

HEAD TO TAIL COUPLING OF 1-(4-HYDROXYPHENETHYL)-7-HYDROXY-6-METHOXY-2-METHYL-1,
2,3,4-TETRAHYDROISOQUINOLINE BY ENZYMIC PHENOLIC OXIDATION

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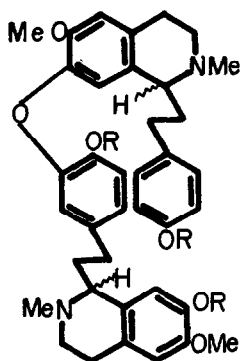
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Since the biogenetic mechanism of morphine was assumed previously in 1925 by Sir Robert Robinson,¹ it has come into the limelight that various kinds of isoquinoline alkaloids would be formed by phenolic oxidative coupling of norlaudanosoline derivatives in the plant.²⁻⁴ These hypotheses have been recognized by application of tracer experiments.⁵⁻⁸ In the previous papers⁹ phenol oxidation of various isoquinolines have been reported, but no attempt to obtain bis-coclaurine type alkaloids which have one or two biphenyl ether linkage has ever been accomplished successfully besides head to head coupling products such as pirocereine¹⁰ and bisbenzylisoquinoline type compounds.^{11,12}

We now wish to report the synthesis of promelanthioidine and/or proisomelanthioidine type¹³ compound (I) by phenol oxidation of 1-phenethylisoquinoline (II) with homogenised potato peels and hydrogen peroxide.

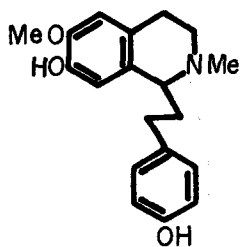
As a preliminary experiment, phenol oxidation of *p*-cresol with the above enzymic catalyst in the presence of hydrogen peroxide was carried out, to give the Pummerer's ketone¹⁴ and di-*p*-cresol, whose structures were identical with the authentic samples, prepared by electrolytic phenol oxidation of *p*-cresol.¹⁵

Secondly, a solution (pH 4.8) of 1-(4-hydroxyphenethyl)-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline^{9d} (II) and ammonium acetate in 10 % acetic acid was oxidised at 5 - 18° for 4 days with homogenised potato peels in the presence of hydrogen peroxide. The reaction mixture was adjusted to pH 8.5 with ammonium hydroxide and washed with chloroform to remove unreacted starting material (II). The resultant aqueous layer was then extracted with *n*-butanol. Removal of the solvent gave a brown solid which was acetylated with acetic anhydride in the presence of potassium carbonate in tetrahydrofuran to

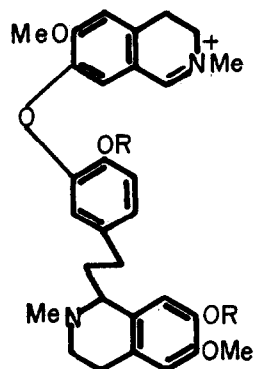


I : R = H

III : R = Ac (M^+ m/e 750)

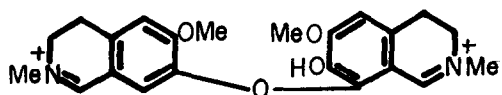


II

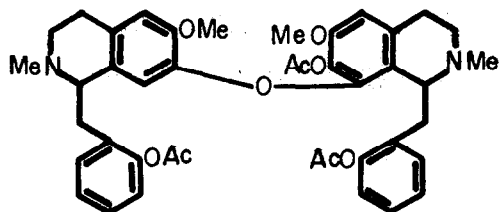


IV : R = H

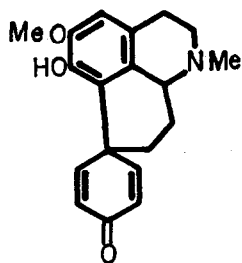
V : R = Ac m/e 587



VI : m/e 191



VII



VIII

afford the acetate (III) in 2 % yield. Its thin layer chromatography showed one spot (Wakogel B-5, chloroform: methanol = 6 : 1). N.m.r. (CCl_4) τ 6.23 (2 x OCH_3), 7.59 (2 x NCH_3), 7.80 (3 x OCOCH_3), 2.8 - 3.5 (11H, multiplet, aromatic protons). The mass spectrum established the molecular weight (M^+ , m/e 750).¹⁶ Further fragment at m/e 587 was assigned to the ion (V). If the head to head coupled compound would be formed, the characteristic fragment ion (VI) should appear at m/e 191 as described in the case of the compound (VII).¹² The lack of this ion also supports the structure of III. Moreover, the possibility of head to head coupling was also excluded because the n.m.r. signal of O-acetyl group was observed as singlet (9H) at τ 7.80, whereas the head to head coupled compound (VII) showed the methyl resonance of C_7 -O-acetyl group (3H) at τ 8.08 as singlet and two other acetyl groups (6H) at τ 7.85.¹² These facts revealed the structure of this compound to be III.

The above triacetyl compound (III) was hydrolyzed with methanolic potassium hydroxide to give the promelanthioidine type phenol base (I) quantitatively, whose recrystallisation from dry tetrahydrofuran-ether gave a pale yellowish powder, m.p. 158 - 161 $^\circ$, ν_{max} . (KBr) 3350 (OH), 2830 (NMe), $\lambda_{\text{max}}^{\text{MeOH}}$ $\mu\mu$ 280. These results reveal the enzymic formation of bisphenethylisoquinoline compound coupled with head to tail as the first example and it is of great interest that no formation of the dienone (VIII)^{9e} has been observed in this enzymic oxidation whereas the inorganic reagents as ferric chloride and potassium ferricyanide generally afford the dienone in comparatively good yield.

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16. The mass spectrum was measured with a Hitachi mass spectrometer RMU-6D equipped with direct inlet system using perfluorokerosene as an internal standard: chamber voltage 70 eV; total emission 80 μ A; evaporation temp., 250°C; ion-chamber temp., 250°C.