SYNTHESES OF LICORICONE AND ITS ISOMER

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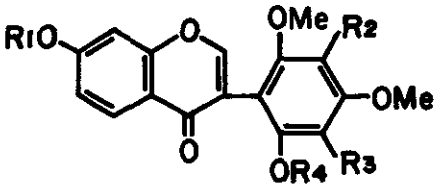
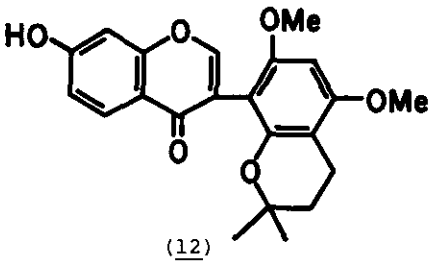
Abstract —— The condensation of 6',7-dibenzoyloxy-2',4'-dimethoxyisoflavone with 2-methyl-3-buten-2-ol, followed by the hydrolysis of the resultant 3'-(3-methyl-2-butenyl)isoflavone afforded licoricone. Its isomer, 5'-(3-methyl-2-butenyl)isoflavone, was also synthesized from 7-benzoyloxy or 6',7-dibenzoyloxyisoflavone in a similar manner.

Licoricone was isolated from the root *Glycyrrhiza uralensis* Fischer. et DC. The structure has been shown to be 6',7-dihydroxy-2',4'-dimethoxy-3'-(3-methyl-2-butenyl)isoflavone (1) on the basis of chemical and spectroscopic studies, and finally determined by an X-ray crystallographic analysis of licoricone monobromoacetate.[1] Licoricone has been characterized as the first naturally occurring isoflavone having the trioxygenated phloroglucinol pattern in the B ring. In the continuation of our studies on the syntheses of isoflavones having 3-methyl-2-butenyl groups in the B ring,[2] we here wish to report an unambiguous synthesis of 1 to confirm the proposed structure of the natural isoflavone and its isomer [6',7-dihydroxy-2',4'-dimethoxy-5'-(3-methyl-2-butenyl)isoflavone] (2).

The formylation of phloroglucinol by N,N-dimethylformamide-phosphorus oxychloride in anhydrous acetonitrile at 30-35 °C, followed by the methylation of the resultant compound with iodomethane in anhydrous acetone under reflux afforded 2-hydroxy-4,6-dimethoxybenzaldehyde [mp 67-68 °C; NMR ($CDCl_3$) δ 10.04 (1H, s, CHO), 12.44 (1H, s, OH)][3] in high yield based on phloroglucinol, which was converted into 2-benzyloxy-4,6-dimethoxybenzaldehyde (3) (mp 89-91 °C). The condensation of

4-benzyloxy-2-hydroxyacetophenone with 3 afforded the chalcone derivative (4) [mp 157-158 °C; NMR ($CDCl_3$) δ 7.78 and 8.35 (each 1H, d, J=16 Hz, CH=)] and the acetylation of 4 led to the acetate derivative (5) (mp 139-140 °C). The oxidative rearrangement of 5 with thallium(III) nitrate in a large amount of methanol, followed by the cyclization of the resultant compound by diluted hydrochloric acid[4] afforded the corresponding isoflavone (6) [mp 100-102 °C; NMR ($CDCl_3$) δ 7.66 (1H, s, 2-H)]. The hydrogenolysis of 6 with palladium charcoal (10%) in methanol-ethyl acetate gave the 6',7-dihydroxyisoflavone (7) (mp 266-268 °C), which was partially benzoylated with benzoyl chloride in pyridine to give 7-benzoyloxy-6'-hydroxyisoflavone (8) [mp 215-216 °C; UV λ_{max} nm (log ε) (EtOH) 260i(4.37), 292sh(3.91), 302 (3.87), (EtOH + AcONa) 262i(4.34), 292sh(3.92), 302 (3.87); NMR ($CDCl_3$) δ 7.54-8.36





(12)

(1) $R_1=R_3=R_4=H$, $R_2=(CH_3)_2C=CHCH_2$
(2) $R_1=R_2=R_4=H$, $R_3=(CH_3)_2C=CHCH_2$
(6) $R_1=R_4=PhCH_2$, $R_2=R_3=H$
(7) $R_1=R_2=R_3=R_4=H$
(8) $R_1=PhCO$, $R_2=R_3=R_4=H$
(9) $R_1=PhCO$, $R_2=R_4=H$, $R_3=(CH_3)_2C=CHCH_2$
(10) $R_1=PhCO$, $R_2=R_3=(CH_3)_2C=CHCH_2$, $R_4=H$
(11) $R_1=R_4=H$, $R_2=R_3=(CH_3)_2C=CHCH_2$
(13) $R_1=R_4=CH_3CO$, $R_2=H$, $R_3=(CH_3)_2C=CHCH_2$
(14) $R_1=R_4=PhCO$, $R_2=R_3=H$
(15) $R_1=R_4=PhCO$, $R_2=(CH_3)_2C=CHCH_2$, $R_3=H$
(16) $R_1=R_4=PhCO$, $R_2=H$, $R_3=(CH_3)_2C=CHCH_2$
(17) $R_1=R_4=CH_3CO$, $R_2=(CH_3)_2C=CHCH_2$, $R_3=H$

Table 1. Mp and UV Spectra of Isoflavones[a]

Compound	Mp (°C)	λ_{max} *nm (log ε)*	
Synthetic licoricone (1)	233-235[b]	(EtOH)	240(4.39), 248(4.38), 285(4.11), 304.5i(4.04)
(Natural)[1]	(250-251)	(EtOH + AcONa)	249.5(4.38), 255.5sh(4.37), 306.5i(3.95), 337.5(3.93)
Synthetic diacetate (17)	146-147[b]	(EtOH)	246sh(4.41), 294(3.86), 302(3.86)
(Natural)[1]	(172-173.5)		

a) i: Inflection point. sh: Shoulder. b) The melting points were measured with a Yanagimoto micro-melting-point apparatus.

Table 2. NMR Spectra of Isoflavones[a]

Compound (Solvent)	2-H	5-H 6-H 8-H	5'-H	$(CH_3)_2C=CHCH_2$	OCH_3	OH or OAc
Synthetic licoricone (1) (DMSO)	8.00(s)	7.91(d_1) 6.93(dd) 6.87(d_2)	6.33(s)	1.64(3H,s,CH_3) 1.70(3H,s,CH_3) 3.19(2H,d_3,CH_2) 5.12(1H,t,CH=)	3.39(s) 3.74(s)	9.67(2H,b, C-6',7)
Synthetic diacetate (17) ($CDCl_3$)	7.84(s)	8.28(d_1) 7.12(dd) 7.26(d_2)	6.49(s)	1.67(3H,s,CH_3) 1.76(3H,s,CH_3) 3.34(2H,d_3,CH_2) 5.17(1H,t,CH=)	3.46(s) 3.79(s)	2.05(s) 2.34(s)

a) Value in δ scale relative to TMS. s: Singlet. d_1, d_2, and d_3: Each doublet; J=9, 2, and 7 Hz, relatively. dd: Double doublet; J=2 and 8 Hz. t: Triplet; J=7 Hz. b: Broad.

(5H, m, C_6H_5CO), 8.97 (1H, s, OH)]. The condensation of 8 with 2-methyl-3-buten-2-ol in the presence of boron trifluoride etherate in anhydrous dioxane afforded 5'-(3-methyl-2-butenyl)isoflavone (9) (mp 164-166 °C) and 3',5'-bis(3-methyl-2-butenyl)isoflavone (10) (oil), which was converted into 6',7-dihydroxy-2',4'-dimethoxy-3',5'-bis(3-methyl-2-butenyl)isoflavone (11) (mp 200-202 °C). The NMR spectrum (DMSO) of 9 showed the presence of two methyl groups as a singlet at δ 1.63 and 1.71, one methylene group as a doublet (J=7 Hz) centering at δ 3.22, and one methine proton as a triplet (J=7 Hz) centering at δ 5.17, respectively. The compound 9 was hydrolyzed with diluted alkali in a nitrogen atmosphere to give 6',7-dihydroxy-2',4'-dimethoxy-5'-(3-methyl-2-butenyl)isoflavone (2) [mp 239-241 °C; UV λ_{max} nm (log ε) (EtOH) 248.5 (4.34), 264 (4.20), 297i(4.01), 304.5sh(3.97), (EtOH + AcONa) 261 (4.40), 289sh(4.06), 341 (3.96); NMR (DMSO) δ 1.61 and 1.68 (each 3H, s, CH_3), 3.20 (2H, d, J=7 Hz, CH_2), 3.64 and 3.79 (each 3H, s, OCH_3), 5.15 (1H, t, J=7 Hz, CH=), 6.26 (1H, s, 3'-H), 6.85 (1H, d, J=2 Hz, 8-H), 6.93 (1H, dd, J=2 and 9 Hz, 6-H), 7.92 (1H, d, J=9 Hz, 5-H), 7.94 (1H, s, 2-H), 8.20 and 10.67 (each 1H, b, OH)]. The compound 2 was cyclized with a small amount of concd hydrochloric acid in methanol to give the chroman derivative (12) (mp 243-245 °C)[5] and also converted into the diacetate (13) (mp 181-182 °C).[6] On the basis of these results, the isoflavone 2 was shown to be an isomer of licoricone.

The exhaustive benzoylation of 7 with benzoyl chloride in pyridine at 63 °C, followed by the condensation of the resultant compound (14) (mp 229-230 °C) with 2-methyl-3-buten-2-ol afforded two compounds (15) (mp 136-138 °C; 12%) and 6',7-

dibenzoyloxy-2',4'-dimethoxy-5'-(3-methyl-2-butenyl)isoflavone (16) (mp 182-184 °C; 31%), which was converted into 2. In this reaction, 39% of the starting material (14) was recovered. The NMR spectrum (DMSO) of 15 showed the presence of one 3-methyl-2-butenyl group and four aromatic protons, respectively. The hydrolysis of 15 with diluted alkali afforded the desired isoflavone (licoricone) (1) (Found: C, 69.02; H, 5.66%. Calcd for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80%). The cyclization of 1 was not caused by the treatment with concd hydrochloric acid in methanol. The compound 1 was subsequently converted into the diacetate (17), whose melting point was depressed by admixture with the diacetate 13. As shown in Table 1 and 2, the NMR and UV spectral data for the synthetic isoflavone 1 and the diacetate 17 are shown to be identical with those of the natural licoricone and its diacetate, respectively.

On the basis of these results, the structure of licoricone was confirmed to be 6',7-dihydroxy-2',4'-dimethoxy-3'-(3-methyl-2-butenyl)isoflavone (1).

REFERENCES AND NOTES

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2. M. Nakayama, S. Hayashi, M. Tsukayama, T. Horie, and M. Masumura, Chem. lett., 1978, 879; M. Tsukayama, K. Fujimoto, T. Horie, Y. Yamashita, M. Masumura, and M. Nakayama, Chem. Lett., 1982, 675.
3. Spectroscopic data and elemental analyses of all compounds agreed with the assigned structures. Melting points are uncorrected.
4. L. Farkas, A. Gottsegen, and M. Nogradi, J. Chem. Soc., Perkin I, 1974, 305.
5. NMR (DMSO) δ 1.13 (6H, s, CH_3 x 2), 1.67 and 2.52 (each 2H, t, J=7 Hz, CH_2), 3.66 and 3.82 (each 3H, s, OCH_3), 6.26 (1H, s, 3'-H), 6.82 (1H, d, J=2 Hz, 8-H), 6.90 (1H, dd, J=2 and 8 Hz, 6-H), 7.80 (1H, s, 2-H), 7.89 (1H, d, J=8 Hz, 5-H), 10.57 (1H, b, OH).
6. NMR ($CDCl_3$) δ 1.65 and 1.70 (each 3H, s, CH_3), 2.03 and 2.34 (each 3H, s, $COCH_3$), 3.18 (2H, d, J=7 Hz, CH_2), 3.72 and 3.84 (each 3H, s, OCH_3), 5.08 (1H, t, J=7 Hz, CH=), 6.41 (1H, s, 3'-H), 7.08 (1H, dd, J=2 and 9 Hz, 6-H), 7.22 (1H, d, J=2 Hz, 8-H), 7.71 (1H, s, 2-H), 8.23 (1H, d, J=9 Hz, 5-H).

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