The Effect of a 10-Methoxyl Group on the Reduction of 3,4-Dehydroyohimbane Chloride

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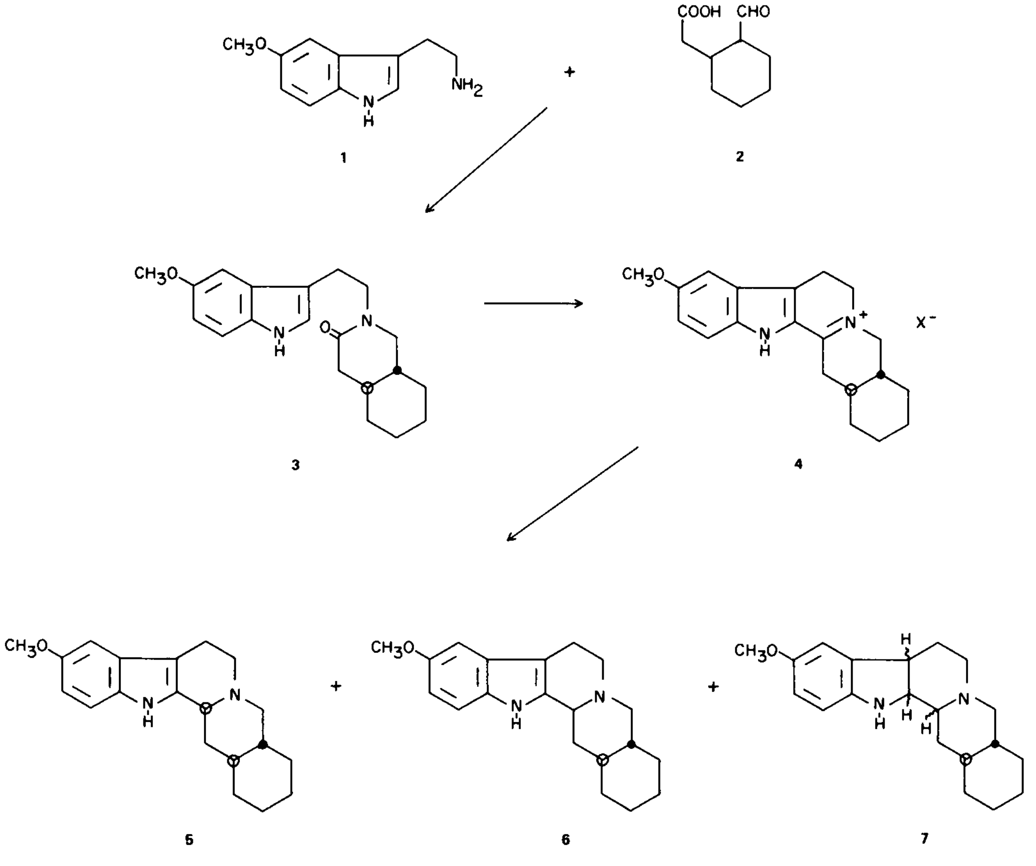
The acetic acid-zinc reduction of 3,4-dehydroyohimbane chloride to a mixture of yohimbane and ψ-yohimbane has been reported by Wenkert and Roychaudhuri (1). More recently we have shown that when the reduction is carried out with perchloric acid the same product was obtained with the *pseudo*-isomer being the predominant product (2). In connection with this work we were interested in obtaining *pseudo*-yohimbane bearing a 10-methoxyl group.

Following the procedure which we had previously utilized for the preparation of (±)-dehydroyohimbane (3), 5-methoxytryptamine (**1**) and 2-formylcyclohexaneacetic acid (**2**) were condensed to give the lactam (**3**) which on subjection to the conditions of the Bischler-Napieralski cyclization afforded (±)-3-dehydro-10-methoxyyohimbane chloride (**4**). Reduction of the dehydro compound (**4**) gave, in addition to the expected (±) 10-methoxyyohimbane (**5**), and (±) 10-methoxy-ψ-yohimbane (**6**), a 17% yield of the dihydroyohimbane (**7**).

The structure assignments were based on the following evidence. The infrared spectrum of (±) 10-methoxy-yohimbane was identical to that of 10-methoxyyohimbane (4). The *pseudo* isomer showed no Bohlmann bands in the infrared and a signal at 4.4 ppm (W_H = 9 cps) in its nmr spectrum, both characteristic of the *cis*-quinolizidine



conformation of *pseudo*-yohimbane which shows no Bohlmann bands and a signal at 4.4 ppm (W_H = 10 cps) (5). The dihydroindole (**7**) has an ultraviolet spectrum similar to that of *p*-anisidine (6), and in 0.1 *N* hydrochloric acid shows the spectrum of the mono-cation, characteristic of two nitrogens separated by less than three carbons (7). In 1 *N* hydrochloric acid the spectrum is a mixture of the mono and di-cation.

We are not in a position to explain the effect of a methoxyl group on the zinc-acid reduction of a 3,4-dehydroyohimbane. However, we have demonstrated that formation of the dihydro compound (**7**) does not go through the indole stage since neither (±) 10-methoxyyohimbane or its ψ-isomer was affected under the conditions used in the reaction.

EXPERIMENTAL (8)

The melting points were determined using a Thomas-Hoover apparatus which had been calibrated against known standards. The infrared spectra were recorded with a Baird Model 455 instrument on chloroform solutions. The ultraviolet spectra were determined using a Beckman DKI spectrophotometer on 95% ethanol solutions. The nmr spectra were determined with a Varian Associates A-60 spectrometer on deuteriochloroform solutions.

trans-Octahydro-2 [2-(5-methoxyindol-3-yl)ethyl]-3(2*H*)-isoquinolinone (**3**).

Using the procedure previously described for *trans*-octahydro-2-[2-(indol-3-yl)ethyl]-3(2*H*)-isoquinolinone (3), 133 g. of 5-methoxy tryptamine and 147 g. of 2-formylcyclohexaneacetic acid gave 136 g. (60%) of a crystalline solid, m.p. 216-217°.

Anal. Calcd. for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.40; H, 8.16; N, 8.76.

(±)-3-Dehydro-10-methoxyyohimbane Chloride (**4**).

A mixture of 48 g. of *trans*-octahydro-2-[2-(5-methoxyindol-3-yl)ethyl]-3(2*H*)-isoquinolinone, 100 ml. of phosphorous oxychloride and 1 l. of benzene was refluxed for 4 hours. Filtration of the cold reaction mixture afforded a solid, m.p. 247° dec. Recrystallization from ethanol gave 41 g. (80%) of a solid, m.p. 302-304°.

Anal. Calcd. for $C_{20}H_{25}ClN_2O$: C, 69.65; H, 7.31; N, 8.12; Cl, 10.28. Found: C, 69.85; H, 7.33; N, 7.94; Cl, 10.03.

Reduction of (±)-3-Dehydro-10-methoxyyohimbane Chloride.

To a refluxing mixture of 38.1 g. of (±)-3-dehydro-10-methoxyyohimbane chloride, 95.4 ml. of perchloric acid, 424 ml. of water and 2.9 l. of methanol was added 95.4 g. of zinc over a 45 minute-interval. After the addition had been completed stirring was continued for an additional 3 hours. The solvent was removed from the reaction mixture *in vacuo* and the residue was treated with 250 ml. of 40% sodium hydroxide and 2.8 l. of methylene chloride. The methylene chloride layer was washed with water, dried over sodium sulfate, and the solvent was removed. Crystallization of the residue from acetonitrile gave 6.7 g. (20%), m.p. 182-185°. Recrystallization first from methanol and then from Skelly solve B gave an analytical sample of (±)-10-methoxyyohimbane (**5**), m.p. 194.5-195.5°; λ max (ethanol) (ε) 225 (29,500), 280 (9,300), 296 mμ sh (8000).

Anal. Calcd. for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.03. Found: C, 77.52; H, 8.41; N, 9.25.

The mother liquor from the acetonitrile crystallization was chromatographed on alumina. Elution with ether gave, after recrystallization from methanol, 5.7 g. (17%) of a solid, m.p. 131-133°. Recrystallization from Skelly solve B gave an analytical sample of (±)-2,7-dihydro-10-methoxyyohimbane (**7**). λ max (ethanol) (ε) 246 (11,700), 315 mμ (3,180); λ max (0.1 *N* hydrochloric acid) (ε) 239 (12,500), 305 mμ (2,600); λ max (1 *N* hydrochloric acid) (ε) 238 (4,100), 278, (1,500), 305 mμ (900).

Anal. Calcd. for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97. Found: C, 77.16; H, 9.00; N, 8.99.

Elution with 5% methanol in chloroform gave after recrystallization from ethanol 1.7 g. (5%) of (±)-10-methoxy-*pseudo*-yohimbane three-quarters ethanolate (**6**), m.p. 125° dec.

Anal. Calcd. for $C_{20}H_{26}N_2O \cdot 3/4C_2H_5OH$: C, 74.85; H, 8.91; N, 8.12. Found: C, 74.59; H, 8.59; N, 8.20.

The hydrobromide formed in ether as a crystalline solid, m.p. 267-269°. Recrystallization from acetonitrile gave an analytical sample, m.p. 268-270°; λ max (ethanol) (ε) 224 (26,600), 281 (9000), 295 mμ sh (8000).

Anal. Calcd. for $C_{20}H_{27}BrN_2O$: C, 61.38; H, 6.95; N, 7.16. Found: C, 61.21; H, 6.95; N, 7.32.

REFERENCES

(1) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, 80, 1613 (1958).

(2) G. C. Morrison, W. A. Cetenko and J. Shavel, Jr., *J. Org. Chem.*, 32, 4089 (1967).

(3) G. C. Morrison, W. A. Cetenko and J. Shavel, Jr., *ibid.*, 31, 2695 (1966).

(4) Supplied by M. von Strandtmann of these laboratories.

(5) G. C. Morrison, unpublished results.

(6) B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, 76, 5603 (1954).

(7) A. R. Battersby and H. F. Hodson, *J. Chem. Soc.*, 736 (1960).

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