Precipitated sticky solid was pressed on the porous plate (1.20 g.) and crystallized from aq. Me_2CO (charcoal) to give (XXII) as colorless needles, m.p. 97~100°. *Anal.* Calcd. for $C_{10}H_{15}N_4Br$: N, 20.67. Found : N, 20.66.

Its picrate was crystallized from 2-butanone as bright yellow needles, m.p. 192.5°. *Anal.* Calcd. for $C_{16}H_{18}O_7N_7Br$: N, 19.60. Found : N, 19.74.

Bromination of Pyrimidines (II~VIII, X~XIII) with NBS——Respective pyrimidine (0.01 mole) and NBS (0.01 mole) were heated in CCl_4 (20 cc.) for the specified period. Solvent was evaporated and the residue, after being treated with water (20 cc.) on a steam bath for 10 min., was crystallized from an appropriate solvent. Reaction time, yield, melting point and analytical data are shown in Table I.

2-Amino-6-methylpyrimidine (XIII)——4-Methyl-6-amino-2-pyrimidinethiol (10.00 g.) and Raney-Ni sludge prepared from 30 g. of alloy under the direction of Mozingo[14] were heated in boiling water (150 cc.) for 2 hr. and Ni was filtered and washed with water. Filtrate was combined with the washings and evaporated under reduced pressure. The residue was pressed on the porous plate (7.45 g., 97%) and crystallized from water (15 cc.) to give the compound (XIII) as colorless plates, m.p. 194~195°. Gabriel and Colman noted m.p. 194~195° for this pyrimidine.[13]

Independent Preparations of Several 5-Bromopyrimidines (XVI~XIX)——2-Amino-4-methyl-5-bromo-6-chloropyrimidine (0.64 g.) and an appropriate chloro- or bromo-aniline (0.4 g.) were heated in water (8 cc.) and conc. HCl (0.5 cc.) for 30 min. The reaction mixture was diluted with water and made alkaline with NH_4OH. Precipitate was crystallized from EtOH or MeOH.

2-Methylthio-4-amino-5-bromo-6-methoxypyrimidine (XXIII)——2-Methylthio-4-chloro-5-bromo-6-aminopyrimidine (1.70 g.) was boiled with MeONa solution prepared from Na (0.20 g.) and MeOH (20 cc.) for 40 min. After the solvent was evaporated, water was added to the residue and the collected product (1.63 g.) was crystallized from MeOH, m.p. 138~140°.

Summary

2-Aminopyrimidines were brominated at their C_5-positions predominantly with NBS in carbon tetrachloride in spite of the presence of an anilino-, haloanilino-, or phenoxy-group at their c_6-positions as substituents.

(Received September 4, 1961)

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[14] R. Mozingo : Org. Syntheses, **21**, 15 (1941).

UDC 547.972.21.3:582.46

165. Koichi Nakazawa : Syntheses of Nuclear-substituted Flavonoids and Allied Compounds. IX.[1] Syntheses of Tetramethyl Ether and Dimethyl Ether of Ginkgetin.

(*Gifu College of Pharmacy*[*1])

In 1941, the author gave a formula $C_{32}H_{22}O_{10}$ for ginkgetin, a flavone compound isolated from the leaves of maidenhair trees (*Ginkgo biloba*), and suggested a structure of biflavonyl (I),[2] two 4′,5,7-trimethoxyflavone skeletones coupled with each other between positions 3 and 8″.

In order to confirm this structure, this author synthesized afterwards a ketonic compound (ketoflavone) (II) derivable from the structure (I) as an alkaline degradation product, and its 6-substituted isomer, both as trimethyl ethers,[3] which differed from

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[*1] Kokonoe-cho, Gifu (中沢浩一).

[1] Part VIII : Yakugaku Zasshi, **76**, 1204 (1956).

[2] K. Nakazawa : *Ibid.*, **61**, 174, 228 (1941).

[3] K. Nakazawa : S. Matsuura : *Ibid.*, **74**, 40 (1954), **75**, 68, 467, 716 (1955).

permethyl ether of the ketoflavone prepared from ginkgetin by aqueous alkaline hydrolysis. A revision of the structure of ginkgetin was, therefore, necessitated by the studies.

Recently, Baker *et al.* have determined the coupling position of the two flavone units of ginkgetin between 3′ and 8″ by the studies of peroxide oxidation, ultraviolet, infrared spectra and biosynthetic considerations, and proposed a new decisive structure (III)[4] for ginkgetin. As to the coupling position of the two units, however, Kawano has also come, about the same time and independently, to the same conclusion[5] as Bakers' from the investigation of alkaline degradation products of trimethyl ether of

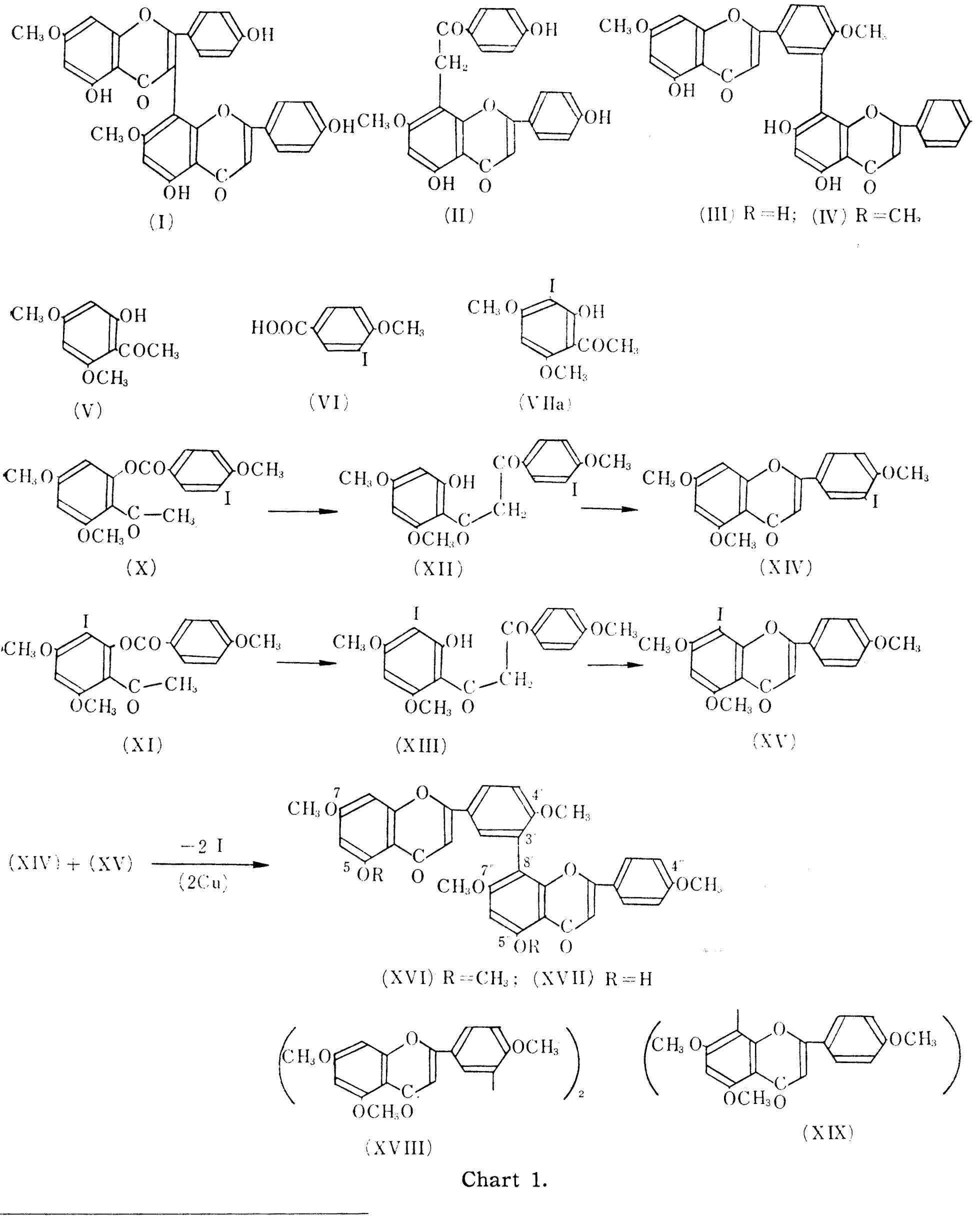

Chart 1.

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[4] W. Baker, A. C. M. Finch, W. D. Ollis, K. W. Robinson : Proc. Chem. Soc. (London), **1959**, 91.

[5] N. Kawano : Chem. & Ind. (London), **1959**, 368.

sciadopitysin (ginkgetin monomethyl ether) (IV) isolated from the leaves of umbrella pine (*Sciadopitys verticillata*).

The author has been carrying out since a decade ago the studies on the syntheses of macromolecular flavonoids including ginkgetin, and has recently succeeded in the syntheses of tetramethyl ether (XVI) and dimethyl ether (XVII) of ginkgetin, identical with natural ginkgetin ethers. The synthetic route to the biflavone (XVI) and (XVII) is shown in Chart 1.

Synthesis of 3′-iodo-4′,5,7-trimethoxyflavone (XIV) : Phloracetophenone was methylated to dimethyl ether (xanthoxylin) (V) by boiling 1 hour with calculated quantity of methyl sulfate in acetone in the presence of potassium carbonate. On the other hand, anisic acid was iodinated[6] by means of iodine in the presence of nitric acid, acetic acid, and sulfuric acid to the known 3-iodoanisic acid (VI), and then the latter was chlorinated to chloride by phosphorus pentachloride. 3-Iodoanisoyl compound (X), prepared by esterification of (V) with 3-iodoanisoyl chloride, was isomerized to diketone (XII) with two moles potassium hydroxide in pyridine by heating for 5 minutes on a steam bath. Excess of alkali decreases the yield. The diketone (XII) was readily cyclized to 3′-iodinated flavone compound (XIV) in the presence of sulfuric acid in acetic acid.

Synthesis of 8-iodo-4′, 5, 7-trimethoxyflavone (XV) : Phloracetophenone dimethyl ether (xanthoxylin) (V) was readily iodinated to 3-iodo-compound (VIIa) by iodination with iodine in the presence of nitric acid in acetic acid. The iodo atom in (VIIa) is assumed to be substituted *ortho* to the hydroxyl group of (V), as the structure of the iodo compound (VIIId) (m.p. 88°), which was obtained from (VIIa) successively by benzylation (VIIb), sodium hypochlorite oxidation (VIIc) and thermal decarboxylation, has been established as benzyl 2-iodo-3,5-dimethoxyphenyl ether (VIIId = IXe) by two unambiguous syntheses : (a) Methyl 2-hydroxy-4,6-dimethoxybenzoate (VIIIa) was benzylated (VIIIb) and saponified, giving 2-benzyloxy-4,6-dimethoxybenzoic acid (VIIIc), from which the iodide (VIIId) was readily obtained by decarboxylative iodination of the silver salt. (b) Methyl 4-hydroxy-2,6-dimethoxybenzoate (IXa)[7] gave the same iodide (IXe) by benzylation (IXb), iodination (IXc), saponification (IXd) and decarboxylation. The silver salt of 4-benzyloxy-2,6-dimethoxybenzoic acid (IXf) yielded by iodination the isomeric 4-iodo compound (IXg) (m.p. 120°). Anisate of VIIa (XI) was isomerized to diketone (XIII), and cyclized to 8-iodinated flavone compound (XV).

Syntheses of tetramethyl ether [5,7,4′,5″,7″,4‴-hexamethoxy-3′,8″-biflavone] (XVI) and dimethyl ether (XVII) of ginkgetin : The condensation of iodinated flavone compounds (XIV and XV) above obtained was finally effected in the presence of copper powder. As the reaction is, however, exothermic in itself and requires elevated temperature for completion in usual method, there were fears at first that in the case of present polymethoxy compounds poor yield would result owing to oxidation and resinification of the product. This was actually the case, namely, in the experiment of the condensation at 260∼300° in the absence of solvent, the product was entirely resinified. But by the investigation on the condensation in solvent, dimethylformamide has proved to be an excellent solvent to prepare the condensation product.

In carrying out the condensation, therefore, the two components and activated natural copper powder[8] were heated at the boiling point (153°) of dimethylformamide, and hot filtrate was mixed with several volumes of ethanol, when sparingly soluble condensation product (XVI) was separated in needles in up to 28% yield according to the activity of copper powder, whereas 3′,3‴-bis- (XVIII) and 8,8″-bis-compound (XIX) formed

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[6] A.N. Nowikow : Chem. Zentr. **1955**, 1947.

[7] E. Fischer, O. Pfeffer : Ann., **389**, 207 (1912).

[8] Organic Syntheses Coll. Vol, III, p. 339 (1955).

in small quantities were dissolved. As to the reaction period, the reaction extent 4~30 hours scarcely changed the yield, and pure product was obtained in short reaction period. The crude product was purified by recrystallization from dimethylformamide, forming colorless prismatic needles.

The properties of the biflavone (XVI) synthesized and purified as above agreed with those of ginkgetin tetramethyl ether.$^{2)}$ The compound is extremely and sparingly soluble in boiling methanol, ethanol and dioxane, and soluble in hot acetic acid, dimethylformamide and pyridine. After drying at 150° for 3 hours *in vacuo* it showed the composition corresponding to $C_{36}H_{30}O_{10}$ and m.p. 238°,[*2] which was undepressed on admixture with natural material (m.p. 238°[*3]), crystallized and dried similarly. The synthetic compound was completely identified with natural material in infrared spectra.

For characterization its dioxime (m.p. 252°) and partial demethylated compound (m.p. 282°) (XVII) were prepared and, found identical respectively with the oxime (m.p. 250°)$^{2)}$ of ginkgetin tetramethyl ether and ginkgetin dimethyl ether (m.p. 282°).$^{2)}$ On partial demethylation of (XVI) by means of aluminum chloride under mild conditions only the two methoxyl groups at positions 5 and 5'' adjacent to carbonyl groups were assumed to be demethylated, forming (XVII). Syntheses of tetramethyl ether and dimethyl ether of ginkgetin have thus been accomplished.

For comparison of biflavones the other two, namely, 3',3'''-bi- (XVIII) (m.p. 354°) and 8,8''-bi-compound (XIX) (m.p. 297°) were prepared by respective self-condensation of 3'-iodo- (XIV) and 8-iodoflavone compound (XV) as for (XVI). The formation of the former was in traces. Infrared spectra of tetramethyl ether (XVI) and dimethyl ether (XVII) of ginkgetin are shown in Fig. 1~2.

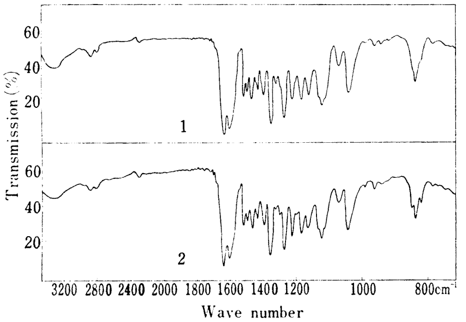


Fig. 1. Infrared Absorption Spectra of Ginkgetin Tetramethyl Ether (KBr disk)
1. natural 2. synthetic

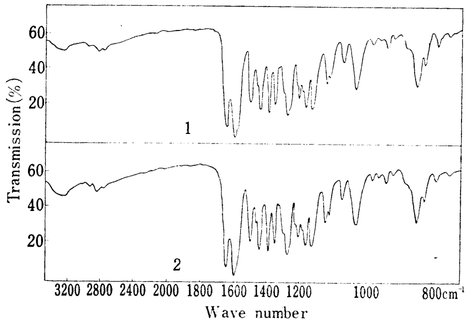


Fig. 2. Infrared Absorption Spectra of Ginkgetin Dimethyl Ether (KBr disk)
1. natural 2. synthetic

Experimental[*4]

I. 3'-Iodo-4',5,7-trimethoxyflavone (XIV)

3-Iodoanisic Acid (VI)——When a mixture of 152.1 g. (1 mole) of anisic acid (powder), 253.8 g. (1 mole) of I_2 (powder), 150 g. of H_2SO_4 and 800 cc. of AcOH was stirred for 90 min. at 40~50° during the dropwise addition of a solution of 100 g. of conc. HNO_3 (65.3% HNO_3) in 150 cc. of AcOH, the iodination of anisic acid proceeded with evolution of N_2O_4. After warming at 50° for 30 min., the reaction mixture was diluted with 1 L. of water, dark, insoluble iodination product was filtered and washed with 10% $Na_2S_2O_4$ solution and water. Dried, tan-colored acid was recrystallized from pyridine-MeOH (1:1) to form colorless needles, m.p. 238°. Yield, 203 g. (73%).

[*2] Air- or low temperature-dried crystals melted at ca. 210° (decomp.). According to C,H-analysis it was proved that they contain a solvent difficult to be removed.

[*3] By the above purification and drying the m.p. became higher than previously reported (228°).$^{2)}$

[*4] All melting points were uncorrected. $FeCl_3$-Reaction were tested in EtOH solutions.

3-Iodoanisoyl Chloride——139 g. (0.5 mole) of 3-Iodoanisic acid was slowly added to a mixture of 114 g. (o.55 mole) of PCl_5 (pea size) and 100 cc. of $CHCl_3$, and afterwards the solution was warmed on a steam bath. After the evolution of HCl gas ceased the solution was filtered and distilled, to afford a product, b.p$_{12\sim13}$ 183~185°. Yield, 138 g. (93%). Distillate soon solidified.

Phloracetophenone 2,4-Dimethyl Ether (Xanthoxylin) (V)——In a 2-necked flask (1 L.) equipped with a reflux condenser and a stirrer were added 126 g. (0.75 mole) of phloracetophenone, 150 g. of K_2CO_3 and 450 cc. of Me_2CO, and with stirring 189 g. (1.5 moles) of Me_2SO_4 was added through the condenser in 50 min. The methylation proceeded with exothermic reaction. After the addition of the methylating agent the mixture was refluxed for 1 hr. on a steam bath, and was then added to 1 L. of water. Solidified product was filtered, washed with water, dried and recrystallized from MeOH to form colorless platechens, m.p. 82~83°. Yield, 114.7 g. (78%). $FeCl_3$-Reaction : purple. Soluble in most organic solvents.

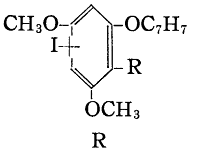
2-Acetyl-3,5-dimethoxyphenyl 3-Iodoanisate (X)——A mixture of 49.0 g. (0.25 mole) of (V), 89.0 g. (0.3 mole) of 3-iodoanisoyl chloride and 120 cc. of pyridine was heated in an oil bath at 110° for 10 min. The cold, solidified product was diluted with 150 cc. MeOH, microcrystalline ester was filtered and washed with MeOH. Gray-colored ester obtained here was almost pure, m.p. 158°. Yield, 86.6 g. (76%). Crystals from Me_2CO form colorless prisms. *Anal.* Calcd. for $C_{18}H_{17}O_6I$: C, 47.36; H, 3.76; I, 27.83. Found : C, 47.76; H, 3.88; I, 27.40.

1-(3′-Iodo-4′ methoxyphenyl)-3-(2′-hydroxy-4″,6″-dimethoxyphenyl)-1,3-propanedione (XII)——When a mixture of 45.6 g. (0.1 mole) of ester (X), 14.0 g. (0.25 mole) of KOH (powder) and 100 cc. of pyridine was heated with stirring on a steam bath for 5 min., a dark brown solution was first formed and then gradually yellow K-compound of the diketone separated to form a thin paste. The cooled reaction mixture was decomposed with 50 cc. of AcOH, and 100 cc. of MeOH was added. Yellow sandy crystals of the diketone was filtered, washed with MeOH and recrystallized from Me_2CO to pale yellow prisms, m.p. 168°. Yield, 18.2 g. (40%). $FeCl_3$-Reaction : yellowish-green. *Anal.* Calcd. for $C_{18}H_{17}O_6I$: C, 47.36; H, 3.76. Found : C, 47.12; H, 3.82.

3′-Iodo-4′,5,7-trimethoxyflavone (XIV)——A hot solution of 45.6 g. (0.1 mole) of diketone (XII) in 600 cc. of AcOH was mixed with 100 g. of 20% H_2SO_4 in AcOH, and after 10 min. the mixture was poured into 2 L. of water. Insoluble colorless needles of the flavone compound were filtered, washed with water, dried and recrystallized from dioxane to colorless slender needles, m.p. 223°. Yield, 39.8 g. (91%). Sparingly soluble in Me_2CO and MeOH, soluble in hot EtOH, dioxane, AcOH and pyridine. $FeCl_3$-Reaction : negative. *Anal.* Calcd. for $C_{18}H_{15}O_5I$: C, 49.31; H, 3.45. Found : C, 49.47; H, 3.69.

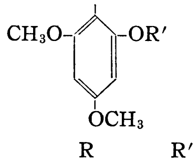
II. 8-Iodo-4′,5,7-trimethoxyflavone (XV)

2′-Hydroxy-3′-iodo-4′,6′-dimethoxyacetophenone (VIIa)——A mixed solution of 127 g. (0.5 mole) of I_2 in 150 cc. of Me_2CO and 98.1 g. (0.5 mole) of (V) in 650 cc. of AcOH was stirred with ice-cooling for 40 min. during the dropwise addition of a solution of 50 g. of conc. HNO_3 (65.3% HNO_3) in 60 cc. of AcOH. The iodination product (VII) crystallized out gradually during the addition to form pasty crystals, which were filtered 30 min. after the addition and washed successively with MeOH, 10% $Na_2S_2O_4$ solution and water. The iodo-compound formed slightly yellow needles from pyridine, m.p. 201°. Yield, 120.8 g. (75%). $FeCl_3$-Reaction : pale brownish-purple. *Anal.* Calcd. for $C_{10}H_{11}O_4I$: C, 37.26; H, 3.44; I, 39.42. Found : C, 37.47; H, 3.62; I, 38.98.

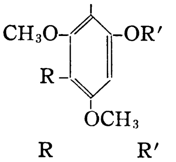


	R
(VIIb)	$COCH_3$
(VIIc)	COOH
(VIId)	H

(VIId)=(VIIId)=(XIe)



	R	R′
(VIIIa)	$COOCH_3$	H
(VIIIb)	$COOCH_3$	C_7H_7
(VIIIc)	COOH	C_7H_7
(VIIId)	I	C_7H_7



	R	R′	R″
(IXa)	$COOCH_3$	H	H
(IXb)	$COOCH_3$	C_7H_7	H
(IXc)	$COOCH_3$	C_7H_7	I
(IXd)	COOH	C_7H_7	I
(IXe)	H	C_7H_7	I
(IXf)	COOH	C_7H_7	H
(IXg)	I	C_7H_7	H

The Structure of (VIIa)——a) Formation of benzyl 2-iodo-3,5-dimethoxyphenyl ether (VIId) from (VIIa). (i) 2′-Benzyloxy-x′-iodo-4′,6′-dimethoxyacetophenone (VIIb) : A mixture of 16.1 g. (0.05 mole) of (VIIa), 7.0 g. (0.055 mole) of benzyl chloride, 15 g. of K_2CO_3 and 35 cc. of dimethylformamide was refluxed in an oil bath for 1 hr. After addidion of water, the precipitate was filtered off and recrystallized from Me_2CO to yield 16.5 g. of colorless needles, m.p. 136°. *Anal.* Calcd. for $C_{17}H_{17}O_4I$: C, 49.49;

H, 4.16. Found : C, 49.75; H, 4.27. (ii) 2-Benzyloxy-x-iodo-4,6-dimethoxybenzoic acid (VIIc) : A mixture of 4.1 g. (0.01 mole) of (VIIb), 22.3 cc. of 10% NaClO and 11 cc. of pyridine was warmed at 60° for 1 hr. with stirring, diluted with H_2O and filtered. The filtrate was acidified with HCl and precipitated acid was recrystallized from benzene to yield needles (2.2 g.), m.p. 183° (decomp.). Insoluble in *n*-C_6H_{14}. *Anal.* Calcd. for $C_{16}H_{15}O_5I$: C, 46.35; H, 3.65. Found : C, 46.75; H, 3.83. (iii) Benzyl 2-iodo-3,5-dimethoxyphenyl ether (VIId) : When 2.1 g. (0.005 mole) of (VIIc) in a small test tube was heated near to the m.p. in an oil bath, it melted with evolution of CO_2. After melting for only 1 min., the melt was recrystallized from *n*-C_6H_{14}, giving colorless prisms (0.45 g.), m.p. 88°. *Anal.* Calcd. for $C_{15}H_{15}O_3I$: C, 48.62; H, 4.08. Found : C, 48.55; H, 4.26. They were proved identical both with (VIIId) and (IXe) by analyses and mixed m.p. determinations. Longer period melting of the acid (VIIc) resulted in resinification of the product with liberation of I_2.

(b) Synthesis of benzyl 2-iodo-3,5-dimethoxyphenyl ether (1). (i) 2-Benzyloxy-4,6-dimethoxybenzoic acid (VIIIc) : 10.6 g. (0.05 mole) of Methyl 2-hydroxy-4,6-dimethoxybenzoate (VIIIa) was benzylated as in (VIIb) with equal quantities of reagents. After addition of water to the reaction mixture, the suspensions were extracted with Et_2O. The extract was washed with 5% KOH, dried over anhyd. $MgSO_4$, and the solvent was evaporated. The oily residue (crude VIIIb) (16.5 g.) was boiled for 15 min. with 200 g. of 20% EtOH-KOH and acidified with HCl. The acid (VIIIc) forms colorless, slender needles from EtOH, m.p. 164° (decomp.). Yield, 8.2 g. *Anal.* Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found : C, 66.65; H, 5.54. Ag salt of the acid : When 10 cc. of *N* $AgNO_3$ was added to a solution of 2.9 g. of (VIIIc) in 100 cc. of 0.1*N* NaOH, the Ag salt precipitated, which was filtered off, washed with water, then with MeOH and dried to yield (3.5 g.) colorless crystalline powder. (ii) Benzyl 2-iodo-3,5-dimethoxyphenyl ether (VIIId) : 1.3 g. of I_2 was added gradually to a mixture of 2.0 g. of the Ag salt and 30 cc. of CCl_4 at 85~70° with stirring. After disappearance of the color of I_2, the reaction mixture was filtered. The filtrate was evaporated to dryness and the crystalline residue was recrystallized from *n*-C_6H_{14} to give colorless prisms (0.7 g.), m.p. 88°. *Anal.* Calcd. for $C_{15}H_{15}O_3I$: C, 48.62; H, 4.08; I, 34.29. Found : C, 48.87; H, 4.23; I, 34.40. They were proved identical with (IXe) by analysis and mixed m.p. determination.

c) Synthesis of benzyl 2-iodo-3,5-dimethoxyphenyl ether (2). (i) Methyl 4-benzyloxy-2,6-dimethoxybenzoate (IXb) : 10.6 g. (0.05 mole) of Methyl 4-hydroxy-2,6-dimethoxybenzoate (IXa)[7] was benzylated as in (VIIb) with equal quantities of reagents and diluted with water. The precipitate was filtered off and recrystallized from MeOH to form colorless needles (13.5 g.), m.p. 99°. *Anal.* Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found : C, 67.92; H, 6.15. (ii) Methyl 3-iodo-4-benzyloxy-2,6-dimethoxybenzoate (IXc) : A mixture of 6.0 g. (0.02 mole) of (IXb) and 5.1 g. of I_2 in 50 cc. of AcOH was iodinated by addition of 2 g. of conc. HNO_3 (65.3% HNO_3) at 50° with stirring. After standing for 2 hr., crystallized iodide was filtered off and recrystallized from ligroin to yield colorless needles (3.1 g.), m.p. 118°. *Anal.* Calcd. for $C_{17}H_{17}O_5I$: C, 47.66; H, 4.00; I, 29.65. Found : C, 47.74; H, 3.98; I, 30.02. (iii) 3-Iodo-4-benzyloxy-2,6-dimethoxybenzoic acid (IXd) : 4.3 g. (0.01 mole) of (IXc) was boiled for 15 min. with 50 g. of 20% EtOH-KOH and acidified with HCl. Precipitated acid was recrystallized from benzene to yield 3.1 g. of colorless plates, m.p. 169° (decomp.). *Anal.* Calcd. for $C_{16}H_{15}O_5I$: C, 46.35; H, 3.65. Found : C, 46.17; H, 3.72. (iv) Benzyl 2-iodo-3,5-dimethoxyphenyl ether (IXe) : 2.1 g. of (IXd) was decarboxylated as in (VIId), giving 1.3 g. of colorless prisms from *n*-C_6H_4 m.p. 88°. *Anal.* Calcd. for $C_{15}H_{15}O_3I$: C, 48.62; H, 4.08. Found : C, 48.69; H, 4.19.

d) Synthesis of benzyl 4-iodo-3,5-dimethoxyphenyl ether (IXg). (i) 4-Benzyloxy-2,6-dimethoxybenzoic acid (IXf) : Six grams (0.02 mole) of (IXb) was saponified as in (VIIIc) with 75 g. of 20% EtOH-KOH. The acid forms colorless small prisms from EtOH (4.1 g.), m.p. 172° (decomp.), *Anal.* Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found : C, 66.83; H, 5.72. Ag salt of the acid : It was prepared from 2.9 g. of (IXf) as in (VIIIc). Colorless crystalline powder. Yield, 2.8 g. (ii) Benzyl 4-iodo-3,5-dimethoxyphenyl ether (IXg) : Two grams of the Ag salt was iodinated as in (VIIId). Colorless plates from ligroin (0.90 g.), m.p. 120°. *Anal.* Calcd. for $C_{15}H_{15}O_3I$: C, 48.62; H, 4.08; I, 34.29. Found : C, 48.89; H, 4.19; I, 34.70.

2-Acetyl-6-iodo-3,5-dimethoxyphenyl Anisate (XI)——A mixture of 80.5 g. (0.25 mole) of (VIIa), 51.2 g. (0.3 mole) of anisoyl chloride and 120 cc. of pyridine was treated similarly as for (X). MeOH-washed reaction product was recrystallized from Me_2CO to form colorless prisms, m.p. 181°. Yield, 80.9 g. (71%). *Anal.* Calcd. for $C_{18}H_{17}O_6I$: C, 47.36; H, 3.76. Found : C, 47.60; H, 3.65.

1-(*p*-Methoxyphenyl)-3-(2″-hydroxy-3″-iodo-4″,6″-dimethoxyphenyl)-1,3-propanedione (XIII)——A mixture of 45.6 g. (0.1 mole) of ester (XI), 11.2 g. (0.2 mole) of KOH (powder) and 100 cc. of pyridine was treated by the same procedure as for (XII). Yellow pasty crystals of the diketone were formed when the cooled thick paste of the reaction mixture was decomposed with 50 cc. of AcOH and on addition 100 cc. of MeOH, which were filtered, washed with MeOH and recrystallized from Me_2CO to pale yellow feather-like crystals, m.p. 166°. Yield, 35.6 g. (78%). $FeCl_3$-Reaction : yellowish-green. *Anal.* Calcd. for $C_{18}H_{17}O_6I$: C, 47.36; H, 3.76. Found : C, 47.27; H, 3.77.

8-Iodo-4′,5,7-trimethoxyflavone (XV)——A hot solution of 45.6 g. (0.1 mole) of diketone (XIII) in 500 cc. of AcOH was mixed with 100 g. of 20% H_2SO_4 in AcOH, of and after 15 min. the mixture was treated similarly as for (XIV). Colorless prisms from dioxane, m.p. 239~240°. Yield, 37.2 g. (85%). Solubility is less than 3′-iodo isomer. Sparingly soluble in MeOH, EtOH and Me_2CO, soluble in hot dioxane, AcOH and pyridine. $FeCl_3$-Reaction : negative. *Anal.* Calcd. for $C_{18}H_{15}O_5I$: C, 49.31; H, 3.45. Found : C, 49.04; H, 3.62.

III. Tetramethyl Ether (XVI) and Dimethyl Ether (XVII) of Ginkgetin.

A mixture of 4.4 g. (0.01 mole) of 3′-iodinated flavone compound (XIV), equal quantity of 8-iodinated isomer (XV), 8.8 g. of freshly activated natural Cu powder[8] and 30 cc. of dimethylformamide was refluxed in a metal bath for 4 hr., filtered hot and washed with 10 cc. of the solvent. EtOH (200 cc.) was added to the combined filtrate and washings and was left overnight, when the sparingly soluble condensed product (XVI) was separated in needles. Yield, 1.83 g. (28%). It was recrystallized from dimethylformamide to form prismatic needles, m.p. 238°(after drying at 150° for 3 hr. *in vacuo*), 1.50 g. Undepressed on admixture with natural ginkgetin tetramethyl ether, recrystallized and dried similarly (m.p. 238°). *Anal.* Calcd. for $C_{36}H_{30}O_{10}$: C, 69.44; H, 4.86. Found : C, 69.02; H, 4.92.

Dioxime——Prepared by 2 hr. boiling of (XVI) with $NH_2OH \cdot HCl$ and AcOK in pyridine. Colorless needles from dioxane-EtOH, m.p. 252°, which remained the same on admixture with the oxime (m.p. 250°)[2] needles of natural material. *Anal.* Calcd. for $C_{36}H_{32}O_{10}N_2$: C, 66.25; H, 4.94; N, 4.29. Found : C, 66.41; H, 4.84; N, 4.39.

Ginkgetin Dimethyl Ether (XVII)——A solution of 1.32 g. (0.002 mole) of (XVI) and equal quantity of $AlCl_3$ in 10 cc. of nitrobenzene was heated for 1 hr. at 110° in an oil bath, and after addition of 2 drops of conc. HCl, was distilled with steam. Remaining yellow powder was filtered and recrystallized from Me_2CO to form yellow needles, m.p. 282°, either alone or in admixture with the specimen of natural material (m.p. 282°).[2] Yield, 0.60 g. $FeCl_3$-Reaction : brownish-purple. *Anal.* Calcd. for $C_{34}H_{26}O_{10}$: C, 68.66; H, 4.41. Found : C, 68.49; H, 4.24.

IV. Other Biflavone Compounds (XVIII, XIX)

3′,3‴-Biflavone Compound (XVIII)——A mixture of 2.2 g. (0.005 mole) of 3′-iodinated flavone compound (XIV), equal quantity of activated natural Cu powder[8] and 8 cc. of dimethylformamide were reacted and treated analogously as for (XVI). Colorless, microscopic needles from dimethylformamide. Yield ca. 10 mg., m.p. 354°. Solubility in organic solvents is extremely small. *Anal.* Calcd. for $C_{36}H_{30}O_{10} \cdot H_2O$: C, 67.47; H, 5.04. Found : C, 67.61; H, 5.19.

8,8″-Biflavone Compound (XIX)——8-iodinated compound (XV) (2.2 g) was self-condensed and treated as above for (XVI). Colorless needles from MeOH. Yield, 0.54 g. (33%), m.p. 297°. Difficult to dissolve in EtOH, Me_2CO and AcOEt, soluble in small quantities in MeOH and dioxane, and soluble in hot AcOH and pyridine. *Anal.* Calcd. for $C_{36}H_{30}O_{10}$: C, 69.44; H, 4.86. Found : C, 69.19; H, 5.08.

Dioxime——Colorless platechen from dioxane, m.p. 294°. *Anal.* Calcd. for $C_{36}H_{32}O_{10}N_2$: N, 4.29. Found : N, 4.21.

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Summary

2-Acetyl-3,5-dimethoxyphenyl 3-iodoanisate (X) and its 6-iodo isomer (XI) were respectively isomerized to diketones (XII, XIII) by means of potassium hydroxide in pyridine, and then cyclized to flavone compounds (XIV, XV), which were finally condensed each other to biflavonyl (XVI) by refluxing in dimethylformamide for 4 hours in the presence of activated natural copper powder. The yield of crude product was 28%. Biflavonyl (XVI) was demethylated to (XVII), when it was treated with aluminum chloride in nitrobenzene at 110° for 1 hour (XVI) and (XVII) were identified respectively with tetramethyl ether and dimethyl ether of ginkgetin in C,H-analyses, mixed melting points and infrared absorption spectra.

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