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

László Töke,* Katalin Honty, Lajos Szabó, Gábor Blaskó, and Csaba Szántay

Institute of Organic Chemistry, Technical University, Budapest, XI. Gellért ter. 4, Hungary

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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]

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.

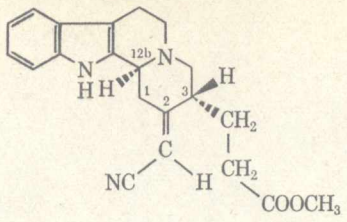
In isomer **4a** the equatorial C_{17} proton is at δ 4.05, while in **4b** the axial C_{17} proton is located higher upfield at δ 3.55. In view of the stable E_t conformation of the two isomers, it follows that the hydroxyl group in **4a** is α while in **4b** it is β. The corresponding O-acylated derivatives **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

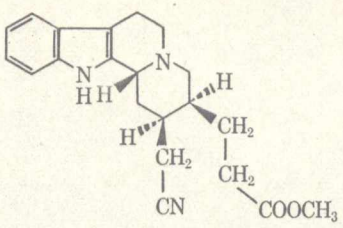
(1) Cs. Szántay, L. Töke, and K. Honty, *Tetrahedron Lett.*, 1665 (1965); L. Töke, K. Honty, and Cs. Szántay, *Chem. Ber.*, **102**, 3248 (1969).

(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).



1



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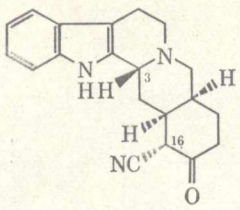

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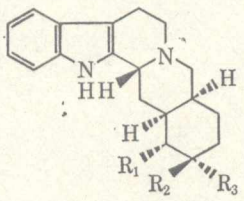
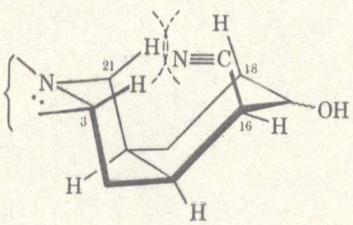


4

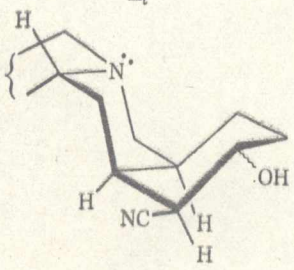
4	R_1	R_2	R_3	4	R_1	R_2	R_3
a	CN	H	OH	f	CN	OTs	H
b	CN	OH	H	g	$CONH_2$	H	OH
c	CN	OH	OAc	h	$CONH_2$	OH	H
d	CN	OAc	H	i	CO_2CH_3	H	OH
e	CN	H	OTs	j	CO_2CH_3	OH	H

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



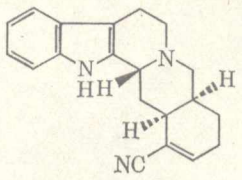
E_t



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.



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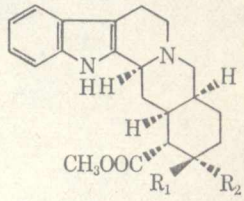


6

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.

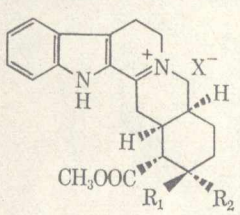
(5) P. E. Aldrich, P. A. Diassi, D. F. Dickel, C. M. Dylion, P. D. Hance, C. F. Huebner, B. Korzun, M. E. Kuehne, L. H. Liu, H. B. McPhillamy, E. W. Robb, D. K. Roychaudhuri, E. Schlittler, A. F. André, E. Van Tamelen, F. L. Weisenborn, E. Wenkert, and O. Wintersteiner, *J. Amer. Chem. Soc.*, **81**,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



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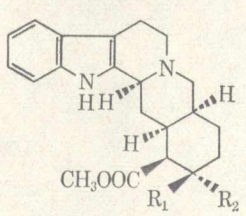

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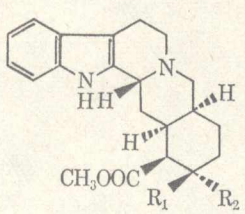

9

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_{c_1} 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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Synthesis of Yohimbines. II. An Alternative Route to Alloyohimbine Alkaloids

László Töke,* Zsuzsa Gombos, Gábor Blaskó, Katalin Honty, Lajos Szabó, József Tamás, and Csaba Szántay

Institute of Organic Chemistry, Technical University, Budapest, XI. Gellért tér 4, Hungary

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Starting from the readily available keto ester **1**, through intermediates **3**, **6a**, **6b**, **6j**, and **6k**, a stereospecific total synthesis of disubstituted alloyohimbanes of type **7** was accomplished. Alloyohimbine (**8m**), α-yohimbine (**8n**), and the other two possible stereoisomers (**8h** and **8i**) were also prepared. In the course of these transformations, the first example of imino ether–enamine tautomerism, neighboring-group participation in the hydrolysis of compounds **6a** and **6b**, and a Knoevenagel condensation under extremely mild experimental conditions were observed and studied.

The route to the synthesis of alkaloids of the alloyohimbine type described in our previous communication[1] utilized a by-product of a catalytic hydrogenation as starting material. Our aim was now to elaborate a high-yield, practical synthesis of alloyohimbine bases.

Condensation of the Keto Ester 1 with Methyl Cyanoacetate and Malononitrile.—The readily available[2] keto ester **1** was the starting material, and the improved mode of preparation of the salt **2** required in its preparation is described in the Experimental Section.

The ketone **1** was condensed with methyl cyanoacetate. It was expected that this reaction would be accompanied by epimerization at C_3, since such a change had been observed earlier in the case of benzo[*a*]quinolizidine derivatives,[3] and had in fact been used successfully by us in the realization of the stereoselective synthesis of corynantheidine.[4] However, under the experimental conditions (NH_4OAc–HOAc, azeotropic removal of water with benzene) which had proven successful with the analog of **1** possessing a C_3 ethyl substituent, the vinyl lactam **4** was obtained instead of the required cyano ester **3a**. Ring E of this lactam may be opened through acid-catalyzed hydrolysis, and the initial ester **1** can be recovered following esterification. Lactam **4** could also be generated by the reaction of the cyano ester **3a** with ammonium acetate.

Using triethylammonium acetate as catalyst, no vinyl lactam **4** was formed. Rather, the desired cyano ester **3a** was produced in low yield, while the dienamine **5a** formed through oxidation was the main product. The structure assigned to the dienamine **5a** was consistent with the spectral data, and could be supported chemically since mercuric acetate oxidation of **3a** yielded **5a**. The behavior of **5a** is similar in many respects to that of its benzo[*a*]quinolizidine analog prepared and studied earlier.[5] It is a yellow substance, resistant to catalytic hydrogenation. On the basis of the temperature dependence of its nmr spectrum, it must be a mixture of *E* and *Z* isomers. Owing to the reduced energy of activation caused by the extensive conjugation, these two isomers are readily interconvertible,[5] the coalescence of the two indole NH signals occurring at 180°.

After a thorough study of the reaction conditions, we finally succeeded in preparing the desired cyano ester **3a** in good yield by carrying out the reaction in triethylammonium acetate as solvent in the presence of phosphorus pentoxide. Under such conditions the reaction proceeded rapidly at room temperature, and there was no need for azeotropic removal of the water formed.

Reduction of **3a** with sodium borohydride gives **6a** in good yield. The nmr spectrum of this product shows that the methoxyl methyl of the R_1 ester group is split into two peaks which are independent of temperature. This phenomenon is a consequence of the new asymmetric center formed following the reduction.[4] There is no need to separate the diastereoisomers, however, since the new asymmetric center disappears in the course of further reactions.

As an alternative to the condensation of **1** with methyl cyanoacetate, the reaction was performed with malononitrile. The product, **3b**, was similarly easy to reduce to **6b**, while its mercuric acetate oxidation product, **5b**, was the analog of the dienamine **5a**.

The remarkably stable imino ether **6c** could be derived from the dinitrile **6b** using base catalysis in an alcoholic medium. The properties of this base, which include the new imino ether–enamine tautomerism observed in association with it, have been reported elsewhere.[6] In an aprotic solvent, **6c** can be converted with 1 mol of water to the ester **6a**. Alternatively, in dry methanol saturated with hydrogen chloride, the acid amide **6e** is obtained. The latter reaction is so easily controlled that, in the preparation of the ester nitrile **6a** from the dinitrile **6b**, it was found expedient to prepare the amide **6e** first, which was subsequently converted to the ester using the dry methanol–hydrogen chloride treatment. The imino ether to amide conversion is presumably an A_{al} process. This assumption is supported by the fact that in DMF solution **6c** alkylates carboxylic acids, thus, *e.g.*, **6g** to **6a**, at room temperature while converting itself to the acid amide **6e**.

The triester **6f** can be prepared either from the amide **6e** or the ester **6a**. Both ester groups of the ester **6a** hydrolyzed with remarkable ease, by simply

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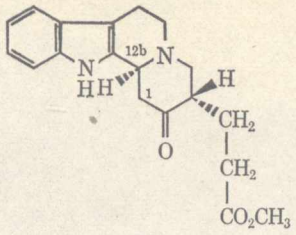
(4) Cs. Szántay and M. Bárczai-Beke, *Chem. Ber.*, **102**, 3963 (1969).

(5) M. Bárczai-Beke, G. Dörnyei, G. Tóth, and Cs. Szántay, *Tetrahedron*, in press.

(6) (a) L. Töke, G. Blaskó, L. Szabó, and Cs. Szántay, *Tetrahedron Lett.*, 2459 (1972). (b) Following our preliminary communication on the imino ether–enamine tautomerization,[6a] Professor H. Ahlbrecht of Giessen, West Germany, was kind enough to draw our attention to some of his still unpublished work relating to the assignments of NH_2 and C=NH proton peaks in the nmr spectra. Further studies on our part initiated by these comments have shown that the spectral assignments for the two functionalities must be contrary to those given by us earlier, so that the ratio of the tautomers should also be reversed.



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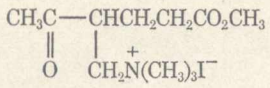

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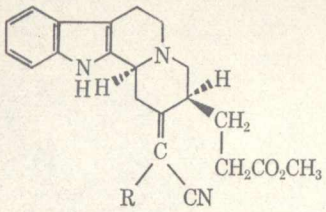

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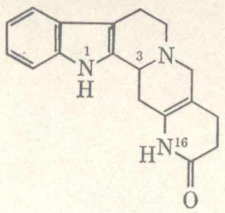

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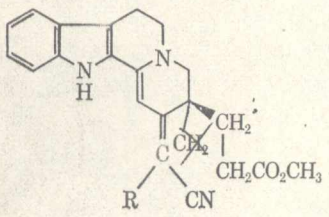

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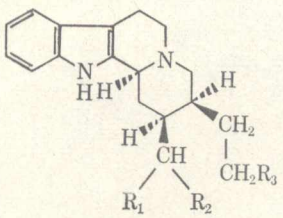
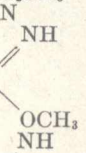
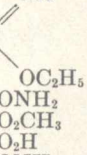


6

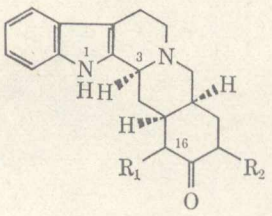
3,5	R
a	CO_2CH_3
b	CN

6	R_1	R_2	R_3
a	CO_2CH_3	CN	CO_2CH_3
b	CN	CN	CO_2CH_3
c		CN	CO_2CH_3
d		CN	CO_2CH_3
e	$CONH_2$	CN	CO_2CH_3
f	CO_2CH_3	CO_2CH_3	CO_2CH_3
g	CO_2H	CN	CO_2H
h	$CONH_2$	CN	CO_2H
i	H	CN	CO_2H
j	H	CN	CO_2CH_3
k	H	CO_2CH_3	CO_2CH_3

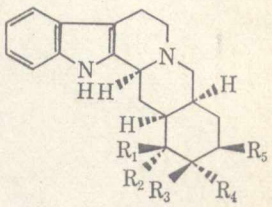
dissolving in alkali at 0° and then acidifying. The precipitate formed is diacid **6g**. This exceedingly rapid hydrolysis could be due to neighboring group participation. A similar behavior is also shown toward alkali by the dinitrile **6b**. However, in this case, the amide **6h** is also present besides the dicarboxylic acid **6g**.

Short boiling of a solution of the diacid **6g** in DMF led, as expected, to decarboxylation and formation of the carboxylic acid nitrile **6i**, which could in turn be converted to the ester nitrile **6j** with diazomethane, or alternatively to the diester **6k** with dry methanol and hydrogen chloride.

Preparation of the Alloyohimbine Skeleton from the Nitrile Ester 6j.—The nitrile ester **6j** can be converted in good yield by potassium *tert*-butoxide in DMSO into the pentacyclic ketone **7a**, which exists as a mixture of keto–enol tautomers both in the solid phase and in solution. From spectral data, the compound must exist in the trans (A_t) conformation. In the allo series, the steric interaction between the C_{21} H, the C_3 H, and the C_{16} substituent, present in the epiallo analogs,[1] is not a factor. There is, therefore, only a minimal difference in energy between an axial and an equatorial C_{16} cyano group in **7a**, so that in an equilibrium mixture both isomers could be present. Accordingly, sodium borohydride reduction of **7a** yielded a 4:1 mixture of the isomeric nitrile alcohols **8a** and **8b**.



7



8

7	R_1	R_2
a	CN	H
b	H	CO_2CH_3
c	H	H
d	CO_2CH_3	H

8	R_1	R_2	R_3	R_4	R_5
a	CN	H	OH	H	H
b	H	CN	OH	H	H
c	CN	H	OAc	H	H
d	H	CN	OAc	H	H
e	H	CN	H	OH	H
f	$CONH_2$	H	OH	H	H
g	H	$CONH_2$	OH	H	H
h	CO_2CH_3	H	OH	H	H
i	H	CO_2CH_3	OH	H	H
j	H	H	OH	H	CO_2CH_3
k	H	H	H	OH	CO_2CH_3
l	H	H	OH	H	CH_2OH
m	H	CO_2CH_3	H	OH	H
n	CO_2CH_3	H	H	OH	H

The spectral characteristics of isomers **8a** and **8b** (Table I) indicate that both exist in the A_t conforma-

TABLE I

SPECTRAL VALUES

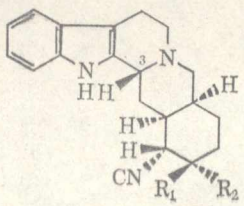
Compd	Nmr,[a] δ: C_{17} proton multiplet	Nmr,[a] δ: C_{17} hydroxyl doublet	Ir,[b] cm^{-1}, Bohlmann bands
8a	3.95	5.05	2815, 2765
8b	3.93	5.15	2810, 2770
8c	5.10		2810, 2760
8d	4.95		2805, 2760

[a] In DMSO-d_6 at 60 MHz. [b] In pyridine.

tion so that the C_{17} OH group can occupy only an axial site. The correctness of this assignment is corroborated by the nmr spectra of the acetylated derivatives **8c** and **8d** (Table I). It can thus be concluded unequivocally that the OH groups in **8a** and **8b** are β, so that attack by borohydride must occur from the convex side of the molecule and is subject to "steric approach control."

The above conclusions are also supported by the chemical behavior of the two compounds. Either isomer when dissolved in alcoholic alkali at room temperature yields a nearly 1:1 mixture of **8a** and **8b**. Under such mild conditions only the carbon atom, adjacent to the nitrile group, can be epimerized. It should be mentioned here that **8a** and **8b** must be primary products of the reduction of the ketone **7a** because no epimerization occurs under the conditions of the reduction. Additionally, the ratio of the reduction products remains unchanged when the reaction with sodium borohydride is carried out in acetic acid.

Further confirmation of the steric assignments can be obtained through correlation with the nitrile alcohols **9a** and **9b** of the epiallo series synthesized

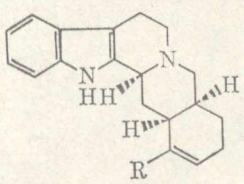


9

9	R_1	R_2
a	OH	H
b	H	OH

earlier.[1] Thus, when the product **9a** was epimerized at C-3 by oxidation with mercuric acetate and subsequent reduction, a product completely identical with **8b** was obtained, proving that in both compounds the C_{17} OH group must be β. On the other hand, similar epimerization of **9b** led to an allo nitrile alcohol which was identical with neither **8a** nor **8b**. For this new nitrile alcohol, structure **8e** can be written.

It will be recalled that the nitrile group in the pentacyclic indole bases could be hydrolyzed in two steps.[1,7] In the first step, treatment of the nitrile with hydrogen peroxide furnished the amide. When the reaction was carried out at room temperature, this transformation occurred at a faster rate than C_{16} isomerization. The unsaturated amide **10b**, which was formed in substan-



10

10	R
a	CN
b	$CONH_2$
c	CO_2CH_3

tial quantities at higher temperature, was present only in trace amounts.

In pyridine solution, the ir spectrum of the amide **8g** shows only weak Bohlmann bands so that the allocis (A_{c1}) conformation must predominate. In the A_t conformation both the carboxamide and the hydroxyl groups must be axial, while in the A_{c1} arrangement they are equatorial.

The hydroxy esters **8h** and **8i** can be prepared from the amides using hydrogen chloride in dry methanol. A by-product of this reaction is apo-α-yohimbine. The chromatographic behaviors of both esters **8h** and **8i** differ from that of natural α-yohimbine or alloyohimbine.

The importance of the synthesis of **8h** and **8i** lies primarily in the fact that all the yohimbine isomers with the allo configuration are now available, thus further enhancing our earlier views on the revision of the stereochemistry of alloyohimbine.

The main spectral features of the isomers in question have been summarized in Table II. For clarity's sake, Table II also includes the data for alloyohimbine (**8m**) and α-yohimbine (**8n**) discussed earlier.[1]

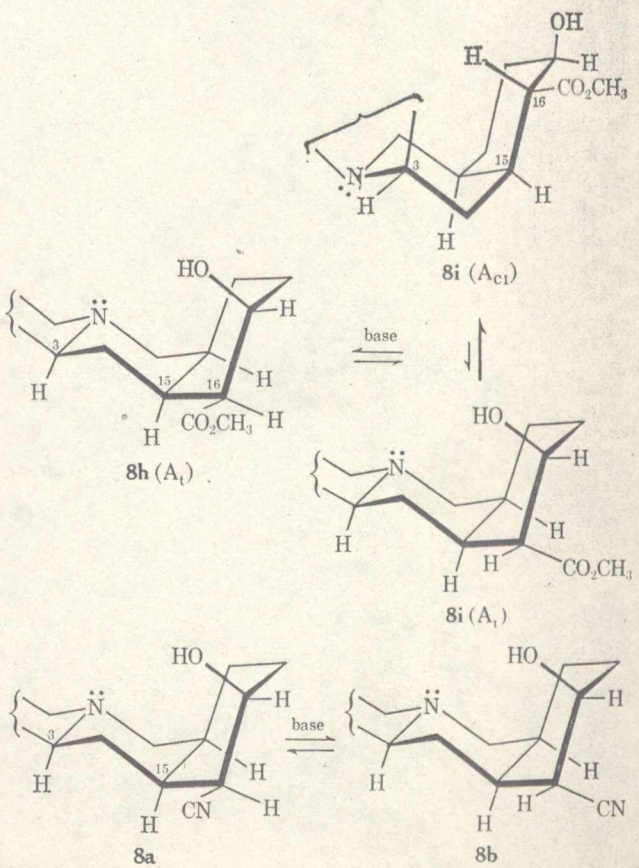
TABLE II
SPECTRAL VALUES

Compd	Nmr, δ: C_{17} proton	Nmr, δ: C_3 proton	Ir,[c] cm^{-1}, Bohlmann bands	Conformation: C_{17} OH	Conformation: C_3 indole ring	Conformation: Skeleton
8h	4.26[a]	3.05	2810, 2760	ax	eq	A_t
8i	3.75[a]	3.95	Very weak	eq	ax	A_{c1}
8m (alloyohimbine)	3.80[b]	3.25	2805, 2760	eq	eq	A_t
8n (α-yohimbine)	3.99[a]	3.15	2805, 2765	eq	eq	A_t

[a] In $CDCl_3$ at 300 MHz. [b] In $CDCl_3$ at 60 MHz. [c] In pyridine.

Epimerization of Yohimbine Isomers.—We have studied the epimerization of yohimbine isomers in 2 *N* methanolic sodium methoxide at room temperature. Under these conditions, only the C_{16} site, adjacent to the carbomethoxy group, can epimerize. Starting with **8h**, its isomer **8i** appeared after a few hours, simultaneously with the elimination product **10c**. Complete equilibration was achieved after about 3 days, with an **8h**:**8i** ratio of about 1:1. Upon further standing, the quantity of **10c** increased. The behavior of the ester alcohols thus bears some similarity to that of the nitrile alcohols **8a** and **8b**, but on the basis of spectral data no full analogy prevails. The transformation **8a** → **8b** occurs between compounds possessing the A_t conformation, and the equilibrium (~1:1) is determined by the small difference in energy between the axial and equatorial positions of the nitrile group (Chart I). It should also be added that the $A_t \rightarrow A_{c1}$ conformational equilibrium also plays an important role (Chart I). Species **8i** is one of those rare sub-

CHART I



(7) L. Töke, K. Honty, and Cs. Szántay, *Chem. Ber.*, **102**, 3248 (1969).

stances with the alloyohimbine skeleton whose C/D ring annelation is cis.

Synthesis of the Alloyohimbine Skeleton from the Diester 6k.—The direction of the Dieckmann cyclization of **6k** was predicated on the conditions used as already established earlier[7] in the case of compounds of analogous structures. When the reaction was carried out in hot toluene in the presence of sodium methoxide or sodium hydride, the enolic pentacyclic ketone **7b** was isolated as the sole product. The compound was readily decarboxylated to the known[8] (±)-alloyohimbone (**7c**). Alternatively, sodium borohydride reduction of **7b** yielded alcohols **8j** and **8k** in a 20:1 ratio, together with a small amount of the diol **8l**. Since neither **8j** nor **8k** was identical with any of the previously prepared yohimbine isomers, the ester function must be linked to C_{18}. The steric arrangement of the hydroxyl group in **8j** and **8k** was not extensively investigated. Rather, with the assumption that "steric approach control" is operative, we attributed structure **8j** to the substance formed in larger quantity.

When the cyclization was carried out at room temperature, the isomer **7d**, alloyohimbinone, was isolated in about 30% yield in addition to **7b**. Ketone **7d**, in analogy to **7b**, is also subjected to keto–enol tautomerism, and again leads to (±)-alloyohimbone (**7c**) upon hydrolysis and decarboxylation.

The optically active form of aloyohimbinone (**7d**) is known[9] from the oxidation of α-yohimbine, and it is reported that it exists completely in the enolic form. This statement, however, is valid only in the solid phase, since in pyridine or chloroform solution the keto form predominates by about 80%. Spectral data indicate that **7d** exists both in the solid phase and in solution as the A_t conformer.

Reduction of **7d** with sodium borohydride furnished three hydroxy esters. The main product proved to be identical with the unnatural base **8h**. The second product was (±)-alloyohimbine[1] (**8m**), while the third product was (±)-α-yohimbine (**8n**). The ratio of the alkaloids was **8h**:**8m**:**8n** = 7:3:2.

Taking into consideration our earlier investigations in the normal yohimbane,[7] epialloyohimbane,[1] and berbane series,[10] it can be stated that the structures and relative quantities of the stereoisomeric alcohols obtained from the sodium borohydride reduction of yohimbinones and their analogs containing nitrile are in accordance with the concept of "steric approach control" in the reduction.

Experimental Section

The infrared spectra were determined on Perkin-Elmer 221 and UR-10 spectrometers. Nuclear magnetic resonance spectra were obtained on a Perkin-Elmer R 12 (60 MHz), Varian A-60, and Varian-300 MHz instruments at Gent and are given in δ units downfield from internal tetramethylsilane. Mass spectra were recorded at 70 eV on a AEI-MS-902 double-focusing instrument using direct insertion probe at a temperature of 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, unless otherwise noted. Silica gel $PF_{254+366}$ and Al_2O_3 $PF_{254+366}$, E. Merck AG, were used for preparative layer chromatography. Silica gel (0.05–0.2 mm, E. Merck, AG) was used for column chromatography, unless otherwise noted. Anhydrous magnesium sulfate was employed as the drying agent. All reactions utilizing strongly basic reagents were conducted under oxygen-free dry nitrogen atmosphere.

4-Dimethylaminomethyl-5-oxocaproic Acid Methyl Ester Methiodide (2) and 4-Methylene-5-oxocaproic Acid Methyl Ester.[2]—A suspension of 138 g (0.6 mol) of diethyl α-acetylglutarate in 600 ml of 2 *N* sodium hydroxide solution was stirred vigorously for 3 hr at room temperature and the unchanged starting material was extracted with ether (2 × 100 ml). A solution of 61 g (0.75 mol) of diethylamine hydrochloride in 102 ml of 22% aqueous formaldehyde (0.75 mol) was added dropwise with stirring into the aqueous phase obtained above. After the reaction mixture was allowed to stand for 48 hr at room temperature it was acidified to pH 3 with concentrated hydrochloric acid and evaporated to dryness *in vacuo*. The resulting viscous oil, which contained sodium chloride, was dissolved in 100 ml of hot ethanol, and the salt was filtered and washed with ethanol (3 × 50 ml). The combined alcoholic solution was dehydrated by azeotroping with benzene (200 ml). The process was repeated several times with a mixture of benzene–ethanol (2:1) while the water content decreased to 3–8% (checking by Karl–Fischer method). The amount of phosphorus pentoxide necessary for the esterification was calculated by the formula

$$P_2O_5\ (\text{mol}) = \frac{\text{water content (\%)} \times \text{weight of crude material}}{18 \times 100} + \text{mol of starting material}$$

The solution of crude material in 300 ml of methanol was added portionwise to the calculated amount of phosphorus pentoxide in 600 ml of methanol with cooling. After the reaction mixture was allowed to stand at room temperature for 24 hr, the solvent was removed *in vacuo*, and the residue was rendered to pH 3 dissolving in saturated sodium bicarbonate solution and extracted with ether (5 × 200 ml). The combined extracts were washed, dried, evaporated, and distilled to give 27 g (28%) of 4-methylene-5-oxocaproic acid methyl ester, bp 70–72° (2 mm).[2]

The above aqueous solution, which was extracted with ether, was cooled and made alkaline with saturated sodium bicarbonate solution and extracted immediately with ether (5 × 500 ml). The combined extracts were dried and evaporated. The obtained oil (38 g) in 10 ml of dry methanol was treated with methyl iodide (19 ml, 0.3 mol) and allowed to stand overnight. The precipitated crystals were collected and washed with dry ether, giving 50 g (25%) of **2**, mp 118–119°.[2]

15,20-Dehydro-16-azayohimbone (4).—To the solution of 1.25 g (3.82 mmol) of **1** in 300 ml of dry toluene was added 0.8 g (10.4 mmol) of ammonium acetate and 2 ml of glacial acetic acid, and the mixture was refluxed for 4 hr. The reaction was followed by tlc [benzene–methanol (8.5:1.5)], R_f 1 > 4. The cooled solution was neutralized with sodium methoxide, washed with water, and dried, and the solvent was evaporated *in vacuo* under nitrogen. The residue (0.95 g, 84%) was crystallized twice from ethanol to give 0.72 g (64%) of **4**, mp 261–262°.

Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.33. Found: C, 73.41; H, 6.54; N, 14.55.

Ir (KBr) 3370 (lactam NH), 3320 (indole NH), 2815, 2750 (Bohlmann bands), 1665 (lactam C=O), 1630 cm^{-1} (C=C); nmr (DMSO-d_6) δ 8.95 (s, 1, lactam NH), 7.45–6.50 (m, 4, aromatic protons).

Hydrolysis and Subsequent Methylation of 4 to 1.—The solution of 12 mg (4.5 × 10^{-5} mol) of **4** in 5 ml of 0.005% aqueous HCl was refluxed for 4 hr, the solvent was evaporated *in vacuo*, and the residue was dried by azeotroping with benzene–ethanol. The salt obtained was suspended in 10 ml of methanol and allowed to stand for 30 min with an excess of ethereal diazomethane, tlc, benzene–methanol (8.5:1.5). The residue (12.2 mg, 91%) after removal of the solvent was crystallized from methanol, mp 207–208°. The identity of the material as **1** was established by ir, tlc, and mixture melting point.[2]

Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.61; H, 6.79; N, 8.58. Found: C, 69.53; H, 6.86; N, 8.65.

Ir (KBr) 3380 (NH), 1721 (CO_2CH_3), 1710 cm^{-1} (C=O).

Methyl 3β-(2-Methoxycarbonylethyl)-1,3,4,7,12,12bα-hexahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-2-ylidenecyanoacetate (3a).—To the solution of 10.4 g (31.7 mmol) of **1** in 42 ml of glacial acetic acid was added 64 ml (460 mmol) of triethylamine, 1.8 g

(8) P. G. Philpott and A. M. Parsons, *J. Chem. Soc.*, 3018 (1958).

(9) J. D. Albright and L. Goldman, *J. Org. Chem.*, **30**, 1107 (1965); J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **89**, 2416 (1967).

(10) L. Szabó, K. Honty, I. Tóth, L. Töke, and Cs. Szántay, *Chem. Ber.*, **105**, 3215 (1972); L. Szabó, K. Honty, L. Töke, and Cs. Szántay, *ibid.*, **105**, 3231 (1972).

(12.6 mmol) of phosphorus pentoxide, and 40 ml (450 mmol) of methyl cyanoacetate. The mixture was stirred at 40–50° for 50 hr under dry nitrogen [tlc, benzene–methanol (8:2), R_f **3a** > **1**], then diluted with cold chloroform (125 ml) at 0°. The extract was washed with 5% sodium hydroxide (2 × 40 ml) and water (2 × 25 ml), dried, and evaporated *in vacuo*. The residue crystallized from methanol (10 ml) on standing to give 10.2 g (80%) of **3a**. An additional 1.3 g (6.4%) of **3a** oxalate was obtained from the mother liquor with methanolic oxalic acid. A recrystallized sample of **3a** exhibited mp 173–174°.

Anal. Calcd for $C_{23}H_{25}N_3O_4$: C, 67.79; H, 6.18; N, 10.31. Found: C, 67.71; H, 6.10; N, 10.24.

Ir (KBr) 3380 (NH), 2820, 2770 (Bohlmann bands), 2260 (C≡N), 1735 (CO_2CH_3), 1600 cm^{-1} (C=C); nmr ($CDCl_3$) δ 8.58 (s, 1, NH), 7.60–7.00 (m, 4, aromatic protons), 4.08 (m, 1, C_1 H_{eq}), 3.85 (s, 3, CO_2CH_3 conj), 3.65 (s, 3, CO_2CH_3).

3β-(2-Methoxycarbonylethyl)-1,3,4,7,12,12α-hexahydro-2*H*,-6*H*-indolo[2,3-*a*]quinolizin-2-ylidenemalononitrile (3b).—To a stirred solution of 16.3 g (50 mmol) of **1** in 40 ml of glacial acetic acid was added 50 ml (360 mmol) of triethylamine, 4 g (28 mmol) of phosphorus pentoxide, and finally 30 g (450 mmol) of malononitrile. The reaction mixture was allowed to stand at room temperature for 2–3 hr under nitrogen. The progress of the reaction was followed by tlc [benzene–methanol (8:2), R_f **3b** > **1**]. The solution was diluted with chloroform (300 ml), the extract was washed thoroughly with 5% sodium hydroxide to remove the acid, and the aqueous layer was reextracted with chloroform (3 × 25 ml). The combined extracts were washed, dried, and evaporated under reduced pressure, giving an oil which was crystallized from methanol (20 ml) on standing (14.9 g, 79.7%). The analytical sample was recrystallized from methanol, mp 158–159°. A further 1.7 g (7.5%) of salt was obtained from the mother liquor with methanolic oxalic acid. The solution of **3b** oxalate (1.7 g, 3.74 mmol) in dioxane (10 ml) was treated with an ethereal solution of diazomethane. After the solvent was evaporated, the residue was crystallized from methanol (4.5 ml) to give 1.19 g of **3b**.

Anal. Calcd for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; N, 14.96. Found: C, 70.63; H, 6.07; N, 14.92.

Ir (KBr) 3380 (NH), 2855, 2825, 2770 w (Bohlmann bands), 2240, 2250 (C≡N), 1740 (CO_2CH_3), 1605 cm^{-1} (C=C); nmr ($CDCl_3$) δ 8.35 (s, 1, NH), 7.6–7.1 (m, 4, aromatic protons), 3.70 (s, 3, CO_2CH_3).

(*E*,*Z*)-Methyl 3β-(2-Methoxycarbonylethyl)-3,4,7,12-tetrahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-2-ylidenecyanoacetate (5a).—A solution of 2.04 g (5 mmol) of **3a** in 20 ml of glacial acetic acid was treated with 4.8 g (15 mmol) of merucry(II) acetate in 20 ml of acetic acid and heated at 100° for 5 min [tlc, chloroform–ether (6:4), R_f **3a** > **5a**]. After cooling the mercury(I) acetate was filtered off, and the solution was neutralized with 40% of sodium hydroxide and extracted with benzene (5 × 150 ml). After removal of the solvent *in vacuo* under nitrogen the residue (1.7 g, 84.7%) was crystallized from methanol, mp 218–219°.

Anal. Calcd for $C_{23}H_{23}N_3O_4$: C, 68.13; H, 5.72; N, 10.36. Found: C, 68.16; H, 5.94; N, 10.45.

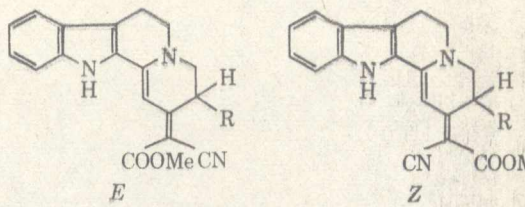
Ir (KBr) 3255 (NH), 2200 (C≡N conj), 1740, 1730 (CO_2CH_3), 1690, 1680 (CO_2CH_3 conj), 1582 cm^{-1} (C=C); nmr ($CDCl_3$) δ 10.27, 9.03 (s, 1, NH), 7.8–7.1 (m, 4, aromatic protons), 6.27 (s, 0.6, C_1H), 3.82 (s, 3, CO_2CH_3 conj), 3.71 (s, 3, CO_2CH_3); nmr ($C_6D_5NO_2$, at 36°) δ 10.40, 10.05 (s, 0.43, 0.57, NH), 7.5–7.0 (m, 4, aromatic protons), 6.43 [s, 0.43, C_1 H (*E*)], 3.84 [s, 0.57, CO_2-CH_3 conj (*Z*)], 3.71 [s, broad, 5.43 (0.43, CO_2CH_3 conj (*E*), 3, CO_2CH_3, 2, C_6 H)] (see Chart II); uv (MeOH) λ_{max} 222 nm (log ε 4.54), 254 (4.06), 346 (4.04), 455 (4.66) 481 (4.76).

3β-(2-Methoxycarbonylethyl)-3,4,7,12-tetrahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-2-ylidenemalononitrile (5b).—Oxidation of 0.75 g (2.0 mmol) of **3b** with 1.95 g (6.12 mmol) of mercury(II) acetate in 40 ml of glacial acetic acid for 5 min at 100° gave on work-up 0.59 g (78.6%) of yellow crystals. Recrystallization from acetone afforded an analytical sample, mp 205–207°.

Anal. Calcd for $C_{22}H_{20}N_4O_2$: C, 70.95; H, 5.42; N, 15.04. Found: C, 70.72; H, 5.56; N, 15.11.

Ir (KBr) 3320 (NH), 2205, 2195 (C≡N conj), 1730 s, 1708 (CO_2CH_3), 1580 cm^{-1} (C=C); nmr (DMSO-d_6) δ 11.9 (s, 1, NH), 7.6–7.1 (m, 4, aromatic protons), 6.15 (s, 1, C_1 H), 3.55 (s, 3, CO_2CH_3); nmr ($C_6D_5NO_2$) δ 10.07 (s, 1, NH), 7.5–7.0 (m, 4, aromatic protons), 6.32 (s, 1, C_1 H), 3.73 (s, 3, CO_2CH_3); uv (MeOH) λ_{max} 221 nm (log ε 4.27), 246 (3.88), 348 (3.98), 448 (4.57), 475 (4.64).

CHART II



R = $CH_2CH_2CO_2CH_3$

Temp, °C	$\Delta\nu_{CO_2CH_3}$ between *E* and *Z* in Hz	Temp, °C	$\Delta\nu_{CO_2CH_3}$ between *E* and *Z* in Hz
36[a]	10.6	119	4.8
63	8.6	138	4.0
82	7.9	155	2.7
100	7.1	T_c = 183	

[a] Determined with a Varian A-60 instrument operated at 60 MHz in $C_6D_5NO_2$.

Methyl 3β-(2-Methoxycarbonylethyl)-1,3,4,7,12,12bα-hexahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-2β-ylcyanoacetate (6a).—To a stirred suspension of 10 g (24.5 mmol) of **3a** in 120 ml of methanol was added 3.7 g (98 mmol) of sodium borohydride gradually during 10 hr at 0°. The reduction was followed by tlc [chloroform–diethyl ether (6:4), R_f **3a** > **6a**]. The mixture was acidified to pH 6 with acetic acid, and the precipitate was collected and dried giving 9.21 g (92%) of **6a**. An analytical sample was recrystallized from methanol, mp 171–173°.

Anal. Calcd for $C_{23}H_{27}N_3O_4$: C, 67.46; H, 6.65; N, 10.26. Found: C, 67.22; H, 6.61; N, 10.04.

Ir (KBr) 3410 (NH), 2800, 2760 (Bohlmann bands), 2250 (C≡N), 1740, 1730 cm^{-1} (CO_2CH_3); nmr ($CDCl_3$) δ 8.15, 7.94 (s, 1, NH), 7.45–6.96 (m, 4, aromatic protons), 3.92, 3.87 (s, 3, CO_2CH_3), 3.68 (s, 3, CO_2CH_3); nmr (DMSO-d_6) δ 10.99, 10.88 (s, 1, NH), 7.15–6.96 (m, 4, aromatic protons), 4.19 (d, 1, J = 1.2 Hz, μ-H of methyl cyanoacetate part), 3.92, 3.87 (s, 3, CO_2CH_3), 3.66 (s, 3, CO_2CH_3).

3β-(2-Methoxycarbonylethyl)-1,3,4,7,12,12bα-hexahydro-2*H*,-6*H*-indolo[2,3-*a*]quinolizin-2β-ylmalononitrile (6b).—To a stirred suspension of 6.04 g (16 mmol) of **3b** in 120 ml of methanol was added 2 g (53 mmol) of sodium borohydride gradually at 0° over a 3-hr period [chloroform–diethyl ether (3:2), R_f **3b** > **6b**]. The mixture was acidified to pH 5 with acetic acid, and the precipitate was collected and dried, giving 5.71 g (94%) of **6b**. An analytical sample was crystallized from dioxane–ether, mp 180–182°.

Anal. Calcd for $C_{22}H_{24}N_4O_2$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.18; H, 6.52; N, 14.48.

Ir (KBr) 3390 (NH), 2820, 2760 (Bohlmann bands), 2255 (C≡N), 1740 cm^{-1} (CO_2CH_3); nmr (DMSO-d_6) δ 10.5 (s, 1, NH), 7.5–6.9 (m, 4, aromatic protons), 3.58 (s, 3, CO_2CH_3).

Methyl Cyano-3β-(2-methoxycarbonylethyl)-1,3,4,7,12,12bα-hexahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-2β-ylacetimidate (6c).—The dinitrile **6b** (2 g, 5.35 mmol) was dissolved in dry methanol (30 ml), and after the addition of 0.10 g (1.85 mmol) of sodium methoxide the solution was refluxed under nitrogen for 1 hr [tlc, benzene–methanol (8:2), R_f **6b** > **6c**]. The resulting crystals were filtered off and washed with methanol (2 × 1 ml), giving 2 g (91.4%) of analytically pure **6c**, mp 214–217°. The material is almost insoluble in common solvents (dioxane, pyridine, DMSO) and it should be stored under vacuum or in a sealed tube.

Anal. Calcd for $C_{23}H_{28}N_4O_2$: C, 67.62; H, 6.91; N, 13.71. Found: C, 67.59; H, 7.02; N, 13.56.

Ir (KBr) 3355 (indole NH), 3295 (NH), 2835, 2810, 2770 (Bohlmann bands), 2250 (C≡N), 1720 (CO_2CH_3), 1670 cm^{-1} (C=N); ir (DMSO) 2190 (C≡N), 1740 (CO_2CH_3), 1675 (C=N), 1660–1630 (NH def), 1600 cm^{-1} (C=C); uv (MeOH) 253 nm (ε 6630), 226 (7200); nmr, see Table III; mass spectrum (70 eV) *m/e* (rel intensity) 408 (18, M^+), 407 (5), 393 (50), 375 (15), 311 (100), 309 (50), 223 (30), 221 (29), 184 (19), 169 (65), 156 (40).

6d was obtained under the same conditions described above, mp 203–205°.

Ir (KBr) 3500–3100 (NH), 2780, 2820 (Bohlmann bands), 2250 (C≡N), 1735 (CO_2CH_3), 1660 cm^{-1} (C=N); ir (DMSO) 2190 (C≡N), 1735 (CO_2CH_3), 1665–1580 cm^{-1} (C=C and C=NH); nmr, see Table IV.

TABLE III

Solvent	Nmr, δ: Indole NH	NH_2[b]	OCH_3	C=NH[b]	Aromatic protons
	10.73 (0.36)[a]	6.65 (0.36)	3.90, 3.95	8.8 (0.72)	7.55–6.95 (4)
DMF-d_7	10.89 (0.28)	6.48 (0.28)	3.80, 3.85		
	11.06 (0.36)		3.63, 3.65		
	11.01	6.63	3.84, 3.87	8.85 (0.30)	7.55–6.97 (4)
DMSO-d_6	11.16	6.54	3.78		
	11.21		3.65		

[a] The sign intensities in parentheses are given in proton units. [b] Assignments for NH_2 and C=NH groups differ from those given in the preliminary communication (ref 6).

TABLE IV

Solvent	Nmr, δ: Indole NH	NH_2[b]	CO_2CH_3	OCH_2CH_3	C=NH[b]	Aromatic protons
DMSO-d_6	10.60	6.41	3.48	3.99 (q, J = 6 Hz)	8.6 (0.30)[a]	7.55–6.95 (m, 4)
	10.65	6.30		4.05 (q, J = 6 Hz)		
	10.80					

[a] The sign intensity in parentheses is given in proton units. [b] Assignments for NH_2 and C=NH groups differ from those given in the preliminary communication (ref 6).

Preparation of 6e from 6c. A.—The solution of 5.3 g (1.3 mmol) of **6c** in 20 ml of dry methanol saturated with hydrogen chloride was refluxed for 1 hr, cooled, filtered, and washed to give 4.85 g (87%) of **6e** HCl, mp 217°.

B.—When a sample of **6c** was allowed to stand under the influence of moisture it was transformed to **6e** over a period of some days. The trace of **6c** was removed by crystallization from methanol to give **6e**, mp 214–215°.

Anal. Calcd for $C_{22}H_{26}N_4O_3$: C, 66.97; H, 6.64; N, 14.20. Found: C, 66.29; H, 6.73; N, 14.42.

Ir (KBr) 3410 (indole NH), 3240–3210 (NH), 2830, 2760 (Bohlmann bands), 2260 (C≡N), 1735 (CO_2CH_3), 1695, 1620 cm^{-1} ($CONH_2$); nmr (DMSO-d_6) δ 11.5 (s, 1, NH), 8.25 (s, 2, NH_2), 7.8–7.1 (m, 4, aromatic protons), 3.67 (s, 3, CO_2CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 394 (85.8, M^+), 393 (65.3), 379 (1.7), 377 (2), 363 (10), 350 (7.2), 319 (12), 318 (13.7), 311 (100), 309 (27.1), 283 (13.1), 184 (44.6), 170 (41), 169 (48), 156 (38).

Preparation of 6a from 6c.—The mixture of 1 g (2.45 mmol) of **6c** in 20 ml of dry dioxane containing 0.5 ml of 10% hydrochloric acid was allowed to stand at room temperature for 30 min [tlc, benzene–methanol (8.5:1.5), R_f **6a** > **6c**]. The resulting crystals (**6a** HCl) were filtered off and dissolved in methanol and the **6a** free base was obtained by the help of an ethereal solution of diazomethane. Most of the solvent was removed *in vacuo* and the residue was crystallized from methanol, affording 0.45 g (45%) of **6a**, mp 171–173°, identical in all respects (ir nmr, tlc spot) with the authentic sample obtained from **32**.

Dimethyl 3β-(2-Methoxycarbonylethyl)-1,3,4,7,12,12bα-hexahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-2β-ylmalonate (6f).—To prepare **6f** triester it is possible to use as starting material **6a**, **6b**, **6c**, or **6e**, respectively. Each of the products was dissolved in dry methanol saturated with hydrogen chloride (50 parts to 1 part of the starting material), refluxed for 1 hr, and then cooled to −5°, hydrogen chloride was introduced, and the reflux was continued. This procedure was repeated while no starting material was detectable on tlc [carbon tetrachloride–methanol (9.0:0.4), R_f **6f** > **6a** > **6b** > **6c** > **6e**]. Most of the solvent was removed *in vacuo* and the residue was crystallized several times from methanol affording **6f**·HCl, mp 205–207°, in an average 50–60% yield.

Anal. Calcd for $C_{24}H_{31}ClN_2O_6$: C, 60.18; H, 6.48; N, 5.85. Found: C, 59.21; H, 6.68; N, 5.97.

Ir (KBr) 3380 (NH), 1745, 1735, 1730 cm^{-1} (CO_2CH_3).

3β-(2-Carboxyethyl)-1,3,4,7,12,12bα-hexahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-2β-ylcyanoacetic Acid (6g). A.—The solution of 3.3 g (8.08 mmol) of **6a** in 40 ml of 15% aqueous sodium hydroxide was allowed to stand at room temperature for 1 hr and then acidified with concentrated hydrochloric acid to pH 4 [tlc, benzene–methanol (8.5:1.5), R_f **6a** > **6g**]. The precipitated **6g** was filtered and washed with dilute hydrochloric acid to give 1.2 g (39%). The mother liquor was evaporated to dryness *in vacuo*, and the residue was treated with DMF (3 × 10 ml). After the solvent was evaporated *in vacuo* (0.6 mm) an additional 1.1 g (35.5%) of material was obtained. The yield was 2.3 g (74.5%). A sample was crystallized from methanol, melted at 214° dec, and was dried *in vacuo* with boiling toluene over phosphorus pentoxide. According its thermoderivatogram the material has a variable amount (*ca.* 1.5–3 mol) of crystal water. The latter cannot be removed without simultaneous decarboxylation, ir (KBr) 3600–2600 (OH, NH polymer association), 2240 (C≡N), 1710 (CO_2H), 1650, 1620 cm^{-1} (CO_2^-).

The material decomposes to **6i** in the mass spectrometer and gives the same spectrogram as **6i**.

B.—The solution of 0.5 g (1.33 mmol) of **6b** in glacial acetic acid (1 ml) was treated with 25% sodium hydroxide solution (10 ml) and allowed to stand at room temperature for 2 hr. After neutralization with concentrated hydrochloric acid to pH 7 and filtering off the resulting crystals, 0.15 g (30%) of **6g** was obtained, identical in all respects (ir, melting point, mass spectrum) with the authentic sample obtained from **6a**. Methylation of the product with an ethereal solution of diazomethane afforded **6a**.

2β-(Cyanocarbamoylmethyl)-1,3,4,7,12,12bα-hexahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-3β-ylpropionic Acid (6h).—The solution of 0.5 g (1.33 mmol) of **6b** in glacial acetic acid (1 ml) was treated with 8 ml of 40% sodium hydroxide. The solid at first precipitated was dissolved after the addition of the whole amount of base. The solution was immediately neutralized with concentrated hydrochloric acid to pH 7 and the crystals separated on cooling were collected to give 0.12 g (24%) of **6h**. An analytical sample was crystallized from methanol, mp 225–227°. Treating **6h** with an ethereal solution of diazomethane, **6e** was obtained.

6h had ir (KBr) 3320 (NH), 2260 (C≡N), 1700–1610 cm^{-1} ($CONH_2$, CO_2H).

2β-Cyanomethyl-1,3,4,7,12,12bα-hexahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-3β-ylpropionic Acid (6i).—The solution of 10 g (26.2 mmol) of **6g** in 30 ml of dry DMF was heated at 150–160° under nitrogen. The decarboxylation was followed by tlc [isoamyl alcohol–methanol–20% ammonia (5:4:2), R_f **6i** > **6g**]. The crystals separated on cooling were filtered off and washed with ethanol to give 6.2 g (70%) of **6i**. After concentration of the mother liquor to near dryness *in vacuo* under nitrogen, 1.8 g (20.4%) of material was obtained. Crystallization of DMF–methanol afforded white crystals, mp 290–292°.

Ir (KBr) 3600–3050 (OH, NH polymer association), 2265 (C≡N), 1700 (CO_2H), 1630–1550 cm^{-1} (CO_2^-); mass spectrum (70 eV) *m/e* (rel intensity) 337 (95, M^+), 336 (100), 319 (8), 318 (8.4), 297 (27), 269 (18), 211 (9.5), 184 (20), 170 (33), 169 (24), 156 (18).

Methyl 2β-Cyanomethyl-1,3,4,7,12,12bα-hexahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-3β-ylpropionate (6j).—The solution of 1 g (2.97 mmol) of **6i** in 20 ml of DMF was treated with an excess of an ethereal solution of diazomethane [tlc, benzene–methanol (8.5:1.5), R_f **6j** > **6i**]. After 1 hr the excess diazomethane was decomposed with acetic acid and the solvent was removed *in vacuo* to give 0.98 g (94%) of **6j**. The analytical sample had mp 158–160° from methanol–ether.

Ir (KBr) 3400 (NH), 2810, 2760 (Bohlmann bands), 2250 (C≡N), 1735 cm^{-1} (CO_2CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 351 (99.4 M^+), 350 (100), 336 (2.6), 320 (11.4), 311 (25.7), 309 (18.2), 283 (16.8), 184 (17.8), 170 (27), 169 (16.4), 156 (12.0).

Methyl 2β-Methoxycarbonylmethyl-1,3,4,7,12,12bα-hexahydro-2*H*,6*H*-indolo[2,3-*a*]quinolizin-3β-ylpropionate (6k).—The solution of 13 g (38.6 mmol) of 6i in 50 ml of saturated methanolic hydrogen chloride was refluxed for 30 min. After cooling the precipitated 6k HCl was washed with cold methanol (5 ml), giving 12.1 g (74.5%) of crude material. The solvent was removed *in vacuo*, and the residue was taken up in ice water (20 ml), made basic with solid sodium hydrogen carbonate, and extracted with ether (5 × 30 ml). Evaporation of the solvent gave an additional 2.1 g (14.2%) of 6k. An analytical specimen prepared from acetone exhibited mp 204°.

Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.74; H, 7.34; N, 7.29. Found: C, 68.55; H, 7.31; N, 7.55.

Ir (KBr) 3385 (NH), 2805, 2770 (Bohlmann bands), 1735, 1710 cm^{-1} (CO_2CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 384 (100, M^+), 383 (95.7), 369 (5.9), 353 (15.3), 311 (12.2), 283 (20), 184 (20), 170 (24.5), 169 (15.2), 156 (11.6).

6k HCl had mp 261–262° from methanol.

Anal. Calcd for $C_{22}H_{29}ClN_2O_4$: C, 62.77; H, 6.94; N, 6.66; Cl, 8.42. Found: C, 62.66; H, 6.84; N, 6.71; Cl, 8.31.

Ir (KBr) 3460 (NH), 3000–2400 (NH^+), 1745 cm^{-1} (CO_2CH_3).

17-Oxoalloyohimban-16-carbonitrile (7a).—A solution of 3.5 g (10 mmol) of 6j (previously dried *in vacuo* with boiling toluene over phosphorus pentoxide) and 6 g (53 mmol) of sublimed potassium *tert*-butoxide in 8 ml of dry DMSO was allowed to stand at room temperature for 12–16 hr in a carefully dried apparatus under nitrogen [tlc, benzene–methanol (8.5:1.5), R_f 6j > 7a]. The dark red solution was acidified with acetic acid to pH 7 and evaporated *in vacuo* (1–2 mm). The residue was treated with chloroform (5 × 50 ml), and the combined extracts were washed, dried, and evaporated to give 2.9 g (91%) of 7a. Recrystallization from methanol–water gave an analytical sample, mp 228–231° dec.

Ir (KBr) 3450–3280 (OH, NH association), 2810, 2760 (Bohlmann bands), 2255 (C≡N), 2210 (C≡N conj), 1735 (C=O), 1665 cm^{-1} (C=C); ir (pyridine) 2810, 2760 (Bohlmann bands), 2210 (C≡N), 1730 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 319 (91, M^+), 318 (100), 291 (3), 290 (3.9), 237 (8.8), 235 (4.5), 223 (8.8), 221 (9.1), 184 (24.3), 170 (24.5), 169 (27.2), 156 (24.2).

17β-Hydroxyalloyohimban-16β-carbonitrile (8a) and 17β-Hydroxyalloyohimban-16α-carbonitrile (8b).—To a stirred suspension of 0.75 g (2.35 mmol) of 7a in 2 ml of ethanol was added gradually 0.14 g (3.5 mmol) of sodium borohydride over a 1-hr period. The reduction was followed by tlc [chloroform–methanol (10:1.4), R_f 7a > 8a > 8b]. After stirring at room temperature for 2 hr the starting material was dissolved and the product began to separate, the pH was brought to 7 with acetic acid, and the precipitate was filtered off (0.5 g, a mixture of 8a and 8b). The mother liquor was evaporated *in vacuo* to dryness, and the residue was treated with water (1 ml) and filtered. An additional 0.2 g (26%) of 8a and 8b was obtained. The mixture of isomers was separated (a) by preparative layer chromatography [silica gel $PF_{254+366}$, chloroform–methanol (100:14), R_f 8a > 8b], (b) by column chromatography over silica. Elution with chloroform and with increasing amounts of methanol (1–4%) in chloroform as eluents gave 40 mg of a mixture of nitrile alcohols with unidentified stereostructure and 0.43 g (57%) of 8a, which upon recrystallization from chloroform–methanol gave colorless crystals, mp 262–263°.

Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.73; H, 7.21; N, 13.07. Found: C, 74.88; H, 7.16; N, 13.21.

Ir (KBr) 3450–3220 (OH, NH association), 2820, 2770 (Bohlmann bands), 2250 (C≡N), 1000 cm^{-1} (COH); ir (pyridine or acetonitrile) 2815, 2765 cm^{-1} (Bohlmann bands); nmr (DMSO-d_6) δ 10.90 (s, 1, NH), 7.60–6.90 (m, 4, aromatic protons), 5.05 (d, 1, J = 4.0 Hz, C_{17} OH), 3.95 (m, 1, C_{17} H); mass spectrum 70 eV) *m/e* (rel intensity) 321 (73.3, M^+), 320 (100), 304 (2.1), 292 (3.7), 223 (5.4), 184 (10.2), 170 (13), 169 (17.2), 156 (9.3).

Also, 0.11 g (14.5%) of 8b was obtained. An analytical sample of the latter was crystallized from chloroform–methanol, mp 226–227°.

Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.73; H, 7.21; N, 13.07. Found: C, 74.65; H, 7.31; N, 13.01.

Ir (KBr) 3550–3200 (OH, NH association), 2820, 2765 (Bohlmann bands), 2245 (C≡N), 1015 cm^{-1} (COH); ir (pyridine) 2810, 2770 cm^{-1} (Bohlmann bands, w); nmr (DMSO-d_6) δ 10.91 (s, 1, NH), 7.60–6.80 (m, 4, aromatic protons), 5.15 (d, broad, 1, C_{17} OH), 3.93 (m, 1, C_{17} H); mass spectrum (70 eV) *m/e* (rel intensity) 321 (87.8, M^+), 320 (100), 304 (3.3), 292 (4.4), 223 (6.3), 184 (12.2), 170 (21), 169 (19.2), 156 (13.8).

Isomerization of 8a to 8b. Alloyohimb-16-ene-16-carbonitrile (10a).—The suspension of 0.80 g (2.4 mmol) of 8a in 2 *N* methanolic sodium methoxide solution (40 ml) was stirred at room temperature for 48 hr under nitrogen. The isomerization was followed by tlc [chloroform–methanol (10:1.6), R_f 10a > 8a > 8b]. The unchanged starting material (70 mg) was filtered off, and the filtrate was diluted with the mixture of chloroform (100 ml), water (10 ml), and acetic acid (2.5 ml). The aqueous layer was extracted with chloroform (5 × 50 ml), and the combined extracts were washed with water (3 × 10 ml), dried, and evaporated. The resultant mixture of 8a, 8b, and 10a was separated by chromatography as previously described; 70 mg (8.7%) of 10a, 100 mg (12.5%) of 8a, and 280 mg (33.7%) of 8b were obtained.

The analytical sample of 10a was crystallized from ethanol, mp 234–235°.

Ir (KBr) 3340 (NH), 2800, 2760 (Bohlmann bands), 2220 (C≡N conj), 1630 cm^{-1} (C=C); mass spectrum (70 eV) *m/e* (rel intensity) 303(100, M^+), 288 (2.1), 275 (2.8), 274 (2.7), 211 (5.0), 210 (3.1), 209 (5.0), 198 (3.8), 197 (4.9), 184 (10), 170 (8.2), 169 (13), 156 (21.4).

17β-Hydroxyalloyohimban-16β-carbonitrile *O*-Acetate (8c).—A mixture of 0.15 g (0.46 mmol) of 8a, 2 ml of anhydrous pyridine, and 0.9 ml (8.7 mmol) of acetic anhydride was allowed to stand at room temperature for 3 days under nitrogen. The dark solution was diluted with ice water (2 ml) and extracted with chloroform (5 × 10 ml). The combined extracts were washed with water (3 × 5 ml) and dried. After the solvents were evaporated, the product was separated by preparative tlc [silica gel $PF_{254+366}$, methylene chloride–methanol (100:14), R_f 8c > 8a]. The yield of 8c was 70 mg (43.5%); crystallized from ethanol it had mp 213–214° [75 mg (50%) of 8a was recovered].

Ir (KBr) 3360 (NH), 2180, 2765 (Bohlmann bands, s), 2245 (C≡N), 1745, 1230 cm^{-1} ($OCOCH_3$); ir (pyridine) 2810, 2760 (Bohlmann bands, s); nmr (DMSO-d_6) δ 10.90 (s, 1, NH), 7.40–6.70 (m, 4, aromatic protons), 5.10 (m, 1, C_{17} H), 1.87 (s, 3, $OCOCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 363 (100, M^+), 362 (108), 320 (5.7), 304 (30), 303 (42), 302 (50), 277 (9.9), 184 (13), 170 (22), 169 (28), 156 (28),

17β-Hydroxyalloyohimban-16α-carbonitrile *O*-Acetate (8d).—A mixture of 0.10 g (0.31 mmol) of 8b, 3.0 ml of anhydrous pyridine, and 0.1 ml (1.0 mmol) of acetic anhydride was allowed to stand at room temperature for 3 days under nitrogen. The product was purified as described earlier for 8c, giving 72 mg (64%) of 8d and 32 mg (32%) of unchanged 8b. Recrystallization from ethanol gave 8d as white crystals, mp 166–168°.

Ir (KBr) 3400 (NH), 2810, 2770 (Bohlmann bands, w), 2245 (C≡N), 1725, 1250 cm^{-1} ($OCOCH_3$); ir (pyridine) 2805, 2760 cm^{-1} (Bohlmann bands, w); nmr (DMSO-d_6) δ 10.80 (s, 1, NH), 7.50–6.90 (m, 4, aromatic protons), 4.95 (m, 1, C_{17} H), 2.00 (s, 3, $OCOCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 363 (100, M^+), 362 (83), 320 (4.7), 304 (32), 303 (24), 302 (33), 184 (9.7), 170 (15.3), 169 (17), 156 (15).

17β-Hydroxyalloyohimban-17β-carboxamide (8f).—To a stirred suspension of 0.12 g (0.37 mmol) of 8a in a mixture of 1 *N* sodium hydroxide (2 ml) and methanol (4 ml), 30% hydrogen peroxide was added dropwise keeping its concentration as low as possible to avoid the formation of *N*-oxide. The stirring was continued for 50–60 hr and the reaction was followed by tlc [chloroform–methanol (10:1.4), R_f 8a > 8f]. Sodium borohydride was added to the solution to decompose the excess hydrogen peroxide, and the white precipitate was collected, washed with water, and dried, giving 94 mg (74%) of white solid. An additional 16 mg (12.6%) of 8f was obtained from the evaporated mother liquor by preparative tlc (Al_2O_3 $PF_{2543+66}$, chloroform–methanol (100:10). Recrystallization from 70% ethanol gave an analytical sample, mp 195° dec.

Ir (KBr) 3350–3150 (OH, NH), 2800, 2760 (Bohlmann bands, s), 1650, 1600 ($CONH_2$), 1010 cm^{-1} (COH); mass spectrum (70 eV) *m/e* (rel intensity) 339 (100, M^+), 338 (70), 337 (15), 321 (79), 320 (53), 295 (14), 277 (15), 223 (16), 221 (13), 209 (20), 197 (16), 195 (12), 184 (53), 170 (24), 169 (34), 156 (34).

17β-Hydroxyalloyohimban-16α-carboxamide (8g).—To the stirred suspension of 0.12 g (0.37 mmol) of 8b in a mixture of 1 *N* sodium hydroxide (1 ml) and methanol (2 ml), 30% hydrogen peroxide was added drop by drop to maintain the concentration of the reagent as low as possible (checking with potassium iodine–starch paper). The reaction was followed by tlc [Al_2O_3 G, chloro-

form–methanol (10:0.5), R_f **8b** > **8g**]. After 15–20 hr of stirring the excess hydrogen peroxide was decomposed with sodium borohydride and the solvent was removed *in vacuo*. The residue was taken up in methanol and purified by preparative tlc [Al_2O_3 $PF_{254+366}$, chloroform–methanol (100:14)] to yield 0.10 g (79%) of **8g**. An analytical sample was crystallized from 70% ethanol, mp 195° dec.

Ir (KBr) 3550–3200 (OH, NH), 2820, 2760 (Bohlmann bands, w), 1670, 1630 ($CONH_2$), 1015 cm^{-1} (COH); ir (pyridine) 2800, 2750 cm^{-1} (Bolhmann bands, w); mass spectrum (70 eV) *m/e* (rel intensity) 339 (100, M^+), 338 (70), 337 (10), 321 (36), 320 (28), 295 (10.5), 277 (7.6), 223 (10.6), 221 (10.6), 209 (10), 197 (9.3), 184 (25), 170 (20), 169 (22), 156 (24).

Oxidation–Reduction on 9a and 9b. A.—Mercury(II) acetate (67 mg, 0.21 mmol) was added in small portions over a period of 10 min to a solution of **9a**[1] (11.7 mg, 0.036 mmol) in glacial acetic acid (3 ml). The mixture was kept at 60° for 8 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*. The residue was taken up in methanol (1 ml), reduced with an excess of sodium borohydride, and subjected to preparative tlc [silica gel $PF_{254+366}$, chloroform–methanol (50:8), R_f **9a** > **8b**]. The identity of the material obtained (3 mg) as **8b** was established by ir, mass spectrum, and tlc [Al_2O_3 G, chloroform–methanol (5.0:0.15), R_f **8a** > **8b** > **9a** > **9b**].

B.—The oxidation was carried out of 30 mg (0.091 mmol) of **9b** and 170 mg (0.53 mmol) of mercury(II) acetate by the method described above to **9a**. The material obtained was reduced with sodium borohydride. After separation of the mixture by preparative tlc [silica gel $PF_{254+366}$, chloroform–methanol (50:8), R_f **8e** > **9b**] 4 mg of **8e** was obtained, mp 268–270° dec.

Ir (KBr) 3410–3370 (OH, NH), 2820, 2760 (Bohlmann bands), 2235 cm^{-1} (C≡N); ir (pyridine) 2805, 2760 (Bohlmann bands), 2245 cm^{-1} (C≡N); mass spectrum (70 eV) *m/e* (rel intensity) 321 (90, M^+), 320 (100), 306 (1.6), 293 (2.2), 292 (3.0), 184 (5), 170 (22), 169 (14), 156 (8).

Alloyohimb-16-ene-16-carboxamide (10b).—The solution of 50 mg (0.44 mmol) of **8f** (or **8g**) in 10 ml of 0.5 *N* sodium hydroxide containing 20 ml of dioxane was refluxed for 12 hr [tlc, Al_2O_3 G, chloroform–methanol (10:0.5), R_f **10b** > **8f** > **8g**]. After cooling the solution was neutralized with concentrated hydrochloric acid and evaporated to dryness. The residue was crystallized from ethanol–water to give 30 mg (63.5%) of **10b**: mp 166–168°; mass spectrum (70 eV) *m/e* (rel intensity) 321 (100, M^+), 320 (65), 277 (9.4), 197 (9.4), 184 (34), 170 (8), 169 (18), 156 (30).

Methyl 17β-Hydroxyalloyohimban-16β-carboxylate (8h).—A solution of 90 mg (0.26 mmol) of **8f** in 20 ml of methanol saturated with hydrogen chloride was refluxed for 12 hr under nitrogen [tlc, chloroform–methanol (10:1.4), R_f **8h** > acid]. The cooled solution was neutralized with sodium methoxide, filtered, and evaporated *in vacuo*, yielding an oil which was purified by preparative tlc [silica gel $PF_{254+366}$, chloroform–methanol (100:15), R_f **8h** > **8f**] to give 60 mg (64%) of **8h**. An analytical sample was obtained by crystallization from methanol, mp 195–197°.

Ir (KBr) 3450–3260 (OH, NH), 2805, 2760 (Bohlmann bands, s), 1735 (CO_2CH_3), 1020 cm^{-1} (COH); ir ($CHCl_3$) 3550–3460 (OH, NH), 3480 (NH), 2810, 2760 (Bohlmann bands, s), 1020 cm^{-1} (COH); nmr ($CDCl_3$, 300 MHz) δ 7.76 (s, 1, NH), 7.42 (d, 1, C_9 H),[11] 7.27 (d, 1, C_{12} H), 7.12–7.01 (m, 2, C_{10} and C_{11} H), 4.26 (s, 1, C_{17} H), 3.82 (s, 3, CO_2CH_3), 3.05 (m, 1, C_3 H);[12] mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M^+), 353 (98), 352 (7), 339 (5.8), 337 (2), 336 (1.3), 335 (2.2), 323 (4.5), 295 (2.8), 279 (1.3), 225 (3.5), 224 (7.5), 223 (5.5), 221 (3.5), 184 (8.5), 170 (9), 169 (12), 156 (7.5).

Methyl 17β-Hydroxyalloyohimban-16α-carboxylate (8i).—The reaction was carried out by the method described for **8h** starting from 60 mg (0.17 mmol) of **8g** in 40 ml of methanol saturated with hydrogen chloride, over a period of 30 hr reflux. Similar work-up gave 38 mg (61%) of **8i**. An analytical specimen was prepared from methanol, mp 223–224°.

Ir ($CDCl_3$) 3480–3350 (OH, NH), 3480 (NH), 2760, 2801 (Bohlmann bands, very weak), 1725 (CO_2CH_3), 1025 cm^{-1} (COH); mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M^+), 353 (98), 339 (5.5), 337 (4.1), 336 (5.3), 335 (5.9), 321 (9.5), 320 (8.6), 305 (1.9), 295 (2), 293 (1.4); nmr (DMSO-d_6) 10.65 (s, 1, NH), 7.4–6.8 (m, 4, aromatic protons), 4.61 (s, 1, OH), 3.97 (m, 1, C_{17} H), 3.60 (s, 3, CO_2CH_3).

Methyl 17-Oxoalloyohimban-16-carboxylate (7d) [(±)-Alloyohimbinone], Methyl 17-Oxoalloyohimban-18-carboxylate (7b), and (±)-Alloyohimbone (7c).—A solution of 1.6 g (4.16 mmol) of **6k** (previously dried *in vacuo* with boiling benzene over phosphorus pentoxide) and 3.0 g (26.8 mmol) of sublimed potassium *tert*-butoxide in 15 ml of dry DMSO was allowed to stand at room temperature in a carefully dried apparatus under nitrogen. After completion of the reaction [about 1 week, tlc chloroform–methanol (10:1.5), R_f **6k** > **7b** > **7d** > **7c**] the pH was brought to 7 with acetic acid and the solvent was removed *in vacuo* (0.5–1 mm) under nitrogen. The residue was triturated with chloroform (5 × 60 ml) and filtered, and the combined extracts were washed with water (2 × 10 ml), dried, and evaporated, giving an amorphous powder which was subjected to preparative tlc [silica gel $PF_{254+366}$, hexane–ethyl methyl ketone–acetone (60:30:10), R_f **7b** > **7d** > **7c**]. When the mixture was separated 0.52 g (36%) of **7b**, 0.18 g (15%) of **7c**, and 0.45 g (30%) of **7d** were obtained.

7b, mp from methanol 276–278°, had ir (KBr) 3400 (NH), 2820, 2775 (Bohlmann bands), 1740 (CO_2CH_3), 1720 cm^{-1} (C=O); ir ($CHCl_3$) 3400 (NH), 2820, 2770 (Bohlmann bands), 1740 (CO_2CH_3, s), 1720 (C=O, s), 1670, 1630 cm^{-1} (enolic β-keto ester, m); ir (pyridine) 1750 (CO_2CH_3, w), 1720 (C=O, w), 1680–1620 cm^{-1} (enolic β-keto ester, s); mass spectrum (70 eV) *m/e* (rel intensity) 352 (100, M^+), 351 (46.8), 335 (6.8), 321 (12.6), 320 (30), 319 (42.8), 293 (37.4), 291 (14.3), 235 (7.4), 223 (10.1), 221 (15), 184 (15.6), 170 (18.9), 169 (22.4), 156 (17.6).

7c, mp from methanol 265–267°, had ir (KBr) 2820, 2760 (Bohlmann bands), 1705 (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 294 (91, M^+), 293 (100), 279 (1.3), 277 (1.5), 265 (2.2), 235 (6.1), 223 (7.1), 211 (6.1), 184 (6.1), 170 (13.8), 169 (18.3), 156 (11.2).

7d, mp 192–193°, had ir ($CDCl_3$) 3480 (NH), 2810, 2770, 2760 (Bohlmann bands), 1750 (CO_2CH_3, shoulder), 1720 (C=O, m), 1660, 1620 cm^{-1} (enolic β-keto ester, m); mass spectrum (70 eV) *m/e* (rel intensity) 352 (100, M^+), 351 (36), 337 (5), 335 (3.4), 321 (18), 320 (66), 319 (70), 293 (34), 291 (5.8), 235 (5.4), 223 (8), 221 (10), 184 (15), 170 (14.5), 169 (23), 156 (30).

Preparation of 7c from 7b.—The solution of 0.15 g (0.42 mmol) of **7b** in 20 ml of hydrochloric acid containing 5 ml of dioxane was refluxed for 3 hr, cooled, and rendered alkaline with 40% sodium hydroxide. The resulting solid was filtered off to give 88 mg (72%) of **7c**, mp 265–267°.[8]

Methyl 17β-Hydroxyalloyohimban-18β-carboxylate (8j), Methyl 17α-Hydroxyalloyohimban-18β-carboxylate (8k), and 17β-Hydroxy-18β-hydroxymethylalloyohimban (8l).—The stirred solution of 0.4 g (1.14 mmol) of **7b** in 15 ml of methanol–DMF (2:1) was treated with sodium borohydride (0.3 g, 6.9 mmol) in small portions at 0°. After a total reaction time of 6 hr [tlc, chloroform–methanol (10:1.5), R_f **7b** > **8j** > **8k** > **8l**] the solution was neutralized with acetic acid and the solvent was removed *in vacuo*. The residue was triturated with chloroform (5 × 50 ml), filtered, washed with water (2 × 10 ml), dried, and concentrated to give a solid (0.3 g, 74%) which was submitted to preparative tlc [silica gel $PF_{254+366}$, chloroform–methanol (100:15)]; 168 mg (42%) of **8j**, 8 mg (2%) of **8k**, and 18 mg (5%) of **8l** were obtained.

8j had mp 143–145°; mass spectrum (70 eV) (rel intensity) 354 (100, M^+), 353 (90), 339 (4.3), 335 (1.2), 323 (5.8), 295 (2.1), 293 (1.0), 223 (3.3), 221 (4.1), 184 (6.4), 170 (8.1), 169 (12), 156 (7.8), 144 (6.5); ir (KBr) 3550–3150 (OH, NH), 2810, 2760 (Bohlmann bands), 1735 (CO_2CH_3), 1045 cm^{-1} (COH).

8k had mp 164–167°; mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M^+), 339 (5.3), 325 (3.1), 323 (6), 184 (15), 170 (28), 169 (37), 156 (20).

8l had mp 192–194°; ir (KBr) 3520–3170 (OH, NH), 1040 cm^{-1} (COH); nmr (DMSO-d_6) δ 10.65 (s, 1, NH), 7.40–6.80 (m, 4, aromatic protons), 4.11 (d, 2, CH_2OH), 3.86 (m, 1, C_{17} OH); mass spectrum (70 eV) *m/e* (rel intensity) 326 (91, M^+), 325 (100), 311 (1.3), 309 (2.6), 307 (3.7), 295 (3.2), 253 (3.3), 223 (3), 221 (6.7), 211 (5.7), 197 (6.3), 184 (11), 169 (36), 156 (15).

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Methyl 17β-Hydroxyalloyohimban-16β-carboxylate (8h), (±)-Alloyohimbine (8m) and (±)-α-Yohimbine (8n) from 7d.—A solution of 0.12 g (0.34 mmol) of **7d** in 10 ml of methanol was reduced with 0.2 g (5.3 mmol) of sodium borohydride over a 5-hr period at 0° [tlc, chloroform–methanol (10:1.5), R_f **7d** > **8n** > **8m** > **8h**]. After neutralization with acetic acid, most of the solvent was removed *in vacuo* and the product was extracted with chloroform (5 × 50 ml). The extracts were combined, washed with water (2 × 10 ml), dried, and evaporated and the resulting mixture of isomers (96 mg, 90%) was separated by (1) preparative tlc [Al_2O_3 G (type E), hexane–ethyl methyl ketone (60:40), R_f **8h** > **8n** ~ **8m**, and then silica gel $PF_{254+366}$, chloroform–methanol (100:15), R_f **8n** > **8m**]; (2) column chromatography over alumina (Brockmann, activity II–III), elution with hexane–ethyl methyl ketone (90:10) and with increasing amount of ethyl methyl ketone (12–20%) as eluents. In another reduction run exactly as above, starting from 0.16 g of **7c**, 32 mg (20%) of **8h**, 10 mg (6%) of **8n**, and 14 mg (9%) of **8m** were obtained.

8h was identical in all respects (ir, mass spectrum, tlc spot) with an authentic sample obtained from **8f**.

8m had mp 136–137° (from ethyl acetate following ether); by mixture melting point, ir, nmr, and tlc spot, **8m** was identical with an authentic sample of (±)-alloyohimbine obtained from **9b**.[1]

8n had ir ($CHCl_3$) identical with that of natural α-yohimbine, 3570 (OH), 3480 (NH), 2805, 2765 (Bohlmann bands), 1730 (CO_2CH_3), 1055 cm^{-1} (COH); nmr ($CDCl_3$ at 300 M-z) δ 7.75 (s, 1, NH), 7.44 (d, 1, C_9 H),[11] 7.28 (d, 1, C_{12} H), 7.15–7.02 (m, 2, C_{10}, C_{11} H), 3.99 (d of t, 1, C_{17} H, J = 26 Hz), 3.84 (s, 3, CO_2CH_3), 3.15 (m, 1, C_3 H);[12] mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M^+), 353 (88), 339 (4.8), 337 (1.6), 335 (1.8), 323 (4.8), 321 (2.9), 320 (2), 295 (5.1), 293 (3.1), 226 (8), 224 (13), 223 (5.6), 221 (5.8), 184 (9.7), 170 (11), 169 (12), 156 (8).

Epimerization of Alloyohimine Isomers. Preparation of 8i (and 10c) from 8h.—**8h** (28 mg, 7.9 × 10^{-1} mmol) in 1 ml of 2 *N* methanolic sodium methoxide solution was allowed to stand at room temperature under nitrogen for 3–4 days. Separation of the mixture by preparative tlc [Al_2O_3 G (type E), hexane–ethyl methyl ketone (60:40), R_f **10c** > **8h** > **8i**] gave 5.5 mg (20%) of **10c**, 5.0 mg (18%) of **8h**, and 11.8 mg (42%) of **8i**.

10c had mp 195–197°, ir (KBr) 3350 (NH), 1700 (CO_2CH_3 conj), 1640 cm^{-1} (C=C); mass spectrum (70 eV) *m/e* (rel intensity) 336 (100, M^+), 335 (99), 321 (23), 206 (15), 197 (11), 191 (12), 184 (17), 169 (14), 165 (26).[12]

8i was identical in all respects with an authentic sample obtained from **8g**.

Preparation of (±)-α-Yohimbine (8n) from (±)-Alloyohimbine (8m).—**8m** (30 mg, 8.1 × 10^{-2} mmol) in 1 ml of 2 *N* methanolic sodium methoxide solution was allowed to stand at room temperature under nitrogen. The progress of the epimerization was followed by tlc [chloroform–methanol (10:1.5), R_f **8n** > **8m**]. After 3–4 days the solution was neutralized with acetic acid, evaporated to dryness, and triturated with chloroform (3 × 2 ml). After the solvent was evaporated, 17.3 mg (58%) of **8n** was obtained, identical with the sample obtained from **7d**.

Thin Layer Chromatographic Behavior of Hydroxy Esters with Alloyohimbane Skeleton.—Al_2O_3 G (Type E), hexane–ethyl methyl ketone (6:4), showed R_f **8h** > **8j** > **8n** > **8i** > **8m** > **8k**; silica gel G, hexane–ethyl methyl ketone–methanol (6:3:1) showed R_f **8n** > **8m** > **8h** > **8i** > **8j** > **8k**.

Registry No.—**1**, 40087-90-9; **2**, 2107-58-6; **2** free base, 2107-57-5; **3a**, 40087-94-3; **3b**, 40087-91-0; **3b** oxalate, 40087-92-1; **4**, 40087-93-2; (*Z*)-**5a**, 40087-95-4; (*E*)-**5a**, 40087-96-5; **5b**, 40087-97-6; **6a**, 39032-75-2; **6b**, 39032-72-9; **6c**, 39032-73-0; **6d**, 39032-74-1; **6e**, 39032-76-3; **6e** HCl, 40037-02-3; **6f** HCl, 40037-03-4; **6g**, 40088-02-6; **6h**, 40088-03-7; **6i**, 40088-04-8; **6j**, 40085-19-6; **6k**, 40088-06-0; **6k** HCl, 40088-07-1; **7a**, 40088-08-2; **7b**, 40088-09-3; **7c**, 40088-10-6; **7d**, 40088-11-7; **8a**, 40088-12-8; **8b**, 40088-13-9; **8c**, 40088-14-0; **8d**, 40088-15-1; **8e**, 40088-16-2; **8f**, 40088-17-3; **8g**, 40088-18-4; **8h**, 40088-19-5; **8i**, 40088-20-8; **8j**, 40088-21-9; **8k**, 40088-22-0; **8l**, 40088-23-1; **8m**, 40085-32-3; **8n**, 40088-25-3; **9a**, 40085-22-1; **9b**, 40085-21-0; **10a**, 40088-28-6; **10b**, 40088-29-7; **10c**, 40088-30-0; diethyl α-acetylglutarate, 1501-06-0; diethylamine hydrochloride, 660-68-4; methyl iodide, 74-88-4; ammonium acetate, 631-61-8; acetic acid, 64-19-7; triethylamine, 121-44-8; phosphorus pentoxide, 1314-56-3; methyl cyanoacetate, 105-34-0; malononitrile, 109-77-3; sodium borohydride, 16940-66-2; sodium methoxide, 124-41-4; potassium *tert*-butoxide, 865-47-4.

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