A NEW ROUTE TO PYRROLO[2,3-b]INDOLES

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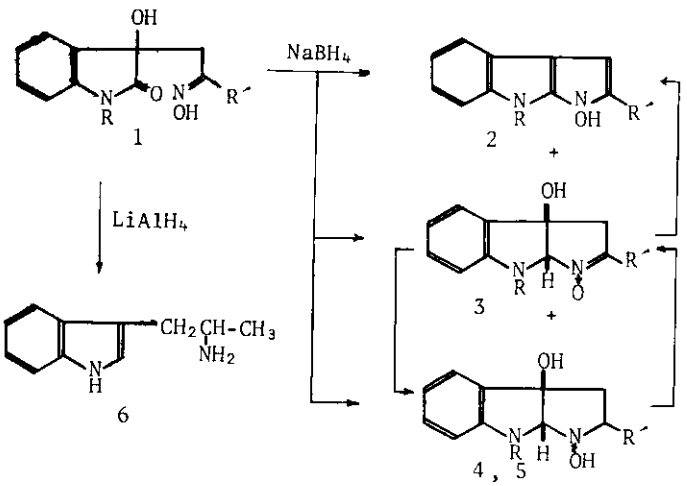
The cyclization of 3-hydroxy-3-2´-hydroxyiminooxindoles (1) to pyrrolo[2,3-b]indole derivatives (2-5) has been described. In the resulting products, 4 and 5 were first isolated five-membered invertomers.

Several cyclizations of indolinones by reduction were frequently employed for the synthesis of tetrahydropyrrolo[2,3-b]indole system.[1-5] However, these cyclizations have been entirely successful only in the case of 1-alkyl derivatives. We now wish to report a convenient synthesis of 3a-hydroxy-tetrahydropyrrolo[2,3-b]indoles and pyrrolo[2,3-b]indoles.

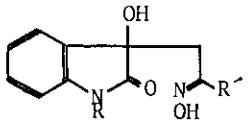
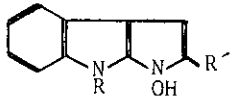
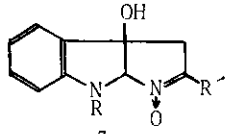
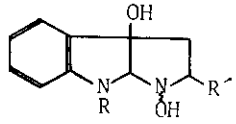
While 3-hydroxy-3-2´-hydroxyiminooxindole derivatives on lithium alanate or on sodium borohydride-aluminium chloride reduction gave α-methyltryptamine (6),[6] reduction with sodium borohydride only gave pyrrolo[2,3-b]indole derivatives. When reduction of 1a was carried out at -10°, 1-hydroxy-2-methylpyrrolo[2,3-b]indole (2a) (mp 210-211°) containing a 14 π-electron system[7] was obtained as main product; nmr (DMSO-d_6) δ 2.68 (s, 3H), 7.68 (s, 1H), 8.75 (s, 1H), 7.49-8.70 (m, 4H), 11.92 (s, 1H); uv max (EtOH) 240 nm (log ε 4.47), 308 nm (log ε 4.06). Elevation of the reaction temperature gave rise to formation of saturated 3a-hydroxy derivatives (3a, 4a and 5a) besides 2a. 3a: mp 171-173°; nmr (DMSO-d_6) δ 1.83 (s, 3H), 5.04



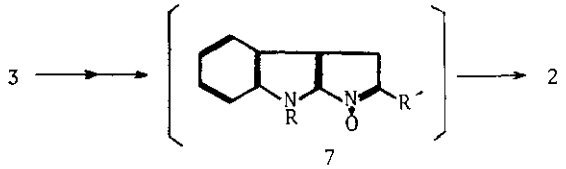
(s, 1H), 6.07 (br. s, 1H), 6.50-7.40 (m, 5H); uv max (EtOH) 230 nm (log ε 4.28), 295 nm (log ε 3.27). 4a: mp 126-128°; nmr (DMSO-d_6) δ 0.99 (d, J=6 Hz, 3H), 1.52 (q, J_1=11.5 Hz, J_2=13 Hz, 1H), 2.21 (q, J_1=8 Hz, J_2=13 Hz, 1H), 3.20 (m, 1H), 4.14 (s, 1H), 5.32 (s, 1H), 6.15 (br. s, 1H), 7.85 (s, 1H), 6.40-7.20 (m, 4H); uv max (EtOH) 241 nm (log ε 4.20), 297 nm (log ε 3.37). 5a: mp 200° (decomp.); nmr (DMSO-d_6) δ 1.05 (d, J=6 Hz, 3H), 1.93 (m, 2H), 2.75 (m, 1H), 4.74 (d, J=1.6 Hz, 1H), 5.50 (s, 1H), 5.95 (s, 1H), 7.01 (d, J=1.6 Hz, 1H), 6.74-7.56 (m, 4H); uv max (EtOH) 240 nm (log ε 3.94), 297 nm (log ε 3.42). On the other hand, 1-methyl-3-hydroxy-3-2´-hydroxyiminopropyloxindole (1b) was converted to 3a-hydroxy-2,8-dimethyl-3a,8a-dihydro-3*H*-pyrrolo[2,3-b]indol-1-oxide (3b) (amorphous) at -10° in nearly quantitative yield, while at room temperature 1b gave a saturated 3a-hydroxy derivative 4b (mp 206-208°, 12.1%) together with 3b. In the same way, 1c and 1d gave 3c and 3d as sole product, respectively (see Table 1).

With the purified 4a or 5a, the interrelation of 4a (or 5a) and 3a was examined. When a solution of 4a (or 5a) was treated with chloranil in THF, 3a

Table 1

 1	Temp. (°C)	Yield (%)  2	 3	 4	5
R=H, R´=Me	-10	55.4	—	0.7	0.6
〃	0-5	21.2	—	26.8	15.0
〃	Room temp.	17.7	5.6	38.3	9.3
〃	〃	4.2	0.5	48.1	10.2
R=R´=Me	-10	—	95.4	—	—
〃	Room temp.	—	65.9	12.1	
R=H, R´=Ph	〃	—	29.3	—	—
R=Me, R´=Ph	〃	—	66.9	—	—

was obtained in nearly quantitative yield. When a solution of 3a was treated with sodium borohydride, 4a and 5a were formed in 43.8% and 24.3% yields, respectively. Compound 3a was slowly dehydrated in dil. hydrochloric acid to the pyrroloindole 2a in high yield. Dehydration might take place on a C-3 hydrogen and then rearrangement of the double bond led to an intermediate 7, which could form the pyrroloindole 2a, *via* the analogous tautomerism on indolenin-*N*-oxide.[8]



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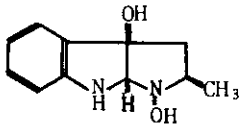
Interestingly 4a and 5a were first isolated five-membered invertomers, whose stereochemistries were showed as $\underline{\underline{4}}$ and $\underline{\underline{5}}$ by their nmr spectra, respectively.



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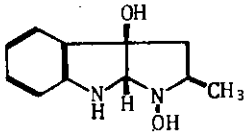
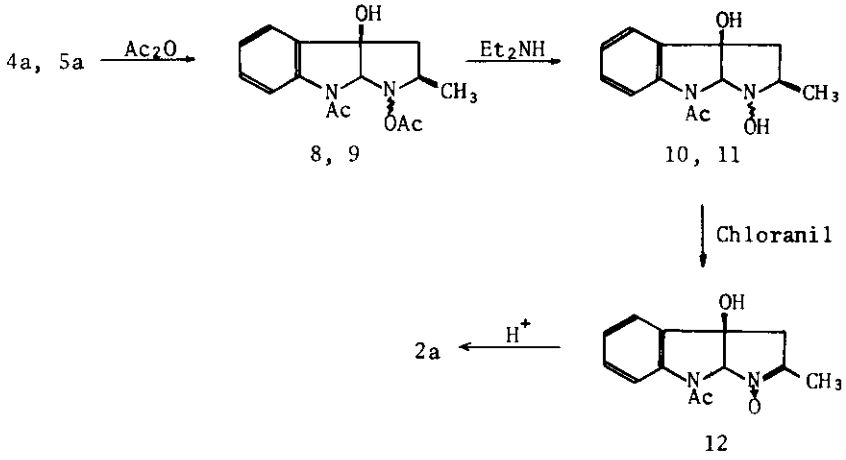


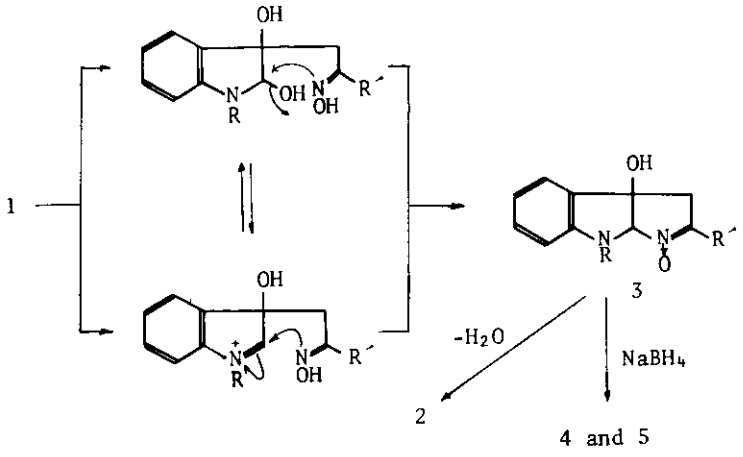
$\underline{\underline{5}}$

Acetylation of tetrahydropyrroloindole 4a and 5a with acetic anhydride gave diacetate 8 (mp 201-203° decomp.) and 9 (mp 177-178°), respectively. When 8 was heated under reflux for 6 h with diethylamine in methanol a partial deacetylated compound 10 (mp 190° decomp.) was obtained in 82% yield. The *N*-acetate 10 was treated with chloranil to give compound 12 (mp 193° decomp.) in quantitative yield, which easily led to the pyrroloindole 2a by treatment with acid.

A likely reaction mechanism was proposed which involved the intramolecular reaction of oxime with imonium intermediate to the 3a-hydroxy-3a,8a-dihydro-3*H*-pyrrolo[2,3-b]indol-1-oxide derivative 3, subsequent reduction or dehydration



to the tetrahydropyrroloindole 4 and 5, and to the pyrroloindole 2, respectively.



Elemental analyses and mass spectral data were consistent with the above formulae.

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