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A Practical Synthesis of 2,3,4,6,7,12-Hexahydroindolo[2,3-a]quinolizine

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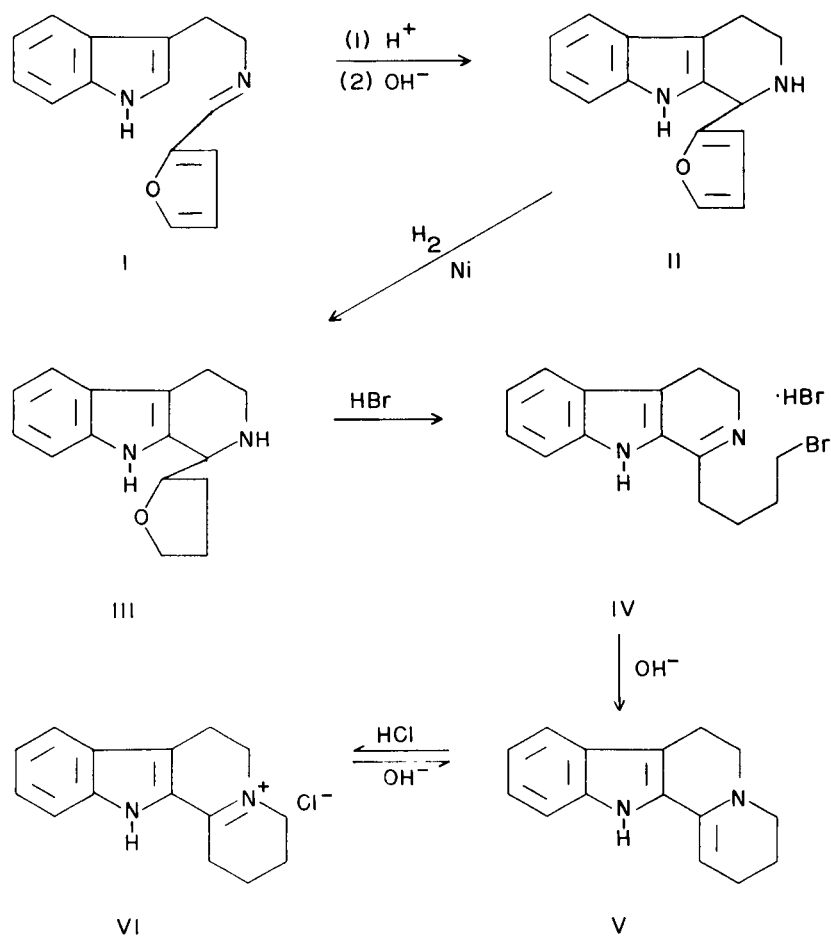
Our interest in the field of indole alkaloids led us to develop a new method for the synthesis of 2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizine (V). This indole enamine is a useful intermediate in the synthesis of compounds having structural features of the eburnamine-vincamine alkaloids.

The Schiff base I (1) was treated with a solution of hydrogen chloride in tetrahydrofuran to give 1-(2'-furyl)-1,2,3,4-tetrahydro- β -carboline (II). Catalytic reduction of II gave the tetrahydrofuryl derivative III which when heated in concentrated hydrobromic acid underwent ring opening and dehydration (cf. IV). The resulting salt was converted into the desired product (V) by treatment with excess potassium hydroxide solution.

All intermediate compounds in the sequence have

been characterized; however, if the synthesis is carried through without purification of intermediates, V can be obtained in 70% over-all yield, based on tryptamine as starting material. This represents a considerable improvement over the yields reported for other procedures (2,3).

The structure of V was confirmed by elemental analysis and spectroscopic determinations. On treatment with alcoholic hydrogen chloride, V was converted into the immonium salt VI. The ultraviolet spectrum of VI shows absorption maxima at 248 and 353 m μ , typical of 1,2,3,4,6,7-hexahydro-12H-indolo[2,3-a]quinolizinium salts (2). Compound VI could not be titrated with 0.1 N sodium hydroxide solution, but when 5 N solution was used the free base form V was regenerated.



EXPERIMENTAL (4)

N-(2-Furfurylidene)tryptamine (I).

A mixture of 409 g. (2.55 moles) of tryptamine and 261 g. (2.72 moles) of freshly distilled 2-furfuraldehyde in 2 l. of benzene was heated under reflux for 4 hours. The water liberated was collected in a Dean-Stark trap. The material which precipitated on cooling was collected, washed with benzene and dried; yield, 534 g. (88%); m.p. 136-137° (reported (1) m.p. 135°). The infrared spectrum (CHCl_3) showed a strong band at 1650 cm^{-1} ($-\text{N}=\text{C}=\text{O}$).

1-(2'-Furyl)-1,2,3,4-tetrahydro- β -carboline (II).

A 265-g. sample (1.11 moles) of the Schiff base (I) was added slowly to a stirred solution of 95 g. of hydrogen chloride in 1.5 l. of cold tetrahydrofuran. The temperature was kept below 10° during the addition. The solution was stirred at room temperature for 2 hours during which time the hydrochloride of II crystallized. The salt was collected and washed with tetrahydrofuran; the compound does not melt below 300°. The hydrochloride was dissolved in 3 l. of cold water and the resulting solution was stirred vigorously at 10° while sodium hydroxide solution was added. The precipitated free base was collected and washed with water; yield, 247 g. (93%); m.p. 132-133°; ν max (CHCl_3), 1020 (ether) and 890 (furan) cm^{-1} . An analytical sample was prepared by recrystallization from ether-pentane; m.p. 134-135°. A mixture melting point with compound I was depressed 105-110°.

Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.58; H, 6.10; N, 11.80.

1-(2'-Tetrahydrofuryl)-1,2,3,4-tetrahydro- β -carboline (III).

A 292-g. sample (1.22 moles) of compound II was dissolved in 1 l. of methanol and hydrogenated at 1500 p. s. i., 100°, using 5 g. of Girdler (G-69, zirconium promoted) nickel catalyst (5). After the reduction was completed (ca. 1 hour) the catalyst was removed and the solvent concentrated *in vacuo*. The residual oil was dissolved in isopropyl alcohol and a solution of hydrogen bromide in isopropyl alcohol was added. The salt was collected, washed with isopropyl alcohol, ethyl acetate and dried; yield 380 g. (96%), m.p. 262-263° (dec.). For analysis, a sample was recrystallized from aqueous isopropyl alcohol; m.p. 267-268° (dec.).

Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O} \cdot \text{HBr}$: C, 55.73; H, 5.94; N, 8.67. Found: C, 55.59; H, 6.10; N, 8.77.

1-(4-Bromobutyl)-3,4-dihydro- β -carboline Hydrobromide (IV).

A 345-g. sample (1.07 moles) of 1-(2'-tetrahydrofuryl)-1,2,3,4-tetrahydro- β -carboline hydrobromide was dissolved in 3.5 l. of 48% hydrobromic acid. The solution was stirred and heated on the steam bath while hydrogen bromide was bubbled into the solution over a 3-hour period. The solution was heated an additional 30 minutes, then allowed to cool. The yellow crystalline product which formed was collected, washed with acetic acid and water and dried; yield 368 g. (93%), m.p. 211-213°; ν max (KCl), 1635, 1575 and 1560 cm^{-1} . The analytical sample was obtained by recrystallization from methanol-ether; m.p. 209-210°.

Anal. Calcd. for $\text{C}_{15}\text{H}_{17}\text{BrN}_2 \cdot \text{HBr}$: C, 46.63; H, 4.66; N, 7.25; Br⁻, 20.70. Found: C, 46.97; H, 4.88; N, 7.25; Br⁻, 21.09 (6).

2,3,4,6,7,12-Hexahydroindolo[2,3-a]quinolizine (V).

To a solution of 368 g. of compound IV in 4 l. of methanol and 2 l. of water at 50° was added a solution of 150 g. of potassium hydroxide in 1 l. of water. A light tan solid formed immediately. The product

was collected and washed thoroughly with water; yield 210 g. (95%); m.p. 161-164°. After recrystallization of a sample from pentane-ether the melting point range widened to 159-167°; ν max (CHCl_3), 3480 (indole N-H) and 1660 cm^{-1} ($-\text{C}=\text{C}-\text{N}-$); λ max (CH_2Cl_2), 242 (ϵ , 19,200), 307 (ϵ , 17,700), sh. 313-317 μm (ϵ , 17,300) (7); n.m.r. (10% CDCl_3) τ 2.05 (N-H, indole), 2.4-3.0 (4 protons, aromatic), 5.08 (1 proton, olefinic), 6.7-7.2 (6 protons) and 7.6-8.2 (4 protons) p.p.m.

Anal. Calcd. for $\text{C}_{15}\text{H}_{16}\text{N}_2$: C, 80.31; H, 7.19; N, 12.50. Found: C, 80.03; H, 7.16; N, 12.45.

1,2,3,4,6,7-Hexahydro-12H-indolo[2,3-a]quinolizinium Chloride (VI).

An 8.82-g. sample of V was dissolved in ether-isopropyl alcohol. Then 15 ml. of 2.7 N hydrochloric acid - isopropyl alcohol was added. The crude salt was collected, washed with ether and dried, yield 9.65 g., m.p. 272-274° (dec.). Recrystallization from ether-isopropyl alcohol gave 6.56 g. of yellow needles, m.p. 272-273° (dec.); ν max (KCl), 1640, 1580 and 1560 cm^{-1} ; λ max (MeOH), 223 (ϵ , 7,600), 248 (ϵ , 10,400) and 353 μm (ϵ , 22,400) (2). The product could not be titrated using 0.1 N sodium hydroxide solution, but was titrated using mercuric acetate-acetic acid as solvent and standard perchloric acid as titrant.

Anal. Calcd. for $\text{C}_{15}\text{H}_{17}\text{ClN}_2$: C, 69.07; H, 6.57; N (basic), 5.36; N (total), 10.73. Found: C, 68.79; H, 6.56; N (basic), 5.35; N (total), 10.67.

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- (3) G. C. Morrison, W. Cetenko and J. Shavel, Jr., *J. Org. Chem.*, 29, 2771 (1964).
- (4) Melting points were taken with a Büchi capillary melting point apparatus and are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 237 grating spectrophotometer; ultraviolet spectra were measured with a Perkin-Elmer Model 202 spectrophotometer. The n.m.r. spectrum was determined at 60 Mc. with a Varian Model A-60 spectrometer.
- (5) It is important that an active nickel catalyst be used in this hydrogenation. In a later run it was found that ruthenium dioxide serves equally well as catalyst for reduction of the furan ring.
- (6) The titration was carried out in aqueous medium using 0.1 N sodium hydroxide solution.
- (7) H. Zinnes, R. A. Comes and J. Shavel, Jr., *J. Org. Chem.*, 30, 105 (1965). The ultraviolet spectrum in methylene chloride was reported for 3-dehydroyohimbane: 233-235 (ϵ , 19,900), 305 (ϵ , 15,200) and 311-312 sh. μm (ϵ , 14,800). When the ultraviolet spectrum of V is run in methanol, strong absorption appears at 353 μm due to formation of indolo[2,3-a]quinolizinium salts from traces of acid in the solvent. This same result was observed when the ultraviolet spectrum of 3-dehydroyohimbane was determined in ethanol.

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