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REDUCTION OF 3-HYDROXY-3-(3-HYDROXYIMINOBUTYL)OXINDOLES WITH SODIUM BOROHYDRIDE IN THE PRESENCE AND IN THE ABSENCE OF COBALT ION

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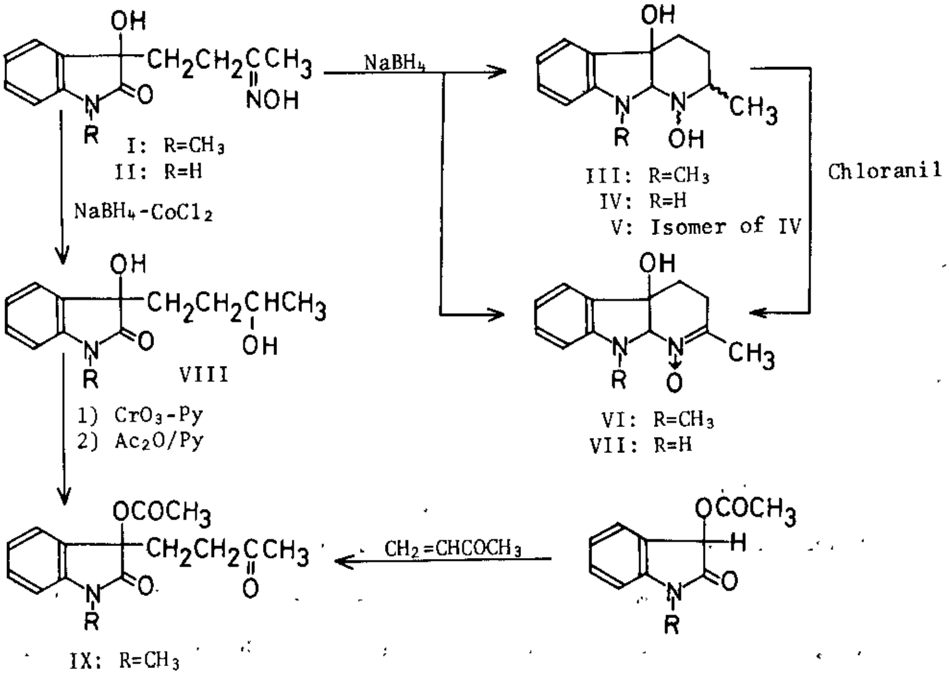
Reduction of 3-hydroxy-3-(3-hydroxyiminobutyl)oxindole (II) and its 1-methyl analog (I) with sodium borohydride afforded the orresponding pyrido[2,3-b]indoles. On the other hand, reduction of I with sodium borohydride in the presence of cobalt ion gave 3-hydroxy-3-(3-hydroxybutyl)-1-methyloxindole (VIII).

Reduction of 3-hydroxy-3-(2-hydroxyiminoalkyl)oxindoles with sodium borohydride has been investigated as a common method for preparing pyrrolo[2,3-b]-indole derivatives[1].

In an extention of this reductive cyclization, we found that 3-hydroxy-3-(3-hydroxyiminobutyl)oxindoles gave different products by conversion of reaction conditions.

When 3-hydroxy-3-(3-hydroxyiminobutyl)-1-methyloxindole (I)[2] was treated with sodium borohydride (13 molar equivalents) in methanol at room temperature, III and VI were obtained in 5.4% and 87.4% yields, respectively. III, mp 146-147°, had the molecular formula $C_{13}H_{18}O_2N_2$ on the basis of elemental analysis and mass spectral results[3]. The ir spectrum of III exhibited no absorption due to $\nu_{C=O}$. The uv spectrum showed absorption maxima at 251 nm (log ε 3.99) and 301 nm (log ε 3.41), which were characteristic of the Ph-N-C-N system. The nmr spectrum[4] of III showed a doublet (3H) at 1.22 ppm due to the secondary methyl group, a singlet (3H) at 2.93 ppm due to the N-methyl group and a singlet (1H) at 4.47 ppm due to the angular methine proton (>N-$\overset{|}{C}$H-N<). These data, together with a positive 2,3,5-triphenyltetrazolium chloride test, are consistent with the structure 1,4a-dihydroxy-2,9-dimethyl-1,2,3,4,4a,9a-hexahydropyrido[2,3-b]-indole for III. VI, amorphous solid, gave a crystalline picrate, mp 98-101°, $C_{13}H_{16}O_2N_2 \cdot C_6H_3O_7N_3$. The nmr spectrum of VI showed singlets at 2.00 ppm (3H), at 3.15 ppm (3H) and at 4.74 ppm (1H), which were assignable to the $\succ$-CH_3, the N-methyl group and the angular methine proton (>N-$\overset{|}{C}$H-N<), respectively. VI was finally proved to be 4a-hydroxy-2,9-dimethyl-3,4,4a,9a-tetrahydropyrido-[2,3-b]indole 1-oxide by conversion of III with chloranil.

On the other hand, when I was treated with sodium borohydride in the presence of cobalt ion[5], a quite different product, the diol (VIII), $C_{13}H_{17}O_3N$, mp 160-162°, was obtained in 53.7% yield. The spectral results suggested the



simple conversion of the oxime group to the hydroxyl function[6]. The structure of VIII was unequivocally confirmed by following manner; VIII was oxidized with chromium trioxide-pyridine complex, followed by acetylation of the resulting ketone with acetic anhydride in pyridine to give 3-acetoxy-1-methyl-3-(3-oxobutyl)oxindole (IX). IX was identical with a sample, which was synthesized separately by the condensation of 3-acetoxy-1-methyloxindole with methyl vinyl ketone.

Treatment of 3-hydroxy-3-(3-hydroxyiminobutyl)oxindole (II) with sodium borohydride in a refluxing isopropyl alcohol, whereas in methanol it was quite unreactive, yielded IV and V in 37.2% and 20.7% yields, respectively. IV, mp 165-167°, showed the molecular formula $C_{12}H_{16}O_2N_2$ on the basis of elemental analysis and mass spectral results. IV exhibited no absorption band at the carbonyl region in its ir spectrum, and showed absorption maxima at 240 nm (log ε 3.88) and 293.5 nm (log ε 3.52) in its uv spectrum. The nmr spectrum showed a doublet (3H) at 1.24 ppm and a singlet (1H) at 4.68 ppm, which were assignable to the secondary methyl group and the angular methine proton (>N-CH-N<). Furthermore, three singlets (each 1H) at 4.80, 6.17 and 9.92 ppm, which were exchangeable for deuterium, were assigned to the protons of hydroxyl and amino groups, respectively. IV showed a positive color test with 2,3,5-triphenyltetrazolium chloride. From these results, the structure of IV was favorably assigned to 1,4a-dihydroxy-2-methyl-1,2,3,4,4a,9a-hexahydropyrido[2,3-b]indole. V, mp 154-155°, showed a striking resemblance to IV on spectral data: mass spectrum, m/e 220 (M^+ for $C_{12}H_{16}O_2N_2$); uv λ_{max} (log ε), 241 nm (3.84), 292 nm (3.38); nmr δ (ppm), 1.20 (3H, d, >CH-$\underline{CH_3}$), 4.58 (1H, s, >N-CH-N<). V was assumed to be a stereoisomer of IV. This assumption was supported by the fact that IV and V afforded the same dehydrogenated product (VII) by treatment with chloranil. The stereochemistry of the two isomers is under investigation.

REFERENCES AND NOTES

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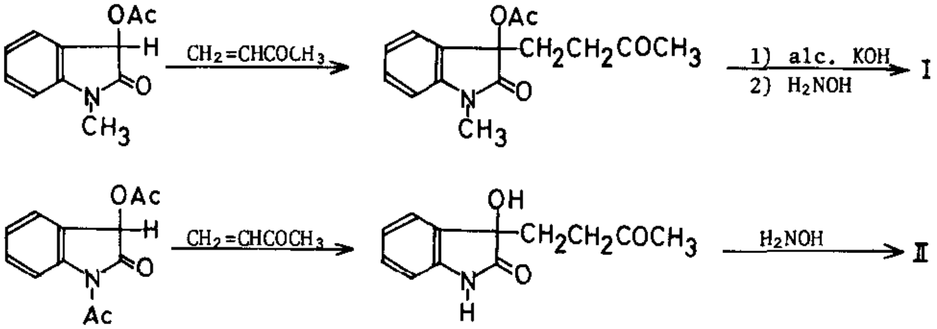
2 Synthesis of key substances I and II was accomplished as shown in following scheme.



3 Satisfactory mass spectra and elemental analyses were obtained on all new compounds.

4 Nmr spectra were taken on a Hitachi R-20 spectrometer. The chemical shifts (δ) were calculated on the basis of TMS as an internal standard.

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