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SYNTHESES OF LICOISOFLAVONE A AND 5'-ALKENYL ISOMER

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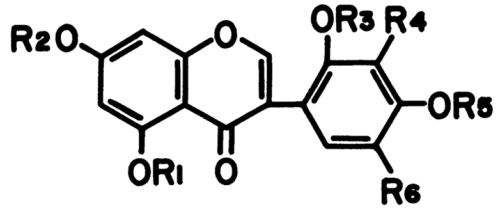
2',4',5,7-Tetrahydroxyisoflavone was partially benzoylated with benzoyl chloride to give 7-benzoyloxy-2',4',5-trihydroxyisoflavone. The condensation of 7-benzoyloxyisoflavone with 2-methyl-3-buten-2-ol, followed by the hydrolysis of the resultant 3'-(3-methyl-2-butenyl)isoflavone afforded licoisoflavone A. Its 5'-(3-methyl-2-butenyl) isomer was also synthesized from 5-benzoyloxyisoflavone.

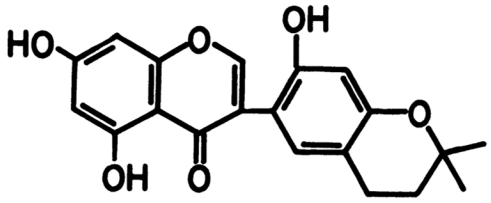
Licoisoflavone A was isolated from the roots of *Glycyrrhiza* spp. (Leguminosae) along with other flavonoids.[1] The structure has been shown to be 2',4',5,7-tetrahydroxy-3'-(3-methyl-2-butenyl)isoflavone (1) on the basis of chemical and spectroscopic studies. In the continuation of our studies on the synthesis of isoflavones having 3-methyl-2-butenyl groups on the B ring,[2] we wish to report an unambiguous synthesis of 1 to confirm the proposed structure of the natural isoflavone and its isomer [2',4',5,7-tetrahydroxy-5'-(3-methyl-2-butenyl)isoflavone] (10).

The condensation of 2,4-dibenzyloxy-6-hydroxyacetophenone with 2,4-dibenzyloxybenzaldehyde gave 2,2',4,4'-tetrabenzyloxy-6'-hydroxychalcone (2) (mp 146-147 °C) as a major product and 2',4',5,7-tetrabenzyloxyflavanone (3) [mp 159-161 °C; NMR ($CDCl_3$) δ 2.83-3.00 (2H, m, 3-H), 5.68-5.94 (1H, m, 2-H)][3] as a minor product. A mixture of 2 and 3 was easily converted into the acetate (4) (mp 113-114 °C) of 2. The oxidative rearrangement of 4 with thallium(III) nitrate[4] in methanol, followed by the hydrolysis of the resultant compound with dilute hydrochloric acid afforded the tetrabenzyloxyisoflavone (5) [mp 178-179 °C; NMR ($CDCl_3$) δ 7.68 (1H, s, 2-H)]. The partial debenzylation of 5 with a small amount of concd hydrochloric acid in acetic acid at 80 °C for 10 min gave the 5-hydroxyisoflavone (6) [mp 117-

119 °C; UV λ_{max} nm (log ε), (EtOH) 260 (4.57), 282.5 (4.20), 323_i(3.65), (EtOH + $AlCl_3$) 273.5 (4.58), 309_i(3.89), 375 (3.65)]. The 5-benzoyloxy derivative (7), which was obtained by the benzoylation of 6 with benzoyl chloride in pyridine, was converted into 5-benzoyloxy-2',4',7-trihydroxyisoflavone (8) [mp 211-213 °C, UV λ_{max} nm (log ε), (EtOH) 273_i(4.42), 250 (4.33), 260.5 (4.32), 301_i(4.00), (EtOH + AcONa) 260.5 (4.43), 297.5_i(4.03), 327 (3.98)] by the hydrogenolysis with palladium charcoal (10%) in methanol-ethyl acetate. The condensation of 8 with 2-methyl-3-buten-2-ol in the presence of boron trifluoride etherate in dry dioxane afforded a 3-methyl-2-butenyl compound (9) (mp 180-182 °C; 20%). The NMR spectrum (DMSO) of 9 showed the presence of two methyl groups as a singlet at δ 1.61, one methylene group as a doublet (J=7 Hz) centering at δ 3.06, one vinyl proton as a triplet (J=7



(1) $R_1=R_2=R_3=R_5=R_6=H$, $R_4=(CH_3)_2C=CHCH_2$
(5) $R_1=R_2=R_3=R_5=C_6H_5CH_2$, $R_4=R_6=H$
(6) $R_1=R_4=R_6=H$, $R_2=R_3=R_5=C_6H_5CH_2$



(11)

(7) $R_1=C_6H_5CO$, $R_2=R_3=R_5=C_6H_5CH_2$ $R_4=R_6=H$
(8) $R_1=C_6H_5CO$, $R_2=R_3=R_4=R_5=R_6=H$
(9) $R_1=C_6H_5CO$, $R_2=R_3=R_4=R_5=H$ $R_6=(CH_3)_2C=CHCH_2$
(10) $R_1=R_2=R_3=R_4=R_5=H$, $R_6=(CH_3)_2C=CHCH_2$
(12) $R_1=R_2=R_3=R_4=R_5=R_6=H$
(13) $R_1=R_3=R_4=R_5=R_6=H$, $R_2=C_6H_5CO$
(14) $R_1=R_3=R_5=R_6=H$, $R_2=C_6H_5CO$ $R_4=(CH_3)_2C=CHCH_2$
(15) $R_1=R_3=R_4=R_5=H$, $R_2=C_6H_5CO$ $R_6=(CH_3)_2C=CHCH_2$
(16) $R_1=R_2=R_3=R_5=CH_3CO$ $R_4=(CH_3)_2C=CHCH_2$, $R_6=H$

Table 1. Mp and UV spectra of Isoflavones[a)]

Compound	Mp (°C)		λ_{max} nm (log ε)
Licoisoflavone A (1) (Natural)[1)]	120-122[b)] (111-113)	(EtOH)	266.5(4.46), 339_i(3.70)
		(EtOH + AcONa)	277(4.53), 330(4.00)
		(EtOH + $AlCl_3$)	269(4.48), 307_i(3.90), 365(3.43)
Tetraacetate (16) (Natural)[1)]	149-150[b,c)] (136-138)	(EtOH)	247(4.42), 296(3.87), 335_i(3.42)

a) i: Inflection point. b) The melting points were measured with a Yanagimoto micro-melting-point apparatus. c) The melting point of the tetraacetate (16) was not depressed by admixture with the natural licoisoflavone A tetraacetate.

Table 2. NMR spectra of Isoflavones[a)]

Compound (Solvent)	2-H	6-H 8-H	5'-H 6'-H	$(CH_3)_2C=CHCH_2$	OH or OAc
Licoisoflavone A (1) (DMSO)	8.11(s)	6.22(d_1) 6.39(d_1)	6.36(d_2) 6.76(d_2)	1.62(3H,s,CH_3) 1.72(3H,s,CH_3) 3.26(2H,d_3,CH_2) 5.21(1H,t,CH=)	8.20, 9.24 10.75, 12.80 (each s or b)
Tetraacetate (16) ($CDCl_3$)	7.76(s)	6.84(d_1) 7.22(d_1)	6.97(d_2) 7.14(d_2)	1.67(6H,s,CH_3x2) 3.22(2H,d_3,CH_2) 5.03(1H,t,CH=)	2.11, 2.28 2.34, 2.40 (each 3H,s)

a) Value in δ scale relative to TMS. s: Singlet. d_1, d_2, and d_3: Each doublet; J=2, 8, and 7 Hz, relatively. t: Triplet. b: Broad.

Hz) centering at δ 5.18, and two aromatic protons at δ 6.33 (1H, s, 3'-H) and 6.66 (1H, s, 6'-H), respectively. The compound 9 was hydrolyzed with dilute alkali in a nitrogen atmosphere at room temperature to yield 2',4',5,7-tetrahydroxy-5'-(3-methyl-2-butenyl)isoflavone (10) [mp 232-234 °C; UV λ_{max} nm (log ε), (EtOH) 266 (4.41), 301_i(4.15), 341_i(3.77), (EtOH + AcONa) 277.5 (4.48), 301_i(4.22), 334.5_i (4.05); (EtOH + $AlCl_3$) 273 (4.44), 313_i(3.93), 374 (3.43); NMR (DMSO) δ 1.67 (6H, s, CH_3 x 2), 3.14 (2H, d, J=7 Hz, $C\underline{H}_2CH=$), 5.26 (1H, t, J=7 Hz, $CH_2C\underline{H}=$), 6.23 and 6.38 (each 1H, d, J=2 Hz, 6- and 8- H), 6.45 (1H, s, 3'-H), 6.83 (1H, s, 6'-H), 8.10 (1H, s, 2-H), 8.70-9.64 (2H, b, OH x 2), 12.96 (1H, s, 5-OH), one OH proton was not observed. Found: C, 67.53; H, 5.05%. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12%]. The compound (10) was cyclized with a small amount of concd hydrochloric acid in methanol to give a chroman derivative (11) (mp 261-262 °C).[5)] The properties of 11 were fully consistent with those of the chroman derivative which was prepared by the condensation of 2,4-dibenzyloxy-6-hydroxyacetophenone with 7-benzyloxy-6-formyl-2,2-dimethylchroman *via* four steps. On the basis of these results, the isoflavone (10) was shown to be an isomer of licoisoflavone A.

The hydrogenolysis of 5 with palladium charcoal (10%), followed by the partial benzoylation of the resultant tetrahydroxyisoflavone (12) (mp 255-256 °C) with benzoyl chloride in pyridine at 0-5 °C gave the 7-benzoyloxyisoflavone (13) [mp 212-213 °C; UV λ_{max} nm (log ε), (EtOH) 256 (4.50), 343_i(3.54), (EtOH + AcONa) 255 (4.50), 341_i(3.60); NMR (DMSO) δ 8.32 (1H, s, 2-H), 7.59-8.22 (m, 5H, 7-C_6H_5CO)]. The condensation of 13 with 2-methyl-3-buten-2-ol afforded two 3-methyl-2-butenyl compounds, (14) (mp 165-167 °C; 18%)[6)] and 7-benzoyloxy-2',4',5-

trihydroxy-5'-(3-methyl-2-butenyl)isoflavone (15) (mp 124-126 °C; 12%), which was converted into 10. The NMR spectrum (DMSO) of 14 showed the presence of one 3-methyl-2-butenyl group and two aromatic protons 5'- and 6'-H as two doublets (each J=8 Hz) centering at δ 6.42 and 6.81, respectively. Therefore, the compound (14) was shown to be 7-benzoyloxy-2',4',5-trihydroxy-3'-(3-methyl-2-butenyl)isoflavone, which was hydrolyzed with dilute alkali to yield the desired isoflavone (licoisoflavone A) (1) (Found: C, 67.55; H, 5.03%. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12%). The compound (1) was subsequently converted into the tetraacetate (16). In Table 1 and 2, the NMR and UV spectral data for licoisoflavone A and the tetraacetate are shown to be identical with those of the synthetic isoflavone (1) and its tetraacetate (16), respectively.

On the basis of these results, the structure of licoisoflavone A was confirmed to be 2',4',5,7-tetrahydroxy-3'-(3-methyl-2-butenyl)isoflavone (1).

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5) NMR (DMSO) δ 1.28 (6H, s, CH_3 x 2), 1.72 and 2.62 (each 2H, t, J=7 Hz, CH_2), 6.18 and 6.82 (each 1H, d, J=2 Hz, 6- and 8-H), 6.20 and 6.82 (each 1H, s, 3'- and 6'-H), 8.08 (1H, s, 2-H), 9.10 and 10.6 (each 1H, bs, OH), 12.88 (1H, s, 5-OH).

6) NMR (DMSO) δ 1.64 and 1.73 (each 3H, s, CH_3), 3.33 (2H, d, J=7 Hz, $C\underline{H}_2CH=$), 5.24 (1H, t, J=7 Hz, $CH_2C\underline{H}=$), 6.42 and 6.81 (each 1H, d, J=8 Hz, 5'- and 6'-H), 6.86 and 7.13 (each 1H, d, J=2 Hz, 6- and 8-H), 7.55-8.25 (5H, m, 7-C_6H_5CO), 8.25 (1H, s, 2-H), 8.28 and 9.38 (each 1H, s, OH), 12.86 (1H, s, 5-OH).

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