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A NEW SYNTHESIS OF WATASENIA PRELUCIFERIN BY CYCLIZATION OF 2-AMINO-3-BENZYL-5-(p-HYDROXYPHENYL)PYRAZINE WITH p-HYDROXYPHENYLPYRUVIC ACID

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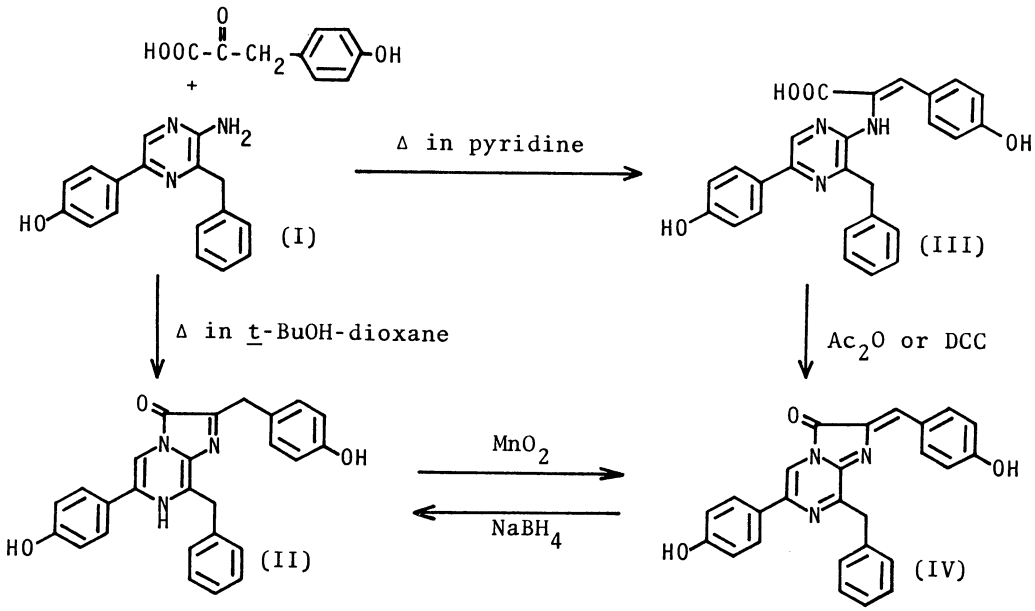
The reaction of 2-amino-3-benzyl-5-(p-hydroxyphenyl)pyrazine with p-hydroxyphenylpyruvic acid gave directly Watasenia preluciferin in a satisfactory yield without any reductive treatment.

Previously we have reported the isolation of a new type of marine luminescent substance, Watasenia preluciferin (II),[1] together with fluorescent compounds, 2-amino-3-benzyl-5-(p-hydroxyphenyl)pyrazine (I)[1] and W. dehydropreluciferin (IV)[2] from the liver, and W. luciferin[3] and W. oxyluciferin[4] from the arm photophores of the luminous squid, Watasenia scintillans (Japanese name: hotaru-ika).

These compounds were subsequently synthesized to confirm their structures as reported earlier;[1~4] for example, W. preluciferin (II) was prepared by condensation of the 2-aminopyrazine (I) with p-acetoxybenzylglyoxal in an acidic medium.

In our continuous effort for the preparation of various luminescent compounds,[1~5] we found that the commercially available p-hydroxyphenylpyruvic acid could react with the 2-aminopyrazine (I) without any reductive treatment to give directly the desired W. preluciferin (II) in a satisfactory yield, whereas a reduction step was involved in our first synthesis of Cypridina luciferin.[6]



A mixture of I (277 mg) and p-hydroxyphenylpyruvic acid (540 mg) in t-butyl alcohol -dioxane (1:1) (1.5 ml) was heated under reflux at 140°C for 25 min. After basified with 10% aq. $NaHCO_3$, the mixture was filtered and the filtrate was evaporated to dryness under vacuum. The soluble portion taken up in CH_2Cl_2-MeOH (3:1) from the residue was chromatographed twice on silica gel [solvent: CH_2Cl_2-acetone (3:1)] to give yellow crystalline W. preluciferin (II) (207 mg, 49%) and its dehydro form (IV) (35.5 mg, 8.4%). Spectral data (UV, IR, NMR, and Mass) of these compounds were indistinguishable with those of natural W. preluciferin (II) and its dehydro form (IV), respectively.

On the other hand, when a mixture of I (1.7 g) and p-hydroxyphenylpyruvic acid (3.3 g) in pyridine (8 ml) was heated at 80°C for 5 h, unstable dehydroamino acid (III) [1.32 g, 49% (corrected yield, 82%)][7] was obtained. The acid (III) was easily converted to W. dehydropreluciferin (IV)[8] by the action of dehydrating agent such as Ac_2O or DCC. For example, a mixture of III (30 mg) and acetic anhydride (7 µl) in dioxane (0.4 ml) was stirred at room temp. for 10 min and the resulting wine red solution was dried up under vacuum. The residue was purified through a silica gel column [solvent: CH_2Cl_2-acetone (1:1)], and then crystallized from hexane to give dark red crystals of IV (22.7 mg, 79%).

The cyclization of the 2-aminopyrazine (I) using commercially available p-hydroxyphenylpyruvic acid instead of p-acetoxybenzylglyoxal[1] is greatly advantageous in the synthesis of W. preluciferin (II). The presence of the 2-aminopyrazine (I), the preluciferin (II), and its dehydro form (IV) in the liver of the luminous squid [1~5] and the synthetic results described here prompt us to make a prediction that in vivo biosynthesis of the preluciferin (II) also involves reaction of the 2-aminopyrazine (I) and p-hydroxyphenylpyruvic acid.

REFERENCES AND NOTES

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6) Y.Kishi, T.Goto, S.Inoue, S.Sugiura, and H.Kishimoto, Tetrahedron Lett., 1966, 3445.
7) III: NMR (ppm in DMSO-d6) 4.25 (2H, s), 6.44 (2H, $\underline{A}_2'X_2'$, J=8 Hz), 6.73 (2H, $\underline{B}_2'Y_2'$, J=8 Hz), 7.0~7.4 (8H, m), 7.64 (2H, $\underline{B}_2'Y_2'$, J=8 Hz), 7.74 (1H, br. s, replaced with D_2O), 8.14 (1H, s). The methyl ester of III: mp (dec.) 208~210°C (from MeOH); NMR (ppm in DMSO-d6) 3.60 (3H, s), 4.28 (2H, s), 6.53 (2H, $\underline{A}_2'X_2'$, J=8 Hz), 6.73 (2H, $\underline{B}_2'Y_2'$, J=8 Hz), 7.0~7.5 (8H, m), 7.71 (2H, $\underline{B}_2'Y_2'$, J=8Hz), 8.09 (1H, br. s, replaced with D_2O), 8.25 (1H, s), 9.46 (1H, br. s, replaced with D_2O), 9.71 (1H, br. s, replaced with D_2O); IR (cm^{-1} in KBr) 1722, 1606, 1583, 1482, 1368, 1245; UV λ_{max}^{MeOH} nm (ε) 287 (33400), 355sh (19800); $\lambda_{max}^{MeOH-NaOH}$ 307 (29600), 368 (27100); MS m/e 453 (M^+); Anal. Calcd. for $C_{27}H_{23}N_3O_4$: C, 71.51, H, 5.11; N, 9.27%. Found: C, 71.47; H, 4.91; N, 8.80%.
8) Interconversion of W. preluciferin (II) and W. dehydropreluciferin (IV), See ref.2.

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