A CONVENIENT SYNTHESIS OF A LINEAR PYRANOISOFLAVONE: SYNTHESES OF ELONGATIN AND ITS ANGULAR ISOMER

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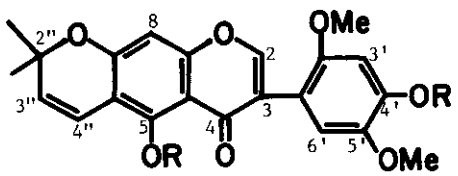
Abstract —— Linear 4',5-dihydroxy-2',5'-dimethoxy-2",2"-dimethyldihydropyrano[5",6"-g]isoflavone, which had been prepared from 6-acetyl-5-benzyloxy-7-hydroxy-2,2-dimethylchroman *via* four steps, was dehydrogenated with DDQ to give elongatin. Its angular isomer was also synthesized from 6-acetyl-7-benzyloxy-5-hydroxy-2,2-dimethylchroman in a similar manner.

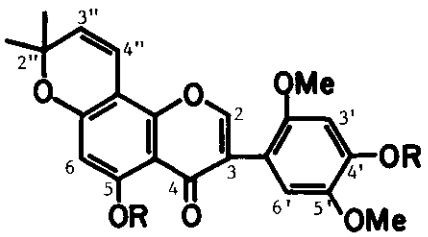
Two different typical pyranoisoflavones, linear and angular pyranoisoflavones, were largely isolated from the Leguminous plants. The structures of angular pyranoisoflavones were determined by their total syntheses.[1] However, the structures of linear pyranoisoflavones have not been determined by their unambiguous total syntheses yet, but assigned on the basis of spectroscopic and chemical studies. Therefore, the present investigation was carried out in order to confirm the proposed structures of naturally occurring linear pyranoisoflavones. A linear pyranoisoflavone, elongatin, was isolated from the roots and aerial parts of *Tephrosia elongata* E. Mey., and the structure has been shown to be 4',5-dihydroxy-2',5'-dimethoxy-2",2"-dimethylpyrano[5",6"-g]isoflavone (1) on the basis of chemical and spectroscopic evidence.[2] We here wish to report an unambiguous synthesis of 1 and also the synthesis of its angular isomer (4',5-dihydroxy-2',5'-dimethoxy-2",2"-dimethylpyrano[5",6"-h]isoflavone) (2).

The formylation of 2-benzyloxy-1,4-dimethoxybenzene, which was prepared from 2,5-dihydroxyacetophenone, by N,N-dimethylformamide-phosphorus oxychloride led to

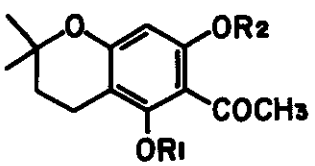
4-benzyloxy-2,5-dimethoxybenzaldehyde (3) (mp 137-139 °C). The partial benzylation of 6-acetyl-5,7-dihydroxy-2,2-dimethylchroman (4) afforded two compounds (5) [mp 120-121 °C; NMR ($CDCl_3$) δ 5.88 (1H, s, 8-H), 14.45 (1H, s, OH)] and (6) [mp 99-100 °C; NMR ($CDCl_3$) δ 6.17 (1H, s, 8-H), 12.77 (1H, s, OH)],[3] respectively. Further spectroscopic evidence favoring structures 5 and 6 was provided by the nuclear Overhauser effect (NOE) measurements on the methylene protons of the benzyl group. As indicated in compound 5, an enhancement of 30% in the proton signal at position C-8 was observed, when the methylene protons were irradiated under NOE conditions.



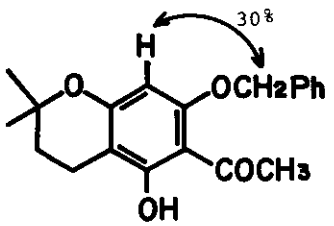
(1) R=H
(18) R=CH_3CO



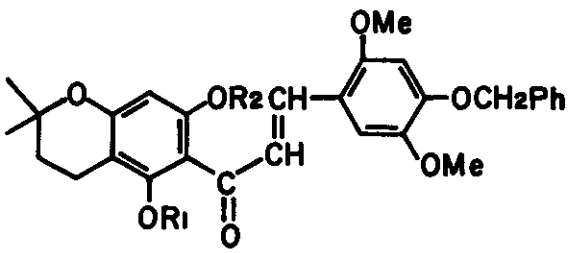
(2) R=H
(11) R=CH_3



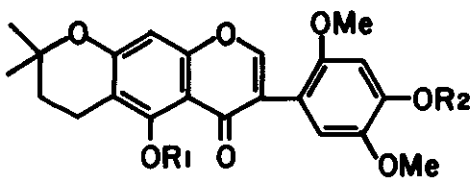
(4) $R_1=R_2=H$
(6) $R_1=PhCH_2$, $R_2=H$
(12) $R_1=H$, $R_2=Ts$
(13) $R_1=PhCH_2$, $R_2=Ts$



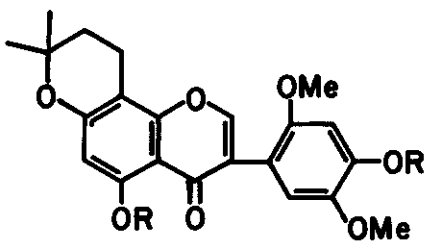
(5)



(7) $R_1=H$, $R_2=PhCH_2$
(8) $R_1=CH_3CO$, $R_2=PhCH_2$
(14) $R_1=PhCH_2$, $R_2=H$
(15) $R_1=PhCH_2$, $R_2=CH_3CO$



(16) $R_1=H$, $R_2=PhCH_2$
(17) $R_1=R_2=H$



(9) R=$PhCH_2$
(10) R=H

However, irradiation at the frequency of the methylene protons in compound 6 did not cause any appreciable enhancement in the proton signal at position C-8. From these results, each structure of compounds 5 and 6 was confirmed to be 7-benzyloxychroman and 5-benzyloxychroman, respectively.

The condensation of 5 with 3 afforded the chalcone derivative (7) (mp 180-182 °C), which was acetylated to give the acetate derivative (8) (mp 111-113 °C). The oxidative rearrangement of 8 with thallium(III) nitrate in methanol,[4] followed by the cyclization of the resultant compound by diluted hydrochloric acid afforded an dihydropyranoisoflavone (9) [mp 182-184 °C; NMR ($CDCl_3$) δ 7.78 (1H, s, 2-H)]. The hydrogenolysis of 9 with Pd-C (10%) in methanol-ethyl acetate afforded 4',5-dihydroxyisoflavone (10) (mp 212-213 °C), which was dehydrogenated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in anhydrous chlorobenzene under reflux to give the angular pyranoisoflavone (2) [mp 173-175 °C; NMR ($CDCl_3$) δ 1.48 (6H, s, CH_3 x 2), 3.72 and 3.86 (each 3H, s, CH_3O), 5.56 (1H, d, J=10 Hz, 3"-CH=), 5.76 (1H, s, 4'-OH), 6.29 (1H, s, 6-H), 6.63 (1H, s, 3'-H), 6.67 (1H, d, J=10 Hz, 4"-CH=), 6.88 (1H, s, 6'-H), 7.86 (1H, s, 2-H), 13.00 (1H, s, 5-OH)]. The methylation of 2 afforded the desired toxicarol isoflavone methyl ether (11) [mp 179-180 °C (lit.,[1b,5] mp 179-181 °C)]. Judging from the above results, the angular pyranoisoflavone 2 was confirmed to be an isomer of natural elongatin.

As described before, the direct benzylation of 4 is not suitable for the preparation of the starting material of elongatin because of a lower yield of 6. Another attempt was carried out in order to find a suitable preparation for 6. 7-Tosyloxychroman (12) (mp 139-140 °C; 72%), which was predominantly prepared from 4 in the presence of potassium carbonate in anhydrous acetone under reflux, was benzylated to give 5-benzyloxy-7-tosyloxychroman (13) (mp 112-113 °C; 89%), and was subsequently hydrolyzed with 10% alkali to give the desired chroman 6 in 85% yield. The condensation of 6 with 3 afforded the chalcone derivative (14) (mp 128-130 °C), which was subsequently converted into the acetate derivative (15) (mp 164-165 °C). The oxidative rearrangement of 15 with thallium(III) nitrate, followed by the cyclization of the resultant compound by diluted hydrochloric acid afforded a linear dihydropyranoisoflavone (16) [mp 150-151 °C; NMR ($CDCl_3$) δ 7.77 (1H, s, 2-H), 13.04 (1H, s, 5-OH)]. The hydrogenolysis of 16 with Pd-C (10%) afforded dihydropyranoisoflavone (17) [mp 181-183 °C (lit.,[2] mp 182-184 °C); NMR ($CDCl_3$) δ 5.80 (1H, s, 4'-OH), 7.78 (1H, s, 2-H), 13.17 (1H, s, 5-OH)], which seems to be dihydroelongatin. The dehydrogenation of 17 with DDQ in anhydrous *o*-dichloro-

benzene under reflux afforded the desired linear pyranoisoflavone (1) [mp 182-184 °C (lit.,[2] mp 181-182 °C); 27%; UV λ_{max} nm (log ε) (EtOH) 228 (4.43), 281 (4.57); NMR ($CDCl_3$) δ 1.48 (6H, s, CH_3 x 2), 3.73 and 3.87 (each 3H, s, CH_3O), 5.59 (1H, d, J=10 Hz, 3"-CH=), 5.76 (1H, s, 4'-OH), 6.32 (1H, s, 8-H), 6.66 (1H, s, 3'-H), 6.74 (1H, d, J=10 Hz, 4"-CH=), 6.88 (1H, s, 6'-H), 7.83 (1H, s, 2-H), 13.20 (1H, s, 5-OH); Found: C, 66.69; H, 5.00%. Calcd for $C_{22}H_{20}O_7$: C, 66.67; H, 5.08%]. The melting point of the synthetic linear pyranoisoflavone 1 was not depressed by admixture with natural elongatin. Pyranoisoflavone 1 was converted into the diacetate (18) [mp 227-228 °C (lit.,[2] mp 226-228 °C); UV λ_{max} nm (log ε) (EtOH) 227 (4.45), 263 (4.57), 239 (4.22), 334i(3.94);[6] NMR ($CDCl_3$) δ 1.47 (6H, s, CH_3 x 2), 2.30 and 2.41 (each 3H, s, CH_3CO), 3.68 and 3.77 (each 3H, s, CH_3O), 5.68 (1H, d, J=10 Hz, 3"-CH=), 6.47 (1H, d, J=10 Hz, 4"-CH=), 6.69 (2H, s, 3'- and 8-H), 6.92 (1H, s, 6'-H), 7.73 (1H, s, 2-H); Found: C, 64.95; H, 5.14%. Calcd for $C_{26}H_{24}O_9$: C, 64.91; H, 5.04%].

On the basis of these results, the structure of elongatin was confirmed to be the linear pyranoisoflavone 1.

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3. Spectroscopic data and elemental analyses of all compounds agreed with assigned structures. Melting points are uncorrected.
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6. i: Inflection point.

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