3 (tubes 12—1).

Hinokiflavone-7,7″-dimethyl Ether (IV)——The precipitates (44 mg) obtained from fraction 1 were crystallized from MeOH–pyridine to give pale yellow prisms (12 mg), mp 280—282° (decomp., uncorr.), giving one spot by TLC (*Rf*: 0.41). IR (KBr) cm^{-1}: 1654, 1603, 1499, 1442, 1358, 1297, 1232, 1202, 1170, 1127, 835. UV λ_{max}^{EtOH} and $\lambda_{max}^{EtOH-NaOH}$ mμ: 271.5, 338. The above prisms (10 mg) were acetylated with Ac_2O (0.2 ml) and AcONa (20 mg) for 1.5 hr in an oil bath at 150°. Water insoluble precipitates obtained were crystallized from EtOH to yield colorless crystals (3 mg), mp 179° (uncorr.). The NMR signals of methyl protons were shown in Table I.

Isocryptomerin (I)——The precipitates (180 mg) obtained from fraction 2 were crystallized from MeOH–pyridine to give pale yellow prisms (73 mg), mp 310°, (decomp., uncorr.), which gave the same *Rf* value (0.37) by TLC and the same IR spectrum with isocryptomerin.[3]

7) H. Miura, *Yakugaku Zasshi*, **87**, 466 (1967).
8) NMR spectra were determined on a Hitachi H–60 instrument with pyridine as solvent and tetramethylsilane as internal reference. UV spectra were measured by a Hitachi ESP–2 Recording Spectrophotometer. HI means hydroiodic acid of d=1.7. Kieselgel G nach Stahl (Merck) was used in TLC. Solvent system: toluene–ethyl formate–formic acid (5:4:1).

Neocryptomerin (V)——The MeOH–pyridine filtrate separated from isocryptomerin was allowed to stand a few days in an ice box after addition of MeOH to give yellow prisms (21 mg), which were recrystallized once from a mixture of MeOH and a small portion of pyridine to yield pale yellow prisms, mp >299—300° (decomp., uncorr.). One spot by TLC (*Rf*: 0.37). IR (KBr) cm^{-1}: 1655, 1606, 1500, 1440, 1365, 1299, 1255, 1230, 1198, 1175, 1158, 1110, 1096, 835. The above prisms (7 mg) were acetylated in the same way as described above in the case of hinokiflavone–7,7″–dimethyl ether and washed with a large amount of water to give white powder (6 mg). The NMR signals of methyl protons of this compound were shown in Table I.

Hinokiflavone (III)——The precipitates (211 mg) obtained from fraction 3 were crystallized from MeOH–pyridine to give pale yellowish brown prisms (141 mg), mp>300°, which gave the same *Rf* value (0.26) by TLC and the same IR spectrum with hinokiflavone.

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Chemistry of Sodium Borohydride and Diborane. V.[1] Reduction of Nitrobenzenes with Sodium Borohydride in Pyridine

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Few examples of the reduction of nitro compounds with borohydrides are found in the literature, and it is generally reported that nitro group is reduced only in exceptional cases.[3]

Nitrobenzene was reduced to azoxybenzene on heating with sodium borohydride at 90—100° in diglyme for 6 hours.[4] Nitrobenzene was also reduced to aniline with lithium borohydride after 18 hours' reflux in tetrahydrofurane.[5] On the reduction of N,N–dimethyl–4–nitrobenzamide with $NaBH_4$–LiCl in refluxing tetrahydrofurane the corresponding azoxybenzene was obtained.[6]

An interesting result was obtained from the reduction of *m*– and *p*–substituted nitrobenzenes with KBH_4 in boiling ethanol and in pyridine at 90°.[7] Under these conditions it was found that some *m*– and *p*–substituted nitrobenzenes carrying a substituent with a positive value of the Hammett sigma constant were reduced to the azoxy compounds but those with a negative sigma constant were not reduced.

No report for converting a nitro compound to the corresponding azo or hydrazo compound with sodium borohydride has been published except as a patent[8] claiming the preparation of azobenzene by treating nitrobenzene with $NaBH_4$–NaOH–$KNi(CN)_4$.

As part of an investigation of the reaction with sodium borohydride in pyridine the reduction of *p*–substituted nitrobenzenes was studied. In the previous paper[9] we reported the reduc-

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5) R.F. Nystrom, S.W. Chaikin, and W.G. Brown, *J. Am. Chem. Soc.*, **71**, 3245 (1949).
6) M. Davis, *J. Chem. Soc.*, **1956**, 3981.
7) H.J. Shine and H.E. Mallory, *J. Org. Chem.*, **27**, 2390 (1962).
8) Dutch Patent 6409225 (1965); *Chem. Abstr.*, **65** 5399*g* (1966).
9) S. Yamada, Y. Kikugawa, and S. Ikegami, *Chem. Pharm. Bull.* (Tokyo), **13**, 394 (1965).