5) **Reaction between V and N-Benzylidenemethylamine**——A mixture of 4.6 g. of V, 3.0 g. of N-benzylidenemethylamine and 20 cc. of glycol was allowed to react, when evolution of CH_3NH_2 was observed. By the same procedures as described in 1), IV was obtained in yield of 6.3 g. (92% yield).

6) **Reaction between V and N-Benzylideneaniline**——A mixture of 4.6 g. of V, 4.5 g. of N-benzylideneaniline and 20 cc. of glycol was heated on a boiling water bath for 6 hr. After standing overnight, a part of IV deposited was filtered and the filtrate was extracted with toluene. After removal of the toluene, aniline, weighing 12 g. (52% yield), was obtained by distillation of the residue. This was proved as its derivative, N,N′-diphenylthiourea, by mixed melting point test.

The authors are grateful of Prof. Emeritus M. Ishidate of the Tokyo University, for his kind encouragement during the course of this work. The authors are also indebted to Miss Y. Saito for the elementary analyses.

Summary

In the presence of ammonia or amine some azomethines were catalytically hydrogenated under high hydrogen pressure to give two kinds of amines according to the equation :

$$ArCH{=}NR + R'NH_2 + H_2 \longrightarrow ArCH_2NHR' + RNH_2$$
$$(R' : \text{H or alkyl})$$

In the pathway of this hydrogenation reaction, the first stage preceding hydrogenation was proposed to be the replacement reaction of amine residue of azomethine by that of ammonia or amine. This was demonstrated using N-benzylidene-4-sulfonamidobenzylamine as azomethine.

(Received February 13, 1962)

UDC 547.972.2/.3

46. Koichi Nakazawa and Manzo Ito : Syntheses of Ring-substituted Flavonoids and Allied Compounds. X.[*1] Synthesis of Ginkgetin.

(*Gifu College of Pharmacy*[*2])

Ginkgetin, $C_{32}H_{22}O_{10}$, a flavone from the leaves of *Ginkgo biloba*, was isolated first by one of the authors (K. N.) who suggested a biflavonyl structure for it[1]. Recently, Baker *et al.*[2] put forward for ginkgetin the structure of 4′,7-dimethoxy-4‴,5,5″,7″-tetrahydroxy-3′,8″-biflavone (I), which consists of two apigenin (4′,5,7-trihydroxyflavone) moieties linked at the 3′- and 8″-positions. In a previous work,[*1] the coupling position of the two flavone units was confirmed by the synthesis of ginketin dimethyl (II) and tetramethyl ethers (III).

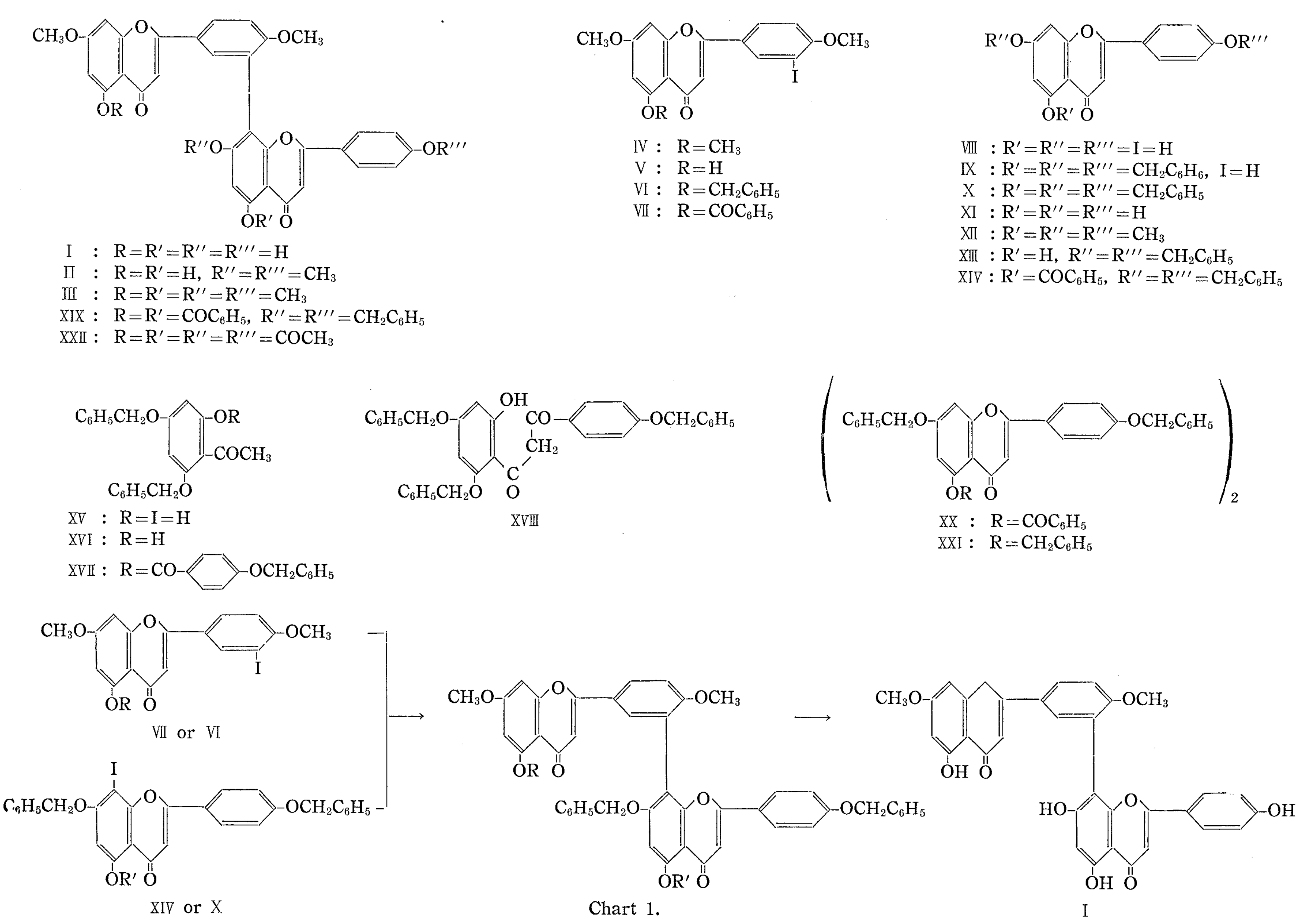
This paper deals with the total synthesis of ginkgetin by the condensation of 3′- and 8-iodinated flavones, (VII or VI) and (XIV or X), in the presence of activated copper powder, without a solvent, followed by removal of the protecting group.

[*1] Part IX. This Bulletin, **10**, 1032 (1962); A preliminary report was published in this Bulletin, **7**, 748 (1959).

[*2] Kokonoe-cho, Gifu (中沢浩一, 伊藤万蔵).

1) K. Nakazawa : Yakugaku Zasshi, **61**, 174, 228 (1941).

2) W. Baker, A. C. M. Finch, W. D. Ollis, K. W. Robinson : Proc. Chem. Soc., 91 (1959).



I : $R=R'=R''=R'''=H$
II : $R=R'=H$, $R''=R'''=CH_3$
III : $R=R'=R''=R'''=CH_3$
XIX : $R=R'=COC_6H_5$, $R''=R'''=CH_2C_6H_5$
XXII : $R=R'=R''=R'''=COCH_3$

IV : $R=CH_3$
V : $R=H$
VI : $R=CH_2C_6H_5$
VII : $R=COC_6H_5$

VIII : $R'=R''=R'''=I=H$
IX : $R'=R''=R'''=CH_2C_6H_6$, $I=H$
X : $R'=R''=R'''=CH_2C_6H_5$
XI : $R'=R''=R'''=H$
XII : $R'=R''=R'''=CH_3$
XIII : $R'=H$, $R''=R'''=CH_2C_6H_5$
XIV : $R'=COC_6H_5$, $R''=R'''=CH_2C_6H_5$

XV : $R=I=H$
XVI : $R=H$
XVII : $R=CO-C_6H_4-OCH_2C_6H_5$

XVIII

XX : $R=COC_6H_5$
XXI : $R=CH_2C_6H_5$

VII or VI

XIV or X

I

Chart 1.

Partial demethylation of 3′-iodo-4′,5,7-trimethoxyflavone[*1] (IV) with aluminum chloride in nitrobenzene gave 5-hydroxy compound (V), which was benzoylated to the benzoate (VII). 4′,5,7-Tribenzyloxyflavone[3] (IX), obtained readily by benzylation of 4′,5,7-trihydroxyflavone (apigenin) (VIII) with benzyl chloride and potassium carbonate in dimethylformamide, was iodinated readily with iodine and nitric acid in acetic acid to the 8-iodinated compound (X). The structure of X was confirmed by the formation of 8-iodo-4′,5,7-trimethoxyflavone[*1] (XII) on debenzylation with 10% sulfuric acid in acetic acid followed by methylation. Partial debenzylation of X with 10% phosphoric acid in acetic acid led to the formation of 5-hydroxy compound (XIII), which gave a dark greenish ferric chloride reaction, and which was benzoylated to the benzoate (XIV). The same debenzylated compound (XIII) was also synthesized from phloracetophenone in another way which involved dibenzylation, iodination, *p*-benzyloxybenzoylation, rearrangement[*3] of the *p*-benzyloxy-benzoyl grouping, and cyclization on treatment with 10% phosphoric acid in acetic acid which accompanied simultaneous debenzylation at 5-position. This route (XV→XVI→XVII→XVIII→XIII) was found to be unsuitable because of its poor yield.

Contrary to the expectation based on the previous successful results in the synthesis of ginkgetin methyl ethers, the components (VII) and (XIV) afforded the 8,8′-bis

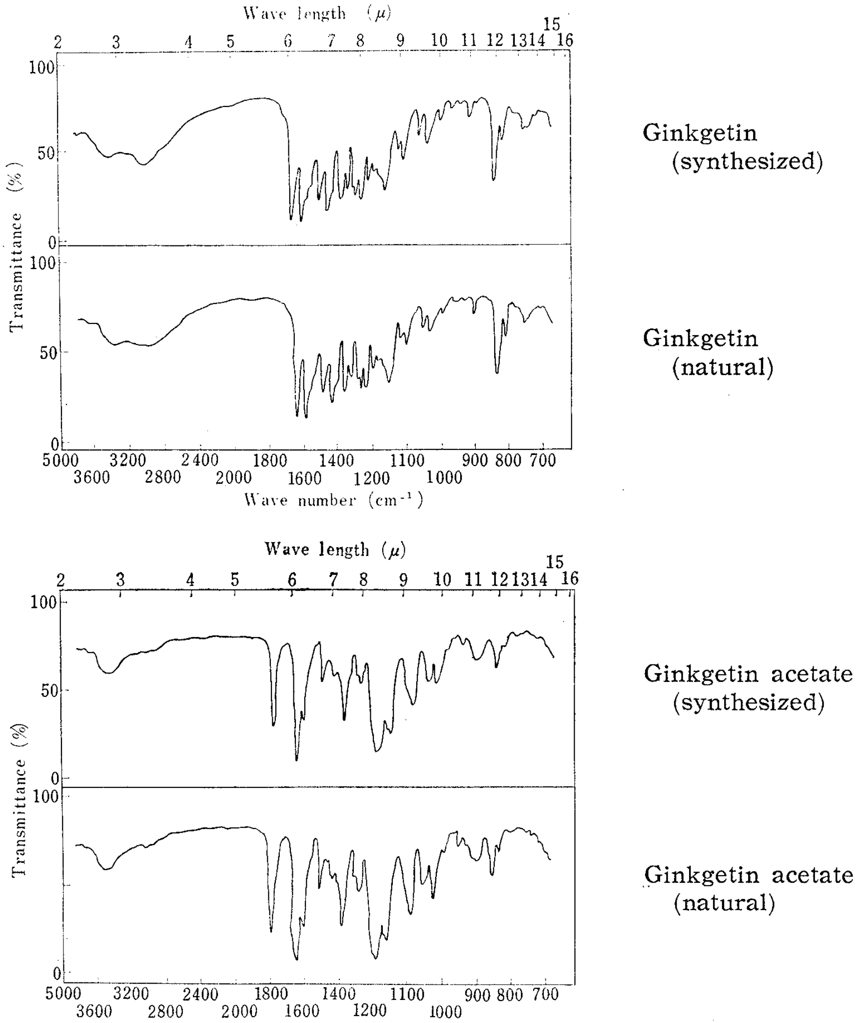


Fig. 1. Infrared Spectra (KBr Disk)

[*3] The iodinated flavone perbenzyl ether (X) gave the diketone (XVIII) by ethanolic alkaline hydrolysis.

3) K. Nakazawa, T. Miyata: Yakugaku Zasshi, 82, 927 (1962).

compound (XX) on treatment with activated copper powder in dimethylformamide. The same result was also obtained in the condensation using the benzyl ether (VI) and the tribenzyl ether (X). However, when the condensation reaction was carried out by heating the mixture without a solvent at 225~230° for 40 minutes, ginkgetin (I) was formed, which separated out as scarcely soluble potasslum salt of brilliant yellow crystals.

The free ginkgetin (I), isolated from the reaction mixture by the procedure described in the experimental part, was recrystallized from methyl ethyl ketone to pale yellow, small plates, m.p. 336°. The tetraacetate of ginkgetin (XXII), colorless needles, m.p. 259°, and the tetramethyl ether (III), m.p. 238°, were prepared. Synthesized ginkgetin and its acetate were respectively identified with the materials of natural origin*[4], by the elementary analysis, mixed fusion, and comparison of their infrared spectra.

The condesations of benzyl ethers (VI) and (X) were carried out as above, at a higher temperature and without a solvent, to yield ginkgetin. The yield of ginkgetin varied depending on the components of condensation, and the highest yield was obtained on using VII and XIV, while the lowest yield was found in the case of VI and X.

Experimental*[5]

I. Synthesis of 3′-Iodinated Flavones

3′-Iodo-5-hydroxy-4′, 7-dimethoxyflavone (V)——43.8 g. (0.1 mol.) of 3′-iodo-5-hydroxy-4′, 7 dimethoxyflavone*[1] (IV) was dissolved in a solution of $AlCl_3$ (20.0 g. (0.15 mol.)) in 100 ml. of nitrobenzene, and heated at 100° for 10 min. After addition of 5 ml. of conc. HCl, the reaction mixture was distilled with steam. The yellow solid that remained was collected by filtration and washed with Me_2CO to yield 39.7 g. (94%) of almost pure 5-hydroxy compound (V), m.p. 218°, which formed yellow needles by recrystallization from pyridine, but melting point was unchanged. $FeCl_3$-reaction, dark purple. *Anal.* Calcd. for $C_{17}H_{13}O_5I$: C, 48.09; H, 3.09. Found : C, 48.44; H, 3.39.

3′-Iodo-5-benzoyloxy-4′,7-dimethoxyflavone (VII)——A mixture of V (21.2 g.), benzoyl chloride (10.5 g.) and pyridine (40 ml.) was heated at 110° for 10 min. When cooled, the solidified mixture was diluted with MeOH, filtered, and washed with MeOH to give colorless plates (25.0 g.), m.p. 236°. $FeCl_3$-reaction, negative. *Anal.* Calcd. for $C_{24}H_{17}O_6I$: C, 54.51; H, 3.24. Found : C, 54.87; H, 3.24.

3′-Iodo-5-benzyloxy-4′,7-dimethoxyflavone (VI)——A mixture of V (10.6 g.), benzyl chloride (3.8 g.), K_2CO_3 (6 g.) and dimethylformamide (50 ml.) was boiled in a metal bath for 30 min., and poured into H_2O. The product collected by filtration was recrystallized from pyridine to colorless needles, m.p. 226°. Yield, 9.5 g. $FeCl_3$-reaction, negative. *Anal.* Calcd. for $C_{24}H_{19}O_5I$: C, 56.00; H, 3.72. Found : C, 56.08; H, 3.71.

II. Synthesis of 8-Iodinated Flavones

8-Iodo-4′,5,7-tribenzyloxyflavone (X)——A solution of IX[3)] (27.0 g. (0.05 mol.)) and I_2 (7.6 g. (0.03 mol.)) in AcOH (200 ml.) was stirred at 60~65° during the dropwise addition of conc. HNO_3 (65.3% HNO_3 (5 g.) during 15 min. The iodination product crystallized out during the reaction to form a paste, which was filtered 1 hr. after the addition of HNO_3, and washed successively with MeOH, 10% Na_2SO_3, and H_2O. The product formed colorless needles (from pyridine+MeOH), m.p. 179°. Yield, 27.6 g. (83%). $FeCl_3$-reaction, negative. *Anal.* Calcd. for $C_{36}H_{27}O_5I$: C, 64.85; H, 4.09; I, 19.05. Found : C, 65.14; H, 4.23; I, 19.18.

Structure of the Iodinated Flavone (X)——Debenzylation : A solution of X (3.3 g.) dissolved in 10% H_2SO_4 (50 ml.) in AcOH at 110°, was heated at 80~90° for 50 min., allowed to stand overnight, and filtered. The filtrate was diluted with H_2O, the precipitate was collected by filtration, washed with H_2O, dried, and acetylated with Ac_2O and pyridine. The acetate was purified by recrystallization from AcOEt to yield colorless needles (0.3 g.), m.p. 245°. *Anal.* Calcd. for $C_{21}H_{15}O_8I$: C, 48.27; H, 2.90. Found : C, 48.37; H, 2.95.

The acetate (0.2 g.) was dissolved in 1 ml. of 10% H_2SO_4 in AcOH at 100° and diluted with H_2O after 2 min. The precipitate was collected by filtration and recrystallized from MeOH to pale yellow needles, m.p. 209°. $FeCl_3$-reaction, greenish purple. *Anal.* Calcd. for $C_{15}H_9O_5I$: C, 45.45; H, 2.29. Found : C, 45.90; H, 2.52.

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*[4] The melting point of natural ginkgetin was higher (336°) than that already reported[1)] after regeneration via its acetate and recrystallization from methyl ethyl ketone.

*[5] *All melting points are uncorrected.*

Methylation : A mixture of 8-iodo-4',5,7-trihydroxyflavone (XI) (0.1 g.) obtained as above, Me_2SO_4 (0.3 g.), K_2CO_3 (0.5 g.) and MeCOEt (3 ml.) was boiled on a steam bath for 5 hr. and filtered while hot. From the filtrate the permethylate was separated and recrystallized from the same solvent to colorless needles, m.p. 238°, either alone or in admixture with 8-iodo-4',5,7-trimethoxyflavone*1 (XII). *Anal.* Calcd. for $C_{18}H_{15}O_5I$: C, 49.31; H, 3.45. Found : C, 49.20; H, 3.55.

5-Hydroxy-8-iodo-4',7-dibenzyloxyflavone (XIII)——(1) Debenzylation of X : A mixture of X (20.0 g. (0.03 mol.)) and 10% H_3PO_4 (160 g.) in AcOH was heated at 110°, becoming a clear, yellow solution, and the debenzylation product began to crystallize out to form a paste. After heating for 10 min., the reaction mixture was diluted with MeOH, and filtered. The solid was washed with Et_2O and recrystallized from pyridine to yellow, slender needles, m.p. 202°. Yield, 12.4 g. (72%). $FeCl_3$-reaction, dark greenish. *Anal.* Calcd. for $C_{29}H_{21}O_5I$: C, 60.38; H, 3.67. Found : C, 60.74; H, 3.87.

(2) Cyclization of the Diketone XVIII with Simultaneous Debenzylation : (i) 2'-Hydroxy-4',6'-dibenzyloxyacetophenone (XV) : A mixture of phloracetophenone (42.0 g.), benzyl chloride (69.6 g.), K_2CO_3 (80 g.) and dimethylformamide (150 ml.) was boiled in a metal bath for 1 hr., and the reaction mixture was poured into H_2O. The sticky product was recrystallized from Me_2CO to colorless needles, melting at 103°. Yield, 49.6 g. $FeCl_3$-reaction, reddish purple. *Anal.* Calcd. for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found : C, 75.86; H, 5.85.

(ii) 2'-Hydroxy-3'-iodo-4',6'-dibenzyloxyacetophenone (XVI) : A solution of XV (34.8 g.) in AcOH (250 ml.) was iodinated with I_2 (14.0 g.) and conc. HNO_3 (65.3% HNO_3) (10.0 g.). Yellowish prisms melting at 196° (26.1 g.) were obtained on recrystallization from pyridine. $FeCl_3$-reaction, dark purple. *Anal.* Calcd. for $C_{22}H_{19}O_4I$: C, 55.69; H, 4.04; I, 26.77. Found. C, 56.10; H, 4.19; I, 26.30.

(iii) 2-(*p*-Benzyloxybenzoyloxy)3'-iodo-4',6'-dibenzyloxyacetophenone (XVII) : XVI (23.7 g.) was esterified with *p*-benzyloxybenzoic anhydride (32,9 g.) and pyridine (80 ml.) by heating at 100° for 10 min. After washing the solidified product with MeOH, colorless prisms of almost pure ester (27.4 g.) melting at 169° were obtained. For analysis it was recrystallized from AcOEt to colorless needles, giving the same melting point as above. $FeCl_3$-reaction, negative. *Anal.* Calcd. for $C_{36}H_{29}O_6I$: C, 63.14; H, 4.27. Found : C, 62.88; H, 4.27.

(iv) 1-(2-Hydroxy-3-iodo-4,6-dibenzyloxyphenyl)-3-(4-benzyloxyphenyl)-1,3-propanedione (XVIII)) : (a) Rearrangement of the ester XVII—The ester XVII (17.1 g.) was heated with KOH (powder) (3.4 g.) in pyridine (50 ml.) at 100° for 5 min. The reaction mixture was acidified with AcOH, and the solidified diketone was recrystallized from benzene to brilliant yellow needles melting at 196° (3.9 g.). $FeCl_3$-reaction, yellowish green. *Anal.* Calcd. for $C_{36}H_{29}O_6I$: C, 63.14; H, 4.27. Found : C, 63.43; H, 4.44.

(b) Ring opening of the flavone X—A solution of the flavone X (6.7 g.) in 1% KOH solution (150 ml.) in EtOH+dioxane (2:1) was boiled for 1 hr. and acidified with AcOH. The yellow product was collected by filtration and recrystallized from benzene to yellow needles (4.4 g.), m.p. 195°, undepressed on admixture with the diketone obtained as above.

(v) 5-Hydroxy-8-iodo-4',7-dibenzyloxyflavone (XIII) : A mixture of the diketone XVIII (6.8 g.) and 10% H_3PO_4 (50 ml.) in AcOH was heated at 110° for 10 min. The pasty product was diluted with MeOH, and recrystallized from pyridine to yellow needles (3.7 g.), m.p. 201°, undepressed on admixture with the product obtained as in (1).

5-Benzoyloxy-8-iodo-4',7-dibenzyloxyflavone (XIV)——XIII (11.5 g.) was benzoylated with BzCl (3.5 g.) and pyridine (50 ml.) by heating at 110° for 10 min. Cooled and solidified mixture was diluted with MeOH. The benzoate formed colorless needles (12.6 g.), m.p. 205°. $FeCl_3$-reaction, negative. *Anal.* Calcd. for $C_{36}H_{25}O_6I$: C, 63.48; H, 3.70. Found : C, 63.78; H, 3.81.

III. Synthesis of Ginkgetin——A mixture of VII (5,8 g. (0.011 mol.)), XIV (6.8 g. (0.010 mol.)) and 6.4 g. (0.1 gram, atom) of freshly prepared activated copper powder was heated in a flask (50 ml.) in a metal bath at 225~230° for 40 min. After cool, the dark brown, fused resinous reaction mixture was extracted several times with boiling $CHCl_3$ and the combined extract was evaporated to a sticky syrup, which was heated with 10% H_2SO_4 (50 g.) in AcOH at 110° for 10 min. to hydrolyze benzoyl and benzyl groups of the product XIX, and poured into H_2O. The dark brown, resinous mass was collected, dissolved in dioxane (50 ml.), mixed with Et_2O (500 ml.) and filtered to remove a brown precipitate. The filtrate was shaken with three 50 ml. portions of 10% K_2CO_3 solution. The combined extract, in which yellow, sandy crystatls of potassium salt of ginkgetin deposited, was filtered after 2~3 hr. and the salt was recrystallized from 10% K_2CO_3 solution to 1.5 g. (25%) of the potassium salt of ginkgetin.

The salt was dissolved in hot H_2O (100 ml.), and acidified with dil. H_2SO_4 to form a colloidal precipitate which was collected by filtration, washed with H_2O, dried, and recrystallized from MeCOEt to pale yellow, small plates melting at 336°. which showed no depression of the melting point on admixture with natural ginkgetin.*4 Yield, 1.19 g. (21%). Synthesized ginkgetin (I) is scarcely soluble in benzene, alcohols, Me_2tO, etc. $FeCl_3$-reaction, brownish purple. Mg+HCl reaction, orange red. *Anal.* Calcd. for $C_{32}H_{22}O_{10}$: C, 67.84; H, 3.91. Found : C, 67.47; H, 4.12,

Reaction of IV (5.7 g.), X (6.7 g.) and activated copper powder (6.4 g.) as above gave only 0.34 g. (6%)

of ginkgetin. When VII (5.8 g.) was substituted for VI (5.7 g.) in the above reaction, the yield of ginkgetin was 0.62 g. (11%).

Acetate XXII : A mixture of ginkgetin (0.2 g.), Ac_2O (1.0 g.) and 1 drop of pyridine was heated at 100° for 10 min. Colorless prisms (from Me_2CO), m.p. 259°, either alone or on admixture with the specimen of natural material. $FeCl_3$-reaction, negative. *Anal.* Calcd. for $C_{40}H_{30}O_{14}$: C, 65.38; H, 4.12. Found : C, 65.34; H, 4.25.

Tetramethyl ether III : Ginkgetin (0.2 g.) was methylated with Me_2SO_4 (5 ml.) and 30% KOH solution. Colorless needles (from dimethylformamide), m.p. 238°, undepressed on admixture with the material of natural origin. $FeCl_3$-reaction, negative. *Anal.* Calcd. for $C_{36}H_{30}O_{10}$: C, 69.44; H, 4.86. Found : C, 69.24; H, 4.90.

Condensation Reaction of VII or VI, and XIV or X in Dimethylformamide (Formation of 8,8-Bis Compounds, XX and XXI)——A mixture of VII (2.9 g.), XIV (3.4 g.), activated copper powder (3.2 g.) and dimethylformamide (20 ml.) was refluxed in a metal bath for 4 hr. and filtered while hot. After standing the filtrate for 3 hr., the crystals which separated out, were collected and recrystallized from EtOH to colorless prisms melting at 170° (0.9 g.), undepressed on admixture with synthetic 8,8-bis compound XX. $FeCl_3$-reaction, negative. *Anal.* Calcd. for $C_{72}H_{50}O_{12}$: C, 78.09; H, 4.56. Found : C, 78.22; H, 4.68.

By using VI (2.9 g.) instead of VII (2.9 g,) and X (3.4 g.) instead of XIV (3.4 g) in the above reaction, the crystals, which separated from the filtrate on dilution with 3 volumes of EtOH and after standing overnight, were recrystallized from EtOH to colorless prisms (0.5 g.), m.p. 158°, undepressed on admixture with synthetic 8,8-bis compound XXI. $FeCl_3$-reaction, negative.

Synthesis of 8,8-Bis Compounds, XX and XXI——A mixture of XIV (0.7 g.), activated copper powder (1 g.) and dimethylformamide (5 ml.) was refluxed for 4 hr., filtered while hot, and needles, which separated from the filtrate, were collected after 3 hr. XX formed colorless prisms, melting at 170°. *Anal.* Calcd. for $C_{72}H_{50}O_{12}$: C, 78.09; H, 4.56. Found : C, 78.30; H, 4.75.

X (0.7 g,) was substituted for XIV (0.7 g,) in the above reaction and dilution of the filtrate with 3 volumes of EtOH, afforded the bis compound XXI as colorless prisms (from EtOH), melting at 159°. *Anal.* Calcd. for $C_{72}H_{54}O_{10}$: C, 80.12; H, 5.05. Found : C, 80.01; H, 5.33.

The authors are grateful to Dr. T. Goto, Assistant Professor of Nagoya University, for measurement of infrared spectra and to Miss K. Masuda for carrying out elemental analysis. They are also indebted to the Ministry of Education for Grant-in-Aid for Fundamental Scientific Research for 1958~1960.

Summary

The condensation of 3′-iodo-5-benzoyloxy-4′,7-dimethoxyflavone and 5-benzoyloxy-8-iodo-4′,7-dibenzyloxyflavone was carried out at 225~230° for 40 minutes, with activated copper powder. The chloroform extract of the reaction mixture was heated with 10% H_2SO_4 in AcOH at 110° for 10 minutes to hydrolyze benzoyl and benzyl groups. The hydrolysate was dissolved in a mixture of dioxane and ether, and shaken with 10% K_2CO_3 solution to obtain yellow, sandy crystalline precipitate of potassium salt of ginkgetin. This salt was purified by recrystallization from 10% K_2CO_3 solution, decomposed with dilute H_2SO_4, and the free ginkgetin obtained was recrystallized from methyl ethyl ketone to pale yellow, small plates, m.p. 336°. Its acetate formed colorless needles, m.p. 259°. Ginkgetin and its acetate synthesized above were respectively identified with the corresponding materials of natural origin.

(Received March 27, 1962)