SYNTHESIS OF HEXA-O-METHYL-6,6"-BINARINGENIN AND -BIAPIGENIN

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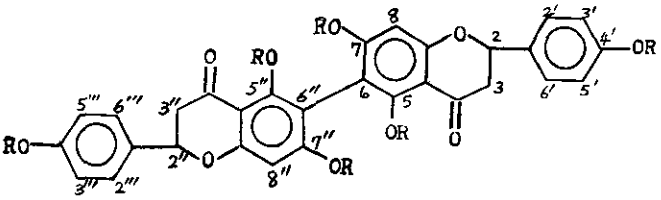
A three-step synthesis of the title compounds starting from 4,4'-dibenzyloxy-2,2', 6,6'-tetramethoxybiphenyl (V) has been accomplished and the proposed structure of 6,6"-binaringenin for succedaneaflavanone is confirmed.

A new biflavanone, (-)-succedaneaflavanone, has been isolated from the seed-kernel of wax-tree, Rhus succedanea, for which the structure has been elucidated as 6,6"-binaringenin (Ia) by means of i.r., u.v., n.m.r. and mass spectroscopy.[1] Dehydrogenation of its hexaacetate (Ic) by NBS[1,2] followed by hydrolysis afforded a new biflavone (III) which is assigned as 6,6"-biapigenin.



(IV) Hexamethyl ether of III

$\uparrow$ methylation

(III) Didehydrosuccedaneaflavanone

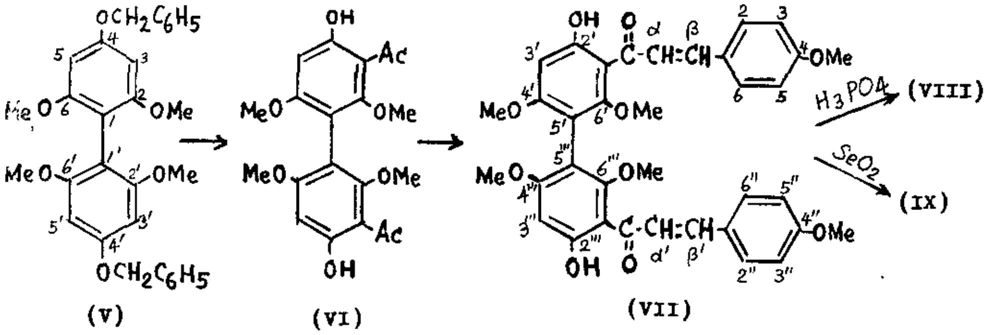
$\uparrow$ OH^-

(Ia) Succedaneaflavanone: R=H

(Ib) Hexamethyl ether: R=Me

(Ic) Hexaacetate: R=Ac $\xrightarrow[NBS]{-4H}$ (II) Didehydrosuccedaneaflavanone hexaacetate

In order to confirm these structures (I and III), a three-step synthesis of hexa-O-methyl-6,6"-binaringenin (VIII) and -biapigenin (IX) is now accomplished from 4,4'-dibenzyloxy-2,2',6,6'-tetramethoxybiphenyl (V).



Benzyl 4-iodo-3,5-dimethoxyphenyl ether under Ullmann reaction gave the symmetrical biphenyl V, m.p. 165-166° (yield 76%), $C_{30}H_{30}O_6$, M^+ m/e 486, negative $FeCl_3$ test, ir(KBr): 2890, 2820 (OMe), 1603, 1500, 1490 (arom.) cm^{-1}; nmr($CDCl_3$-TMS): δ 3.71 (s, OMe-2,2',6,6'), 6.40 (s, H-3,3',5,5'), 5.15 (s, four benzyl protons), 7.50 (s, ten arom. protons).

Hoesch reaction on V with CH_3CN, $ZnCl_2$ and HCl in dry $CHCl_3$-Et_2O (1:1) gave the key product VI, m.p. 230-232° (60%), $C_{20}H_{22}O_8$, M^+ m/e 390; purple in $FeCl_3$ test ; ir(KBr): 2650 (OH), 1620 (CO), 1580, 1490 (arom.) cm^{-1}; nmr ($CDCl_3$-TMS): δ 2.63 (s, Ac-3,3'), 3.38 (s, OMe-2,2'), 3.71 (s, OMe-6,6'), 6.31 (s, H-5,5'), 13.68 (s, OH-4,4').

Reaction of VI with two moles of p-anisaldehyde in presence of alkali gave bichalcone (VII), m.p. 191-192° (58%), $C_{36}H_{34}O_{10}$, M^+ m/e 626; dark brown in $FeCl_3$ test; ir (KBr): 2570 (OH), 1630 (chalcone CO), 1603, 1560, 1530, 1500 (arom.) cm^{-1}; nmr ($CDCl_3$-TMS): δ 3.48 (s, OMe-6',6"'), 3.73 (s, OMe-4',4"'), 3.78 (s, OMe-4,4"), 6.35 (s, arom. H-3',3"'), 6.88 (d, J=9 Hz, H-3,5,3",5"), 7.55 (d, J=9 Hz, H-2,6,2",6"), 7.83 (s, H-α,α',β,β'), 14.88 (s, OH-2',2"').

Acidic cyclization of VII by refluxing with alcoholic H_3PO_4 for three weeks gave VIII, m.p. 257-258° (35%), $C_{36}H_{34}O_{10}$, M^+ m/e 626, negative FeCl test; ir(KBr): 2890, 2930, 2790 (OMe), 1678 (flavanone CO), 1598, 1585, 1560, 1500 (arom.) cm^{-1}; nmr ($CDCl_3$-TMS): δ 2.80-3.18 (m, H-3,3"), 3.63 (s, OMe-5,5"), 3.72 (s, OMe-7,7"), 3.82 (s, OMe-4',4"'), 5.43 (dd, J=13, 3 Hz, H-2,2"), 6.38 (s, H-8,8"), 6.95 (d, J=9 Hz, H-3',5',3"',5"'), 7.39 (d, J=9 Hz, H-2', 6', 2"',6"').

Oxidative cyclization of VII with SeO_2 in dioxane followed by preparative TLC gave IX, m.p. 304-306° (28%), $C_{36}H_{30}O_{10}$, negative $FeCl_3$ test; ir (KBr): 2890, 2800 (OMe), 1648 (flavone CO), 1603, 1580, 1500 (arom.) cm^{-1}; nmr ($CDCl_3$-TMS): δ 3.70 (s, OMe-5,5"), 3.78 (s, OMe-7,7"), 3.83 (s, OMe-4',4"'), 6.58 (s, H-3,3") 6.83 (s, H-8,8"), 6.98 (d, J=9.1 Hz, H-3',5',3"',5"'), 7.80 (d, J=9.1 Hz, H-2',6',2"',6"').

The induced change in the chemical shift (ppm) owing to the addition of $Eu(FOD)_3$ on IX represented by S-value was listed in Table 1. The S-values of OMe-5,5" in IX showed near value (3.87 ppm) with that of OMe-5 in agathisflavone hexamethyl ether (2.14 ppm[4]) and OMe-5" in robustaflavone hexamethyl ether (2.64,[5] 2.17 ppm[6]). The S-values of OMe-7,7", 4,4"; H-3,3"; 8,8"; 2',6',2"',6"' 3',5',3"',5"' (Table 1) showed no much difference from the previously reported values.[4-6]

Table 1. N.m.r. Spectral Data and S-values for Hexa-O-methyl-6,6"-biapigenin

Protons	Chemical shifts (δ)	S-values by $Eu(FOD)_3$
OMe-5,5"	3.70	3.87
7,7"	3.78	1.15
4',4"'	3.83	0.06
H-3,3"	6.58	0.84
8,8"	6.83	1.23
2',6',2",6"	7.80	0.07
3',5',3"',5"'	6.98	-0.08

Spectra were taken on a Varian T-60 instrument in $CDCl_3$ using TMS as internal standard.

On change of solvent from CDCl to 66% $C_6D_6/CDCl_3$, the most upfield signal (δ 3.70) of the six methoxyl groups in IX [δ 3.70 (s, 6H), 3.78 (s, 6H) and 3.83 (s, 6H)] moved downfield (9 cps) as that of OMe-5 signal in agathisflavone[7] and OMe-5" signal in robustaflavone;[5] the other two signals (δ 3.78 and 3.83) moved upfield (39 and 29 cps respectively). The above evidence clearly indicated that IX was composed of two apigenin units joined by an interflavonyl linkage of C_6-$C_{6"}$.

The synthetic compounds VIII and IX were identical in all respects (m.p., mixed m.p., i.r., n.m.r., mass spectra, and t.l.c.) with the hexamethyl ethers Ib and IV (m.p. 308-310°) respectively. Thus, it has definitely established that succedaneaflavanone (Ia) is 6,6"-linked binaringenin.

Satisfactory analytical date were obtained for all the above compounds.

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