THE STRUCTURE OF LISETIN: THE SYNTHESIS OF ISOLISETIN DIMETHYL ETHER

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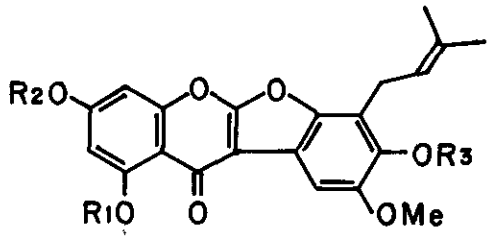
Abstract —— Isolisetin dimethyl ether (3) was prepared by oxidative cyclization of the isoflavone derivative (7) derived from 2-hydroxy-4,6-dimethoxyacetophenone and 5-benzyloxy-6-formyl-8-methoxy-2,2-dimethylchroman via three steps. The compound (3) was also obtained by the same reaction of 2',4'-dihydroxy-5,7,5'-trimethoxy-3'-(3-methyl-2-butenyl)isoflavone (12), followed by cyclization of the resultant compound (13) Lisetin (1) was synthesized by way of piscerythrone (2) and converted into isolisetin dimethyl ether (3) in succession.

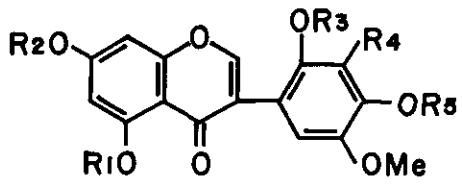
Lisetin has been isolated from the root of Jamaican Dogwood, Piscidia erythrina L., along with piscerythrone and piscidone.[1] The structure has been shown to be a benzopyrone-benzofuran compound, a unique type of natural product, bearing 3-methyl-2-butenyl group as shown in 1 on the basis of chemical and spectroscopic evidence, and by the partial synthesis from natural piscerythrone.[1] We wish to report that isolisetin dimethyl ether (3) is synthesized to confirm the proposed structure of natural lisetin and then lisetin (1) is prepared by way of piscerythrone (2)[2] by an unambiguous method.

2,4-Dihydroxy-5-methoxybenzaldehyde (mp 151-152 °C), prepared by hydrogenolysis of 2,4-dibenzyloxy-5-methoxybenzaldehyde[2] with palladium charcoal (10%), was converted into 2,4-dihydroxy-5-methoxy-3-(3-methyl-2-butenyl)benzaldehyde (mp 106-107 °C) with 2-methyl-3-buten-2-ol in the presence of boron trifluoride etherate in dry dioxane.[2,3] The cyclization of the 3-(3-methyl-2-butenyl)benzaldehyde derivative with hydrochloric acid in methanol afforded an oily chroman derivative. The NMR ($CDCl_3$) spectrum exhibited the presence of methylene protons as two



(1) $R_1=R_2=R_3=H$

(13) $R_1=R_2=Me$, $R_3=H$

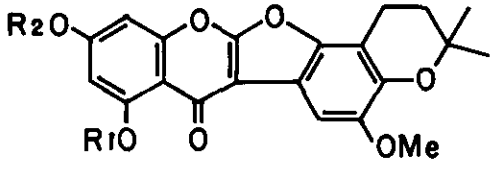


(2) $R_1=R_2=R_3=R_5=H$,
$R_4=(CH_3)_2C=CHCH_2$

(10) $R_1=R_2=Me$, $R_3=R_5=C_6H_5CH_2$,
$R_4=H$

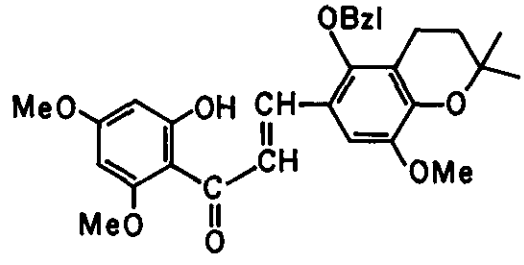
(11) $R_1=R_2=Me$, $R_3=R_4=R_5=H$

(12) $R_1=R_2=Me$, $R_3=R_5=H$,
$R_4=(CH_3)_2C=CHCH_2$

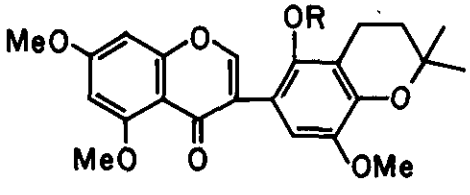


(3) $R_1=R_2=Me$

(14) $R_1=R_2=H$

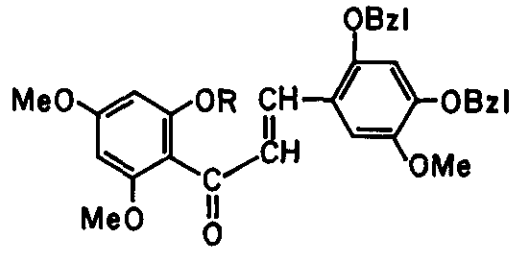


(5)



(6) $R=C_6H_5CH_2$

(7) R=H



(8) R=H

(9) $R=CH_3CO$

$Bzl=C_6H_5CH_2$

triplets (J=7 Hz) centering at δ 1.83 and 2.73 ppm, one chelate proton of hydroxyl group at δ 11.60 ppm, and one aromatic proton at δ 6.77 ppm, confirming the product to be 6-formyl-5-hydroxy-8-methoxy-2,2-dimethylchroman. The chroman was then converted into 5-benzyloxy-6-formyl-8-methoxy-2,2-dimethylchroman (4) (mp 164-165 °C) with benzyl chloride in dimethylformamide in the presence of anhydrous potassium carbonate. The condensation of 2-hydroxy-4,6-dimethoxyacetophenone with 4 in the presence of piperidine in ethanol gave the corresponding chalcone (5). The oxidative rearrangement of the crude chalcone (5) by thallium nitrate in methanol, followed by the hydrolysis of the resultant compound with dilute hydrochloric acid afforded an isoflavone derivative (6) (mp 188-189 °C), and 6 was then debenzylated by the catalytic hydrogenolysis to give a 2'-hydroxyisoflavone derivative (7) [mp 235-236 °C; NMR (DMSO) δ 6.60 (1H, s, 6'-H), 8.17 (1H, s, 2-H), 8.48 (1H, s, OH)]. The isoflavone derivative (7) was transformed by the oxidative cyclization with alkaline potassium ferricyanide into the desired isolisetin dimethyl ether (3) [mp 278-279 °C (lit,[1] mp 268-270 °C); IR (KBr) 1660 cm^{-1}; UV λ_{max} nm (log ε) (EtOH) 257 (4.49), 275_{sh} (4.26), 304 (4.12), 326 (4.11); NMR ($CDCl_3$) δ 1.44 (6H, s, CH_3 x 2), 1.89 and 2.98 (each 2H, t, J=7 Hz, CH_2), 3.88, 3.92, and 3.97 (each 3H, s, OCH_3), 6.41 and 6.55 (each 1H, d, J=2 Hz, Arom H), 7.50 (1H, s, Arom H); Found: C, 67.04; H, 5.55%. Calcd for $C_{23}H_{22}O_7$: C, 67.31; H, 5.40%]. The spectral data and the melting point of 3 were fully consistent with those of isolisetin dimethyl ether derived from natural lisetin.[1] The compound (3) was also prepared by an alternate procedure. The condensation of 2-hydroxy-4,6-dimethoxyacetophenone with 2,4-dibenzyloxy-5-methoxybenzaldehyde gave the corresponding chalcone (8) (mp 152-153 °C), which was then converted into the acetate (9) (mp 137-138 °C). The oxidative rearrangement of 9 by thallium nitrate, followed by the hydrolysis of the resultant compound afforded an isoflavone derivative (10) (mp 172-173.5 °C). The hydrogenolysis of 10 gave 2',4'-dihydroxy-5,7,5'-trimethoxyisoflavone (11) (mp 203.5-204.5 °C). The condensation of 11 with 2-methyl-3-buten-2-ol in the presence of boron trifluoride etherate in dry tetrahydrofuran yielded an isoflavone bearing one 3-methyl-2-butenyl group (12) (mp 183.5-185 °C). The NMR (DMSO) spectrum of 12 showed the presence of one aromatic proton at δ 6.59 ppm, methylene protons as a doublet (J=7 Hz) centering at δ 3.29 ppm, and one vinyl proton as a triplet (J=7 Hz) centering at δ 5.20 ppm. The oxidation of 12 with potassium ferricyanide, followed by the cyclization of the resultant compound (13) [mp 237-238.5 °C;

NMR (DMSO) δ 7.28 (1H, s, Arom H), 8.80 (1H, s, OH)] with hydrochloric acid in acetic acid afforded the desired compound (3), which was identical with the specimen (3) synthesized above. On the basis of these results, the structure of 12 was revealed to be 2',4'-dihydroxy-5,7,5'-trimethoxy-3'-(3-methyl-2-butenyl)-isoflavone.

Natural piscerythrone (2) has already been converted into lisetin (1),[1] and by use of the same procedure, piscerythrone (2), which was synthesized by the method described in the previous paper,[2] was transformed into the corresponding benzopyrone-benzofuran derivative (1) [mp 286-289 °C dec. (lit,[1] mp 283-286 °C dec.); IR (KBr) 1653 cm^{-1}; UV λ_{max} nm (log ε) (EtOH) 259 (4.48), 285 (4.28), 344 (4.13); NMR (DMSO) δ 1.67 and 1.80 (each 3H, s, CH_3), 3.45 (2H, d, J=7 Hz, CH_2CH=), 3.88 (3H, s, OCH_3), 5.30 (1H, t, J=7 Hz, CH_2CH=), 6.27 and 6.49 (each 1H, d, J=2 Hz, Arom H), 7.16 (1H, s, Arom H), 12.81 (1H, s, OH); Found: C, 66.10; H, 4.80%. Calcd for $C_{21}H_{18}O_7$: C, 65.96; H, 4.75%]. The treatment of 1 with hydrochloric acid in acetic acid gave readily isolisetin (14) [mp 292-294 °C; NMR (DMSO) δ 1.86 and 2.86 (each 2H, t, J=7 Hz, CH_2)], which was further converted into isolisetin dimethyl ether (3) with dimethyl sulfate. The properties of this compound were identical with those of isolisetin dimethyl ether (3) synthesized above. Consequently, the structure of lisetin was shown to be the structure as shown in (1).

References

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