CHEMISTRY LETTERS, pp. 879-882, 1978. Published by the Chemical Society of Japan

SYNTHESIS OF PISCERYTHRONE

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5,7,2',4'-Tetrahydroxy-5'-methoxyisoflavone (6) prepared from 2,4,2',4'-tetrabenzyloxy-6'-hydroxy-5-methoxychalcone (2) by way of three steps was partially benzoylated to give 7-benzoyloxy-5,2',4'-trihydroxy-5'-methoxyisoflavone (7). The condensation of 7 with 2-methyl-3-buten-2-ol afforded 7-benzoyloxy-5,2',4'-trihydroxy-5'-methoxy-3'-(3-methyl-2-butenyl)isoflavone (8), which was hydrolyzed to give piscerythrone (1).

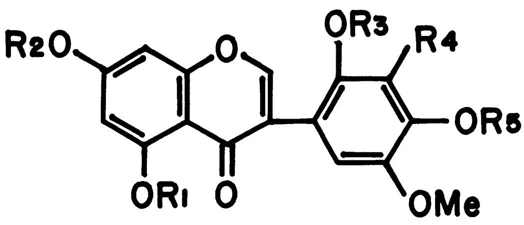
Piscerythrone has been isolated from the root of Jamaican Dogwood, *Piscidia erythrina* L., along with several other isoflavones.[1] The structure has been shown to be 5,7,2',4'-tetrahydroxy-5'-methoxy-3'-(3-methyl-2-butenyl)isoflavone (1) on the basis of chemical and spectroscopic evidence.[1] The isoflavone 1 is one of the unique isoflavones bearing a 3-methyl-2-butenyl group in the B ring. In our previous papers,[2] we reported on the high selectivity of 7-benzoyloxyisoflavones for the introduction of a 3-methyl-2-butenyl group into the B ring of isoflavones. In continuation of our studies on the synthesis of isoflavones, we wish to report an unambiguous synthesis of 1 to confirm the proposed structure of the natural isoflavone.

The partial benzylation of 2,5-dihydroxyacetophenone[3] with benzyl chloride in acetone in the presence of potassium carbonate gave 5-benzyloxy-2-hydroxyacetophenone, which was converted into 5-benzyloxy-2-methoxyacetophenone with dimethyl sulfate in acetone in the presence of potassium carbonate. The oxidation of 5-benzyloxy-2-methoxyacetophenone with hydrogen peroxide, followed by the benzylation afforded 2,4-dibenzyloxy-1-methoxybenzene. The formylation of the benzene derivative by

N,N-dimethylformamide-phosphoryl chloride in 1,2-dichloroethane yielded 2,4-dibenzyloxy-5-methoxybenzaldehyde [mp 115-117 °C; IR (KBr) 1650 cm^{-1}; NMR ($CDCl_3$) δ 6.55 (1H, s), 7.35 (1H, s), 10.35 (1H, s, CHO)]. The condensation of 2,4-dibenzyloxy-6-hydroxyacetophenone with the benzaldehyde derivative in the presence of piperidine in ethanol gave 2,4,2',4'-tetrabenzyloxy-6'-hydroxy-5-methoxychalcone (2) [mp 132-134 °C; NMR ($CDCl_3$) δ 7.80 and 8.19 (each 1H, d, J=16 Hz, CH=CH)]. The oxidative rearrangement of the acetate (3) [mp 110-112 °C] of 2 by thallium nitrate in methanol, followed by the hydrolysis with dilute hydrochloric acid[4] afforded two isoflavones 7,2',4'-tribenzyloxy-5-hydroxy-5'-methoxyisoflavone (4) [mp 141-143 °C; NMR ($CDCl_3$) δ 4.88 (2H, s, $C_6H_5CH_2$), 5.11 (4H, s, $C_6H_5CH_2$ x 2), 7.84 (1H, s, 2-H), 13.00 (1H, s, 5-OH)] and 5,7,2',4'-tetrabenzyloxy-5'-methoxyisoflavone (5) [mp 151-152 °C; NMR ($CDCl_3$) δ 4.85, 5.08, 5.10, and 5.18 (each 2H, s, $C_6H_5CH_2$), 7.76 (1H, s, 2-H)], which were converted into 5,7,2',4'-tetrahydroxy-5'-methoxyisoflavone (6) [mp 259-260 °C; NMR (DMSO) δ 3.64 (3H, s, OCH_3), 6.17 and 6.35 (each 1H, d, J=2 Hz, 6- and 8-H), 6.38 (1H, s, 3'-H), 6.73 (1H, s, 6'-H), 8.16 (1H, s, 2-H), 8.82 and 9.08 (each 1H, bs, OH), 13.07 (1H, s, 5-OH)] by the hydrogenolysis with palladium charcoal (10%) in methanol-ethyl acetate. The partial benzoylation of the isoflavone (6) with benzoyl chloride in pyridine[2] gave 7-benzoyloxyisoflavone derivative (7) [mp 229-231 °C; UV λ_{max} nm (log ε), (EtOH) 299 (4.04), (EtOH + AcONa) 300 (4.06); NMR (DMSO) δ 7.48-8.27 (5H, m, C_6H_5CO)]. The condensation of 7 with 2-methyl-3-buten-2-ol in the presence of boron trifluoride etherate[2,5] in dry dioxane afforded a prenyl compound (8) [mp 142-143.5 °C]. The NMR spectrum ($CDCl_3$) of 8 showed the presence of two methyl groups as a singlet at 1.68 and 1.80 ppm, one methylene group as a doublet (J=7 Hz) centering at 3.45 ppm, and one vinyl proton as a triplet (J=7 Hz) centering at 5.26 ppm. Furthermore, 8 was cyclized with hydrochloric acid in acetic acid to give two chroman derivatives (9) [mp 249-250 °C; NMR (DMSO) δ 1.30 (6H, s, CH_3 x 2), 1.75 and 2.65 (each 2H, t, J=7 Hz, CH_2 x 2)] and (10) [mp 182-184 °C; NMR (DMSO) δ 1.20 (6H, s, CH_3 x 2), 1.70 and 2.63 (each 2H, t, J=7 Hz, CH_2 x 2)]. The oxidative cyclization of 10 with alkaline potassium ferricyanide, followed by the methylation of the resultant compound afforded also a compound (11) [mp 271-273 °C], whose properties (mp and spectral data) were fully consistent with those of isolisetin dimethyl ether.[1] On the basis of these results, the compound 8 was shown to be 7-benzoyloxy-5,2',4'-trihydroxy-5'-methoxy-3'-(3-methyl-2-butenyl)isoflavone.

The compound 8 was hydrolyzed with dilute alkali in a nitrogen atmosphere at room temperature to yield the desired isoflavone (piscerythrone) (1) [mp 182.5-

183.5 °C (lit,1) mp 183.5-184.5 °C); IR (KBr) 3410, 1650 cm^{-1}; UV λ_{max} nm (log ε) (EtOH) 267 (4.38), 295$_{sh}$ (4.22), 335 (3.88); NMR (DMSO) δ 1.60 (3H, s, CH$_3$), 1.70 (3H, s, CH$_3$), 3.23 (2H, d, J=7 Hz, C$\underline{H}_2$CH=), 3.67 (3H, s, OCH$_3$), 5.13 (1H, t, J=7 Hz, CH$_2$C$\underline{H}$=), 6.19 and 6.36 (each 1H, d, J=2 Hz, 6- and 8-H), 6.55 (1H, s, 6'-H), 8.19 (1H, s, 2-H), 7.90, 8.54, and 10.94 (each 1H, s, OH), 13.00 (1H, s, 5-OH); Found: C, 65.35; H, 5.32%. Calcd for $C_{21}H_{20}O_7$: C, 65.61; H, 5.24%]. The properties of this synthetic isoflavone (1) were fully consistent with those of natural piscerythrone.



(1) $R_1=R_2=R_3=R_5=H$

$R_4=(CH_3)_2C=CHCH_2$

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

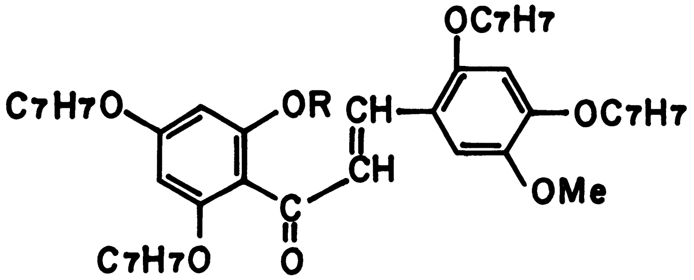
(5) $R_1=R_2=R_3=R_5=C_6H_5CH_2$, $R_4=H$

(6) $R_1=R_2=R_3=R_4=R_5=H$

(7) $R_1=R_3=R_4=R_5=H$, $R_2=C_6H_5CO$

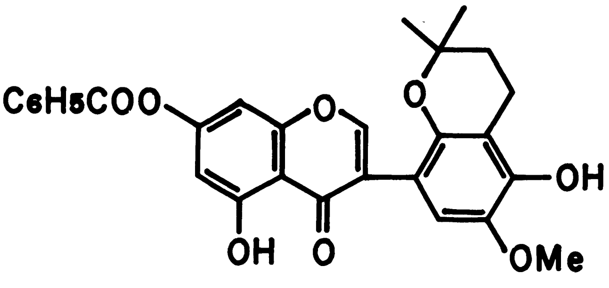
(8) $R_1=R_3=R_5=H$, $R_2=C_6H_5CO$

$R_4=(CH_3)_2C=CHCH_2$

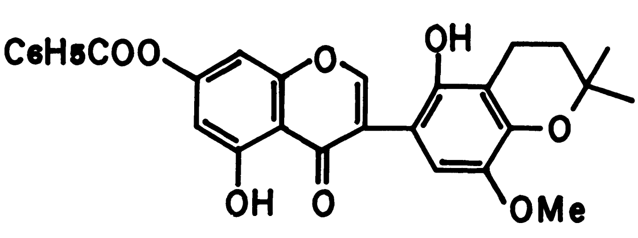


(2) R=H

(3) $R=CH_3CO$



(9)



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(Received June 12, 1978)