66%), mp 54–57°. Material that had been recrystallized several times from ether–pentane mixtures melted at 55–56°. The infrared spectrum (CCl_4) showed significant bands at 1793, 1662, 1294, 1100, 1061, and 950 cm^{-1} and was identical in all respects with that of the natural material. The nmr spectrum (3% in CCl_4, calibrated) showed absorption at 6.32 (doublet, J = 2.3 Hz), 5.80 (doublet, J = 2.0 Hz), 4.97 (doublet, J = 8.3 Hz), 4.33 (multiplet), 3.57 (multiplet), 1.32, and 0.90 ppm (triplet) [lit.[3] (3% in CCl_4), 6.36 (doublet, J = 2.17 Hz), 4.98 (doublet, J = 8.54 Hz), 4.33 (multiplet), and 3.59 (multiplet)].

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.69; H, 8.26.

The synthetic and natural avenaciolide gave identical thin layer chromatograms on silica gel H being eluted with 20% ether in benzene (v/v).

Registry No.—**1**, 26057-70-5; **7**, 99-11-6; **8**, 6973-55-3; **9**, 39949-60-5; **10**, 39949-61-6; **11**, 39949-62-7; **12**, 39971-68-1; **15**, 39949-63-8; **16**, 39949-64-9; **26**, 39949-65-0; **27**, 39949-66-1; **28**, 39949-67-2; **32**, 39949-68-3; **33**, 39949-69-4; **33** free acid, 39949-70-7; **34**, 39949-71-8; **35**, 39949-88-7; **36**, 39949-89-8; **40**, 39949-90-1; dibenzyl heptylmalonate, 39949-91-2; diethyl heptylmalonate, 607-83-0; benzyl alcohol, 100-51-6; nonanoic anhydride, 1680-36-0; tricarballylic acid, 99-14-9.

Acknowledgment.—The authors would like to thank Drs. J. J. Ellis and F. H. Stodola for a culture of *Aspergillus fischeri* var. glaber, and Mr. P. C. Watts and Mr. L. G. Duquette for technical assistance. Thanks are due also to Dr. J. Martin for suggestions that contributed to the success of this work.

Synthesis of Yohimbines. I. Total Synthesis of Alloyohimbine, α-Yohimbine, and Their Epimers. Revised Structure of Natural Alloyohimbine

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The first total synthesis of alloyohimbine (**6a**) and its isomers **4i**, **4j**, and **8b** has been accomplished. Sodium borohydride reduction of the keto nitrile **3** yielded alcohols **4a** and **4b**, epimeric at C_{17}. The diastereoisomers **4i** and **4j** belonging to the epiallo series were derived from **4a** and **4b**. Epimerization of **4i** at C_3 furnished **6a** which proved to be identical with naturally occurring alloyohimbine except for melting point and optical activity. Compound **6a** could be converted to α-yohimbine under mild conditions, characteristic of those used for epimerization at C_{16}. On the basis of these facts, the structures for alloyohimbine and epialloyohimbine should be revised to **6a** and **4i**, respectively. The hydroxy ester **4j** does not lend itself to facile epimerization at C_3, and has not yet been found in nature.

Two products had been obtained from the catalytic reduction of the unsaturated nitrile ester **1** which had been prepared in the course of the total synthesis of yohimbine.[1] The main product, the trans 2,3-disubstituted nitrile ester, was used for the synthesis of yohimbine. It stood to reason, therefore, to utilize the cis fused isomer **2**, which was the minor product, for the preparation of yohimbines of the allo series, especially so since such bases had not been heretofore synthesized.

The nitrile ester **2** was converted in almost quantitative yield to the pentacyclic ketone **3** using potassium *tert*-butoxide in DMSO. This ketone is strongly enolized both in the solid and dissolved states, and on the basis of its spectral properties must exist mainly in the epiallo-trans (E_t) conformation.[2]

In the course of the earlier sodium borohydride reduction of the analogous ketone nitrile belonging to the normal series, three different nitrile alcohols were isolated out of the theoretically possible four. Under similar conditions (DMF–methanol), **3** furnished only two products, **4a** and **4b**, in a ratio of about 2:3.

From spectral evidence, both **4a** and **4b** must exist in the E_t conformation (Table I). It is also possible to establish the stereochemistry of the C_{17} hydroxyl function from the chemical shift of the C_{17} proton.[3]

(1) Cs. Szántay, L. Töke, and K. Honty, *Tetrahedron Lett.*, 1665 (1965); L. Töke, K. Honty, and Cs. Szántay, *Chem. Ber.*, **102**, 3248 (1969).

(2) (a) W. F. Trager, C. M. Lee, and A. H. Becket, *Tetrahedron*, **23**, 365 (1967). (b) For the meaning of the symbols for the corresponding conformations of yohimban derivatives, see Cs. Szántay, *Magy. Kém. Lapja*, **26**, 490 (1971).

(3) J. D. Albright, L. A. Mitscher, and L. Goldman, *J. Org. Chem.*, **28**, 38 (1963).

TABLE I

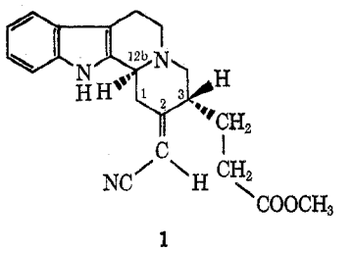
NMR AND IR DATA

	Nmr,[a] δ		Ir,[b] cm^{-1}	Conformation		
Compd	C_{17} proton multiplet	C_{17} hydroxyl doublet	Bohlmann bands	C_{17} H	C_{17} OH	Skeleton
4a	4.05	5.25	2815, 2775, 2760	e[c]	a	E_t[d]
4b	3.55	5.45	2815, 2775	a[c]	e	E_t
4c	5.15		2815, 2775	e		E_t
4d	4.85		2815, 2780	a		E_t

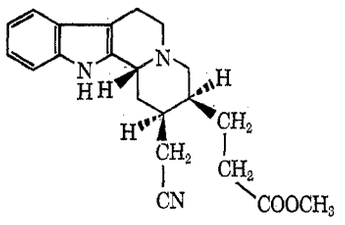
[a] In DMSO-d_6 at 60 MHz. [b] In pyridine. [c] a = axial, e = equatorial. [d] See ref 2b.

In isomer **4a** the equatorial C_{17} proton is at δ 4.05, while in **4b** the axial C_{17} proton is located higher upfield at δ 3.55. In view of the stable E_t conformation of the two isomers, it follows that the hydroxyl group in **4a** is α while in **4b** it is β. The corresponding O-acylated derivatives **4c** and **4d** were also prepared, and their spectra confirmed the correctness of the C_{17} assignments since the signals for the α protons are now shifted to δ 5.15 and 4.85, respectively. In accordance with the steric assignments, the rate of O-acetylation of **4b** was larger by an order of magnitude than that for the similar reaction of **4a**.

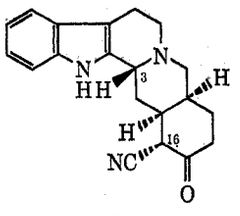
It had been observed in the course of the yohimbine synthesis[1] that the analogs of **4a** and **4b** belonging to the normal series readily epimerized at C-16, bearing the nitrile group, in the presence of aqueous alcoholic alkali at room temperature or under gentle heating. The ΔG value calculated from the equilibrium constants was in good agreement with the energy difference of a



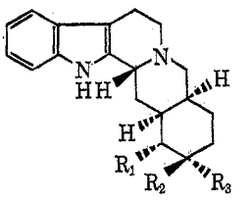
1



2



3

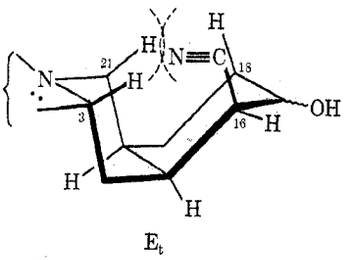


4

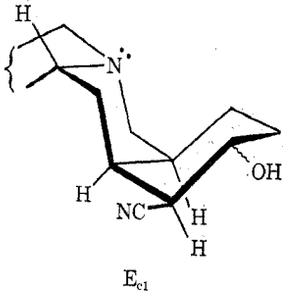
4	R_1	R_2	R_3	4	R_1	R_2	R_3
a	CN	H	OH	f	CN	OTs	H
b	CN	OH	H	g	$CONH_2$	H	OH
c	CN	OH	OAc	h	$CONH_2$	OH	H
d	CN	OAc	H	i	CO_2CH_3	H	OH
e	CN	H	OTs	j	CO_2CH_3	OH	H

nitrile group in the axial and equatorial positions of a cyclohexane system.[4] On the other hand, isomers **4a** and **4b** belonging to the epiallo series could not be epimerized with alcoholic alkali. This result can be readily rationalized by the realization that, if the nitrile group were to epimerize to the β position, it would interact with the axial hydrogens at C_3 and C_{21} in the E_t conformation (Chart I). If the molecule were to take the epiallo-cis (E_{c_1}) conformation to evade such steric interaction, then the indole ring would be placed in an axial position. One can see, then, that the energy difference between the α and β nitrile epimers would be much larger than the value of ~0.2 kcal/mol observed in the normal series.

CHART I



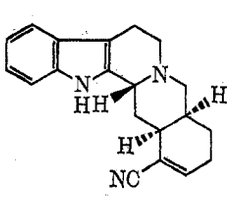
E_t



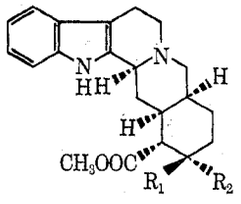
E_{c_1}

It should be mentioned, by way of comparison, that 3-epi-α-yohimbine (**9b**) in which the C_{16} substituent is β exists entirely in the epiallo-cis (E_{c_1}) conformation, and Bohlmann bands indicative of the E_t conformation are completely absent.

Neither can the epimerization of the nitrile alcohols be brought about by hot methanolic alkali. However, **4a** is converted relatively quickly, in about 30 min, to the unsaturated nitrile **5**, whereas **4b** undergoes this dehydration over a period of about 8 hr. This difference in rates of elimination is again in agreement with the structural assignments made.



5



6

6	R_1	R_2
a	H	OH
b	OH	H

The difference in the elimination rates when the tosylates **4e** and **4f** are heated in DMF parallels that for their hydroxyl precursors. This trend can also be observed in the mass spectra. In contradistinction to the spectrum of **4f**, the molecular peak of **4e** is not observed; rather only the ion for the dehydro species **5** is recorded.

By analogy with the behavior of the tosylate of 3-epi-α-yohimbine,[5] it was expected that in pyridine a quaternary salt could be derived from **4e**. The fact that such a transformation did not occur may be attributed to the elimination reaction in the nitrile proceeding at a considerably faster rate than that for the corresponding ester, so that quaternization does not appear as a concurrent reaction.

An answer can now be given as to why only two isomers are formed in the reduction of the ketone **3** belonging to the epiallo series, while it will be recalled that three alcohols are formed in the corresponding reaction in the normal series.

Considering the stereochemistry depicted in Chart I, in the ketone **3** the nitrile group can occupy solely an α position, contrary to the analogous keto nitrile belonging to the normal series where the nitrile in a β configuration is also present at equilibrium. It follows that attack by sodium borohydride leads to two alcohols, with a slight preference for attack from the convex side of the molecule.

As a further step in the synthesis, the nitrile groups in **4a** and **4b** were converted to ester functions. Similarly, in the normal series, direct hydrolysis did not yield the required results. Rather, the acid amides **4g** and **4h** were prepared using hydrogen peroxide in

(4) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965, p 44.

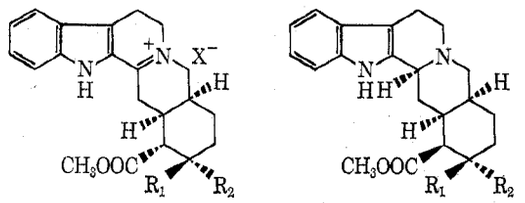
(5) P. E. Aldrich, P. A. Diassi, D. F. Dickel, C. M. Dylion, P. D. Hance, C. F. Huebner, B. Korzun, M. E. Kuehne, L. H. Liu, H. B. McPhillamy, E. W. Robb, D. K. Roychaudhuri, E. Schlittler, A. F. André, E. Van Tamelen, F. L. Weisenborn, E. Wenkert, and O. Wintersteiner, *J. Amer. Chem. Soc.*, **81**, 2481 (1959).

alkaline methanol, and from them the free acids were obtained by boiling with aqueous hydrochloric acid. Esterification of the two acid with diazomethane gave rise to esters **4i** and **4j**. Noteworthy was the observation that the isomers containing the C_{16}, C_{17} substituents in the cis relationship (**4a**, **4g**) hydrolyze more rapidly than in the trans compounds (**4b**, **4h**) on account of the effect of the hydroxyl group.

However, in the course of the hydrolysis of the acid amide **4g** with hydrochloric acid, epimerization at the C_3 site also occurred, so that in addition to **4i** belonging to the epiallo series, a smaller quantity of **6a** of the allo configuration was also formed. That **4i** and **6a** actually differ only at C_3 was proven by mercuric acetate oxidation, which furnished the same immonium salt, **7b**. Reduction of this salt with sodium borohydride gave **6a** as the main product, while **4i** was recovered from the zinc in acetic acid reduction.

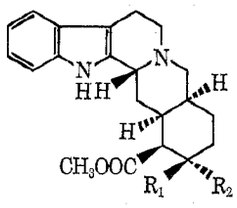
Boiling with acid of **6a** with the allo configuration and subsequent methylation provided a 1:3 mixture of **6a** and **4i**, identical with that derived from the boiling with acid and methylation of the amide **4g**.

Following all of these transformations, it was somewhat unexpected to find that the chromatographic, spectral, and chemical properties of **6a** were identical with those of natural alloyohimbine to which the structure **8a** had been attributed in the literature.[6] The original structural assignment had been based on the finding that on boiling with potassium *tert*-butoxide alloyohimbine was converted to α-yohimbine (**8b**), the



7

8



9

7, 8, 9,	R_1	R_2
a	OH	H
b	H	OH

structure of which had been firmly established.[7] Indeed, under such conditions, epimerization of the C_{17} hydroxyl can occur, as for example in the preparation of β-yohimbine from yohimbine. Thus, alloyohimbine was considered to be the C_{17} epimer of α-yohimbine.

To eliminate this apparent contradiction, we tried to bring about under mild conditions the epimerization of natural alloyohimbine, as well as of **6a** which we had synthesized. It was found that alloyohimbine can be readily converted to α-yohimbine at room temperature using sodium methoxide as base. Under such mild conditions, only the more acidic C_{16} hydrogen α to the carbomethoxy group can be pulled. For instance, yohimbine cannot epimerize under such conditions to β-yohimbine.

It follows then that the structural assignment for alloyohimbine, also strongly supported by nmr data, must be revised to **6a**. A corollary is that 3-epialloyohimbine is now correctly represented by expression **4i**. According to the literature, 3-epialloyohimbine should be represented by expression **9a**. The ir spectrum[7] of this alkaloid clearly shows Bohlmann ir bands, so that the molecule would then exist in the E_t conformation. Such a steric arrangement, however, would mean that the β carbomethoxy group would strongly interfere with the hydrogens at C_3, C_{18}, and C_{21}.

In support of our new assignments, it should be noted that Weisenborn indicated[8] as early as 1957 that epimerization at C_{16} of 3-epi-α-yohimbine (**9b**) occurred upon treatment with sodium methoxide to afford 3-epi-16-epi-α-yohimbine. The latter compound should be renamed 3-epialloyohimbine and must be represented by **4i**. Using Weisenborn's conditions, we have found that **9b** could be completely isomerized to the natural antipode of **4i**.

It is interesting to note that in the original literature[9] on alloyohimbine structure **6a** was considered as a possibility for the alkaloid, but was then rejected.

Another result of our stereochemical revisions concerns the nomenclature of the depyrroloalloyohimbine earlier synthesized by us.[10] The proper name for this berban derivative should now be 10,11-dimethoxydepyrrolo-14-epi-α-yohimbine.

From the hydroxy nitrile **4b**, we have also prepared, through the intermediacy of the amide **4h**, the methyl ester **4j**, which proved to be a very stable material, and did not epimerize even on boiling with concentrated acid. Sodium borohydride reduction of its Δ-3 immonium salt yielded, in addition to **6b**, which possesses the alloyohimbine skeleton, a substantial quantity of the isomer **4j**. Such a result could be expected since in **6b** either the indole ring (A_{c1} conformer) or the C_{16} and C_{17} substituents on ring E (A_t conformer) must be in axial positions.

Following the present synthesis of alloyohimbine and 3-epialloyohimbine the total synthesis of all known yohimbine alkaloids can now be considered to have been achieved, especially since the conversions alloyohimbine → α-yohimbine[7] and α-yohimbine → 3-epi-α-yohimbine[11] are already known from the literature.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer 221 and UR-10 spectrometer. Nuclear magnetic resonance spectra were obtained on a Perkin-Elmer R 12 (60 MHz) and on a Varian 300-MHz instrument located in Belgium, and are given in δ units downfield from internal tetramethylsilane. Mass spectra were recorded at 70 eV on AEI MS-902 double-focusing instrument

(6) J. E. Saxton in "The Alkaloids, Chemistry and Physiology," Vol. VII, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1960, p 55, and R. H. F. Manske, *ibid.*, Vol. VIII, 1965, p 705, and references cited therein.

(7) M. M. Janot, R. Goutarel, E. W. Warnhoff, and A. Le Hir, *Bull. Soc. Chim. Fr.*, 637 (1961).

(8) F. L. Weisenborn, *J. Amer. Chem. Soc.*, **79**, 4818 (1957).

(9) A. Le Hir, M. M. Janot, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 1027 (1953).

(10) L. Szabó, K. Honty, L. Töke, and Cs. Szántay, *Chem. Ber.*, **105**, 3231 (1972).

(11) F. L. Weisenborn and P. A. Diassi, *J. Amer. Chem. Soc.*, **78**, 2022 (1956).

using direct insertion probe at 120–150°. High-resolution mass measurements were accurate to within 2 ppm.

Thin layer chromatography (tlc) was performed on silica gel G, E. Merck AG; silica gel $PF_{254+366}$, E. Merck AG, was used for preparative layer, and silica gel (0.05–0.2 mm), E. Merck AG, for column chromatography, unless otherwise noted.

Anhydrous magnesium sulfate was employed as the drying agent. All reactions utilizing strongly basic reagents were conducted in an oxygen-free dry nitrogen atmosphere. Melting points are uncorrected.

17-Oxo-3-epialloyohimban-16α-carbonitrile (3).—A solution of 3.35 g (9.5 mmol) of **2** (previously dried *in vacuo* with boiling toluene over phosphorus pentoxide for 12 hr) and 3.14 g (28 mmol) of sublimed potassium *tert*-butoxide in 15 ml of dry DMSO was allowed to stand at room temperature for 12 hr, in a carefully dried apparatus under nitrogen. In the meantime the potassium salt of **3** began to separate. The reaction mixture was poured into 100 ml of ice water made acidic to pH 7.5. The precipitate was collected, washed with water and then with methanol, and dried to give 2.95 g (97%) of crude product of satisfactory purity for use in the next step without further purification. Recrystallization from DMF–water gave an analytical sample, mp 285° dec.

Anal. Calcd for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.83; N, 13.16. Found: C, 74.94; H, 6.60; N, 12.99.

Ir (KBr) 3450–3050 (OH, NH), 2170 (C≡N conj), 2220 (C≡N, w), 1720 (C=O, w), and 2750 and 2810 cm^{-1} (Bohlmann bands); ir (DMF) 2200 cm^{-1} (C≡N).

17α-Hydroxy-3-epialloyohimban-16α-carbonitrile (4a) and 17β-Hydroxy-3-epialloyohimban-16α-carbonitrile (4b).—To a stirred suspension of 0.73 g (2.29 mmol) of **3** in 40 ml of DMF–methanol (1:1) under nitrogen was added 0.17 g (4.5 mmol) of sodium borohydride in small portions during 1 hr. Stirring was continued for an additional 3 hr and the progress of the reaction was followed by tlc (chloroform–methanol 5.0:0.7, R_f **4b** > **3** > **4a**). The excess of sodium borohydride was decomposed with acetic acid and the solvent was removed *in vacuo*. The residue was dissolved in water and basified with concentrated ammonium hydroxide to pH 8.5. The solid separating on cooling was washed with water to give 0.70 g (95%) of a mixture of **4a** and **4b** which was chromatographed over alumina (Brockmann, activity II–III). Elution with chloroform–methanol (99:1) afforded 0.27 g (37%) of **4b** which upon recrystallization from ethanol gave colorless crystals, mp 275° dec.

Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.73; H, 7.21; N, 13.07. Found: C, 74.77; H, 7.29; N, 13.25.

Ir (KBr) 3500–3100 (OH, NH), 2820, 2760 (Bohlmann bands), 2240 cm^{-1} (C≡N); ir (pyridine) 2815, 2775 (Bohlmann bands), 2245 cm^{-1} (C≡N); nmr (DMSO-d_6) δ 10.80 (s, 1, NH), 5.45 (d, 1, OH, J = 6 Hz, C_{17} OH), 3.55 (m, 1, C_{17} H).

Further elution with chloroform–methanol (98:2) gave 0.22 g (30%) of **4a** which was recrystallized from ethanol to give white needles, mp 265° dec.

Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.73; H, 7.21; N, 13.07. Found: C, 74.61; H, 7.31; N, 13.49.

Ir (KBr) 3420 (OH), 3340 (NH), 2820, 2760 (Bohlmann bands), 2250 cm^{-1} (C≡N); ir (pyridine) 2815, 2775, 2760 (Bohlmann bands), 2243 cm^{-1} (C≡N); nmr (DMSO-d_6) δ 10.85 (s, 1, NH), 5.25 (d, 1, J = 6 Hz), C_{17} OH), 4.05 (m, 1, C_{17} H).

17α-Hydroxy-3-epialloyohimban-16α-carbonitrile O-Acetate (4c).—A mixture of 0.10 g (0.31 mmol) of **4a**, 3.0 ml of anhydrous pyridine, and 0.3 ml (2.9 mmol) of acetic anhydride was allowed to stand at room temperature for 48 hr under nitrogen. The solid which separated was removed by filtration and washed with 2 ml of ether–petroleum ether (bp 30–60°) (1:1) to give 74 mg (68%). Crystallization from 15 ml of dioxane–water (1:1) gave 40 mg (36%) of **4c**: mp 290° dec; ir (KBr) 3360 (NH), 2815, 2780 (Bohlmann bands), 2245 (C≡N), 1740, 1230 cm^{-1} (OCO-CH_3); ir (pyridine) 2815, 2774 (Bohlmann bands), 2245 cm^{-1} (C≡N); nmr (DMSO-d_6) δ 10.95 (s, 1, NH), 5.15 (m, 1, C_{17} H), 2.05 (s, 3, $OCOCH_3$); mass spectrum (70 eV) m/e (rel intensity) 363 (100, M^+), 362 (95), 320 (14), 304 (30), 303 (15), 302 (22), 277 (1.8), 276 (2.8), 184 (15), 170 (30), 169 (23), 156 (21).

17β-Hydroxy-3-epialloyohimban-16α-carbonitrile O-Acetate (4d).—A mixture of 0.10 g (0.31 mmol) of **4b**, 3.0 ml of anhydrous pyridine, and 0.3 ml (2.9 mmol) of acetic anhydride was allowed to stand at room temperature for 24 hr under nitrogen. The dark solution was diluted with ice water and made basic with concentrated ammonium hydroxide. The solid was filtered and crystallized from ethanol to give 70 mg (68%) of **4d**: mp 268–270° dec; ir (KBr) 3350 (NH), 2815, 2770 (Bohlmann bands), 2245 (C≡N), 1745, 1245 cm^{-1} ($OCOCH_3$); ir (pyridine) 2815, 2780 (Bohlmann bands), 2250 cm^{-1} (C≡N); nmr (DMSO-d_6) δ 10.85 (s, 1, NH), 4.85 (m, 1, C_{17} H), 2.0 (s, 3, $OCOCH_3$); mass spectrum (70 eV) m/e (rel intensity) 363 (100, M^+), 362 (77), 320 (2.3), 304 (28), 303 (1.8), 302 (16), 277 (1.7), 276 (2.7), 184 (9.5), 170 (17), 169 (16), 156 (13).

17α-Hydroxy-3-epialloyohimban-16α-carbonitrile O-Tosylate (4e).—A solution of 24.8 mg (0.077 mmol) of **4a** and 40 mg (0.21 mmol) of *p*-toluenesulfonyl chloride in 2 ml of dry pyridine was allowed to stand at room temperature for 12 hr under nitrogen. The product was separated by preparative tlc (methylene chloride–methanol (100:8), R_f **4e** > **4a**), yielding 9.5 mg of **4e**, mp 290° dec, which could not be obtained crystalline: mass spectrum (70 eV) m/e (rel intensity) 303 (90.3, M^+), 302 (100), 288 (2.4), 275 (2.7), 274 (2.9), 235 (1.5), 221 (3.6), 211 (6.7), 209 (6.2), 197 (5.2), 184 (13.8), 170 (11), 169 (17.6), 156 (27.2). Boiling **4e** (2 mg) in 1 ml of dry pyridine for 3 hr gave no change, while during the reflux in DMF for 1 hr elimination occurred and **5** was obtained as the sole product [tlc, chloroform–methanol (5.0:0.2), R_f **4e** > **5** > **4a**].

17β-Hydroxy-3-epialloyohimban-16α-carbonitrile O-Tosylate (4f).—The conversion of 34.4 mg (0.107 mmol) of **4b** to **4f** was accomplished under the same conditions as for the preparation of **4e**. The yield of **4f** was 10 mg, mp 310° dec, which could not be obtained crystalline: mass spectrum (70 eV) m/e (rel intensity) 475 (1.4, M^+), 303 (94.9), 302 (100), 288 (2.3), 275 (2.8), 274 (3.2), 221 (3.7), 211 (6.7), 209 (6.2), 198 (4.1), 197 (5.5), 184 (13.2), 170 (10.7), 169 (16.5), 156 (26.4).

4f (2 mg) was refluxed in pyridine (1 ml). No product was formed after 3 hr. Reflux was continued in DMF. Analysis of the mixture by tlc showed that it consisted of **4f** and **5** in the ratio 4:6 after 11 hr [chloroform–methanol (5.0:0.2), R_f **4f** > **5** > **4b**)].

16,17-Dehydro-3-epialloyohimban-16-carbonitrile (5).—A solution of 10 mg (0.031 mmol) of **4a** in 5 ml of 1 *N* ethanolic potassium ethoxide solution was refluxed under nitrogen for 3 hr. After cooling the separated crystals were collected and recrystallized from ethanol to give **5** as colorless needles (8 mg, 85%): mp 233–235°; ir (KBr) 3340 (NH), 2210 (C≡N conj), 1630 cm^{-1} (C=C); mass spectrum (70 eV) m/e (rel intensity) 303 (100, M^+), 302 (98), 288 (2.4), 275 (2.6), 274 (2.5), 221 (3), 211 (5.8), 209 (5.6), 198 (3.9), 197 (4.8), 184 (12), 170 (8.5), 169 (13.6), 156 (25).

17α-Hydroxy-3-epialloyohimban-16α-carboxamide (4g).—To a stirred mixture of methanol (28 ml), 1 *N* sodium hydroxide (5.0 ml), and 15% hydrogen peroxide solution (1.7 ml) was added 0.23 g (0.71 mmol) of **4a**. The suspension was refluxed under nitrogen to the disappearing of the starting material [about 75 min, tlc chloroform–methanol (5.0:1.5), R_f **4a** > **4g**]. The excess of the reagent was destroyed with sodium borohydride and the solvent was evaporated *in vacuo*. The tan residue was taken up with ice water (1.5 ml), filtered, and washed with water (2 × 0.5 ml), giving 0.20 g (79%) of white crystals of **4g**. An analytical sample was prepared by recrystallization from chloroform–methanol (100:1.5), mp 280–285° dec.

Anal. Calcd for $C_{20}H_{25}N_3O_2 \cdot H_2O$: C, 67.21; H, 7.61; N, 11.75. Found: C, 67.01; H, 7.38; N, 11.95.

Ir (KBr) 3450–3150 (OH, NH), 2820, 2760 (Bohlmann bands), 1665, 1590 cm^{-1} ($CONH_2$); mass spectrum (70 eV) m/e (rel intensity) 339 (100, M^+), 338 (52), 321 (5), 295 (16), 277 (14), 267 (2.2), 235 (3.6), 223 (7.4), 221 (7), 209 (6), 197 (6), 184 (12), 170 (13), 169 (17), 156 (10).

17β-Hydroxy-3-epialloyohimban-16α-carboxamide (4h).—A solution of **4b** (0.24 g, 0.74 mmol) in methanol (23 ml), 1 *N* sodium hydroxide (7.0 ml), and 15% hydrogen peroxide (1.6 ml) was stirred and refluxed for about 75 min, after which time tlc showed the complete disappearance of **4b** [chloroform–methanol (5.0:1.5), R_f **4b** > **4h**]. Sodium borohydride was added to the solution to decompose excess hydrogen peroxide. Most of the solvent was then removed under reduced pressure, and the residue obtained was taken in cold water, washed, and filtered to give 0.19 g (73%) of **4h**. Recrystallization from chloroform–petroleum ether gave colorless crystals, mp 256–259° dec.

Anal. Calcd for $C_{20}H_{25}N_3O_2 \cdot H_2O$: C, 67.21; H, 7.61; N, 11.75. Found: C, 67.64; H, 7.36; N, 11.46.

Ir (KBr) 3450–3150 (OH, NH), 2800, 2760 (Bohlmann bands), 1660, 1615 cm^{-1} ($CONH_2$); mass spectrum (70 eV) m/e (rel intensity) 339 (100, M^+), 338 (65), 321 (6), 295 (12), 277 (8),

267 (2.2), 235 (3.6), 223 (10), 221 (9.2), 209 (5.8), 197 (6.5), 184 (15), 170 (15), 169 (18.5), 156 (11).

Methyl 17β-Hydroxy-3-epialloyohimban-16α-carboxylate (4j).—A solution of 0.25 g (0.70 mmol) of **4h** in 40 ml of 18% hydrochloric acid was refluxed for 7–8 hr under nitrogen [tlc, benzene–methanol (4.0:1.7), R_f **4h** > the acid]. The solvent was removed *in vacuo* and after azeotropic removal of water with benzene and crude acid was suspended in methanol (5 ml) and treated with an excess of an ethereal solution of diazomethane. After 60 min the excess of the reagent was decomposed with acetic acid and the solvent was removed again. The residue was refluxed with 2 × 25 ml of chloroform and filtered and the combined extracts were concentrated to a small volume. The crude product was purified by chromatography on silica. Elution with methylene chloride–methanol (98:2) yielded 0.10 g (40.5%) of **4j** which upon recrystallization from methanol afforded colorless needles, mp 232–233°.

Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.40; N, 7.92. Found: C, 71.10; H, 7.44; N, 8.03.

Ir (KBr) 3500–3200 (OH, NH), 2820, 2780 (Bohlmann bands), 1740 (CO_2CH_3), 1060 cm^{-1} (COH); ir ($CHCl_3$) 3620 (OH), 3470 (NH), 2815, 2775 (Bohlmann bands), 1730 (CO_2CH_3), 1050 cm^{-1} (COH); nmr ($CDCl_3$ at 300 MHz) δ 7.76 (s, 1, NH), 7.42 (d, 1, C_9 H), 7.27 (d, 1, C_{12} H), 7.12–7.0 (m, 2, C_{10}, and C_{11} H), 3.83 (m, 1, C_{17} H), 3.80 (s, 3, CO_2CH_3), 3.55 (m, 1, C_3 H); mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M^+), 353 (99), 339 (12), 337 (3.1), 335 (1.6), 325 (2.5), 323 (1.3), 305 (4.5), 295 (2.7), 277 (2.0), 184 (1.5), 170 (15), 169 (19), 156 (11), 144 (8.5).

Methyl 17α-Hydroxy-3-epialloyohimban-16α-carboxylate (4i) and Methyl 17α-Hydroxyalloyohimban-16α-carboxylate [6a, (±)-Alloyohimbine].—4g (0.11 g, 0.31 mmol) was refluxed in 20 ml of 18% hydrochloric acid for 4 hr [tlc, chloroform–methanol (5.0:1.5), R_f **4g** > acid] under nitrogen and then evaporated to dryness. The residue was dehydrated by azeotroping with benzene. The solid, which showed two spots on tlc, was taken up with methanol (5 ml) and treated with excess of an ethereal solution of diazomethane. After 60 min the excess reagent was destroyed with acetic acid. The residue after removal of solvents was treated with boiling chloroform (2 × 25 ml) and a small amount of insoluble material filtered off. The filtrate was taken to dryness *in vacuo*, leaving the mixture of **4i** and **6a**, which was separated by chromatography on silica; elution with methylene chloride–acetone (80:20) yielded **6a** (15 mg, 13%). Recrystallization from ethyl acetate following from ether gave an analytical sample of **6a**: mp 136–137°; ir (KBr) 3550–3200 (OH, NH), 2805, 2750 (Bohlmann bands), 1725 (CO_2CH_3), 1050 cm^{-1} (COH); ir ($CHCl_3$) identical with that of an authentic sample of natural alloyohimbine, 3615 (OH), 3470 (NH), 2805, 2760 (Bohlmann bands), 1715 (CO_2CH_3), 1050 cm^{-1} (COH); nmr ($CDCl_3$) δ 8.57 (s, 1, NH), 7.65–7.05 (m, 4, aromatic protons), 3.80 (axial C_{17} H signal coincident with methoxycarbonyl signal total intensity equivalent to four protons), 3.25 (m, 1, C_3 H); mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M^+), 353 (95), 339 (4.8), 337 (1.9), 335 (1.4), 323 (4.9), 295 (7.3), 277 (1.5), 267 (1.7), 184 (6.7), 170 (12), 169 (14), 156 (9.0), 144 (9.6).

Further elution with methylene chloride–acetone (65:35) afforded **4i** (50 mg, 43.7%). An analytical sample was recrystallized from ethyl acetate: mp 223–224° (sublimed at 226.5°); ir (KBr) 3550–3350 (OH, NH), 3460 (NH), 2815, 2775 (Bohlmann bands), 1720 (CO_2CH_3), 1060 cm^{-1} (COH); ir ($CHCl_3$) 3650–3500 (OH, NH), 3480 (NH), 2815, 2775 (Bohlmann bands), 1725 (CO_2CH_3), 1050 cm^{-1} (COH); nmr ($CDCl_3$ at 300 MHz) δ 7.72 (s, 1, NH), 7.45 (d, 1, C_9 H), 7.28 (d, 1, C_{12} H), 7.14–7.04 (m, 2, C_{10} and C_{11} H), 4.23 (s, 1, C_{17} H), 3.82 (s, 3, CO_2CH_3), 3.48 (m, 1, C_3 H); mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M^+), 353 (98), 339 (8.5), 337 (2.1), 335 (1.4), 323 (4.6), 295 (8.4), 277 (1.9), 267 (2.0), 184 (8.4), 170 (18), 169 (21), 156 (13), 144 (12).

***3-Epi-α-yohimbine* (9b).**[11]—To a solution of 60 mg (0.17 mmol) of natural α-yohimbine (**8b**) in 4 ml of glacial acetic acid held at 60° was added 215 mg (0.67 mmol) of mercury (II) acetate. The course of the oxidation was followed by tlc [chloroform–methanol (5.0:0.5), under an ammonia atmosphere, R_f **8b** > the immonium salt of **8b**]. After completion of the reaction (*ca.* 90 min) the mercury(I) acetate was removed by filtration and washed with acetic acid (5 ml). The filtrate was heated to boiling, hydrogen sulfide gas was introduced, and the sulfides were filtered off. Zinc dust (0.30 g) was added to the solution, the reflux was continued for 2.5 hr, and the solution was filtered and evaporated to dryness *in vacuo*. The residue was dissolved in water. Basification with concentrated ammonia followed by ethereal extraction yielded a crude product which was purified by chromatography on silica. Elution with chloroform gave 13.5 mg of α-yohimbine (**8b**). Then chloroform–methanol (90:10) eluted a 3,4-secoyohimbine fraction. Further elution with chloroform–methanol (85:15) afforded 10.8 mg of 3-epi-α-yohimbine (**9b**).

8b had mp 235–236°; mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M^+), 353 (93), 339 (5.5), 337 (2), 336 (1.5), 335 (1.9), 323 (6), 295 (7.1), 184 (10), 170 (12), 169 (13), 156 (8.4).

9b had mp 225°; mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M^+), 353 (94), 339 (10), 337 (3.9), 335 (2.6), 323 (6.3), 297 (9.3), 295 (10), 184 (18), 170 (19), 169 (21).

3,4-Secoyohimbine had mass spectrum (70 eV) *m/e* (rel intensity) 356 (100, M^+), 355 (40), 341 (5.1), 339 (6.8), 335 (49), 325 (8), 297 (53), 264 (8.5), 250 (12), 225 (23), 223 (14).

Oxidation–Reduction of 4i and 4j. A.—Mercury(II) acetate (71 mg, 0.22 mmol) was added in small portion over a period of 10 min to a solution of **4i** (10 mg, 0.028 mmol) in glacial acetic acid (9 ml). The mixture was kept at 60° for 10 hr under nitrogen and then filtered. The filtrate was heated to boiling, hydrogen sulfide gas was introduced, the insoluble sulfides were filtered off, and the solvent was evaporated *in vacuo*, giving a yellow oil (**7b**) which was halved.

(1) A suspension of the 3-dehydro compound and a large excess of zinc dust (five to six times the weight of the 3-dehydro compound) in glacial acetic acid was refluxed for 2 hr. The mixture was filtered, the solvent was removed *in vacuo*, and the residue was dissolved in water and made basic with concentrated ammonia. The base was extracted exhaustively with chloroform, and the extract was washed, dried, and evaporated. The residue was separated by preparative tlc [benzene–ethanol (40:10), developed twice, R_f **6a** > **4i**]. It consisted of **4i** and **6a** in the ratio of 3:2.

(2) Sodium borohydride was added gradually to a solution of **7b** acetate in methanol till the starting material disappeared. Analysis of the reaction mixture by tlc [methyl ethyl ketone–hexane–methanol (1.5:3:0.5), R_f **6a** > **4i** or Al_2O_3-G, chloroform–methanol (5.0:0.15), R_f **6a** > **4i**] showed that it consisted mostly of **6a**.

B.—The oxidation was carried out on 10 mg of **4j** by the method described above to **7b**. The material obtained (**7a**) was reduced with sodium borohydride. Analysis of the mixture by tlc [Al_2O_3 G, chloroform–methanol (5.0:0.15)], showed that it consisted of **4j** and **6b** in the ratio of 4:1.

Epimerization of Alloyohimbine (6a) to α-Yohimbine (8b).—Natural alloyohimbine (15 mg) in 3 ml of 2 *N* methanolic sodium methoxide solution was allowed to stand at room temperature under nitrogen for 4 days. Separation of the mixture by preparative tlc [chloroform–methanol (100:16), R_f **8b** > **6a**] gave 5.6 mg of α-yohimbine (**8b**). The product was shown to be identical in all respects (ir, mass spectrum, tlc spots) with the authentic natural α-yohimbine.

Epimerization of 3-Epi-α-yohimbine (9b) to 3-Epialloyohimbine (4i).—3-Epi-α-yohimbine (**9b**) (1 mg) in 1.5 ml of 2 *N* methanolic sodium methoxide solution was heated at 60° under nitrogen. The isomerization was followed by tlc [chloroform–methanol (5.0:0.5), R_f **4i** > **9b**]. After 80 min the ratio of **9b** and **4i** was 3:2 and in 2 hr **9b** was completely converted to one of the enantiomers of **4i**.

Registry No.—**2**, 40085-19-6; **3**, 40085-20-9; **4a**, 40085-21-0; **4b**, 40085-22-1; **4c**, 40085-23-2; **4d**, 40085-24-3; **4e**, 40085-25-4; **4f**, 40085-26-5; **4g**, 40085-27-6; **4h**, 40085-28-7; **4i**, 40085-29-8; **4j**, 40085-30-1; **5**, 40085-31-2; **6a**, 40085-32-3; **8b**, 131-03-3; **9b**, 483-09-0; 3,4-seco-α-yohimbine, 39990-62-0.

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