SYNTHESIS OF THE ALKALOID YOHIMBINE

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Reaction scheme: yohimbon (I) → carboethoxyyohimbon (II) → hydroxy ester (III) → yohimbolcarboxylic acid (IV) → yohimbine (V).

Figure 1: Reaction scheme: yohimbon (I) → carboethoxyyohimbon (II) → hydroxy ester (III) → yohimbolcarboxylic acid (IV) → yohimbine (V).

Abstract

Full Text

CHEMISTRY

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SYNTHESIS OF THE ALKALOID YOHIMBINE

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In our communication ([1]) on synthetic studies in the field of the alkaloid yohimbine (V), the preparation of apoyohimbine from yohimbine and formic acid ester was described. This solved one of the principal problems in the synthetic preparation of the active principle of the bark of *Corynanthe Johimbe* trees—the reproduction of the hydrogenated ring E, corresponding in structure and arrangement of atoms to the natural alkaloid yohimbine (V). However, the synthesis of apoyohimbine carried out by us does not yet make it possible to proceed to the preparation of yohimbine, since the construction of 16 α-carbomethoxy-17 α-hydroxyyohimbane (V) from 16 α-carbomethoxy-yohimben-16 is very difficult.

In the present work we have established that yohimbon (I) reacts with diethyl carbonate to form carboethoxyyohimbon (II). By reduction of the ester obtained to III, followed by saponification to IV and esterification, the methyl ester of yohimbolcarboxylic acid, the alkaloid yohimbine (V), was obtained.

The reaction of ethyl carbonate with the base yohimbon (m.p. 296–298°) (I) in the presence of sodium ethoxide in dry benzene proceeds slowly, and the heating necessary for its completion causes some resinification and decomposition of the substance. Under the same conditions, in the interaction of yohimbon and dimethyl carbonate, we were unable to obtain an analytically pure substance. The best results were achieved by carrying out the condensation of yohimbon with a large excess of diethyl carbonate with shaking for 3–4 days at 18–20°. After separation of the unreacted yohimbon, removal of the solvent in vacuo, and treatment of the condensation product with water, the sodium salt

the enol form are decomposed with acetic acid. The precipitate that separates is extracted with chloroform. Ethyl yohimboncarboxylate (II) is a yellowish crystalline substance. The melting point of the unpurified base is 98–105°. Yield

60% of theory.

Hydrochloride, m.p. 241-243° (from 70% ethyl alcohol).

Found %:	C 65.68; 65.33;	H 6.20; 6.34;	N 6.72; 6.88			
$C_{22}H_{27}O_3N_2Cl$.	Calculated %:			C 65.59;	H 6.78;	N 6.9

Ethyl yohimboncarboxylate (II) was subjected to catalytic hydrogenation in anhydrous ethyl alcohol in the presence of platinum oxide at 35-40° and 80 atm. The reduction product gives no coloration with ferric chloride solution. Yield of ethyl yohimbolcarboxylate (III) 93% of theory. M.p. 178-184° (decomp.) (from 60% ethyl alcohol).

Found %:	C 71.73; 71.72;	H 7.47; 7.72;	N 7.58; 7.97			
$C_{22}H_{28}O_3N_2$.	Calculated %:			C 71.74;	H 7.61;	N 7.61

Hydrochloride, m.p. 275-280° (decomp.); (repeated crystallization from 70% ethyl alcohol).

Found %:	C 65.08; 65.20;	H 7.17; 7.14;	N 7.91; 6.92			
$C_{22}H_{29}O_3N_2Cl$.	Calculated %:			C 65.26;	H 7.22;	N 6.9

This hydrochloride of base III proved to be identical with the hydrochloride of the ethyl ester of yohimbic acid, obtained by saponification of the natural alkaloid yohimbine with potassium hydroxide in 70% methanol followed by esterification with ethyl alcohol.

Melting point of the hydrochloride 279-281° (decomp.) (from 70% ethyl alcohol).

Found %:	C 65.23; 65.18;	H 7.25; 7.32;	N 6.96; 6.84			
$C_{22}H_{29}O_3N_2Cl$.	Calculated %:			C 65.26;	H 7.22;	N 6.9

A mixed sample of the hydrochlorides of the ethyl esters of natural and synthetic yohimbolcarboxylic acids showed no depression (m.p. 277-280° (decomp.)).

The natural alkaloid yohimbine is the methyl ester of 16α-carboxy-17α-hydroxyyohimbane (V). We therefore carried out the conversion of the ethyl ester of 15-carboxy-17-oxoyohimbane (III), obtained by us from yohimbon, into the methyl ester. For this purpose the ethyl ester of the isomeric β-hydroxy

acids was saponified with a solution of potassium hydroxide in 60% methanol. The acid was isolated. M.p. 245–249° (decomp.) (from water).

Found %:	C 70.48; 70.20;	H 7.08; 6.81;	N 8.20; 8.33			
$C_{20}H_{24}O_3N_2$.	Calculated %:			C 70.59;	H 7.06;	N 8.24

After esterification of β-hydroxy acid IV with methanol saturated with hydrogen chloride, we obtained the hydrochloride of methyl yohimbolcarboxylate (V). The compound obtained was purified via the base (aqueous ammonia), the tartrate (alcoholic solution of (+)-tartaric acid), again the base (aqueous ammonia), and crystallization from 70% ethyl alcohol. Methyl yohimbolcarboxylate—needle-shaped crystals.

M.p. 234–236.5° (decomp.) (deforms at 226°).

Found %:	C 71.10;	H 7.23;	N 7.63		
$C_{21}H_{26}O_3N_2$.	Calculated %:		C 71.14;	H 7.34;	N 7.91

Hydrochloride, m.p. 299–302° (deforms at 294°).

Found %:	C 64.42;	H 6.92;	N 6.86		
$C_{21}H_{27}O_3N_2Cl$.	Calculated %:		C 64.50;	H 6.91;	N 7.17

A mixed sample with the hydrochloride of the natural alkaloid yohimbine (m.p. 298–300°) gave no depression.

Thus, the work carried out by us completes the total synthesis of the alkaloid yohimbine, since previously this synthesis had been carried out only as far as yohimbone ([2]) and apoyohimbine ([1]).

To confirm the identity of the arrangement of the carbomethoxy and hydroxy groups in ring E of natural and synthetic yohimbines, we applied the method used by G. Fodor to establish the spatial configuration in a series of tropane alkaloids ([3]).

The ethyl ester of yohimbolcarboxylic acid (III) synthesized by us was reduced with lithium aluminum hydride in dry tetrahydrofuran to yohimbol alcohol (VI). Yield 39.5% of theory. M.p. 194–199°.

Found, %:	C 73.53; 73.41;	H 7.77; 7.68;	N 8.59; 8.63		
$C_{20}O_{26}O_2N_2$. Calculated, %:	C 73.57;	H 7.97;	N 8.59		

structural scheme: conversion of VI to VII

Figure 2: structural scheme: conversion of VI to VII

Hydrochloride, m.p. 282-284° (from 70% ethanol).

Found, %:	C 66.20;	H 7.73;	N 7.60
$C_{20}H_{27}O_2N_2Cl$. Calculated, %:	C 66.21;	H 7.45;	N 7.72

Yohimbol alcohol was also obtained by us by reduction of yohimbine with lithium aluminum hydride under analogous conditions. Hydrochloride, m.p. 283-285.

Found, %:	C 66.60;	H 7.46;	N 7.75
$C_{20}H_{27}O_2N_2Cl$ Calculated, %:	C 66.21;	H 7.45;	N 7.72

A mixed sample of both substances gave no depression of the melting point.

Further, synthetic yohimbol alcohol (VI), on reaction with benzaldehyde in the presence of *p*-toluenesulfonic acid, gave the *p*-toluenesulfonate of the benzylidene derivative VII.

M.p. 283-286°.

Found, %:	C 69.51;	69.54;	H 6.43;	6.73;	N 4.46;	4.55
$C_{34}H_{38}O_5N_2S$. Calculated, %:	C 69.62;		H 6.48;		N 4.78	

Yohimbol alcohol (VI), obtained by reduction of the natural alkaloid yohimbine (V), on reaction with benzaldehyde under the same conditions gave an analogous cyclic acetal.

Found, %:	C 69.50;	69.86;	H 6.15;	6.52;	N 4.61;	4.73
$C_{34}H_{38}O_5N_2S$. Calculated, %:	C 69.62;		H 6.48;		N 4.78	

A mixed sample of the synthetic *p*-toluenesulfonate of the benzylidene derivative (m.p. 283-285°) with the *p*-toluenesulfonate of the cyclic acetal synthesized from the natural alkaloid yohimbine (m.p. 282-285°) gave no depression of the melting point.

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Note: Figure translations are in progress. See original paper for figures.