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Syntheses of Ring-substituted Flavonoids and Allied Compounds. XI.[1] Synthesis of Hinokiflavone

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Permethylated 3-nitrobisflavonyl ether (XXIV), the key-intermediate for the synthesis of the proposed structure (XXX), was prepared by the condensation of 8-hydroxy-4′,5,7-trimethoxyflavone (XX) with 4′-iodo-3′-nitro-5,7-dimethoxyflavone (XXIII) in DMSO in the presence of K_2CO_3 at 110° for 1 hr. The nitro ether was reduced by $Na_2S_2O_4$ in aq. DMF, diazotized and decomposed with 50% H_3PO_2 to give XXVII, which proved to be different from pentamethyl ether of natural hinokiflavone.

An alternative bisflavone with 4′,6″-coupling positions has now been synthesized in a similar route described above. XXXIV was condensed with XXIII to 3′-nitro ether (XXXV), which was reduced, diazotized and decomposed to give permethylated ether (XXXVIII), identical with permethyl ether of natural hinokiflavone.

The synthesized methyl ether was finally demethylated by means of HI·Ac_2O at 130—140° for 3 hr to give 4‴,5,5″,7,7″-pentahydroxy-4′,6″-bisflavonyl ether (XLII) identical with natural hinokiflavone.

4′,8″-Bisflavone (XXVII) was converted into a bisflavone (XLII) identical with natural hinokiflavone, when heated with HI·Ac_2O as above (Wessely–Moser rearrangement).

In recent years a number of bisflavones having the skeleton of 4′,5,7-trihydroxyflavone (apigenin) have been isolated from the leaves of *Coniferae*. They are classified into bisflavonyls (ginkgetin,[3] sciadopitysin,[4] *etc.*) and bisflavonyl ethers (hinokiflavone[5] and its methyl ethers[6]). Structure for ginkgetin (I) was already confirmed by synthesis.[1]

This paper deals with a synthesis of hinokiflavone, a bisflavonyl ether from the leaves of *Chamaecyparis obtusa* Endl., for which structure (XXX) has been proposed.[5] It was now revised by this work, however, to the alternative structure (XLII) having the 4′,6″-ether linkage.

The key step in the synthesis of the bisflavonyl ethers is the Ullmann condensation between appropriate aromatic halogenide and phenolate for the formation of diaryl ether linkage. Difficulty in this condensation reaction usually arises from the low reactivity of aromatic helogenide compared with the phenolate.

Attempted synthesis of the pentamethyl ether (XXVII)[7] of the proposed structure (XXX) by the Ullmann condensation between 4′-hydroxy-5,7-dimethoxyflavone[8] (IV) and

1) Part X: K. Nakazawa and M. Ito, *Chem. Pharm. Bull.* (Tokyo), **11**, 283 (1963).
2) Location: *Mitahora, Gifu.*
3) K. Nakazawa, *Yakugaku Zasshi*, **61**, 174; 228 (1941).
4) N. Kawano, *Yakugaku Zasshi*, **76**, 457 (1956); *Chem. Ind.* (London), **1959**, 368, 852.
5) Y. Fukui and N. Kawano, *J. Am. Chem. Soc.*, **81**, 6331 (1959); N, Kawano and Y. Fukui, *Yakugaku Zasshi*, **80**, 749 (1960); Y. Fukui, *ibid.*, **80**, 752, 756 (1960).
6) H. Miura, N. Kawano, and A.C. Waiss Jr., *Chem. Pharm. Bull.* (Tokyo), **14**, 1404 (1966); H. Miura, *Yakugaku Zasshi*, **87**, 871 (1967).
7) When the present work was in progress, a paper entitled "Synthesis of Hinokiflavone Pentamethyl Ether" by the same condensation reaction has appeared in brief report in S.K. Krishnan, V.V. Murti, and T.R. Seshadri, *Current Sci.* (India), **35** (3), 64 (1966).
8) H.S. Mahal and K. Venkataraman, *J. Chem. Soc.*, **1936**, 569. This flavone has now readily prepared from 2-hydroxy-4,6-dimethoxyacetophenone by *p*-benzyloxybenzoylation, rearrangement and cyclization with sulfuric acid in acetic acid.

8-iodo-4′,5,7-trimethoxyflavone[9] (V) under a variety of conditions was unsuccessful, and the reactions resulted in formation of resinous products without obtaining the condensation product.

This difficulty, however, could be overcome by activation of the halogen substituent by introduction of a nitro group *ortho* to it as illustrated by the following example.

A Model Experiment for the Formation of Diaryl Ether Linkage

The Ullmann condensation between methyl 4-iodo-3-nitrobenzoate (VI) and methyl 4-hydroxybenzoate (VII) in dimethylsulfoxide (DMSO) in the presence of potassium carbonate at 105—110° for 1 hr, followed by the steps outlined in the Chart 1, afforded readily 4,4′-dicarbomethoxydiphenyl ether (X).[10] Thus this model route provides a valuable method for the synthesis of diaryl ethers and could be applied to the synthesis of hinokiflavone and its allied compounds.

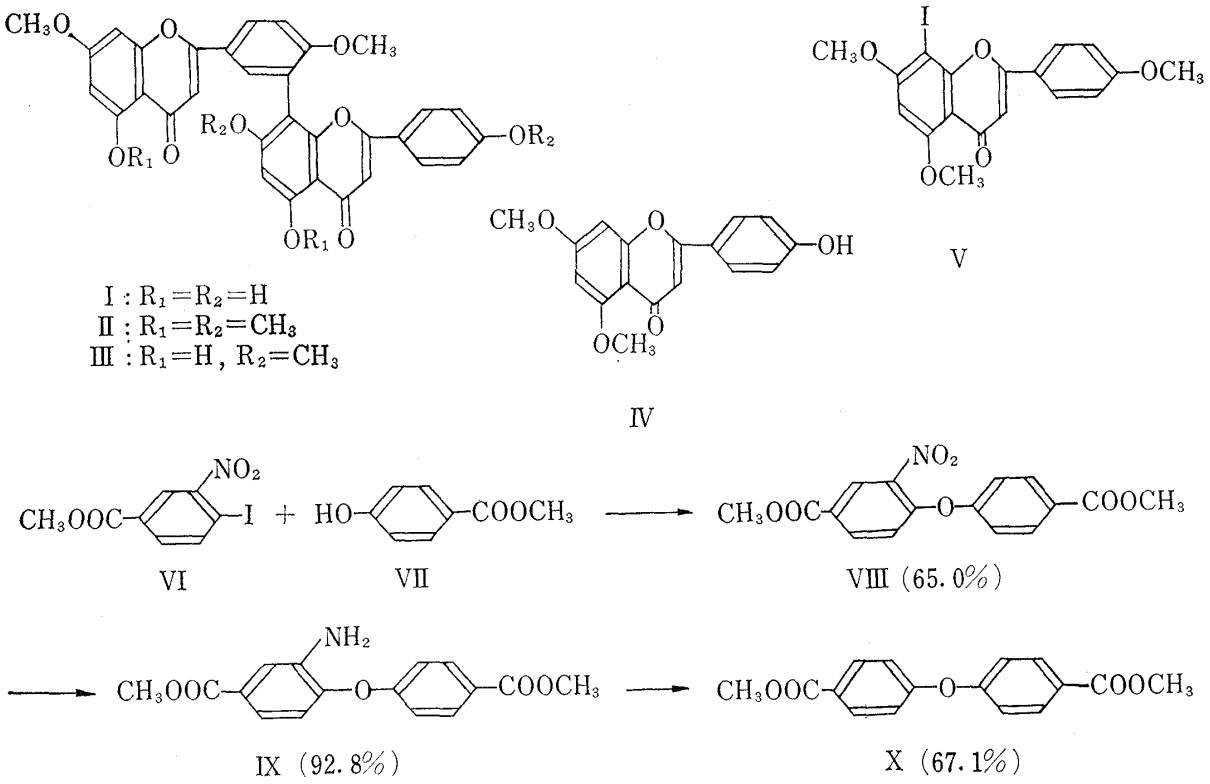

Chart 1

Synthesis of 4′,8″-Bisflavonyl Ethers

Synthesis of the pentamethyl ether (XXVII) from 3,6-dihydroxy-2,4-dimethoxyacetophenone (XI) by a 11-step sequence (or from pyrogallol by a 16-step sequence) was carried out according to the route shown in Chart 2.

2,3-Dihydroxy-4,6-dimethoxyacetophenone (XV),[11] was readily prepared in the present study from 3,6-dihydroxy-2,4-dimethoxyacetophenone (XI)[12] by selective monoacetylation at low temperature, methylation with dimethyl sulfate and partial demethylation with alumi-

9) K. Nakazawa, *Chem. Pharm. Bull.* (Tokyo), **10**, 1032 (1962).
10) T.H. Golden, *J. Chem. Soc.*, **1961**, 1604; *cf.* M. Tomita, *Yakugaku Zasshi*, **57**, 609 (1937).
11) P.D. Gardner, W.J. Horton, and R.E. Pincock, *J. Am. Chem. Soc.*, **78**, 2541 (1956); V.J. Horton and M.G. Stout, *J. Org. Chem.*, **27**, 830 (1962). This phenol, however, could be conveniently prepared by the route as shown in Chart 2.
12) F. Mauthner, *J. Prakt. Chem.*, **147**, 288 (1936).

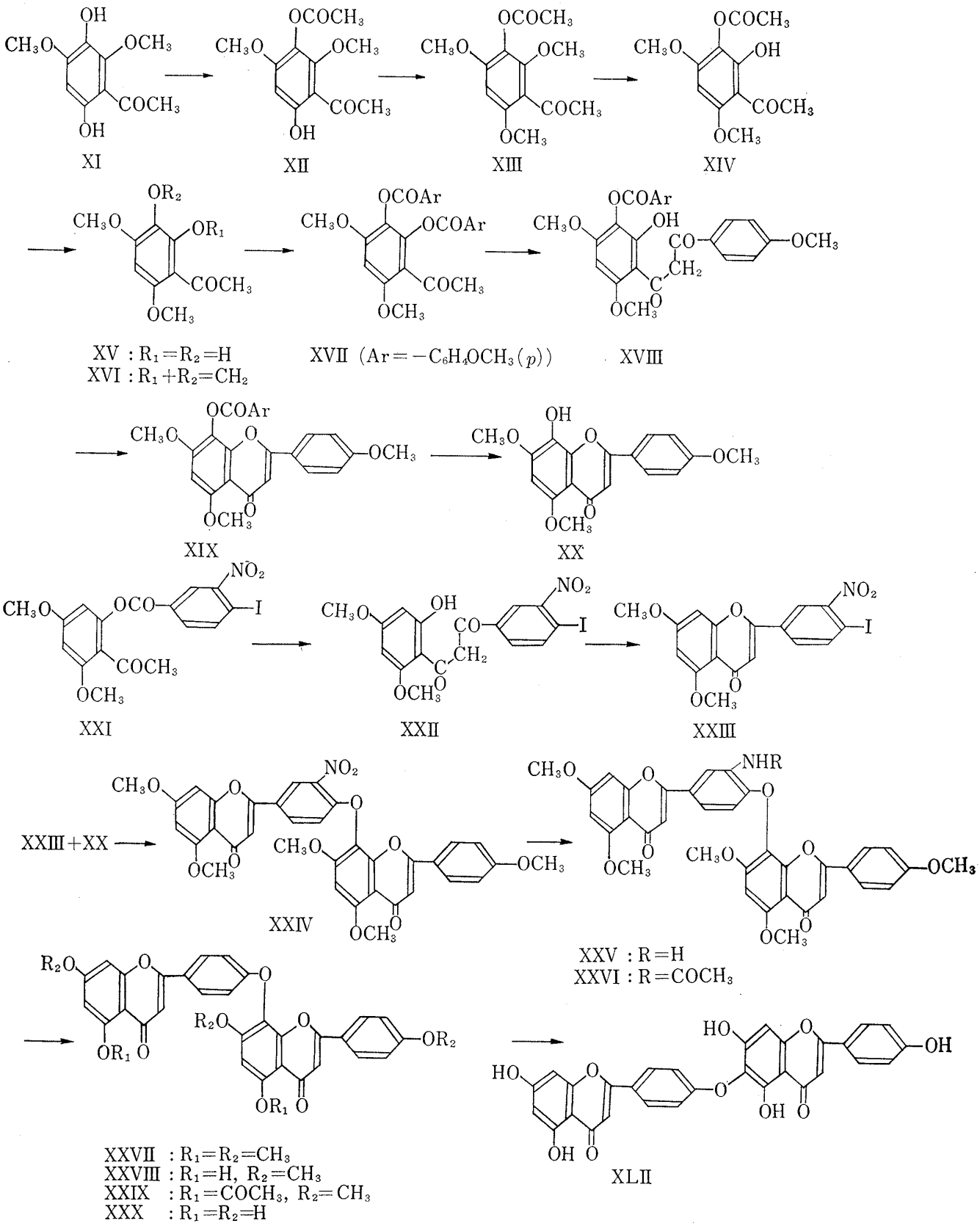

Chart 2

num chloride followed by saponification. This dihydric phenol is reversely monoacetylated to XIV, and gives methylene derivative (XVI).

By the authors procedure[9] dianisate (XVII) was isomerized to diketone (XVIII) by means of potassium hydroxide in pyridine and cyclized to XIX, followed by saponification to give 8-hydroxy-4′,5,7-trimethoxyflavone (XX).

Similarly, 4′-iodo-3′-nitro-5,7-dimethoxyflavone (XXIII) was obtained from 2-hydroxy-4,6-dimethoxyacetophenone by 4-iodo-3-nitrobenzoylation, isomerization and cyclization.

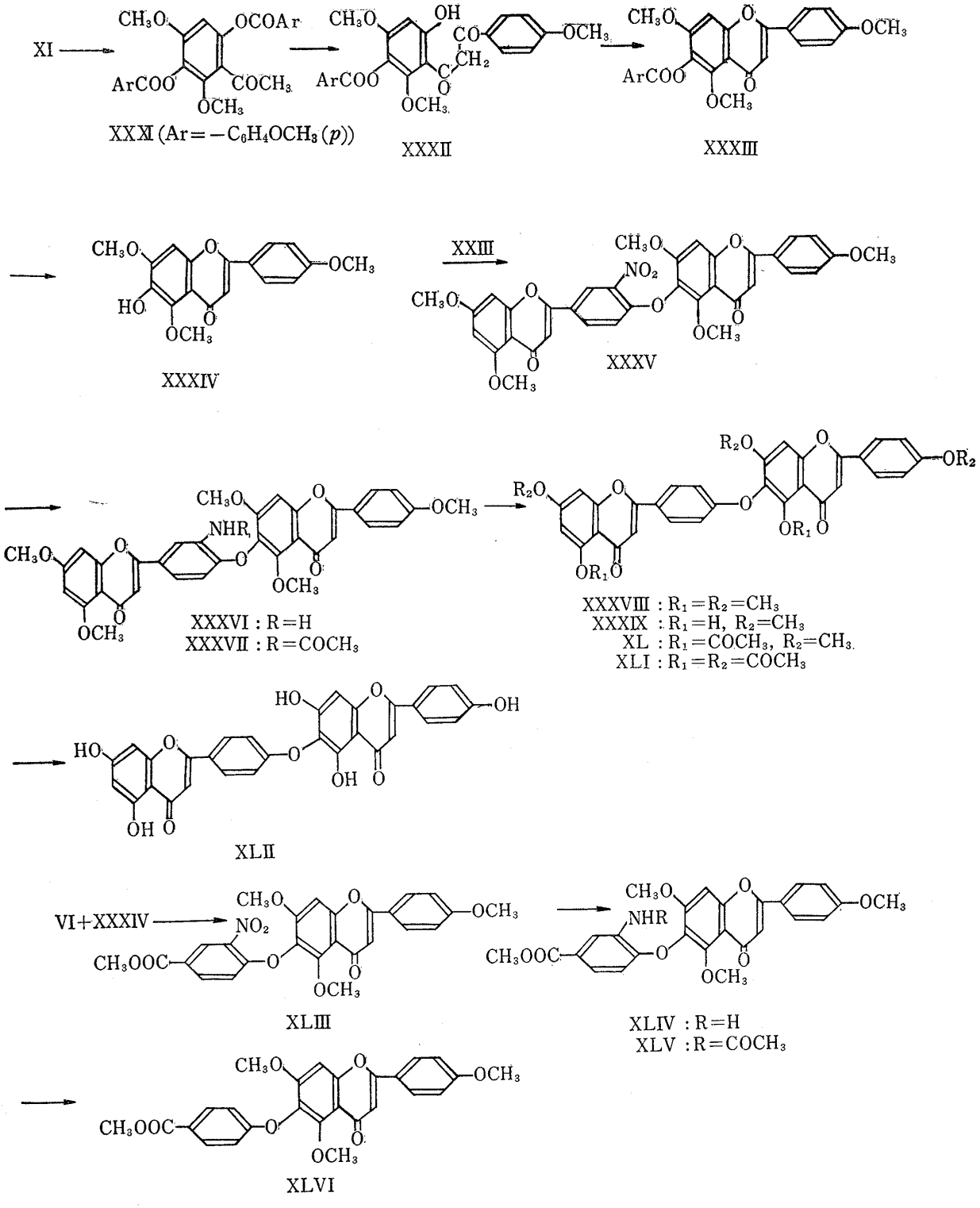

Chart 3

4‴,5,5″,7,7″-pentamethoxy-3′-nitro-4′,8″-bisflavonyl ether (XXIV) was prepared in 85.3% yield by coupling of 8-hydroxyflavone (XX) with iodonitroflavone (XXIII) in DMSO in the presence of potassium carbonate.

3′-Aminobisflavonyl ether (XXV), formed by reduction of nitrobisflavonyl ether (XXIV) with sodium hydrosulfite in aqueous dimethylformamide (DMF), was diazotized and reduced with 50% hypophosphorous acid to give the pentamethoxybisflavonyl ether (XXVII). The pure product (mp 268°) was isolated from the reaction mixture by chromatography on activated alumina using chloroform as a solvent in 45.4% yield. The melting point of this compound was depressed on admixture with hinokiflavone pentamethyl ether (mp 260°) prepared from the natural flavone, and their infrared spectra were different.

For characterization the pentamethyl ether (XXVII) was partially demethylated by aluminum chloride to give 5,5″-dihydroxyflavone (XXVIII), which forms yellow needles (mp 279°) and its acetate (XXIX) is colorless needles (mp 258°).

Synthesis of 4′,6″-Bisflavonyl Ethers (Hinokiflavone and Its Methyl Ethers)

Since the structure of hinokiflavone pentamethyl ether proved to be different from XXVII, synthesis of another isomer (XXXVIII) and its demethylation product (XLII) was carried out, as shown in Chart 3, by a similar route described above.

4‴,5,5″,7,7″-Pentamethoxy-3′-nitro-4′-,6″-bisflavonyl ether (XXXV) was prepared in 80.3% yield, similarly as in XXIV, by condensation of 6-hydroxyflavone (XXXIV)[13] with iodonitroflavone (XXIII) in DMSO in the presence of potassium carbonate.

3′-Nitrobisflavonyl ether (XXXV) was reduced to amine (XXXVI), which was diazotized and reduced with 50% hypophosphorus acid to give 4‴,5,5″,7,7″-pentamethoxy-4′,6″-bisflavonyl ether (hinokiflavone pentamethyl ether) (XXXVIII). After purification on activated alumina using chloroform as a solvent, the product was obtained in 34.4% yield, which melted at 260°. The melting point was undepressed on admixture with natural hinokiflavone pentamethyl ether (mp 260°)[5] and their infrared spectra were superimposable. The structure XXXVIII was also supported by nuclear magnetic resonance spectrum.

5,5″-Dihydroxyflavone (XXXIX) was obtained in yellow needles (mp 290°) on demethylation of the pentamethyl ether (XXXVIII) by aluminum chloride. Its acetate (XL) forms colorless needles (mp 250°).

4‴,5,5″,7,7″-Pentahydroxy-4′-6″-bisflavonyl ether (hinokiflavone) (XLII) was prepared by heating the pentamethyl ether (XXXVIII) with a mixture of hydriodic acid and acetic anhydride and purified through its acetate (mp 251°). The product was pale yellow needles, mp 343° (decomp.). This could lead reversely to the pentamethyl ether (XXXVIII) by complete methylation with dimethyl sulfate. The synthetic demethylated product (XLII) and its acetate (XLI) were shown to be identical with natural hinokiflavone[5] and its acetate,[5] respectively, by elementary analyses, mixed melting points determination and comparison of their infrared spectra.

Thus the structure of hinokiflavone (XLII) was established.

Formation of Hinokiflavone by Demethylation of 4′,8″-Bisflavonyl Ether (XXVII) with Simultaneous Rearrangement

4′,8″-Bisflavonyl ether (XXVII) was demethylated by means of a mixture of hydriodic acid and acetic anhydride to a product, which formed after purification through its acetate pale yellow needles (mp 343°) and proved to be identical with natural hinokiflavone. This indicates that 4′,8″-bisflavonyl ether (XXVII) was converted into 4′,6″-bisflavonyl ether (hinokiflavone) (XLII) during the demethylation by means of hydriodic acid under condi-

13) M.G. Stout, H. Reich, and M.N. Huffman, *J. Pharm. Sci.*, **53**, 192 (1964). The preparation of 6-hydroxyflavone (XXXIV), however, has now improved over the published procedures by the smooth route outlined in Chart 3.

tions which may be expected to bring about a Wessely–Moser rearrangement[14–21] in flavonoids, coumarins, xanthones, *etc.*

Synthesis of 6-(4″-Carbomethoxyphenoxy)-4′,5,7-trimethoxyflavone

This flavonyl phenyl ether (XLVI) (mp 206°) was synthesized by coupling of 6-hydroxyflavone (XXXIV) with methyl 4-iodo-3-nitrobenzoate (VI), reduction and deamination. It was identified with the complete methyl ether ester of an alkaline degradation product[5] of natural hinokiflavone by undepression of mixed fusion and identity of their infrared spectra.

The bisflavonyl ethers synthesized above (XXIV, XXV, XXVII, XXXV, XXXVI, XXXVIII, XLII, *etc.*) are extremely less soluble in conventional solvents, and sometimes difficulty was experienced in obtaining satisfactory C.H. analysis as observed in ginkgetin (I)[1,3] and its methyl ethers (II, III).[9] This may be caused by tenacious retention of water or solvent of crystallization.

Experimental[22]

A Novel Synthesis of 4,4′-Dicarbomethoxydiphenyl Ether (X) 4,4′-Dicarbomethoxy-3-nitrodiphenyl Ether (VIII)——A mixture of methyl 4-iodo-3-nitrobenzoate (VI) (30.7 g, 0.1 mole), methyl 4-hydroxybenzoate (VII) (15.2 g, 0.1 mole), K_2CO_3 (27.6 g, 0.2 mole) and DMSO (50 ml) was heated with occasional stirring at 100° for 1 hr, and was poured into water (300 ml). Gray precipitate was filtered, washed with water and recrystallized from acetone to give (VIII) (21.8 g, 65.0%) as pale yellow, small needles, mp 120—121°. *Anal.* Calcd. for $C_{16}H_{13}O_7N$: C, 58.01; H, 3.96; N, 4.23. Found: C, 58.28; H, 4.22; N, 4.20.

3-Amino-4,4′-dicarbomethoxydiphenyl Ether (IX)——In a solution of VIII (33.5 g, 0.1 mole) in AcOH (120 ml), $SnCl_2+2H_2O$ (67.7 g, 0.3 mole) and 35% HCl (75 ml) were dissolved with stirring and the resulting warm solution was, after keeping 2 hr, made strongly alkaline with 40% KOH. Separated milky amine was taken up in ether, the ethereal solution was washed with water, dried over $MgSO_4$ and evaporated leaving crystallized amine (IX) (28.4 g, 92.8%). An analytical sample was prepared by recrystallization from C_6H_6 as colorless prisms, mp 81°. *Anal.* Calcd. for $C_{16}H_{15}O_5N$: C, 63.78; H, 5.02. Found: C, 63.76; H, 5.01.

4,4′-Dicarbomethoxydiphenyl Ether (X)——A solution of IX (15.2 g, 0.05 mole) and 35% HCl (30 g) in DMF (80 ml) was diazotized with 10% $NaNO_2$ (34.5 g, 0.05 mole). After addition of 50% H_3PO_2 (100 ml), the mixture was allowed to stand overnight to deposite deaminated product, which was filtered, washed with MeOH and recrystallized from C_6H_6 to yield X (9.6 g, 67.1%) as colorless needles, mp and mixed mp with an authentic sample[9] 156°. *Anal.* Calcd. for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93. Found: C, 67.17; H, 5.04.

Synthesis of 4′,8″-Bisflavonyl Ethers (XXVII, XXVIII, XXIX) 3-Acetoxy-6-hydroxy-2,4-dimethoxyacetophenone (XII)——A mixture of 3,6-dihydroxy-2,4-dimethoxyacetophenone (XI)[11] (106.1 g, 0.5 mole), Ac_2O (200 ml) and AcONa (41.0 g) was heated with occasional stirring at 60° for 1 hr, and was poured into water (500 ml) to decompose excess Ac_2O. Gray crystals were separated by filtration, washed with water and MeOH to yield the acetate (XII) (102.0 g, 80.2%), mp 110°. An analytical sample was recrystallized from MeOH to form colorless needles, mp 112°. $FeCl_3$–reaction, purple. *Anal.* Calcd. for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.42; H, 5.51.

3-Acetoxy-2,4,6-trimethoxyacetophenone (XIII)——A mixture of XII (127.6 g, 0.5 mole), acetone (400 ml), K_2CO_3 (207 g, 1.5 mole) and Me_2SO_4 (126.1 g, 1 mole) was refluxed for 15 hr, and was poured into water (1 liter). Crude crystals of the product were filtered and recrystalized from C_6H_6 to yield XIII as colorless prisms (114.0 g, 85.0%), mp 110°. $FeCl_3$–reaction, negative. *Anal.* Calcd. for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 58.17; H, 5.92.

3-Acetoxy-2-hydroxy-4,6-dimethoxyacetophenone (XIV)——A solution of $AlCl_3$ (33.3 g, 0.25 mole) in $C_6H_5NO_2$ (250 ml) at 80° was mixed with a solution of XIII (67.1 g, 0.25 mole) in $C_6H_5NO_2$ (50 ml), and, after heating at 100° for 5 min, the mixture was poured onto cracked ice (1 kg) containing 35% HCl (20 ml).

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14) F. Wessely and G.H. Moser, *Monatsh.*, **56**, 97 (1930).
15) S.K. Mukerjee and T.R. Seshadri, *J. Sci. Ind. Res.*, **13B**, 400 (1934).
16) R.C. Shah and C.R. Mehta, *Current Sci.*, **6**, 503 (1938).
17) R.C. Shah, C.R. Mehta, and T.S. Wheeler, *J. Chem. Soc.*, **1938**, 1555.
18) S. Hattori, *Nippon Kagaku Zasshi*, **60**, 875 (1939).
19) K. Nakazawa, *Yakugaku Zasshi*, **59**, 530 (1939).
20) E.M. Philbin, J. Swirski, and T.S. Wheeler, *J. Chem. Soc.*, **1956**, 4409.
21) D.M.X. Donnelly, P.B. Green, E.M. Philbin, F.T.B. Smyth, and T.S. Wheeler, *Chem. Ind.* (London), **1958**, 892.
22) All melting points are uncorrected. $FeCl_3$–reaction was tested in ethanolic solutions.

The resulting aqueous slurry of the product was washed several times with ether, filtered, washed with water and dried to give the crude demethylated product (XIV) (33.0 g, 51.9%), mp 175°. An analytical sample was obtained by recrystallization from AcOH as colorless needles, mp 180°. $FeCl_3$–reaction, reddish purple. *Anal.* Calcd. for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.75; H, 5.82.

From the unified ether washings, crude dihydric phenol (XV) (11.9 g, 22.4%), mp 158°, was recovered by extraction with 5% KOH followed by acidification.

2,3-Dihydroxy-4,6-dimethoxyacetophenone (XV)——A solution of XIV (101.6 g, 0.4 mole) in 10% KOH (500 ml) was allowed to stand at room temperature for 1 hr. The alkaline solution was acidified with HCl to precipitate yellow crystals of XV, which were filtered, washed with water and dried (76.0 g, 89.5%), mp 163°. It was sufficiently pure for next step. It forms brilliant yellow prisms from C_6H_6, mp 164—165° (lit.[10] mp 165.2—166.5°). $FeCl_3$–reaction, light green, on addition of alkali turned reddish. *Anal.* Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.67; H, 5.66.

Monoacetate (XIV)——The dihydric phenol (XV) (2.1 g) was acetylated at 60° with Ac_2O (5 ml) and AcONa (1 g). Colorless needles (2.0 g) from AcOH, mp and mixed mp with XIV 180°.

Methylene Ether (XVI)——XV (2.1 g) was heated with CH_2Br_2 (2.2 g), K_2CO_3 (3.0 g) and DMSO (15 ml) at 130° for 1 hr. Colorless needles, mp 95°, from C_6H_6–ligroin. $FeCl_3$–Reaction, negative. *Anal.* Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 59.11; H, 5.47.

2,3-Dianisoyloxy-4,6-dimethoxyacetophenone (XVIII)——XV (63.6 g, 0.3 mole) was anisoylated with anisoyl chloride (112.5 g, 0.66 mole) and pyridine (250 ml) by heating at 100° for 5 min. After cooling the mixture was diluted with MeOH to separate the product (XVII), which was filtered, washed with MeOH to give the crude anisate (93.0 g, 64.5%), mp 190°. Colorless needles from AcOH, mp 208°. *Anal.* Calcd. for $C_{26}H_{24}O_9$: C, 64.99; H, 5.04. Found: C, 64.87; H, 5.32.

1-(3′-Anisoyloxy-2′-hydroxy-4′,6′-dimethoxyphenyl)-3-(4″-methoxyphenyl)-1,3-propanedione (XVIII)——When a mixture of XVII (96.1 g, 0.2 mole), pulverized KOH (16.8 g, 0.3 mole) and pyridine (250 ml) was heated with strong stirring to 90—95° for 1 min, a brown–violet solution first formed was soon solidified to a thick, yellow paste of K salt of the diketone (XVIII). The mixture was decomposed with AcOH (20 ml) and MeOH (500 ml), and the sandy, yellow crystals were filtered and washed with MeOH to yield XVIII (67.0 g, 69.7%), mp 202°. From DMF yellow prisms of pure diketone, mp 209°, were obtained. *Anal.* Calcd. for $C_{26}H_{24}O_9$: C, 64.99; H, 5.04. Found: C, 64.96; H, 5.15.

8-Anisoyloxy-4′,5,7-trimethoxyflavone (XIX)——A boiling solution of XVIII (96.1 g, 0.2 mole) in AcOH (800 ml) was mixed with 20% H_2SO_4 in AcOH (100 g) and the resulting red solution was poured into water (2 liter). The crystalline paste was filtered, washed with water to yield the anisoylated flavone (82.8 g, 89.5%), mp 228°. It forms colorless prisms from AcOH, mp 228°. *Anal.* Calcd. for $C_{26}H_{22}O_8$: C, 67.52; H, 4.80. Found: C, 67.59; H, 4.83.

8-Hydroxy-4′,5,7-trimethoxyflavone (XX)——XIX (46.2 g, 0.1 mole) was dissolved in 10% KOH (MeOH–H_2O 1:1) (250 ml) by boiling for 1 hr to a red–orange solution, and acidified with HCl to separate yellow paste of the flavone (XX). It was filtered, washed with water and MeOH to give XX (23.0 g, 70.1%), mp 230°. Recrystallization from AcOH gave yellow prisms, mp 235°. $FeCl_3$–reaction, negative. Mg+HCl reaction, dark orange. *Anal.* Calcd. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91. Found: C, 65.61; H, 5.13.

2-(4′-Iodo-3′-nitrobenzoyloxy)-4,6-dimethoxyacetophenone (XXI)——A mixture of 2-hydroxy-4,6-dimethoxyacetophenone (98.1 g, 0.5 mole), 4-iodo-3-nitrobenzoyl chloride (155.7 g, 0.5 mole) and pyridine (180 ml) was heated at 100° for 5 min, and then diluted with MeOH (450 ml) and water (150 ml) to give crude crystals of XXI. It forms yellow needles from MeOH (153.1 g, 65.0%), mp 140°. *Anal.* Calcd. for $C_{17}H_{14}O_7NI$: C, 43.31; H, 3.00; N, 2.97; I, 26.95. Found: C, 43.21; H, 3.21; N, 3.10; I, 26.55.

1-(2′-Hydroxy-4,6-dimethoxyphenyl)-3-(4″-iodo-3″-nitrophenyl)-1,3-propanedione (XXII)——A mixture of XXI (94.2 g, 0.2 mole), pulverized KOH (33.6 g, 0.6 mole) and pyridine (200 ml) was heated with strong stirring at 90—95° for 1 min. After cooling AcOH (25 ml) and MeOH (200 ml) was added to give yellow crystals of the diketone (43.4 g, 46.0%). It forms yellow plates from C_6H_6, mp 168°. *Anal.* Calcd. for $C_{17}H_{14}O_7NI$: C, 43.31; H, 3.00. Found: C, 43.01; H, 3.30.

4′-Iodo-3-nitro-5,7-dimethoxyflavone (XXIII)——Cyclization of XXII was effected by mixing a boiling solution of XXII (47.1 g, 0.1 mole) in AcOH (250 ml) with 20% H_2SO_4 in AcOH (25 g). The flavone was obtained from DMF in yellow needles (25.1 g, 55.5%), mp 266°. Mg+HCl–reaction, negative. *Anal.* Calcd. for $C_{17}H_{12}O_6NI$: C, 45.03; H, 2.67. Found: C, 45.26; H, 2.88.

3′-Nitro-4‴,5,5″,7,7″-pentamethoxy-4′,8″-bisflavonyl Ether (XXIV)——A mixture of iodonitroflavone (XXIII) (27.7 g, 0.05 mole), 8-hydroxyflavone (XX) (16.4 g, 0.05 mole), K_2CO_3 (20.7 g) and DMSO (150 ml) was heated at 100° for 1 hr with occasional stirring, and was added to water (500 ml). Dark, gray product was filtered, washed with water, dried and recrystallized from DMF to yield colorless prisms (28.3 g, 85.3%), mp 275°. *Anal.* Calcd. for $C_{35}H_{27}O_{12}N$: C, 64.30; H, 4.17; N, 2.14. Found: C, 64.30; H, 4.49; N, 2.04.

3′-Amino-4‴,5,5″,7,7″-pentamethoxy-4′,8″-bisflavonyl Ether (XXV)——Since 3′-nitrobisflavonyl ethers (XXIV, XXXV) are less soluble in solvents and precipitated from solutions with metallic salts and/or inorganic acids (HCl, H_2SO_4, *etc.*), the reduction of these nitroflavones was carried out in different manner from that described in the model experiments (VIII→IX).

To a stirring suspension of XXIV (13.0 g, 0.02 mole) in a solution of DMF (400 ml), water (200 ml) and AcOH (50 ml), was added $Na_2S_2O_4$ (19 g) at 80—90° in a period of 20 min. After further stirring for 40 min AcONa (10 g) was dissolved in the mixture, and after cooling for 2 hr the crystals of the amine were filtered and recrystallized from DMF to give the pure amine (XXV) as colorless prisms (11.7 g, 92.4%), mp 295°. *Anal.* Calcd. for $C_{35}H_{29}O_{10}N+\frac{1}{2}H_2O$: C, 66.43; H, 4.78. Found: C, 66.88; H, 4.75.

Acetate (XXVI)——Colorless prisms from $CHCl_3$+acetone mp 323°. *Anal.* Calcd. for $C_{37}H_{31}O_{11}N$: C, 66.74; H, 4.70. Found: C, 66.95; H, 4.82.

4‴,5,5″,7,7″-Pentamethoxy-4′,8″-bisflavonyl Ether (XXVII)——A solution of XXV (6.2 g, 0.01 mole) in DMF (250 ml) and 10% HCl (50 ml) was diazotized with 10% $NaNO_2$ (7 g), and after addition of 50% H_3PO_2 (20 ml), the reaction mixture was kept standing overnight to deposite crude crystals of the bisflavonyl ether (XXVII), which were filtered, washed with water, dried and chromatographically purified on activated Al_2O_3 (25 g) using $CHCl_3$ as a solvent and an eluent to give XXVII (2.8 g, 45.4%), mp 268°. Mg+HCl, reaction, red–orange. It forms colorless microscopic needles from DMF. The mp was depressed on admixture with pentamethyl ether of natural hinokiflavone (mp 260°) and the IR spectrum was differed from that of the latter. *Anal.* Calcd. for $C_{35}H_{28}O_{10}$: C, 69.05; H, 4.64. Found: C, 69.07; H, 4.73. IR ν_{max}^{KBr} cm^{-1}: 1645 (C=O). NMR (10% solution in $CDCl_3$) τ: 2.17 and 2.94 ($2\times2H$, A_2B_2, $J\cong9$ cps, 1,4-disubst. benzene); 2.55 and 3.20 (as above); 3.44—3.47 ($3\times1H$, singlet, 3,3″and 6″); 3.49 and 3.63 ($2\times1H$, AB, $J=2.5$ cps, 6 and 8); 5.95, 6.02, 6.06, 6.12 and 6.22 ($5\times3H$, singlet, 5 OCH_3).

5,5″-Dihydroxy Compound (XXVIII)——A solution of XXVII (0.6 g) and $AlCl_3$ (0.5 g) in $C_6H_5NO_2$ (10 ml) was heated at 100—110° for 1 hr, and after addition of conc. HCl (one drop) was distilled with steam to separate yellow powder, which was filtered and recrystallized from DMF to form pale yellow needles (0.4 g), mp 279°. $FeCl_3$–reaction, dark green. *Anal.* Calcd. for $C_{33}H_{24}O_{10}$: C, 68.27; H, 4.17. Found: C, 68.37; H, 4.29.

Acetate (XXIX)——Colorless prisms from MeCN, mp 258°. *Anal.* Calcd. for $C_{37}H_{28}O_{12}$: C, 66.86; H,4.25. Found: C, 67.11; H, 4.45.

Synthesis of 4′,6″-Bisflavonyl Ethers (Hinokiflavone and Its Methyl Ethers) (XXXVIII, XXXIX, LXI, LXII)

4′,6″-Bisflavonyl ethers were prepared similarly by the procedure employed above for the synthesis of 4′,8″-isomers (XXVII, XXVIII, XXIX).

2,5-Dianisoyloxy-4,6-dimethoxyacetophenone (XXXI)——3,6-Dihydroxy-2,4-dimethoxyacetophenone (XI) (63.6 g, 0.3 mole) was anisoylated under identical conditions as described in the preparation of XVII. There were obtained ochre–yellow crystals of the anisate (XXXI) (108.5 g, 75.3%), mp 207°. For analysis a sample was recrystallized from AcOH to give colorless needles, mp 208°. *Anal.* Calcd. for $C_{26}H_{24}O_9$: C, 64.99; H, 5.04. Found: C, 65.29; H, 5.12.

1-(5′-Anisoyloxy-2′-hydroxy-4′,6′-dimethoxyphenyl)-3-(4″-methoxyphenyl)-1,3-propanedione (XXXII)——Anisate (XXXI) (96.1 g, 0.2 mole) was isomerized by means of pulverized KOH (17 g) in pyridine (250 ml) to the diketone (XXXII). Resinous product was recrystallized from acetone–MeOH to form brilliant yellow needles (61.9 g, 64.4%), mp 128°. Analytical sample from acetone forms yellow prisms, mp 145°. $FeCl_3$–reaction, green. *Anal.* Calcd. for $C_{26}H_{24}O_9$: C, 64.99; H, 5.04. Found: C, 65.26; H, 5.00.

6-Anisoyloxy-4′,5,7-trimethoxyflavone (XXXIII)——To a boiling solution of XXXII (96.1 g, 0.2 mole) in AcOH (300 ml) was added 20% H_2SO_4 (AcOH) (50 ml), and the red sloution was poured into warer (2 Liter) to afford the crude flavone (86.5 g, 93.5 %). It forms colorless needles by recrystallization from DMF, mp 235°. *Anal.* Calcd. for $C_{26}H_{22}O_8$: C, 67.52; H, 4.80. Found: C, 67.42; H, 4.72.

6-Hydroxy-4′,5,7-trimethoxyflavone (XXXIV)——Anisoylated flavone (XXXIII) (92.4 g, 0.2mole) was dissolved in 15 % KOH (MeOH) (400 ml) by boiling for 2.5 hr, and the red sloution was acidified with HCl to give the yellow crystals of XXXIV, which were recrystallized to yield yellow prisms (50.3 g, 76.6%) mp 220—221° (lit[12]. mp 217—218°). Mg+HCI—reaction, red–orange. *Anal.* Calcd. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91. Found: C, 65.63; H, 5.11.

3′-Nitro-4‴,5,5″,7,7″-pentamethoxy-4′,6″-bisflavonyl Ether (XXXV)——A mixture of iodonitroflavone (XXIII) (45.5 g, 0.1 mole), 6-hydroxyflavone (XXXIV) (33.0 g, 0.1 mole), K_2CO_3 (70 g) and DMSO (300 ml) was heated at 100° for 1 hr. By recrystallization of the product from DMF XXXV was obtained as colorless prisms (52.5 g, 80.3 %), mp 283°. *Anal.* Calcd. for $C_{35}H_{27}O_{12}N+\frac{1}{2}H_2O$: C, 63.42; H, 4.26; N, 2.12. Fornd: C, 63.21; H, 4.44; N, 2.01.

3′-Amino-4‴,5,5″,7,7″-pentamethoxy-4′,6″-bisflavonyl Ether (XXXVI)——A stirring suspension of XXXV (16.2 g, 0.025 mole) in DMF (600 ml), water (300 ml) and AcOH (60 ml) was reduced at 80—90° by adding $Na_2S_2O_4$ (25 g) over a 30 min period, after further stirring for 50 min AcONa (12.5 g) was added to the reaction mixture, and cooled to separate the amine (XXXVI). Pure amine was obtained from DMF as clolrless plates (11.0 g, 70.2 %), mp 272°. *Anal.* Calcd. for $C_{35}H_{29}O_{10}N+H_2O$: C, 65.50; H, 4.87. Found: C, 65.68; H, 5.00.

Acetate (XXXVII)——Colorless needles from $CHCl_3$+acetone, mp 275°. *Anal.* Calcd. for $C_{37}H_{31}O_{11}N$: C, 66.74; H, 4.70. Found: C, 66.54; H. 4.85.

4‴,5,5″,7,7″-Pentamethoxy-4′,6″-bisflavonyl Ether (Hinokiflavone Pentamethyl Ether) (XXXVIII)——A solution of the amine (XXXVII) (12.4 g, 0.02 mole) in DMF (500 ml) and 10% HCl (100 ml) was diazotized with 10% $NaNO_2$ (14 g) and after addition of 50% H_3PO_2 (40 ml) the mixture was kept standing

overnight. The product precipitated by addition of water was purified by chromatography on activated Al_2O_3 (50 g) using $CHCl_3$ as a solvent and an eluent to yield XXXVIII (4.1 g, 34.4%), mp 260°. It forms colorless microscopic prisms from DMF. Mg+HCl-reaction, orange. The mp of the synthetic bisflavonyl ether (XXXVIII) was undepressed on admixture with natural hinokiflavone pentamethyl ether, mp 260°. *Anal.* Calcd. for $C_{35}H_{28}O_{10}+\frac{1}{2}H_2O$: C, 68.05; H, 4.74. Found: C, 68.27; H, 5.07. IR ν_{max}^{KBr} cm^{-1}: 1640 (C=O). NMR (10% solution in $CDCl_3$) τ: 2.16 and 3.00 ($2\times2H$, A_2B_2, $\tau\cong9$ cps, 1,4-disubst. benzene); 2.21 and 3.00 (as above); 3.11 (1H, singlet, 8″); 3.42 (1H, singlet, 3 or 3″); 3.44 (1H, singlet, 3 or 3″); 3.48 and 3.65 ($2\times1H$, AB, $J=2.5$ cps, 6 and 8); 6.07—6.11 (15H, 5 OCH_3).

5,5″-Dihydroxy Compound (XXXIX)——A solution of XXXVIII (0.6 g) and $AlCl_3$ (0.5 g) in $C_6H_5NO_2$ (10 ml) was heated at 100—110° for 1 hr, and after addition of conc. HCl (one drop) was distilled with steam to remain the demethylated product (XXXIX). It forms from DMF yellow prisms, mp 290°. $FeCl_3$-reaction, brownish violet. *Anal.* Calcd. for $C_{33}H_{24}O_{10}$: C,68.27; H, 4.17. Found: C, 68.16; H, 4.34.

Acetate (LX)——Colorless plates from MeCN, mp 250°. *Anal.* Calcd. for $C_{37}H_{28}O_{12}$: C, 66.86; H, 4.25. Found: C, 67.06; H, 4.33.

4‴,5,5″,7,7″-Pentahydroxy-4′,6″-bisflavonyl Ether (Hinokiflavone) (LXII)——Pentamethoxybisflavonyl ether (XXXVIII) (3.0 g, 0.005 mole) was boiled with a solution of HI ($d=1.7$) (40 g) and Ac_2O (8 ml) at 130—140° for 3 hr, and after decolorization with $Na_2S_2O_4$ yellow precipitate was filtered, washed with water, dried and acetylated. The acetate (LXI) was obtained as colorless, microscopic needles (1.2 g) from MeCN. The mp and mixed mp with material of natural origin recrystallized from MeCN by the author, 251°. *Anal.* Calcd. for $C_{40}H_{28}O_{15}$: C, 64.15; H, 3.77. Found: C, 64.14; H, 3.94. IR ν_{max}^{KBr} cm^{-1}: 1780 (C=O of OAc), 1640 (C=O).

A solution of the acetate (LXI) (0.75 g) in 10% KOH (MeOH–H_2O 1:1) (5 ml) was kept standing for 30 min at room temperature and acidified with HCl to precipitate LXII, which was filtered, washed with water, dried and recrystallized from AcEt to yield microcrystals of yellow needles, mp 343° (decomp.), either alone or on admixture with the specimen of natural hinokiflavone. $FeCl_3$-reaction, brownish purple. Mg+HCl-reaction, light orange. *Anal.* Calcd. for $C_{30}H_{18}O_{10}+\frac{1}{2}H_2O$: C, 65.79; H, 3.50. Found: C, 65.95; H, 3.68. IR ν_{max}^{KBr} cm^{-1}: 1650 (C=O).

Complete Methylation of the Synthetic Hinokiflavone (LXII) to the Pentamethyl Ether (XXXVIII)——A mixture of LXII (0.5 g), AcEt (100 ml), K_2CO_3 (5 g) and Me_2SO_4 (2.0 g) was refluxed for 10 hr and was filtered. The filtrate was evaporated to yellowish residue, which was purified by chromatography on activated Al_2O_3 using $CHCl_3$ as a solvent and an eluent to give methylated product (0.3 g), mp and mixed mp with XXXVIII, 260°.

Formation of Hinokiflavone (LXII) by Demethylation of 4′,8″-Bisflavonyl Ether (XXVII)——Demethylation of XXVII (0.6 g) was carried out by boiling with a solution of HI ($d=1.7$) (8 ml) and Ac_2O (1.6 ml) at 130—140° for 3 hr and demethylated product was treated in the same manner described above for (LXII), giving from MeCN acetate (0.2 g), mp 251°. Saponification of the acetate (0.15 g) gave demethylated product from AcEt as microscopic needles, mp 343° (decomp.), undepressed on admixture of natural hinokiflavone.

Synthesis of 6-(4″-carbomethoxyphenyloxy)-4′,5,7-trimethoxyflavone (LXVI) 6-(4″-Carbomethoxy-2″-nitrophenyloxy)-4′,5,7-trimethoxyflavone (LXIII)——Condensation of methyl 4-iodo-3-nitrobenzoate (VI) (7.7 g, 0.025 mole) and 6-hydroxyflavone (XXXIV) (8.2 g, 0.025 mole) was effected by heating the mixture in DMSO (40 ml) in the presence of K_2CO_3 (10 g) at 100° for 1 hr. The condensation product was obtained from DMF in colorless needles (5.3 g, 41.8%), mp 226°. *Anal.* Calcd. for $C_{26}H_{21}O_{10}N$: C, 61.54; H, 4.17; N, 2.76. Found: C, 61.78; H, 4.17; N, 2.65.

6-(4″-Carbomethoxy-2″-aminophenyloxy)-4′,5,7-trimethoxyflavone (LXIV)——To a mixture of LXIII (5.1 g, 0.01 mole), DMF (80 ml), water (40 ml) and AcOH (15 ml) $Na_2S_2O_4$ (9.5 g) was added at 80—90° with stirring for 30 min, and after additional stirring for 40 min AcONa (10 g) was dissolved. The reaction mixture was allowed to stand overnight to crystallize the amine. Recrystallized from DMF it was obtained as colorless plates (1.5 g, 31.4%), mp 246°. *Anal.* Calcd. for $C_{26}H_{23}O_8N$: C, 65.40; H, 4.86. Found: C, 65.13; H, 5.02.

Acetate (LXV)——Colorless, small needles from $CHCl_3$+MeOH, mp 255°. *Anal.* Calcd. for $C_{28}H_{25}O_9N$: C, 64.73; H, 4.85. Found: C, 64.50; H, 4.86.

6-(4″-Carbomethoxyphenyloxy)-4′,5,7-trimethoxyflavone (LXVI)——A solution of LXIV (0.5 g) in DMF (20 ml) and 10% HCl (10 ml) was diazotized with 10% $NaNO_2$ (0.7 ml) and after addition of 50% H_3PO_2 (3 ml) the mixture was left to stand overnight. Separated crystallized product was filtered, and purified from C_6H_6 to give LXVI in colorless, small needles (0.4 g, 83.3%), mp and mixed mp with material of natural orgin[3] 206°. Mg+HCl-Reaction, orange. *Anal.* Calcd. for $C_{26}H_{22}O_8$: C, 67.52; H, 4.80. Found: C, 67.34; H, 4.87. IR ν_{max}^{KBr} cm^{-1}: 1715 (C=O of $COOCH_3$), 1645 (C=O).

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