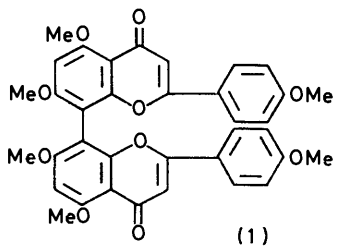
Synthesis of Hexa-*O*-methyl-cupressuflavone and -agathisflavone

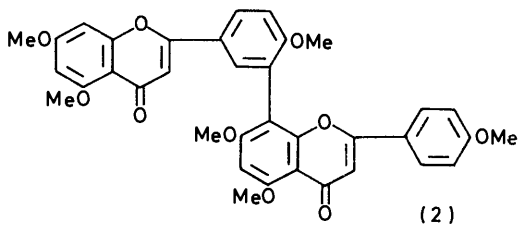
By **Shigeki Moriyama, Masayoshi Okigawa,** and **Nobusuke Kawano,*** Faculty of Pharmaceutical Sciences, Nagasaki University, Nagasaki, Japan 852

Syntheses of hexa-*O*-methyl-cupressuflavone (1) and -agathisflavone (7) (4',4''',5,5'',7,7''-hexamethoxy-8,8''-biflavone and -6,8''-biflavone, respectively) are described starting from 3,3'-diacetyl-2,2'-dihydroxy-4,4',6,6'-tetramethoxybiphenyl (9) and 3,3'-diacetyl-2,4'-dihydroxy-2',4,6,6'-tetramethoxybiphenyl (8) respectively.

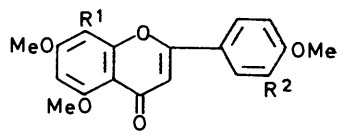
SYNTHETIC hexa-*O*-methylcupressuflavone (1) was first reported by Nakazawa [1] as a by-product in the synthesis of hexa-*O*-methylamentoflavone (2) from tri-*O*-methyl-8-iodoapigenin (3) and tri-*O*-methyl-3'-iodoapigenin (4) although the name of cupressuflavone was later given by Seshadri [2] when 8,8-linked biapigenin was isolated from *Cupressus* plants. Isolation of 7-*O*-methylagathisflavone (5) and 4''',7-di-*O*-methylagathisflavone (6) from *Agathis palmerstonii* has been reported and the structure of agathisflavone was proposed as a new 6,8-linked biapigenin on the basis of spectral data.[3] Hexa-*O*-methylagathisflavone (7) has only been synthesized by Wessely–Moser rearrangement [4] of hexa-*O*-methylcupressuflavone (1) with hydrogen iodide followed by methylation.[5] We now report syntheses of compound (7) starting from an asymmetrically substituted biphenyl (8), and of hexa-*O*-methylcupressuflavone (1) from a symmetrical compound (9).[6]



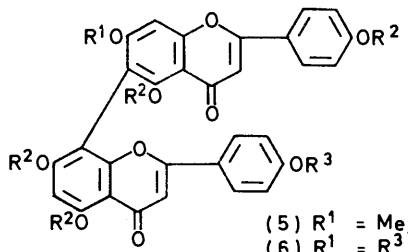
(1)



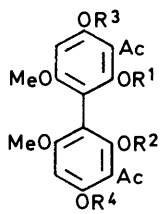
(2)



(3) R^1 = I, R^2 = H
(4) R^1 = H, R^2 = I



(5) R^1 = Me, R^2 = R^3 = H
(6) R^1 = R^3 = Me, R^2 = H
(7) R^1 = R^2 = R^3 = Me



(8) R^1 = R^4 = H, R^2 = R^3 = Me
(9) R^1 = R^2 = H, R^3 = R^4 = Me
(10) R^1 = R^2 = Me, R^3 = R^4 = H
(17) R^1 = H, R^2 = R^3 = R^4 = Me

Friedel–Crafts reaction of 2,2',4,4',6,6'-hexamethoxybiphenyl with acetic anhydride and anhydrous aluminum chloride in nitrobenzene gave compound (9), *m/e* 390, whose n.m.r. data (Table) showed the presence of two acetyl and four methoxy-groups substituted symmetrically. The structure (9) is preferable to the other

[1] K. Nakazawa, *Chem. and Pharm. Bull. (Japan)*, 1962, **10**, 1032.
[2] V. V. S. Murti, P. V. Raman, and T. R. Seshadri, *Tetrahedron*, 1967, **23**, 397.
[3] A. Pelter, R. Warren, J. N. Usmani, R. H. Rizvi, M. Ilyas, and W. Rahman, *Experientia*, 1969, **25**, 351.
[4] F. Wessely and G. H. Moser, *Monatsh.*, 1930, **56**, 97.
[5] A. Pelter, R. Warren, B. K. Handa, K. K. Chexal, and W. Rahman, *Indian J. Chem.*, 1971, **9**, 98.
[6] Recently, S. Ahmad and S. Razaq reported the synthesis of hexa-*O*-methylcupressuflavone (*Tetrahedron Letters*, 1971, 4633); our results were presented at the 91st annual meeting of the Pharmaceutical Society of Japan, Fukuoka, April 1971, and published in *Tetrahedron Letters*, 1972, 2105.

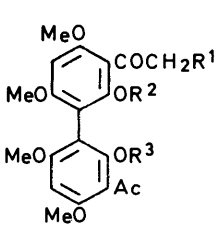
possible structure (10) because the *ortho*-positions of biphenyl will be more easily demethylated than the *para*-positions, owing to steric hindrance. Nuclear

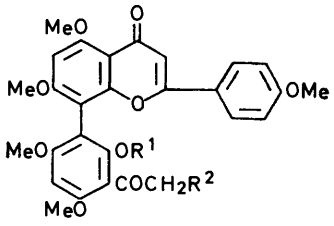
N.m.r. data * (δ) of biphenyl derivatives

Compound	(9)	(8)	(17)
Ac	2·62 (6H)	2·67 (6H)	2·52, 2·65
OMe	3·80 (6H)	3·48, 3·73	3·48, 3·76, 3·81
	3·93 (6H)	3·83, 3·96	3·86, 3·96
Aromatic H	6·06 (2H)	6·10, 6·28	6·07, 6·36
OH	13·94 (2H)	13·55, 13·95	13·98

* All signals are singlets and spectra are taken in $CDCl_3$ solution.

Overhauser effect studies on this compound also supported structure (9): when the methoxy-protons were irradiated (δ 3·93), a signal increase (20%) was found in the aromatic proton (δ 6·06) and irradiation of the other





(11) R^1 = H, R^2 = R^3 = An (14) R^1 = R^2 = H
(12) R^1 = An, R^2 = R^3 = H (15) R^1 = An, R^2 = H
(13) R^1 = R^3 = An, R^2 = H (16) R^1 = H, R^2 = An

An = *p*-MeO·C_6H_4CO

methoxy-protons (δ 3·80) caused a 17% increase in the same aromatic proton signal.

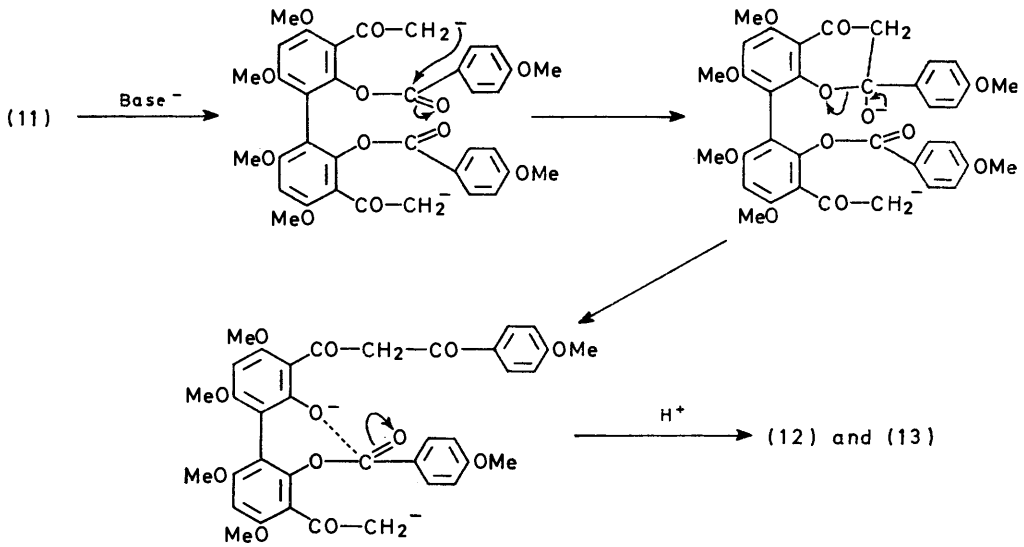
Compound (9), on treatment with *p*-anisoyl chloride in pyridine gave an anisoyl ester (11), which was subjected to Baker–Venkataraman rearrangement [7] to give two compounds (12) and (13) in 25 and 5% yield respectively, together with 42% recovery of starting material.

[7] W. Baker, *J. Chem. Soc.*, 1933, 1381; H. S. Mahal and K. Venkataraman, *ibid.*, 1934, 1767.

Compound (12) has one acetyl, five methoxy-, and a *p*-substituted phenyl group, showing that one of the two anisoyl groups was lost while the other had migrated. The n.m.r. spectrum of the other product (13) showed the presence of one acetyl, six methoxy-, and two *p*-substituted phenyl groups. Ring closure of the former compound (12) afforded a flavone derivative (14), which was again treated with anisoyl chloride in pyridine to give an ester (15), also obtained by ring closure of the other product (13). The Baker–Venkataraman rearrangement of the ester (15) to a diketone (16) and subsequent ring closure furnished pale yellow crystals, m.p. 293—294°, which were identical with hexa-*O*-methylcupressuflavone (mixed m.p. and spectral comparison).

In order to synthesize hexa-*O*-methylagathisflavone (7) in a similar way it was necessary to obtain an asymmetrically substituted biphenyl (8). Prolonged treatment with acetyl chloride and anhydrous aluminium chloride in ether of 2,2′,4,4′,6,6′-hexamethoxybiphenyl gave three compounds, which were separated by silica gel column chromatography. One of them (15% yield) was identical with compound (9). The other two (23 and 16% yield) were characterized as 3,3′-diacetyl-2,4′-dihydroxy-2′,4,6,6′-tetramethoxybiphenyl (8) and 3,3′-diacetyl-2-hydroxy-2′,4,4′,6,6′-pentamethoxybiphenyl (17) respectively, by n.m.r. spectral data (Table).

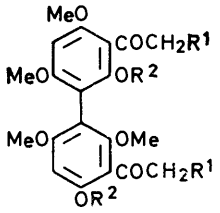
Starting from compound (8), Baker–Venkataraman rearrangement of the dianisoyl ester (18) to a β-diketone (19), followed by ring closure, afforded a compound of m.p. 262—265°, identical with hexa-*O*-methylagathisflavone (7) by mixed m.p. and comparisons of spectral data. Since the i.r. spectrum of the compound



Mechanism of Baker–Venkataraman rearrangement

(19) showed no absorption corresponding to the ester carbonyl group, both the anisoyl groups of the ester (18) seem to migrate in one step to give the β-diketone (19). This finding differs greatly from the rearrangement of the former ester (11) to give the β-diketone products

(12) and (13). The mechanism of the Baker–Venkataraman rearrangement has been considered by Henecka.[8] In the case of compound (11) nucleophilic attack of phenolate anion from the rear-side seems to be effective in preventing further rearrangement and also in promoting the elimination of the anisoyl group (Scheme).



(18) R^1 = H, R^2 = An
(19) R^1 = An, R^2 = H

An = *p*-MeO·C_6H_4CO

The fact that compound (12) was obtained along with 42% recovery of the starting material (11) can also be explained by phenolate anion attack from the rear-side. Consequently, the Baker–Venkataraman rearrangement of the ester (11) affords the products (12) and (13), whereas compound (18), which has no such structural relationship, can undergo both rearrangements to give the diketone (19) without interruption.

EXPERIMENTAL

N.m.r. spectra were recorded with Hitachi H-60 and JEOL PS-100 instruments using tetramethylsilane as internal reference in deuteriochloroform. Mass spectra were obtained from a JEOL JMS-01SG double focus high resolution instrument. T.l.c. was carried out by using silica gel G according to Stahl (Merck) and the following solvent systems were used: benzene–ethyl acetate, 4 : 1 (S-1), benzene–ethyl acetate, 3 : 2 (S-2), and toluene–ethyl formate–formic acid, 5 : 4 : 1 (TEFF). U.v. and i.r. spectral data are given in Supplementary Publication No. SUP 21068 (2 pp.).*

3,3′-*Diacetyl*-2,2′-*dihydroxy*-4,4′,6,6′-*tetramethoxybiphenyl* (9).—A mixture of 2,2′,4,4′,6,6′-hexamethoxybiphenyl (1 g), acetic anhydride (5 ml), nitrobenzene (15 ml), and powdered anhydrous aluminium chloride (1 g) was heated in an oil-bath at 140° for 1 h. After cooling, 20% hydrochloric acid (50 ml) was added and nitrobenzene was removed by steam-distillation. The residue was extracted with chloroform and the chloroform layer was washed with water, dried, and evaporated to yield the diacetylbiphenyl (9) as *needles* (from chloroform–ethanol) (230 mg, 20%), m.p. 253—257° (Found: C, 61·3; H, 5·6. $C_{20}H_{22}O_8$ requires C, 61·55; H, 5·7%), *m/e* 390 (M^+), R_F 0·40 (S-1).

3,3′-*Diacetyl*-2,2′-*bis*-p-*anisoyloxy*-4,4′,6,6′-*tetramethoxybiphenyl* (11).—A mixture of (9) (500 mg), pyridine (2 ml), and *p*-anisoyl chloride (450 mg) was heated in an oil-bath at 125—130° for 2 h. The cooled mixture was extracted with chloroform and the chloroform layer was treated with dilute hydrochloric acid to remove pyridine, washed with water, dried, and evaporated to give the diester (11) as *plates* (from chloroform–methanol) (530 mg, 62%), m.p. 263—265° (Found: C, 65·85; H, 5·35. $C_{36}H_{34}O_{12}$ requires C, 65·65; H, 5·2%), R_F 0·37 (S-1), δ 2·48 (6H, s, Ac), 3·56 (6H, s, OMe), 3·81 (12H, s, OMe), 6·23 (2H, s, aromatic), 6·82 (4H, d, *J* 10 Hz), and 7·86 (4H, d, *J* 10 Hz).

Baker–Venkataraman Rearrangement of the Diester (11).—A mixture of (11) (1 g), sodium amide (2 g), and dry toluene (50 ml) was heated at 110—120° for 6 h with occasional stirring. After adding dilute hydrochloric acid to decompose the excess of sodium amide, the mixture was extracted with chloroform and the chloroform layer was washed with water, dried, and evaporated to give a mixture which showed three spots on t.l.c., two of them being positive to the $FeCl_3$ colour reaction. The mixture was chromatographed on silicic acid (Mallinckrodt 100 mesh). Elution with benzene–ethyl acetate (99 : 1, 98 : 2, and 95 : 5 successively) gave (i) 3-*acetyl*-3′-p-*anisoylacetyl*-2,2′-*dihydroxy*-4,4′,6,6′-*tetramethoxybiphenyl* (12) as yellow needles (200 mg) (from chloroform–methanol), m.p. 260—264° (Found: C, 63·85; H, 5·4. $C_{28}H_{28}O_{10}$ requires C, 64·1; H, 5·4%), R_F 0·51 (S-2), δ 2·63 (3H, s, Ac), 3·58, 3·78, 3·81, 3·88, and 3·93 (each 3H, s, OMe), 5·98 and 6·06 (each 1H, s, aromatic), and 6·96 and 7·96 (each 2H, d, *J* 10 Hz); (ii) 3-*acetyl*-3′-p-*anisoylacetyl*-2-p-*anisoyloxy*-2′-*hydroxy*-4,4′,6,6′-*tetramethoxybiphenyl* (13) as yellow needles (56 mg) (from chloroform–methanol), m.p. 212—215°, R_F 0·45 (S-2), δ 2·53 (3H, s, Ac), 3·70, 3·75, and 3·90 (each 3H, s, OMe), 3·80 (9H, s, OMe), 6·48 and 6·52 (each 1H, s, aromatic), 6·72, 6·83, 7·75, and 7·80 (each 2H, d, *J* 10 Hz), and 14·00 (1H, s, OH); and (iii) starting material (11) as needles (420 mg), m.p. and mixed m.p. 264—265°, R_F 0·37 (S-1), negative colour reaction with $FeCl_3$ solution.

8-(3-*Acetyl*-2-*hydroxy*-4,6-*dimethoxyphenyl*)-4′,5,7-*trimethoxyflavone* (14).—The β-diketone (12) (100 mg) was added to a mixture (1 ml) of conc. sulphuric acid and acetic acid (1 : 4 w/w) and kept on a steam-bath for 5 min. The resulting dark red solution, after cooling, was poured into cold water to yield a yellow precipitate, which was collected, washed with water, and crystallized from chloroform–methanol to give the flavone (14) as *needles* (56 mg), m.p. 230—232° (Found: C, 66·6; H, 5·05. $C_{28}H_{26}O_9$ requires C, 66·35; H, 5·0%), R_F 0·50 (TEFF), δ 2·73 (3H, s, Ac), 3·79, 3·83, and 3·91 (each 3H, s, OMe), 4·05 (6H, s, OMe), 6·13 (1H, s, aromatic), 6·53 and 6·55 (each 1H, s), 6·82 and 7·47 (each 2H, d, *J* 10 Hz), and 14·10 (1H, s, OH).

8-(3-*Acetyl*-2-p-*anisoyloxy*-4,6-*dimethoxyphenyl*)-4′,5,7-*trimethoxyflavone* (15).—The flavone (14) (100 mg), anhydrous pyridine (0·4 ml), and anisoyl chloride (45 mg) were mixed and kept at 125—130° for 50 min. The cooled mixture was poured into cold water and extracted with chloroform. The chloroform layer was washed with dilute hydrochloric acid and water, dried, and evaporated. The residue gave the flavone (15) as *prisms* (50 mg) (from chloroform–methanol), m.p. 160—165° (Found: C, 67·75; H, 5·0. $C_{36}H_{32}O_{11}$ requires C, 67·5; H, 5·05%), R_F 0·53 (TEFF), δ 2·58 (3H, s, Ac), 3·69, 3·75, 3·78, 3·83, 3·93, and 3·99 (each 3H, s, OMe), 6·30 (1H, s), 6·57 (2H, s), and 6·73, 6·91, 7·60, and 7·65 (each 2H, d, *J* 10 Hz).

Compound (13) (100 mg) was added to a mixture (1 ml) of conc. sulphuric acid and acetic acid (1 : 4 w/w) and kept on a steam-bath for 20 min. Treatment as for compound (14), gave prisms (65 mg), m.p. 162—165°, which were identical (t.l.c., mixed m.p., i.r., and n.m.r.) with compound (15).

* For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1973, Index issue.

[8] H. Henecka, 'Chemie der Beta-Dicarbonylverbindungen,' Springer Verlag, Berlin, 1950, p. 150.

Baker–Venkataraman Rearrangement of the Flavone (15).—A mixture of compound (15) (100 mg), powdered potassium hydroxide (200 mg), and dry pyridine (0·5 ml) was heated at 120° for 2 h with stirring. The mixture was mixed with water and an excess of hydrochloric acid and extracted with chloroform. The chloroform layer was washed with water, dried (Na_2SO_4), and evaporated to give 8-(3-p-*anisoylacetyl*-2-*hydroxy*-4,6-*dimethoxyphenyl*)-4′,5,7-*trimethoxyflavone* (16) as yellow needles (37 mg) (from chloroform–methanol), m.p. 255—257° (Found: C, 67·3; H, 5·2. $C_{36}H_{32}O_{11}$ requires C, 67·5; H, 5·05%), R_F 0·43 (S-2).

Hexa-O-*methylcupressuflavone* (1).—Compound (16) (50 mg) was added to a mixture (0·5 ml) of conc. sulphuric acid and acetic acid (1 : 4) and treated as described in the preparation of (15) from (13), to afford a product, which was chromatographed on silicic acid and recrystallized from chloroform–ethyl acetate to give pale yellow needles (26 mg), m.p. 293—294° (Found: C, 69·5; H, 5·05. Calc. for $C_{36}H_{30}O_{10}$: C, 69·45; H, 4·85%), δ 3·78, 3·86, and 4·12 (each 6H, s, OMe), 6·57 and 6·59 (each 2H, s), and 6·77 and 7·30 (each 4H, d, *J* 9 Hz), mixed m.p. 293—294° with authentic hexa-*O*-methylcupressuflavone (1).

Friedel–Crafts Reaction of 2,2′,4,4′,6,6′-*hexamethoxybiphenyl*.—To a solution of anhydrous aluminum chloride (13·2 g) in dry ether (70 ml; ice-cold) was added 2,2′,4,4′,6,6′-hexamethoxybiphenyl (2·2 g) and then slowly acetyl chloride (3 ml) dropwise. The mixture, after stirring for 15 h at room temperature, was refluxed for 5 h and poured into dilute (10%) hydrochloric acid (*ca.* 90 ml). Ether was evaporated off and the mixture was warmed on a steam-bath for 1 h. The cooled mixture was extracted with chloroform and the chloroform layer was washed with water, dried, and evaporated to give a mixture (1·5 g) which showed three spots on t.l.c. The mixture was chromatographed on silicic acid. Elution with benzene–ethyl acetate (98 : 2) gave needles of 3,3′-*diacetyl*-2,4′-*dihydroxy*-2′,4,6,6′-*tetramethoxybiphenyl* (8) (600 mg, 23%), m.p. 185—186° (from chloroform–ethanol) (Found: C, 61·3; H, 5·4. $C_{20}H_{22}O_8$ requires C, 61·55; H, 5·85%), R_F 0·51 (S-1), *m/e* 390 (M^+). Elution with benzene–ethyl acetate (97 : 3) gave needles (from chloroform–ethanol) (400 mg, 15%), m.p. 254—257°, identical (t.l.c., mixed m.p., and n.m.r.) with compound (9). Elution with benzene–ethyl acetate (96 : 4) gave needles of 3,3′-*diacetyl*-2-*hydroxy*-2′,4,4′,6,6′-*pentamethoxybiphenyl* (17) (420 mg, 16%), m.p. 213—215° (Found: C, 62·5; H, 5·85. $C_{21}H_{24}O_8$ requires C, 62·35; H, 6·0%), R_F 0·29 (S-1), *m/e* 404 (M^+), n.m.r. data in the Table.

3,3′-*Diacetyl*-2,4′-*bis*-p-*anisoyloxy*-2′,4,6,6′-*tetramethoxybiphenyl* (18).—A mixture of compound (8) (500 mg), dry pyridine (2 ml), and anisoyl chloride (480 mg) was refluxed for 2 h and treated as described in the preparation of (11) from (9) to give the diester (18) as *needles* (660 mg), m.p. 174—177° (Found: C, 65·25; H, 5·0. $C_{36}H_{34}O_{12}$ requires C, 65·65; H, 5·2%), R_F 0·29 (S-1), δ 2·32 and 2·59 (each 3H, s, Ac), 3·47 and 3·58 (each 3H, s, OMe), 3·85 (9H, s, OMe), 3·93 (3H, s, OMe), 6·47 and 7·00 (1H, s), and 6·83, 6·91, 7·75, and 8·05 (each 2H, d, *J* 10 Hz).

Baker–Venkataraman Rearrangement of Compound (18).—A mixture of compound (18) (50 mg), powdered potassium hydroxide (100 mg), and dry pyridine (0·3 ml) was heated at 80—90° for 40 min with stirring. The mixture was mixed with ice–water, acidified with hydrochloric acid, and extracted with chloroform. The chloroform layer was washed with water, dried, and evaporated to give 3,3′-*bis*-p-*anisoylacetyl*-2,4′-*dihydroxy*-2′,4,6,6′-*tetramethoxybiphenyl* (19) as yellow crystals (23 mg), m.p. 108—112° (from ethanol) (Found: C, 65·2; H, 5·45. $C_{36}H_{34}O_{12}$ requires C, 65·65; H, 5·2%), R_F 0·56 (S-2).

Hexa-O-*methylagathisflavone* (7).—Compound (19) (50 mg) was added to a mixture (0·5 ml) of conc. sulphuric acid and acetic acid (1 : 4) and kept on a steam-bath for 30 min. The resulting dark red solution, after cooling, was mixed with ice–water (50 ml) to yield a precipitate, which was collected, washed with water, chromatographed on silicic acid, and crystallized from chloroform–ethyl acetate to give needles (7) (37 mg), m.p. 262—265°, no m.p. depression on admixture with an authentic sample of hexa-*O*-methylagathisflavone obtained by the Wessely–Moser rearrangement of hexa-*O*-methylcupressuflavone (1), R_F 0·43 (TEFF) (Found: C, 69·2; H, 5·0. Calc. for $C_{36}H_{30}O_{10}$: C, 69·45; H, 4·85%), δ 3·61, 3·76, 3·80, 3·88, 3·90, and 4·07 (each 3H, s, OMe), 6·52, 6·55, 6·66, and 6·92 (each 1H, s), and 6·80, 7·04, 7·40, and 7·92 (each 2H, d, *J* 10 Hz).

[4/655 *Received*, 1*st April*, 1974]