gel gives a light blue fluorescence under UV. ν_{max}^{KBr} (cm^{-1}): 1716 (coumarin lactone CO), 1637 (3,4-double bond in conjugation with CO), 1260 (ether), 1586, 878 (furan ring peak due to out-of-plane deformation vibration of C-H) and 753 (C-H in-plane deformation vibration in furanocoumarin). NMR (δ in ppm): 1.79 (6H, *s*, methyls), 4.73 (2H, *d*, *J* 7 Hz, Ar–O–$\underline{CH_2}$–CH=), 5.59 (1H, coupled *t*, *J* 7 Hz,–O–CH$_2$–$\underline{CH}$=), 6.32 (1H, *d*, *J* 9.5 Hz, H-3), 7.72 (1H, *d*, *J* 9.5 Hz, H-4), 6.88 (1H, *s*, H-5), 7.06 (1H, *d*, *J* 2 Hz, H-3'), 7.65 (1H, *d*, *J* 2 Hz, H-2').

Dealkylation of heratomin. Heratomin (200 mg) was heated under reflux with 4% HCl in EtOH (20 ml) for 30 min. The mixture was diluted with H_2O (80 ml) and the solid, which separated, crystallized from EtOH to yield phenol (**2**), as needles, mp 253–254° (M$^+$ 202). (Found: C, 64.9; H, 2.8. $C_{11}H_6O_4$ requires: C, 65.3; H, 3.0%).

Methylation of phenol (**2**). A solution of phenol (50 mg) in MeOH (10 ml) was treated with an ethereal solution of CH_2N_2. After 24 hr the solvent was evaporated and the residue crystallized from Me_2CO–petrol giving sphondin as needles, mp 191–192° (mmp, superimposable IR, NMR, MS, Co-TLC).

Heratomol. It crystallized from MeOH, as needles, mp 253–255°. Found: C, 64.8; H, 2.9. $C_{11}H_6O_4$ requires C, 65.3; H, 3.0%. M$^+$ 202. It did not depress the mp of 6-hydroxyangelicin (2) (the dealkylated product of heratomin). R_f 0.20 [Si gel, C_6H_6–Me_2 CO (9:1)]. On Si gel this gives a light blue fluorescence under UV.

Methylation of heratomol. It was methylated in the usual way with CH_2N_2. The methyl ether, mp 192–193°, was found to be identical with sphondin (mmp, Co-TLC, IR, NMR, MS).

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THE SYNTHESIS OF AFZELIN, PAEONOSIDE AND KAEMPFEROL 3-*O*-β-RUTINOSIDE

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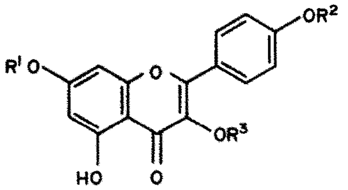
Key Word Index—Kaempferol glycosides; synthesis; afzelin; paeonoside.

Abstract—The structure of afzelin (kaempferol 3-*O*-α-L-rhamnopyranoside) and paeonoside (kaempferol 3,7-bis-*O*-β-D-glucopyranoside) has been confirmed by total synthesis. Synthetic kaempferol 3-*O*-β-rutinoside had a mp of 190–192° suggesting that those natural kaempferol 3-*O*-rhamnoglucosides which melt in the same range are also 3-*O*-β-rutinosides.

In this paper we report the unambigous synthesis of three kaempferol glycosides with the purpose of supporting thereby the structures of the corresponding natural products.

The isolation of afzelin, a kaempferol 3-*O*-rhamnoside has been reported from at least nine different sources, the first being in 1950 by King and Acheson from an *Afzelia* sp. [1]. Due to their quite similar mp's (mainly 172–174°) it has been generally assumed that these rhamnosides are identical and except in two cases [2,3], it has been assumed that the sugar moiety is in the α-pyranoside form (**1**). For substances isolated from *Aesculus hippocastanum* [2] and *Galega officinalis* [3], rhamnofuranoside structures were postulated.

We prepared **1** by coupling 7,4'-di-*O*-benzylkaempferol (**2**) [4] with α-benzoyl-bromorhamnose [5] to give, after saponification, the dibenzyl ether (**3**), which was converted to kaempferol 3-*O*-α-L-rhamnopyranoside (**1**), mp



(1) $R^1 = R^2 = H, R^3 = \alpha$-L-Rha
(2) $R^1 = R^2 = CH_2Ph, R^3 = H$
(3) $R^1 = R^2 = CH_2Ph, R^3 = \alpha$-L-Rha
(4) $R^1 = R^3 = \beta$-D-Glc, $R^3 = H$
(5) $R^1 = R^3 = H, R^2 = CH_2Ph$
(6) $R^1 = R^3 = \beta$-D-Glc $R^2 = CH_2Ph$
(7) $R^1 = R^2 = H, R^3 = \beta$-rutinosyl
(8) $R^1 = R^2 = CH_2Ph, R^3 = \beta$-rutinosyl

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‡ Kaempferol 3-*O*-(3-*O*-α-L-rhamnopyranosyl-β-D-glucopyranoside) from *Rungia repens*; the disaccharide is called rungiose.

172–174° by catalytic hydrogenation. A sample of natural **1** could not be obtained.

The isolation of the 3,7-bis-*O*-glycoside of kaempferol, called paeonoside was reported in 1961 by Egger [6] from *Paeonia albiflora*. A synthesis of kaempferol 3,7-bis-*O*-β-D-glucopyranoside (**4**) has now been accomplished by coupling 4′-*O*-benzylkaempferol (**5**) with a large excess of α-acetobromoglucose, saponification and debenzylation of the resulting benzylbisglucoside **6**. A correspondence in mp and superimposable IR-spectra proved the identity of the natural and synthetic products.

The situation concerning kaempferol 3-*O*-β-rutinoside is rather confused. Hukuti seems to be the first who claimed this structure for a substance, mp 223–224° (as the dihydrate) isolated from *Calystegia japonica* [7]. Hattori and Shimokoriyama confirmed Hukuti's hypothesis by identifying rutinose in the enzymic hydrolysate of the glycoside by PC [8]. Another kaempferol 3-*O*-rhamnoglucoside, first isolated by Kobayashi and Hayashi in 1952 [9], showed mp 156–158° (as the tetrahydrate) and mp 182–185° (as the dihydrate). A survey of the literature revealed almost fifty references concerning the isolation of kaempferol 3-*O*-rhamnoglucosides from plant material. About twenty contained mp data which except for rungioside[‡] (mp 256°) fell into two categories, namely those grouping around 190 and around 220° resp. Both contained substances which were claimed to be rutinosides.

Our synthesis of kaempferol 3-*O*-β-rutinoside (**7**) carried out (see Experimental) as that of the corresponding rhamnoside (**1**) furnished a product of mp 190–192° that was identified by chromatography and IR spectroscopy with samples of kaempferol 3-*O*-rhamnoglucosides isolated by Bodalski *et al.* from *Peucedanum oreoselinum* [10] and in our laboratory from *Eupatorium seratinum* [11].

On this basis we feel justified in regarding those kaempferol 3-*O*-rhamnoglucosides which melt around 190° to be β-rutinosides. Further it is probable that those melting around 220°, including nicotiflorin from *Nicotiana silvestris* [12] and Hukuti's compound [7], are the corresponding neohesperidosides, since the kaempferol 3-*O*-glycoside containing the third possible α-rhamnopyranosyl-glucose i.e. rungiose, had a mp of 256°.

EXPERIMENTAL

*7,4′-Dibenzyloxy-3,5-dihydroxyflavone-3-O-α-L-*rhamnopyranoside (**3**). To a soln of 7,4′-dibenzyloxy-3,5-dihydroxyflavone (**2**) [4] (0.47 g) in quinoline (20 ml) anh. calcium sulphate (1.0 g), silver oxide (0.30 g) and in two portions α-benzoylbromorhamnose [5] (1.07 g) was added with stirring. After 4 hr the mixture was diluted with $CHCl_3$ (100 ml), extracted several times with 5% aq. H_2SO_4, washed, dried and evaporated. Residue was treated with 0.1 N NaOMe for 24 h, the soln evaporated and the residue extracted after acidification with dil. HCl with EtOAc. The extract was washed, dried, evaporated, the residue chromatographed on Si gel with C_6H_6–EtOAc (18:1) as eluant and crystallized from 80% aq. EtOH to yield **3** (94 mg, 15%) as small, pale yellow platelets of mp 186–188°. (Found: C, 68.41; H, 5.48. $C_{35}H_{32}O_{10}$ requires: C, 68.62; H, 5.27%).

3,5,7,4′-Tetrahydroxyflavone-3-O-α-L-rhamnopyranoside; kaempferol-3-O-α-L-rhamnopyranoside, afzelin (**1**). Catalytic hydrogenation of **2** over palladium–charcoal catalyst afforded **1** yellow prisms of mp 172–174° (lit. [1] 172–174°), $[\alpha]_D^{25}$ −230° (*c* 1.0, DMF).

*4′-Benzyloxy-3,5,7-trihydroxyflavone-3,7-bis-O-β-D-*glucopyranoside (**6**). 4′-Benzyloxy-3,5,7-trihydroxyflavone [4] (**5**) (0.76 g) was coupled with acetobromoglucose (1.65 g) and worked up as described under **3** to afford after saponification **6** (0.35 g) as yellow needles of mp 229–231°. (Found: C, 58.13; H, 5.38. $C_{34}H_{36}O_{16}$ requires: C, 58.28; H, 5.18%).

3,5,7,4′-Tetrahydroxyflavone 3,7-bis-O-β-D-glucopyranoside, kaempferol-3,7-bis-O-β-D-glucopyranoside, paeononside (**4**). Debenzylation of **6** gave the free glucoside as yellow platelets (from 90% EtOH) of mp 239–242° (lit. [6] 233°) (Found: C, 48.55; H, 4.99. $C_{27}H_{30}O_{16}\cdot 3H_2O$ requires C, 48.79; H, 5.46%). Deca-acetate: Colourless plates, mp 186–188°. (Found: C, 54.74; H, 4.88%).

7,4′-Dibenzyloxy-3,5-dihydroxyflavone-3-β-(6-O-α-L-rhamnopyranosyl-D-glucopyranoside) (**8**). Coupling of **2** (0.6 g) as described under **3** with acetobromorutinose [13] (2.0 g) gave after the usual work-up and saponification **8** (0.27 g, 27%), mp 152–154° (from EtOH). (Found: C, 63.13; H, 5.67. $C_{41}H_{42}O_{15}$ requires C, 63.56; H, 5.46%).

3,5,7,4′-Tetrahydroxyflavone-3-O-(6-O-α-L-rhamnopyranosyl-β-D-glucopyranoside), kaempferol-3-O-β-rutinoside (**7**). The foregoing dibenzyl ether (**8**), (0.25 g) gave on catalytic hydrogenation **7** (0.1 g, 54%), mp 190–192° (from aq. MeOH). The analytical sample was dried at 110° i.v. $[\alpha]_D^{25}$ −52° (*c* 1.0, pyridine). (Found C, 53.50; H, 4.98. $C_{27}H_{30}O_{15}$ requires: C, 54.55; H, 5.09%).

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