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A NOVEL FORMATION OF THE INDOLE DERIVATIVES BY PHENOLIC OXIDATIVE COUPLING

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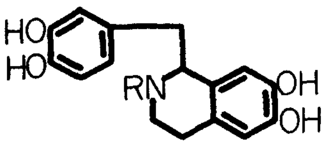
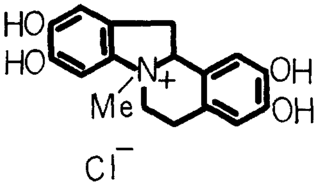
Extensive studies have been published recently on the phenolic oxidative coupling reactions. We are currently investigating the phenolic oxidative coupling reaction of 1,2,3,4-tetrahydroisoquinolines, leading to the total syntheses of a variety of isoquinoline alkaloids. Robinson and Sugasawa[1] reported that oxidation of laudanosoline (Ia) with chloranil resulted in the bond formation between the carbon and nitrogen atoms to afford 5,6,12,12a-tetrahydro-2,3,9,10-tetrahydroxy-7-methyldibenzo[b,g]pyrrocolinium chloride (II) in good yield. By oxidation of norlaudanosoline (Ib) with potassium ferricyanide, Harley-Mason[2] obtained 5,6-dihydro-2,3,9,10-tetrahydroxydibenzo-[b,g]pyrrocoline (III) which was, further, oxidised readily to the corresponding aromatic dibenzopyrrocoline (IV). Furthermore, Harley-Mason and co-workers[3,4] reported that the 3,4-dihydroxyphenethylamine derivatives were oxidised with a variety of oxidising agents to afford the corresponding 2,3-dihydroindole-5,6-quinones.

Concerning the formation of indole nucleus through phenolic oxidative coupling reaction, since a few examples have hitherto been reported[1-6], we now wish to report an interesting results of the oxidative coupling of the compound (Va) and (Ve) with ferric chloride in order to examine whether the intramolecular coupling between the carbon-C_6 and amino-nitrogen would occur or not, leading to an alternative synthesis of indole derivatives.

At first, 3-benzyloxy-4-methoxyphenethylamine (Vb) was debenzylated with ethanolic hydrochloric acid to afford 3-hydroxy-4-methoxyphenethylamine (Va)[7] in good yield. Oxidation of the above phenolic amine (Va) (1.5 g.) with 4.1 molar equivalents of ferric chloride hexahydrate was carried out at room temperature for 20 hr. in a current of nitrogen, to give 5-hydroxy-6-methoxyindole (VIa) (160 mg.; 10.6 %), which was recrystallised from benzene-hexane to afford colourless needles, m.p. 110 - 111° (Found: C, 66.63; H, 5.61. $C_9H_9NO_2$ requires C, 66.24; H, 5.56), $\nu_{max.}$ ($CHCl_3$) 3500 (OH), 3450 cm.$^{-1}$ (NH), (δ) (in $CDCl_3$) 3.93 (3H, s, $OC\underline{H}_3$), 5.43 (1H, m,



(I) a R = Me
b R = H



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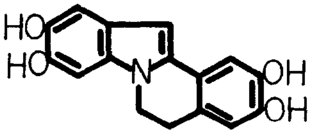

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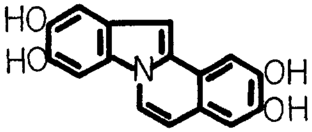

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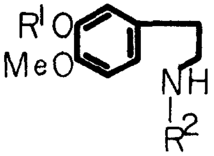
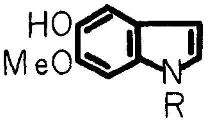
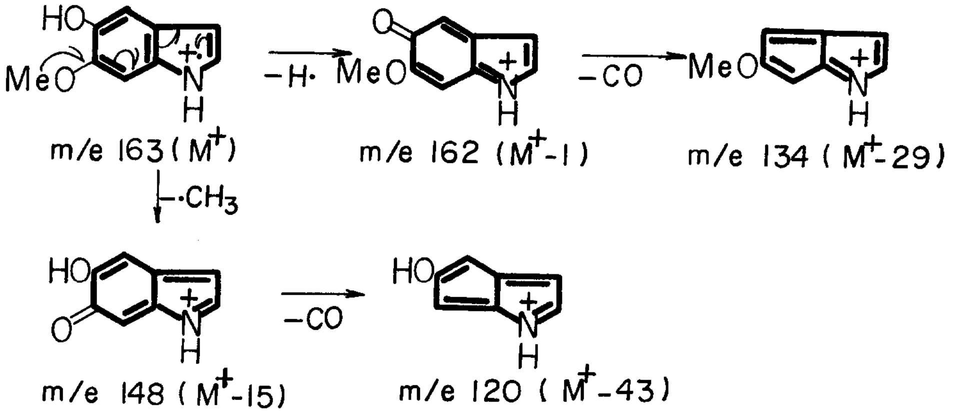


(V) a $R^1 = R^2 = H$
b $R^1 = CH_2Ph, R^2 = H$
c $R^1 = CH_2Ph, R^2 = COMe$
d $R^1 = CH_2Ph, R^2 = Et$
e $R^1 = H$, $R^2 = Et$

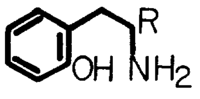


(VI) a R = H
b R = Et

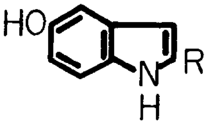
O<u>H</u>, disappeared with deuterium oxide), 6.43 (1H, C_3-<u>H</u>), 6.88 (1H, s, C_4-<u>H</u>), 7.06 (1H, C_2-<u>H</u>), 7.12 p.p.m. (1H, s, C_7-<u>H</u>), m/e 163 (M^+, base peak), 162 (M^+-1), 148 (M^+-15), 134 (M^+-29), 120 (M^+-43). The fragment ion species of the mass spectrum of (VIa) in details were observed as shown as follow.



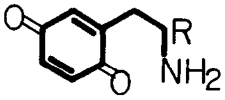
Secondly, lithium aluminium hydride reduction of N-(3-benzyloxy-4-methoxyphenethyl)-acetamide[7] (Vc) in tetrahydrofuran gave 3-benzyloxy-4-methoxyphenethylamine (Vd) as a yellowish oil, whose oxalate was recrystallised from ethanol gave colourless needles, m.p. 186 - 187° (Found: C, 64.28; H, 6.88; N, 3.67. $C_{18}H_{23}NO_2.(CO_2H)_2$ requires C, 63.98; H, 6.71; N, 3.73 %). The above ethylamine derivative (Vd) was debenzylated with ethanolic hydrochloric acid to afford an expected phenolic amine (Ve), whose oxidation under the similar conditions as above afforded 1-ethyl-5-hydroxy-6-methoxyindole (VIb). Since the compound (VIb) could not be crystallised, it was chromatographed on silicic acid to give a pale yellowish gum, $\nu_{max.}$ ($CHCl_3$) 3500 cm.$^{-1}$ (OH), m/e 191 (M^+), 190 (M^+-1), 176 (M^+-15, base peak), 162 (M^+-29), 148 (M^+-43). The mass spectrum of (VIb) showed the closely similar fragmentations to that of the above compound (VIa) and supported the structure of (VIb) to be corect.



(VII) a R = Ph
b R = H



(VIII) a R = Ph
b R = H

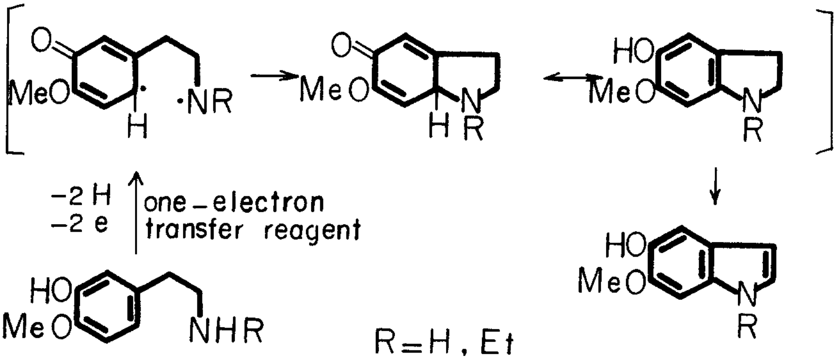


(IX) a R = Ph
b R = H

Teuber[8] reported that 1-amino-1-phenyl-2-(2-hydroxyphenyl)ethane (VIIa) was oxidised with potassium nitrosodisulphonate (Fremy reagent) to 5-hydroxy-2-phenylindole (VIIIa) through the p-quinone derivative (IXa) as an intermediate.

2-Hydroxyphenethylamine[9] (VIIb) was treated with ferric chloride under a variety of conditions in order to investigate whether the formation of the p-quinone derivative (IXb) would be possible or not, leading to the formation of the indole derivative (VIIIb), but only a starting material was recoverd and no trace of the expected compound (VIIIb) was detected.

These results supported the formation of VIa and VIb to proceed as shown as follow.



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