ACTA CHEMICA SCANDINAVICA **10** (1956) 1414—1421

Dehydrogenation of Alkaloids of the Yohimbine Type with *tert.*-Butyl Hypochlorite. Conversion of Yohimbine to Pseudoyohimbine

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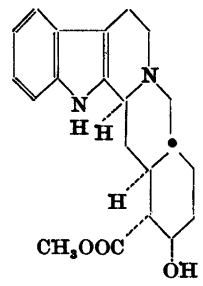
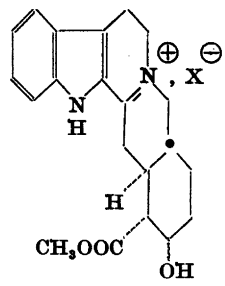
The dehydrogenation of alkaloids of the yohimbine type with *tert.*-butyl hypochlorite is described and the structure of the dehydrogenation products discussed.

It is shown that catalytical hydrogenation of dehydroyohimbine under alkaline conditions leads to the formation of a mixture of yohimbine and pseudoyohimbine.

In a recent communication Weisenborn and Diassi [1] describe the oxidation of yohimbine (I) with mercuric acetate to salts of Δ^3-dehydroyohimbine (II).



I



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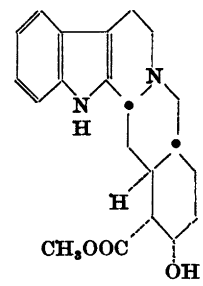


III

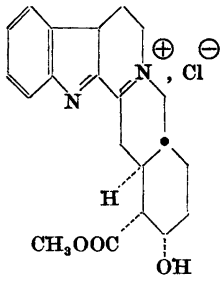
Other alkaloids of the yohimbine type containing an axial hydrogen at C_3 were oxidized in the same manner, while compounds containing an equatorially oriented hydrogen failed to react.

Catalytical reduction of II with platinum in methanol gave only yohimbine, while reduction with zinc and hydrochloric acid yielded a mixture of yohimbine (I) and pseudoyohimbine (III).

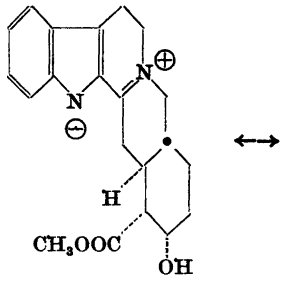
In this paper, it is shown that the same dehydrogenation can be accomplished in good yield with *tert.*-butyl hypochlorite in methylene chloride. By this method, the following compounds have been oxidized: Yohimbine, pseudoyohimbine, corynanthine, α-yohimbine, apoyohimbine, and deserpidine.

It will be seen that compounds containing an axial hydrogen at C_3 (yohimbine, corynanthine, α-yohimbine, and apoyohimbine) as well as compounds with an equatorially oriented hydrogen atom (pseudoyohimbine and deserpidine) can be dehydrogenated in this way.

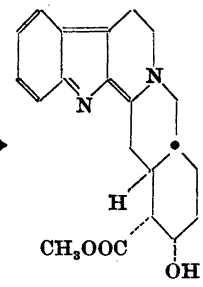
The fact that in the infrared spectrum of Δ^3-dehydroyohimbine chloride no band appears in the NH-region while, on the other hand, all N-unsubstituted indole derivatives are characterized by an intense sharp band at 2.9 μ, suggests that the structure of this compound is better represented by formula IV than by formula II.



IV



V

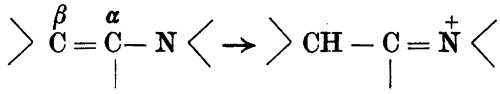


Va

The dehydroyohimbine base is proposed to be a resonance hybrid of the limiting structures V and Va.

The difference between the chromophoric systems in IV and V ⟷ Va is clearly demonstrated by the ultraviolet spectra (curves 1 and 2, Fig. 1).

In this connection it is worth mentioning Leonards [2] observation, that the transformation



takes place when an α,β-unsaturated amine is converted to its salt.

The formulae IV and V ⟷ Va involve a difference between the ultraviolet spectra of the methiodide and the salts of dehydroyohimbine. It is seen from Fig. 1 (curves 1 and 3) that, actually, such a difference is present.

The choice between the structures VI and VII for dehydroyohimbine methiodide was made by catalytical reduction of this compound. The result that the hydrogenation product turned out to be a mixture of yohimbine methiodide and pseudoyohimbine methiodide indicates that VII is the correct structure.

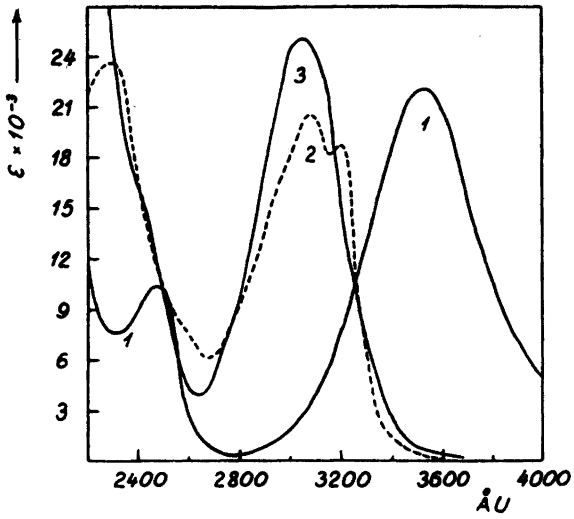
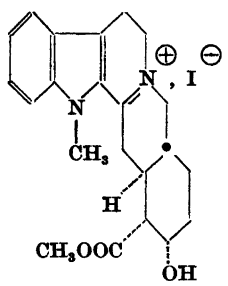
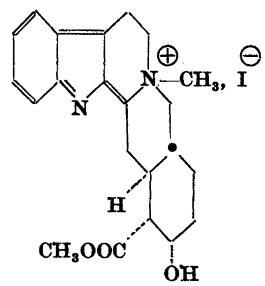


Fig. 1. Ultraviolet absorption spectra.
Curve 1. Dehydroyohimbine chloride.
» *2. The dehydroyohimbine base.*
» *3. Dehydroyohimbine methiodide.*



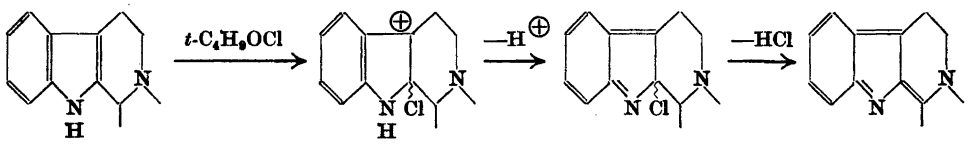
VI



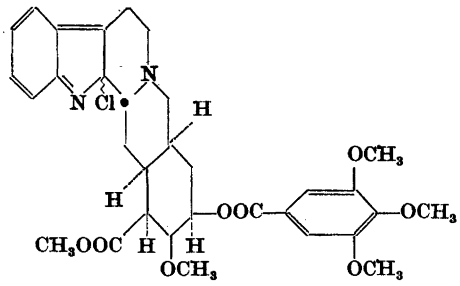
VII

By dehydrogenation of deserpidine a chlorodeserpidine was isolated as an intermediate. This compound was smoothly transformed to dehydrodeserpidine chloride by short treatment with methanolic hydrogen chloride.

The intermediary formation of chloro compounds by dehydrogenation with *tert.*-butyl hypochlorite may be explained by assuming the following reaction sequence:



The assignment of formula VIII to chlorodeserpidine is supported by the experimental findings mentioned below.



VIII

1) The infrared spectrum contains no band in the NH-region (2.9 μ).
2) The substance does not show the oxidizing properties which would be expected for N-chlorodeserpidine.
3) Catalytical reduction with platinum in ethylene glycol monomethyl ether yields only deserpidine.
4) Hydrogen chloride is readily eliminated with the formation of dehydrodeserpidine chloride.

Catalytical reduction of Δ^3-dehydrodeserpidine chloride with platinum in methanol afforded the hitherto unknown compound 3-isodeserpidine, isolated as the nitrate.

We are able to confirm Weisenborn and Diassi's [1] observation that reduction of salts of dehydroyohimbine with hydrogen and platinum in methanol gives only yohimbine. The same result is obtained with sodium borohydride in methanol.

If, however, the catalytical reduction is carried out in basic solution a mixture of yohimbine and pseudoyohimbine is obtained. With Raney nickel in ethylene glycol monomethyl ether the yield of pseudoyohimbine was approximately 50 %.

The influence of the solvent and the catalyst appears from Table 1. It will be seen that the formation of pseudoyohimbine is favoured by a low dielectric constant of the solvent.

EXPERIMENTAL

All melting points are corrected.

Dehydroyohimbine

A stirred solution of 17.7 g (0.05 mole) of yohimbine and 7 ml of triethylamine in 350 ml of dry methylene chloride was cooled to $-10°$ C and, during 45 min, a solution of 7 ml of *tert.*-butyl hypochlorite in 50 ml of dry carbon tetrachloride was added. The cooling bath was removed and, after standing for about 15 min, the resulting solution was washed with two 50 ml portions of water, and dried. The solvent was evaporated *in vacuo* and the oily residue dissolved in 75 ml of absolute ethanol. After acidification with ethanolic hydrogen chloride, the dehydroyohimbine chloride was crystallized by addition of ether.

Yield of crude product: 17.4 g. Recrystallization from methanol-ether gave 17.0 g of yellow needles, m. p. 268–270° C (decomp.). $[\alpha]_D^{20}$ + 213° (1 % in water). Ultraviolet absorption spectrum: λ_{max}^{EtOH} 246 mμ, log ε 4.03; 355 mμ, log ε 4.35. (Found: C 64.68; H 6.40; Cl 9.27; N 7.40. Calc. for $C_{21}H_{25}Cl\,N_2O_3$: C 64.86; H 6.48; Cl 9.12; N 7.21).

The iodide was obtained by addition of aqueous potassium iodide to a methanolic solution of the chloride. Recrystallization from methanol gave yellow needles; m. p. 276–277° C (decomp.). (Found: C 52.36; H 5.22; I 26.17; N 5.83. Calc. for $C_{21}H_{25}I\,N_2O_3$: C 52.50; H 5.25; I 26.42; N 5.83).

The dehydroyohimbine base was precipitated from a solution of 5.0 g of dehydroyohimbine chloride in 50 ml of methanol by addition of concentrated aqueous sodium hydroxide followed by water. Yield of crude product: 3.7 g, m. p. 174–176° C (decomp.). Recrystallization from methanol-water yielded pale yellow crystals, m. p. 176–178° C (decomp.). (Found: C 71.46; H 7.06; N 7.74. Calc. for $C_{21}H_{24}N_2O_3$: C 71.57; H 6.86; N 7.95).

The following alkaloids were dehydrogenated in the same way as yohimbine:

Pseudoyohimbine [3]. Yield of dehydroyohimbine chloride: 65 %. The I. R.-spectrum was identical with the I.R.-spectrum of dehydroyohimbine chloride prepared from yohimbine.

Apoyohimbine [4]. Yield of dehydroapoyohimbine chloride: 73 %. Recrystallization from alcohol-ether gave yellow needles, m. p. 284–285° C (decomp.). (Found: C 67.81; H 6.44; Cl 9.74; N 7.76. Calc. for $C_{21}H_{23}Cl\,N_2O_3$: C 68.01; H 6.25; Cl 9.56; N 7.55). Ultraviolet absorption spectrum: λ_{max}^{EtOH} 246 mμ, log ε 3.95; 355 mμ, log ε 4.31.

Corynanthine *. Yield of dehydrocorynanthine chloride after recrystallization from methanol-ether: 66 %. M. p. 227–229° C (decomp.). Ultraviolet absorption spectrum: λ_{max}^{EtOH} 247 mμ, log ε 4.03; 353 mμ, log ε 4.35. (Found: C 63.62; H 6.63; Cl 8.98; N 7.25. Calc. for $C_{21}H_{25}Cl\,N_2O_3$, ½ CH_3OH: C 63.78; H 6.72; Cl 8.76; N 6.92).

α-Yohimbine *. Dehydro-α-yohimbine chloride was isolated in 77 % yield as a yellow amorphous powder. A crystalline perchlorate was obtained by addition of aqueous sodium perchlorate to a methanolic solution of the chloride. Recrystallization from water gave m. p. 206–208° C. (Weisenborn and Diassi [1] report m. p. 211–212° C). Ultraviolet absorption spectrum: λ_{max}^{EtOH} 246 mμ, log ε 4.01; 355 mμ, log ε 4.33.

Chlorodeserpidine (VIII)

To a stirred solution of 1 734 mg (0.003 mole) of deserpidine ** and 0.45 ml of triethylamine in 30 ml of dry methylene chloride a solution of 0.45 ml of *tert.*-butyl hypochlorite in 5 ml of carbon tetrachloride was added at −10° C during a period of 15 min. After standing for another 15 min. at 0° C, the resulting solution was washed with two 10 ml portions of water, and dried. The solvent was removed *in vacuo* and the solid residue recrystallized from ethanol to give 1 400 mg (76 %) of white crystalline material. M. p. 189–193° C (decomp.). Recrystallization from *iso*propanol raised the melting point to 191–196° C (decomp.). $[\alpha]_D^{20}$ −184.5° in chloroform (c = 1). Ultraviolet absorption spectrum: λ_{max}^{EtOH} 266 mμ, log ε 4.14. (Found: C 62.69; H 6.27; Cl 5.67; N 4.65. Calc. for $C_{33}H_{37}ClN_2O_8$: C 62.69; H 6.08; Cl 5.78; N 4.57).

Dehydrodeserpidine chloride

A suspension of 400 mg of chlorodeserpidine in 6 ml of methanol was acidified with strong methanolic hydrogen chloride and the resulting clear solution was refluxed for five minutes. After cooling dehydrodeserpidine chloride was precipitated as an amorphous powder. Yield: 380 mg. Crystallization from water afforded yellow crystals, m. p. 185–187° C (decomp.).

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* Kindly supplied by E. Merck AG., Darmstadt.

** Supplied by S. B. Penick & Co., New York.

Ultraviolet absorption spectrum: λ_{max}^{MeOH} 252 mμ, log ε 4.19; 260—265 mμ (shoulder), log ε 4.07; 355 mμ, log ε 4.36. (Found: C 60.13; H 6.60; Cl 5.68; N 4.61. Calc. for $C_{32}H_{37}ClN_2O_3$, 1½ H_2O: C 60.05; H 6.30; Cl 5.54; N 4.38).

Dehydroyohimbine methiodide (VII)

2.5 g of dehydroyohimbine base were dissolved in a mixture of 20 ml of absolute ethanol and 10 ml of methyl iodide. After standing overnight in the dark, 1.87 g of a crystalline methiodide were obtained, which were recrystallized from ethanol. M. p. 213—215° C (decomp.). Ultraviolet absorption spectrum: λ_{max}^{MeOH} 305 mμ, log ε 4.35. (Found: C 52.66; H 5.81; I 24.80; N 5.82. Calc. for $C_{22}H_{27}I N_2O_3$, ½ H_2O: C 52.48; H 5.61; I 25.21; N 5.57).

Hydrogenation of dehydroyohimbine methiodide

A solution of 988 mg of dehydroyohimbine methiodide in 30 ml of ethylene glycol monomethyl ether was hydrogenated at *ca.* 60° C under one atm. of hydrogen in the presence of 200 mg of a platinum oxide catalyst.

When the theoretical amount of hydrogen had been absorbed, the catalyst was removed by filtration and the filtrate evaporated to dryness. The light yellow sirupy residue crystallized on scratching in the presence of a few ml of acetone. The solid was filtered and washed with acetone to give 890 mg of a mixture of yohimbine methiodide and pseudoyohimbine methiodide, which was dissolved in 20 ml of boiling methanol. After cooling yohimbine methiodide crystallized upon seeding while pseudoyohimbine methiodide remained in solution. Filtration and washing with methanol yielded 150 mg of pure yohimbine methiodide which softened at 240—242° C and thereafter was gradually decomposed. The infrared spectrum was indistinguishable from the spectrum of authentic yohimbine methiodide.

Addition of ether to the filtrate afforded 580 mg of pseudoyohimbine methiodide, m. p. 271—272° C (decomp.). The melting point of a mixture with an authentic sample was undepressed and their infrared spectra were identical.

Hydrogenation of chlorodeserpidine (VIII) to deserpidine

A solution of 307 mg (0.0005 mole) of chlorodeserpidine (VIII) in 10 ml of dioxan was shaken at room temperature in the presence of 30 mg of platinum oxide under one atm. of hydrogen. When the theoretical amount of hydrogen had been absorbed (30 min.), the catalyst was removed by filtration and the solution evaporated to dryness under reduced pressure. The residue was dissolved in 10 ml of methanol and the resulting solution basified with aqueous ammonia. Addition of water yielded 220 mg of white crystalline material. M. p. 224—226° C (decomp.). After recrystallization from methanol the melting point was 225—227° C (decomp.) alone and by admixture with deserpidine. $[\alpha]_D^{20}$ —135° in chloroform (c = 1). Schlittler *et al.*[5] report for deserpidine: $[\alpha]_D^{24,5}$ —137° ± 1 in chloroform.

3-Isodeserpidine

235 mg of dehydrodeserpidine chloride were dissolved in 10 ml of methanol and hydrogenated at room temperature under one atmosphere of hydrogen in the presence of 20 mg of a platinum oxide catalyst.

When the theoretical amount of hydrogen had been absorbed (15 min.), the catalyst was removed by filtration. The solution was basified with aqueous ammonia and the hydrogenation product precipitated as a white amorphous powder by addition of water.

The amorphous base was converted to a crystalline nitrate by careful acidification of an ethanolic solution with nitric acid. Filtration and washing with ethanol and ether yielded 170 mg which melted at 189—194° C (decomp.). Recrystallization from ethanol raised the melting point to 194—198° C (decomp.). Ultraviolet absorption spectrum: λ_{max}^{EtOH} 271 mμ, log ε 4.26. (Found: C 58.34; H 6.55; N 6.47. Calc. for $C_{32}H_{39}N_3O_{11}$, H_2O: C 58.25; H 6.28; N 6.37).

The substance was readily distinguishable from deserpidine nitrate [6] by its low melting point, its optical rotation ($[\alpha]_D^{20}$ −153° in pyridine (c = 1)), and its high R_F value in the paper chromatographic system described below.

For deserpidine nitrate Mac Phillamy *et al.*[6] report m. p. 254—260° C (decomp.). The optical rotation was found to be $[\alpha]_D^{20}$ −138° in pyridine (c = 1).

Reduction of dehydroyohimbine

a) With sodium borohydride. To a stirred solution of 777 mg of dehydroyohimbine chloride in 20 ml of methanol was added drop by drop 1 ml of a 10 % methanolic solution of sodium borohydride. From the resulting colourless solution the reduction product was precipitated by addition of 50 ml of water. The precipitate was filtered off, washed with water and dried. Yield: 525 mg of white crystals, m. p. 234—235.5° identified as yohimbine by mixed melting point and by optical rotation $[\alpha]_D^{20}$ +102° in pyridine (c = 1).

b) Catalytically. A series of catalytical hydrogenations were carried out with the aim to study the influence of the solvent, the catalyst, and the addition of base on the content of pseudoyohimbine in the hydrogenation product. The general procedure is described below and the results are summarized in Table 1.

Table 1. Catalytical hydrogenation of dehydroyohimbine chloride.

Solvent	Dielectric constant of the solvent	Catalyst	Mole equivalent triethylamine added	Yield of pseudoyohimbine %
Methanol	32.6	PtO_2 (100 mg)	0	0
—	—	—	1	26
—	—	—	2	27
Ethylene glycol monomethyl ether	16.0	—	2	34
Dioxan *	2.2	—	2	47
Methanol	32.6	5 % Pd on $CaCO_3$ (1.0 g)	2	20
—	—	Raney nickel (*ca.* 0.5 g)	2	30
Ethylene glycol monomethyl ether	16.0	Raney nickel (*ca.* 0.5 g)	2	48

*) In this experiment dehydroyohimbine acetate was dehydrogenated since the chloride was insoluble in dioxan.

General procedure. 1.554 g (0.004 mole) of dehydroyohimbine chloride were dissolved in 40 ml of the appropriate solvent. The catalyst and the base were added and the resulting mixture was shaken at room temperature under one atmosphere of hydrogen. When the theoretical amount of hydrogen had been absorbed (5—60 min.) the catalyst was removed by filtration and the filtrate concentrated *in vacuo* to a volume of 10 ml. The solution was made alkaline with aqueous ammonia and the hydrogenation product precipitated by addition of water. The crystalline precipitate was filtered, washed with water and, after drying, treated with 10 ml of boiling methanol. By this treatment, the yohimbine went into solution, while the highly insoluble pseudoyohimbine, after cooling, was collected on a filter and washed with methanol. From the filtrate the yohimbine was precipitated by addition of water.

The pseudoyohimbine was identified by its melting point (266—268° C (decomp.). and its optical rotation $[\alpha]_D^{20}$ +28° in pyridine (c = 1).

Paper chromatography

It was found that two of the paper chromatographic systems described by Bush [7] for the separation of steroids were well suited for the separation and identification of alkaloids of the yohimbine type.

The relatively polar alkaloids such as yohimbine, corynanthine, and α-yohimbine were best separated in the B5 system, while the B3 system was more convenient for the relatively non-polar alkaloids such as reserpine, deserpidine, and isodeserpidine.

Whatman No. 1 paper was used and the chromatograms were run at 32° C for three hours after equilibration overnight.

The alkaloids were located on the dried papers by their ultraviolet fluorescence after irradiation with ultraviolet light for about ten min. Quantities ranging from 0.5 to about 5 μg could be detected by this method.

It was necessary to use known alkaloids as controls, since the R_F values varied with the amount of material applied.

Acknowledgment. The authors wish to express their gratitude to Dr. E. Frederiksen and Dr. E. Juhl Nielsen for their kind encouragement and advice. We are also indebted to Dr. P. Mørch for the ultraviolet and infrared spectra and to Mr. G. Cornali for the microanalyses.

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Received July 11, 1956.