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Conversion of Yohimbine into β-Yohimbine and 3-*epi*-β-Yohimbine

W. O. GODTFREDSEN and S. VANGEDAL

Leo Pharmaceutical Products, Copenhagen, Denmark

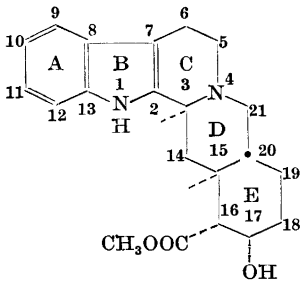
A four step conversion of yohimbine into β-yohimbine is described. Epimerization of β-yohimbine at C_3 affords a new yohimbine stereoisomer, 3-*epi*-β-yohimbine. Finally, the correlation between R_F-values and conformations of some yohimbine stereoisomers is discussed.

Three of the four possible 16-carbomethoxy-17-hydroxy-(—)-yohimbanes are known, *viz.* yohimbine, corynanthine, and β-yohimbine *.

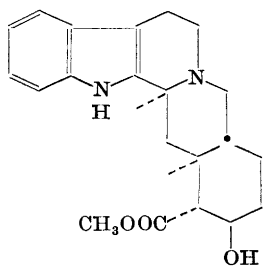
In yohimbine (I) the 16-carbomethoxy group is equatorially and the 17-hydroxyl group axially oriented [2,3]. Corynanthine is the 16-epimer of yohimbine [4] and, consequently, β-yohimbine must contain an equatorial 17-hydroxyl group. The 16-carbomethoxy group is considered to be of equatorial conformation since β-yohimbic acid is not epimerized by prolonged treatment with alkali [5].

In the following, a four step conversion of yohimbine (I) into β-yohimbine (II) will be described.

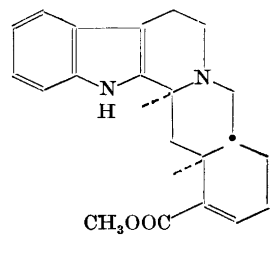
The first step, which consists in dehydration of yohimbine (I) to apoyohimbine (III), is well known [6].



I



II

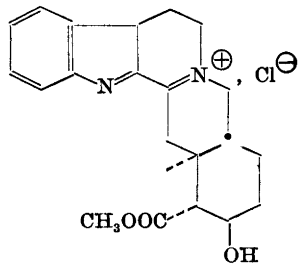


III

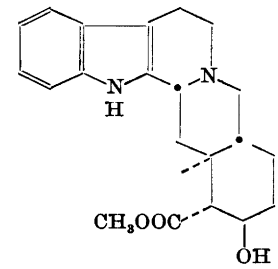
* The fourth stereoisomer is possibly represented by the alkaloid Serpine [1].

Treatment of apoyohimbine (III) with sodium methoxide in boiling methanol causes addition of methanol to the 16,17-double bond with the formation of a 16-carbomethoxy-17-methoxy-(—)-yohimbane, which upon heating with 48 % hydrobromic acid and subsequent esterification of the resulting 16-carboxy-17-hydroxy-(—)-yohimbane with diazomethane yields β-yohimbine, identical in every respect with an authentic sample.

In a previous paper [7] the dehydrogenation of alkaloids of the yohimbine type with *tert*-butyl hypochlorite was described. When β-yohimbine (II) is dehydrogenated in this way 3-dehydro-β-yohimbine chloride (IV) is obtained in good yield.



IV



V

Reduction of this compound with zinc and 50 % acetic acid according to Weisenborn and Diassi [8] yields a mixture of β-yohimbine (II) and a new yohimbine stereoisomer, 3-*epi*-β-yohimbine (V). For the separation of these two epimers their different solubilities in acetone were utilized. While β-yohimbine is readily soluble in this solvent, 3-*epi*-β-yohimbine forms a practically insoluble solvate.

The new yohimbine stereoisomer crystallizes nicely from alcohol, ethyl acetate, and benzene, but in solvated forms from which the solvent, in spite of intensive drying, could not be completely removed. For analysis the recrystallized material was therefore sublimed.

The melting point (203—204°C) and the optical rotation ($[\alpha]_D^{25}$ —83° in pyridine (c = 1)) seem to exclude that 3-*epi*-β-yohimbine is identical with any of the unidentified yohimbine isomers isolated from *Rauwolfia* species.

Table 1. R_F-values in Bush's B5-system.

Substance	R_F-value	D/E ring juncture	Orientation of the		
			C_3-hydrogen	16-carbomethoxy group	17-hydroxyl group
Corynanthine [4]	0.37	*trans*	axial	axial	axial
β-Yohimbine [5]	0.43	—	—	equatorial	equatorial
Yohimbine [2,3]	0.55	—	—	equatorial	axial
Allo-yohimbine [11]	0.67	*cis*	—	axial	equatorial
α-Yohimbine [12]	0.79	—	—	equatorial	equatorial
3-*epi*-β-Yohimbine	0.28	*trans*	equatorial	equatorial	equatorial
Pseudo-yohimbine [2]	0.40	—	—	equatorial	axial

In accordance with the equatorial orientation of the hydrogen atom at C_3, 3-*epi*-β-yohimbine is not dehydrogenated by mercuric acetate [8].

It has previously been pointed out [7] that Bush's B5 system [9] is well suited for paper chromatographic separation of alkaloids of the yohimbine type; in Table 1, the R_F-values of seven yohimbine stereoisomers are given. It will be seen that a substance containing an equatorial hydroxyl group is absorbed more strongly than its axial epimer (β-yohimbine — yohimbine; 3-*epi*-β-yohimbine — *pseudo*yohimbine), a phenomenon which is well known from the steroid series [10]. In addition, it appears from the table that compounds with an equatorial hydrogen atom at C_3 have lower R_F-values than their C_3-epimers (3-*epi*-β-yohimbine—β-yohimbine; *pseudo*yohimbine—yohimbine), and that compounds with an axial 16-carbomethoxy group are absorbed more strongly than their equatorial epimers (corynanthine — yohimbine; *allo*yohimbine — α-yohimbine).

EXPERIMENTAL

All melting points are corrected.

16-Carbomethoxy-17-methoxy-(—)-yohimbane (β-yohimbine methyl ether)

Apoyohimbine (22.4 g) and methyl acetate (25 ml) were added to a sodium methoxide solution containing 12.0 g of sodium in 350 ml of absolute methanol, and the mixture was refluxed for three days. The resulting clear solution was cooled and the crystals were collected on a filter and washed with methanol and water. Addition of water to the filtrate gave a further crop of crystals.

The combined precipitates were dissolved in 10 % acetic acid, reprecipitated with aqueous ammonia, and dried over P_2O_5 to give 21.7 g of white crystals with m.p. 196—200 °C. Recrystallization from *iso*propanol yielded 21.6 g of a product containing one mole of *iso*propanol. M.p. 204—206 °C (sealed tube). $[\alpha]_D^{20}$ −49° in pyridine (c = 1). (Found: C 70.05; H 8.57; N 6.40. Calc. for $C_{22}H_{28}N_2O_3$, C_3H_7OH: C 70.06; H 8.47; N 6.54).

Three recrystallizations from benzene gave solvent free crystals with m.p. 214.5—215.5 °C (sealed tube). $[\alpha]_D^{20}$ −54.5°±1 in pyridine (c = 1). (Found: C 71.53; H 7.76; N 7.68. Calc. for $C_{22}H_{28}N_2O_3$: C 71.71; H 7.66; N 7.60).

β-Yohimbine (II).

β-Yohimbine methyl ether, C_3H_7OH (2.0 g), was triturated in a mortar with a few ml of 48 % hydrobromic acid. The resulting paste was transferred to a 100 ml round-bottomed flask fitted with a reflux condenser; freshly distilled 48 % hydrobromic acid (20 ml) was added, and the mixture was heated cautiously with occasional shaking. When the excessive foaming which occurred during the first period of heating had ceased (about 30 min), the mixture was refluxed until a clear solution was obtained (another 30 min).

The solution was evaporated *in vacuo* and the last traces of hydrobromic acid were removed by drying over potassium hydroxide The residue was dissolved in methanol (30 ml) and excess of an ethereal solution of diazomethane was added. The solution was warmed on the steam bath to expel excess reagent and then evaporated *in vacuo* to a volume of 20 ml. After standing, 1.3 g of white plates, m.p. 234.5—235.5°C, were collected by filtration. Recrystallization from methanol raised the melting point to 236—237°C, and this was not depressed by admixture with an authentic sample of β-yohimbine, 2 CH_3OH. The I.R.-spectra of the two products and their R_F-values were identical too.

The optical rotation was found to be: $[\alpha]_D^{23}$ −42° in pyridine (c = 1). Le Hir and Goutarel [5] report $[\alpha]_D^{18}$ −46.6° in pyridine (c = 0.5).

3-Dehydro-β-yohimbine chloride (IV).

To a stirred solution of 1 360 mg (3.25 mmoles) of β-yohimbine, 2 CH_3OH and 0.50 ml of triethylamine in 25 ml of dry methylene chloride, a solution of 0.50 ml of *tert*-butyl hypochlorite in 5 ml of carbon tetrachloride was added at −25 °C during a period of 10 min. The cooling bath was removed and, after standing for about 15 min, the solution was washed with two 10 ml portions of water, and dried. The solvent was removed *in vacuo*, the residue dissolved in 5 ml of methanol, and the solution acidified with methanolic hydrogen chloride. Upon standing, 1 025 mg of yellow needles m.p. 267—269 °C (decomp.) were obtained. Recrystallization from methanol raised the melting point to 268—269.5 °C (decomp.). Ultraviolet absorption spectrum: λ_{max}^{MeOH} 246 mμ, log ε 4.03; 354 mμ, log ε 4.38. (Found: C 63.97; H 6.74; Cl 9.06. Calc. for $C_{21}H_{25}ClN_2O_3$, ½ CH_3OH: C 63.78; H 6.72; Cl 8.76).

3-*epi*-β-Yohimbine (V)

Zinc dust (800 mg) was added to a solution of 3-dehydro-β-yohimbine chloride, ½ CH_3OH (1 600 mg) in 50 % acetic acid (40 ml) and the mixture was shaken at room temperature until all zinc had dissolved (about 4 h). After addition of crushed ice, the solution was made alkaline with conc. aqueous ammonia (pH 9) and extracted three times with 30, 15 and 10 ml, respectively, of methylene chloride.

The combined extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo* The residue was treated with 20 ml of boiling acetone to bring the β-yohimbine into solution. Cooling, filtration and washing with acetone gave 680 mg of crude 3-*epi*-β-yohimbine. Recrystallization from absolute ethanol afforded 505 mg of pure material which sintered at 141—142 °C (loss of solvent) and melted at 203—204 °C (dec.).

Recrystallizations from ethyl acetate and benzene gave also solvated forms and, for analysis the material was therefore sublimed. The sublimed material had m.p. 203—204 °C (decomp.) and $[\alpha]_D^{25}$ −83° in pyridine (c = 1).

Ultraviolet absorption spectrum: λ_{max}^{EtOH} 225 mμ, log ε 4.54; 282 mμ, log ε 3.88; 290 mμ, log ε 3.81. λ_{min}^{EtOH} 248 mμ, log ε 3.29; 288 mμ, log ε 3.80. (Found: C 70.99; H 7.25; N 7.71. Calc. for $C_{21}H_{26}N_2O_3$: C 71.16; H 7.39; N 7.90).

The acetone filtrate, containing mainly β-yohimbine, was evaporated to dryness *in vacuo* and the residue dissolved in 10 ml of boiling methanol. After cooling, 660 mg of β-yohimbine, 2 CH_3OH, m.p. 233—235 °C, were recovered.

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