Synthetic Studies Related to the Yohimbine Alkaloids

FREDERICK E. ZIEGLER AND JAMES G. SWEENY[1]

Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut 06520

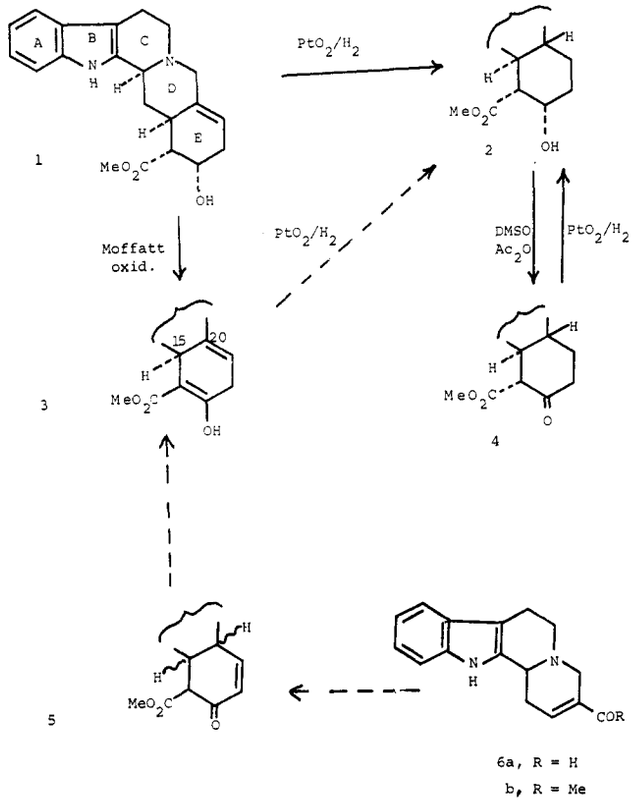
Received April 14, 1969

An approach to the synthesis of yohimbine (**2**) an dmethyl 17-hydroxyyohimb-17,19-diene-16-carboxylate (**3**) is described. The structures derived from the ring E forming reaction are discussed.

The isolation of 19-dehydroyohimbine (**1**) by Djerassi and coworkers[2] and its subsequent reduction to yohimbine (**2**) and oxidation to methyl 17-hydroxyyohimb-17,19-diene-16-carboxylate (**3**) prompted us to explore a synthetic route to this class of unsaturated yohimbine bases. These observations, coupled with our own that catalytic reduction of yohimbinone (**4**) over platinum oxide gave yohimbine as the sole reduction product, lent substance to the belief that **3** might well be converted in one step to yohimbine.

A synthetic route to pentacyclic **3** was our immediate objective without due regard to the relative configuration at C-3 and C-15. If the hydrogens at these centers were to be established in a *trans* configuration, it was felt that acid-catalyzed epimerization[3] at C-3 would establish the requisite *cis* substitution pattern. Since it is mandatory that the hydrogen at C-15 be axially oriented,[4] it follows that the *cis* stereoisomer, having the bulky indole moiety equatorially oriented, would be more stable than the *trans*.

SCHEME I



1 2 3 4 5

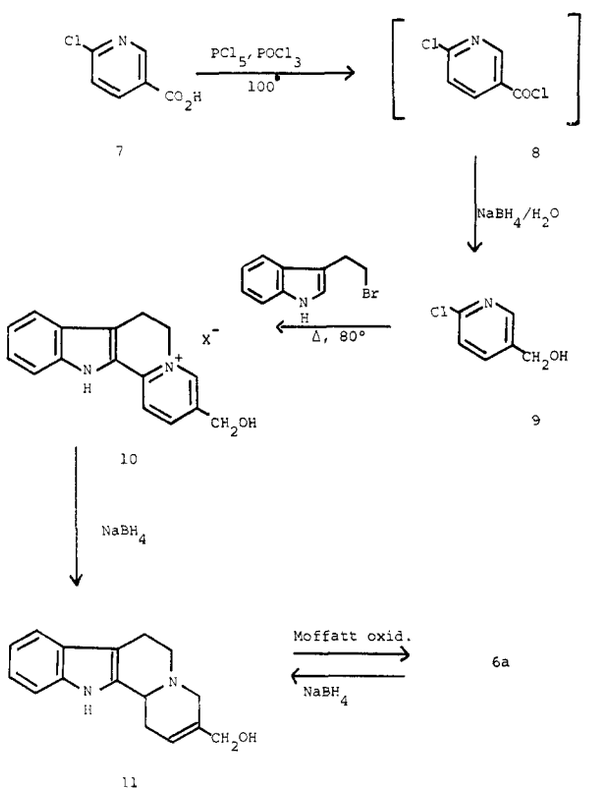
6a, R = H

b, R = Me

Ring E of pentacyclic **3** can be formally derived by the Michael addition of methyl acetoacetate to the α,β-unsaturated aldehyde **6a** followed by aldolization to afford enone ester **5**. Under the alkaline conditions of such a condensation, deconjugation of the enone to the β,γ isomer might well be expected and give rise to the enolic β-keto ester **3** or its stereoisomer.

To test this hypothesis, the aldehyde **6a** was prepared as depicted in Scheme II. The position of the double bond in the allylic alcohol **11** follows from its mass spectral pattern,[5] while the aldehyde displayed a carbonyl at 1685 cm^{-1}.

SCHEME II



7 8 9 10 11 6a

With the appropriate aldehyde at our disposal, the condensation with methyl acetoacetate was conducted under mild alkaline conditions. The thin layer chromatogram indicated the presence of two enolic products (positive $FeCl_3$ test), one of which predominated over the other. Crystallization afforded the major component A in the pure state. On the other hand, when a stronger alkaline medium was employed, the product distribution was reversed, affording the other component, B, as the major product, which could be

(1) National Institutes of Health Predoctoral Fellow, 1966–1969.

(2) R. R. Arndt and C. Djerassi, *Experientia*, **21**, 566 (1965).

(3) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958); N. J. Dastoor, A. A. Gorman, and H. Schmid, *Helv. Chim. Acta*, **50**, 213 (1967).

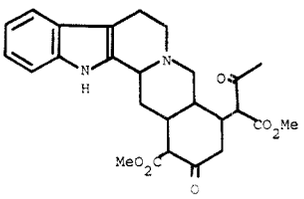
(4) Taking 19-dehydroyohimbine as a case in point, it is impossible to have the C-15–C-16 bond bound axially to ring D. Since C-15, C-20, C-19, and C-18 lie in a plane, the ring size is insufficient to tolerate such strain.

(5) F. E. Ziegler and J. G. Sweeny, *Tetrahedron Lett.*, 1097 (1969). The position of the double bond has been established in other cases; see E. Wenkert, R. A. Massy-Westropp, and R. G. Lewis, *J. Amer. Chem. Soc.*, **84**,, 3732 (1962); F. E. Ziegler and J. G. Sweeny, *J. Org. Chem.*, **32**, 3216 (1967).

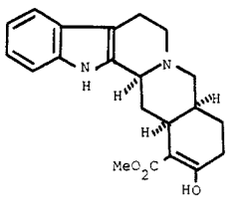
obtained by direct crystallization. Treatment of A with excess sodium methoxide in methanol yielded B. Comparison (tlc) of these two products with an authentic sample[6] of pentacyclic **3** showed neither of the components to be identical with it.

High-resolution mass spectrometry supported our suspicion that A and B were stereoisomers, since both compounds had the same molecular ion, in agreement with an empirical formula $C_{26}H_{30}N_2O_6$ (mol wt 466). This was in accord with pentacyclic **3** (mol wt 350) plus methyl acetoacetate (mol wt 116) insofar as the molecular weight was concerned. It is apparent that the two materials are isomeric and that compound A is the product formed under kinetically controlled conditions, whereas B is its thermodynamic isomer formed under equilibrating conditions.

The most likely site for the attachment of a second mole of methyl acetoacetate would be at C-19, by Michael addition to the enone ester **5**, indicating that the rate of addition of the second mole of methyl acetoacetate is faster than deconjugation. The gross structure of the isomers can be represented by structure **12**. Attempts to reverse the second Michael addi-



12



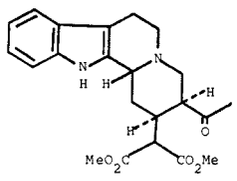
13

tion met with failure. The attempt at isolating the initial adduct and effecting acid-catalyzed[7] aldolization was likewise unsuccessful. No intermediate of this type could be detected during the course of the reaction, implying that the initial adduct rapidly undergoes aldolization and conversion to products. The addition of dimethyl malonate to the unsaturated ketone **6b** has been shown[8] to proceed smoothly, wherein the aldol condensation does not present itself.

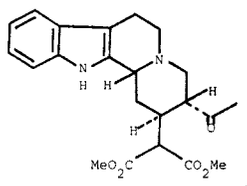
The ultraviolet spectra of the two isomers were identical in ethanol and 0.1 *N* sodium hydroxide solution with the spectrum of methyl 17-hydroxy-20α-yohimb-16-ene-16-carboxylate (**13**).[9] Consequently, the structure **12** must be altered to include one enolic β-keto ester chromophore.

Acid hydrolysis of either isomer A or B produced the same monodecarboxylated product, $C_{24}H_{28}N_2O_4$ (mol wt 408), which indicated that isomerization was also occurring in acid medium. The ultraviolet spectrum was identical in both neutral and alkaline media (negative $FeCl_3$ test), indicative of the loss of the enolic chromophore. More vigorous hydrolysis afforded a small amount of bisdecarboxylated material, $C_{22}H_{26}N_2O_2$ (mol wt 350), which displayed the fragments M − C_2H_3O (acetyl), M − C_3H_5O (acetonyl), and 349 − C_3H_6O (acetone) in its high-resolution mass spectrum, confirming the presence of a side chain[10] in the orignal isomers.

Winterfeldt[8] has demonstrated that the addition of dimethyl malonate to the enone **6b** proceeds with axial entry[11] of the nucleophilic reagent, thereby establishing a *trans* relationship between the C-3 and C-15 hydrogen atoms with the *epiallo* isomer **14** being the kinetic product while the thermodyanmic isomer is of the pseudoconfiguration **15**.



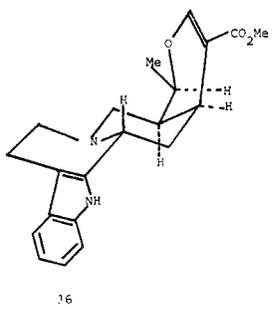
14



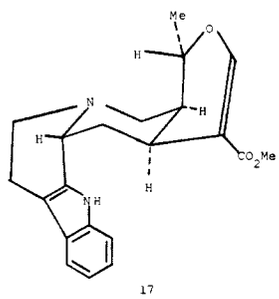
15

The solution infrared spectra of the two isomers were particularly informative. Isomer B displayed the presence of *trans* bands in the 2900–2700-cm^{-1} region, indicating that the hydrogen at C-3 is *trans* diaxial to the electron pair of the basic nitrogen,[12] whereas isomer A was found to be devoid of absorption in this region of the spectrum. Clearly, the pentacyclic thermodynamic isomer B cannot be of the pseudoconfiguration as is the tetracyclic **15**, since tetracyclics and pentacyclics[12] of the pseudoconfiguration do not shown *trans* bands. In addition, isomer A, although it does not display *trans* bands, cannot be of the pseudoconfiguration, since the D/E juncture is formed at the tetracyclic stage under kinetic conditions. Therefore, both isomers can be assigned to the *epiallo* configuration and the center of epimerization is relegated to C-19.

Although yohimbines of the *epiallo* configuration do not show *trans* bands, the heteroyohimbine mayumbine (**16**), which is of the *epiallo* configuration with a C-19β (equatorial) methyl substituent, does display *trans* bands.[13] On the other hand, akuammigine (**17**) is also of the *epiallo* configuration with a C-19α (equatorial) methyl and does not reveal *trans* bands.[13] Consequently, the C-19 equatorial group influences the conformation of each of these *epiallo* isomers.



16



17

With a *cis* D/E ring juncture, it can be argued that the enolic chromophore belongs to the β-keto ester of ring E, in accord with the enolic properties of methyl

(6) We wish to thank Professor Djerassi for providing us with a sample of this material.

(7) M. Mousseron, R. Jacquier, A. Fontaine, and R. Zagdoun, *Bull. Soc. Chim. Fr.*, 1254 (1954).

(8) E. Winterfeldt, H. Radunz, and T. Korth, *Chem. Ber.*, **101**, 3172 (1968).

(9) (a) Uv λ_{max} (EtOH) 289 (ϵ 6700), 282 sh (ϵ 9200), 264 (ϵ 12,700), and 224 mμ (ϵ 38,100); λ_{max} (0.1 *N* NaOH) 283 (ϵ 23,200) and 215 mμ (ϵ 57,400).[9b] (b) J. D. Albright and L. Goldman, *J. Org. Chem.*, **30**, 1107 (1965).

(10) H. Budzikiewicz, C. Djerassi, and D. Williams "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, Chapter 3; "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. I, Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 5.

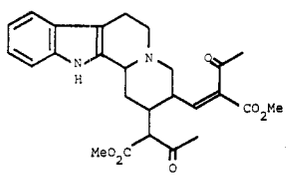
(11) R. A. Abramovitch and D. L. Struble, *Tetrahedron*, **24**, 357 (1968).

(12) E. Wenkert and D. K. Roychaudhuri, *J. Amer. Chem. Soc.*, **78**, 6417 (1956); F. Bohlmann, *Chem. Ber.*, **92**, 1798 (1959).

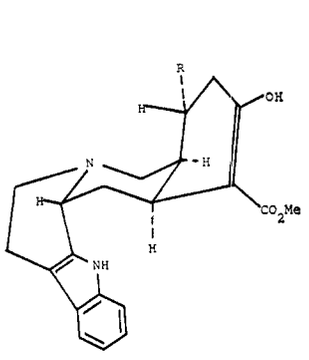
(13) M. Shamma and J. M. Richey, *J. Amer. Chem. Soc.*, **85**, 2507 (1963).

17-hydroxy-20α-yohimb-16-ene-16-carboxylate (**13**) and the nonenolic properties of ring-E β-keto esters, such as yohimbinone (**4**),[9] having a *trans* fused D/E juncture. These data are in accord with previously reported[14] enolization behavior of ring E.

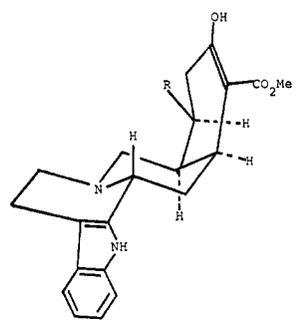
The mode of epimerization of C-19 can be envisaged as proceeding *via* the alkylidene acetoacetic ester **18**. The complete stereochemical formulations of isomers A and B are therefore represented by **19a** and **b**, respectively, both having the *epiallo* configuration.



18



19a



19b

R = CH(COMe)CO_2Me

In retrospect, the monodecarboxylated product **20** can be defined as 3β,20α,19β-(2-methylacetoacetyl)-yohimb-17-one, while the bisdecarboxylated material **21** is 3β,20α,19β-acetonylyohimb-17-one.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are corrected. The infrared spectra were determined on Perkin-Elmer 421 and 237B spectrometers. Ultraviolet spectra were recorded on a Cary 11S recording spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60 or A-60A spectrometer with tetramethylsilane as internal standard. Mass spectra were recorded on an AEI MS-9 spectrometer. Elemental analyses were determined by Alfred Bernhardt or Galbraith Laboratories. Unless stated otherwise, magnesium sulfate was used as the drying agent.

Reduction of Yohimbinone (4) to Yohimbine (2).—To a solution of 74 mg (0.22 mmol) of yohimbinone[15] in 15 ml of methanol and 1 ml of acetic acid was added 20 mg of platinum oxide, and the mixture was hydrogenated at atmospheric pressure and room temperature for 24 hr. An additional 20 mg of platinum oxide was added (the system was first evacuated to remove hydrogen) and reduction was continued for an additional 24-hr period. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. Dilution of the residue with 10 ml of dilute aqueous sodium carbonate was followed by extraction with three 10-ml portions of chloroform. Drying, filtering, and concentrating the extracts afforded an oil. Examination of the oil on tlc (4:1 methanol–benzene) showed only yohimbine and none of its 17β isomer, β-yohimbine. Trituration of the oil with ether gave 33 mg of a light yellow solid, which upon recrystallization from ether produced 18 mg of yohimbine, mp 236–240°. Comparison with an authentic sample, mp 233–237° (prepared from the hydrochloride, lit.[16] mp 235–236°, mmp 232–236°), showed the two materials to have superimposable solution infrared spectra.

2-Chloro-5-hydroxymethyl Pyridine (9).—A mixture of 7.0 g (0.044 mol) of 6-chloronicotinic acid,[17] 10.0 g (0.048 mol) of phosphorus pentachloride, and 5 ml (8.37 g, 0.055 mol) of phosphorus oxychloride was heated for 1 hr at 100° and cooled, and the solvent was removed *in vacuo* to yield a light yellow solid.

To a stirred solution of 6.0 g (0.16 mol) of sodium borohydride in 100 ml of water cooled with an ice bath was added the aforementioned yellow solid in small portions, at such a rate as to maintain the temperature below 20°. The reaction mixture was stirred for 1 hr, saturated with sodium chloride, and extracted with five 40-ml portions of ether. The extracts were dried, filtered, concentrated, and distilled, affording 5.66 g of chloro alcohol: bp 120° (0.4 mm); mp 39–40°; ir ($CHCl_3$) 3320 cm^{-1}; nmr ($CDCl_3$) δ 4.60 (s, 2 H), 4.78 (broad s, 1 H), 7.16 (d, 1 H, J = 12 Hz), 7.54 (q, 1 H, J = 6 and (12 Hz), and 8.13 (d, 1 H, J = 6 Hz).

Anal. Calcd for C_6H_6ClNO: C, 50.17; H, 4.18; Cl, 24.74; N, 9.76. Found: C, 50.12; H, 4.27; Cl, 24.63; N, 9.85.

6,7-Dihydro-3-hydroxymethyl-12H-indolo[2,3-a]quinolizinium chloride (10).—The salt was prepared by the method of Ban.[18] A mixture of 2.05 g (0.009 mol) of tryptophyl bromide and 2.64 g (0.0018 mol) of 2-chloro-5-hydroxymethyl pyridine (**9**) was heated under a nitrogen atmosphere at 90° for 3 hr. The resulting cake was triturated with 15 ml of methanol and filtered, affording 1.42 g (43%) of salt, mp 295–305° dec. Although this material was a mixture of chloride and bromide salts, it was suitable for subsequent steps. A sample was completely converted to the chloride salt by elution of a methanol solution through a column of IRA-400 ion-exchange resin (chloride form), yielding the chloride salt from methanol: mp >310°; uv λ_{max} (MeOH) 390 (ε 14,300), 314 (ε 14,200), and 254 mμ (ε 7500).

Anal. Calcd for $C_{16}H_{15}ClN_2O$: C, 67.05; H, 5.24; Cl, 12.39; N, 9.77. Found: C, 66.95; H, 5.51; Cl, 12.14; N, 9.61.

1,4,5,6,7,12b-Hexahydro-3-hydroxymethylindolo[2,3-a]quinolizine (11).—To a stirred solution of 1.00 g (0.026 mol) of sodium borohydride in 200 ml of 80% aqueous methanol containing 0.5 g of sodium carbonate maintained at 5° was added 7.76 g (0.0236 mol) of pyridinium salt **10** in small portions, in order to moderate the reaction mixture. After the addition was complete, stirring was continued for an additional 0.5 hr and the solution was then concentrated *in vacuo* to a volume of 50 ml. The residue was diluted with 250 ml of saturated brine and extracted with four 75-ml portions of ethyl acetate. The extracts were dried, filtered, and concentrated, giving 5.40 g (90%) of a light yellow solid, mp 228–230°. A sample recrystallized from methanol had mp 234–236°; ir (KBr) 3250 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 254 (46), 253 (18), 171 (16), 170 (100), 169 (62), 143 (12), and 142 (13).

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.18; H, 7.05; N, 11.23.

1,4,5,6,7,12b-Hexahydro-3-formylindolo[2,3-a]quinolizine (6a).—To 150 ml of dry dimethyl sulfoxide (from barium oxide) was added 3.00 g (0.012 mol) of allylic alcohol **11**, 7.48 g (0.0364 mol) of dicyclohexylcarbodiimide, and 1.80 g (0.0184 mol) of orthophosphoric acid, and the solution was allowed to stand at room temperature overnight.[19] The reaction mixture was diluted with 550 ml of methylene chloride[9b] and filtered *in vacuo*. The residual filter cake was suspended in 200 ml of 50% aqueous acetic acid and stirred for 0.5 hr. Insoluble dicyclohexylurea was removed by filtration, the filtrate was basified in the cold with concentrated ammonia, and the mixture was extracted with five

(14) J. D. Albright, L. A. Mitscher, and L. Goldman, *J. Org. Chem.*, **28**, 38 (1963); C. Szantay, L. Töke, and K. Honti, *Tetrahedron Lett.*, 1665 (1965).

(15) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **89**, 2416 (1967).

(16) M.-M. Janot, R. Goutarel, E. W. Warnhoff, and A. LeHir, *Bull. Soc. Chim. Fr.*, 637 (1961).

(17) Pure, commercially available 6-hydroxynicotinic acid (Aldrich Chemical) may be successfully employed, while practical 6-hydroxynicotinic acid (City Chemical) can be purified by conversion to 6-chloronicotinic acid by the procedure of L. R. Fibel and P. E. Spoeri, *J. Amer. Chem. Soc.*, **70**, 3909 (1948).

(18) Y. Ban and M. Seo, *Tetrahedron*, **16**, 5 (1961).

(19) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5670 (1965).

50-ml portions of chloroform. The extracts were dried, filtered, and concentrated, affording, upon trituration with ether, 1.84 g (62%) of the aldehyde as a red-orange solid:[20] mp 179–183° dec; ir ($CHCl_3$) 3470 and 1685 (conjugated CHO) cm^{-1}.

Reduction of α,β-Unsaturated Aldehyde 6a to Allylic Alcohol 11.—To a stirred solution of 100 mg (0.40 mmol) of α,β-unsaturated aldehyde in 50 ml of methanol maintained at 5° was added 100 mg (2.64 mmol) of sodium borohydride. The reaction mixture was stirred for 1 hr, concentrated to 10 ml, and diluted with 100 ml of saturated brine, which in turn was extracted with three 25-ml portions of ethyl acetate. The extracts were dried, filtered, and concentrated to give an oil which, upon crystallization from methanol, yielded 88 mg (88%) of a white solid, mp 229–231°. The product had a superimposable solution infrared spectrum with a sample of allylic alcohol **11** (*vide supra*).

Methyl 3β,20α-17-Hydroxy-19α-(2-methylacetoacetyl)yohimb-16-ene-16-carboxylate (19a).—To 1.84 g (0.0073 mol) of α,β-unsaturated aldehyde **6a** dissolved in 150 ml of dry methanol (from magnesium methoxide) was added 2.52 g (0.0217 mol) of methyl acetoacetate and 211 mg (9.17 mg-atoms) of Na dissolved in 50 ml of dry methanol. After refluxing for 3 hr under nitrogen, the mixture was cooled, treated with 1.5 ml of acetic acid, and taken to dryness. The residue was taken up in 100 ml of chloroform, washed with 50 ml of water, and extracted with three 50-ml portions of 1% aqueous sodium hydroxide. The combined alkaline extracts were neutralized with acetic acid and then adjusted to *ca.* pH 8 with sodium bicarbonate. The alkaline solution was extracted with four 40-ml portions of chloroform. The extracts were dried, filtered, and concentrated, giving a light yellow solid which, upon recrystallization from methanol, produced 515 mg (15.2%) of a white solid: mp 211–214°; ir ($CHCl_3$) 3570, 3460, 2920, 1725, 1660, and 1625 cm^{-1}; uv λ_{max} (EtOH) 290 (ε 6900), 283 (ε 8000), 261 (ε 13,000), and 225 mμ (ε 39,400), and λ_{max} (0.1 *N* NaOH) 284 (ε 22,400) and 220 mμ (ε 52,200); mass spectrum (70 eV) *m/e* (rel intensity) 467 (28), 466 (100), 465 (61), 435 (16), 434 (38), 433 (34), 184 (54), 171 (14), 170 (33), 169 (30), 156 (23), and 144 (14).

Methyl 3β,20α-17-Hydroxy-19β-(2-methylacetoacetyl)yohimb-16-ene-16-carboxylate (19b).—To a solution of 1.00 g (0.0040 mol) of α,β-unsaturated aldehyde **6a** in 125 ml of dry methanol maintained under nitrogen was added 464 mg (4.00 mmol) of methyl acetoacetate and 276 mg (12.00 mg-atoms) of Na dissolved in 25 ml of methanol. After refluxing for 3 hr, the reaction mixture was worked up as previously described (*vide supra*), yielding 230 mg (12.5%) of a white solid: mp 280–290° dec; ir ($CHCl_3$) 3480, 2925, 2820, 2770, 1735, 1660, and 1620 cm^{-1}; uv λ_{max} (EtOH) 290 (ε 6900), 282 (ε 8980), 260 (ε 13,000), and 226 mμ (ε 41,800) and λ_{max} (0.1 *N* NaOH) 282 (ε 23,200) and 218 mμ (ε 58,000); mass spectrum (70 eV) *m/e* (rel intensity) 467 (23), 466 (77), 465 (19), 435 (38), 434 (100), 433 (62), 408 (11), 223 (21), 221 (19), 184 (15), 170 (23), 169 (34), and 156 (33).

Epimerization of 19a to 19b.—To a dry methanol solution of 100 mg (0.215 mmol) of isomer **19a** maintained under a nitrogen atmosphere was added 5 mg (0.217 mg-atoms) of Na dissolved in 20 ml of methanol The solution was refluxed for 18 hr, cooled, neutralized with 1 drop of acetic acid, and concentrated. The residue was diluted with 20 ml of water and extracted with three 20-ml portions of chloroform. The extracts were dried, filtered, and concentrated, yielding a light brown oil. Trituration with methanol gave 19 mg (19%) of a light tan solid, mp 280–287° dec. Comparison of the product on tlc (4:1 benzene–methanol) with a sample of **19b** showed them to be identical. Both materials had superimposable solution infrared spectra.

3β,20α,19β-(2-Methylacetoacetyl)yohimb-17-one (20) from 19a.—A mixture of 300 mg (0.644 mmol) of isomer **19a**, 8 ml of acetic acid, 8 ml of concentrated hydrochloric acid, and 24 ml of water was refluxed for 3 hr. The cooled mixture was poured into a mixture of 25 ml of concentrated ammonium hydroxide and 100 g of ice. After neutralization with acetic acid and adjustment of the pH to 8 with sodium bicarbonate, the solution was extracted with three 50-ml portions of chloroform and the extracts were dried, filtered, and concentrated. Trituration of the residue with methanol afforded 63 mg (38%) of a white solid: mp 297–302° dec; ir ($CHCl_3$) 3470, 3260, 2910, 2850, 2780, 1730, and 1710 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 409 (24), 408 (100), 407 (76), 393 (8), 349 (7), 223 (8), 221 (7), 184 (7), 170 (10), 169 (13), 156 (12), and 143 (17); uv λ_{max} (MeOH) 290 (ε 6260), 283 (ε 7650), and 226 mμ (ε 37,500).

3β,20α,19β-(2-Methylacetoacetyl)yohimb-17-one (20) from 19b.—Hydrolysis of 300 mg of isomer **19b** as described above afforded 59 mg (22%) of a white solid, mp 298–303° dec. Comparison with the product from the previous experiment showed the two materials to have superimposable solution infrared spectra and identical R_f values on tlc (4:1 benzene–methanol). A mixture melting point determination was undepressed.

3β,20α,19β-Acetonylyohimb-17-one (21).—A mixture of 284 mg (0.61 mmol) of **20**, 8 ml of acetic acid, 8 ml of concentrated hydrochloric acid, and 24 ml of water was refluxed for 24 hr. Upon cooling, the solution was poured into 25 ml of concentrated ammonium hydroxide and 25 ml of ice. Extraction with five 50-ml portions of chloroform, followed by drying, filtration, and evaporation of the extracts of the organic layer, gave a semisolid material which, upon elution from Florisil with 5% methanol–chloroform, afforded 20 mg (9%) of a light tan solid: mp 254–256° dec; ir ($CHCl_3$) 3475, 2920, 2850, 2815, 2765, and 1710 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 351 (22), 350 (100), 349 (97), 307 (9), 293 (8), 291 (4.5), 184 (21), 170 (18), 169 (21), and 156 (15).

Registry No.—**6a**, 21577-56-0; **9**, 21543-49-7; **10**, 21543-50-0; **11**, 21543-51-1; **19a**, 21559-54-6; **19b**, 21559-55-7; **20**, 21559-56-8; **21**, 21559-57-9.

Acknowledgment.—The authors wish to thank the National Science Foundation (Grant GP-5828), the National Cancer Institute of the National Institutes of Health (Grant CA-08869), and Eli Lilly and Co. for financial support of this work. We are deeply indebted to Professor Walter McMurray of the Yale Medical School for both recording and stimulating discussion of the mass spectra.

(20) A satisfactory elemental analysis could not be obtained for this compound, since all attempts at further purification only decreased its purity. The material was homogeneous on tlc except for impurities near the origin.