

## 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**),  $\alpha$ -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<sup>1</sup> 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<sup>2</sup> 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<sub>3</sub>, since such a change had been observed earlier in the case of benzo[*a*]quinolizidine derivatives,<sup>3</sup> and had in fact been used successfully by us in the realization of the stereoselective synthesis of corynantheidine.<sup>4</sup> However, under the experimental conditions (NH<sub>4</sub>OAc-HOAc, azeotropic removal of water with benzene) which had proven successful with the analog of **1** possessing a C<sub>3</sub> 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.<sup>5</sup> 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,<sup>5</sup> the coalescence of the two indole NH signals occurring at 180°.

(1) L. Töke, K. Honty, L. Szabó, G. Blaskó, and Cs. Szántay, *J. Org. Chem.*, **38**, 2496 (1973).

(2) Cs. Szántay, L. Töke, K. Honty, and Gy. Kalas, *J. Org. Chem.*, **32**, 423 (1967).

(3) A. Brossi and O. Schnider, *Helv. Chim. Acta*, **45**, 1899 (1962).

(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.

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.

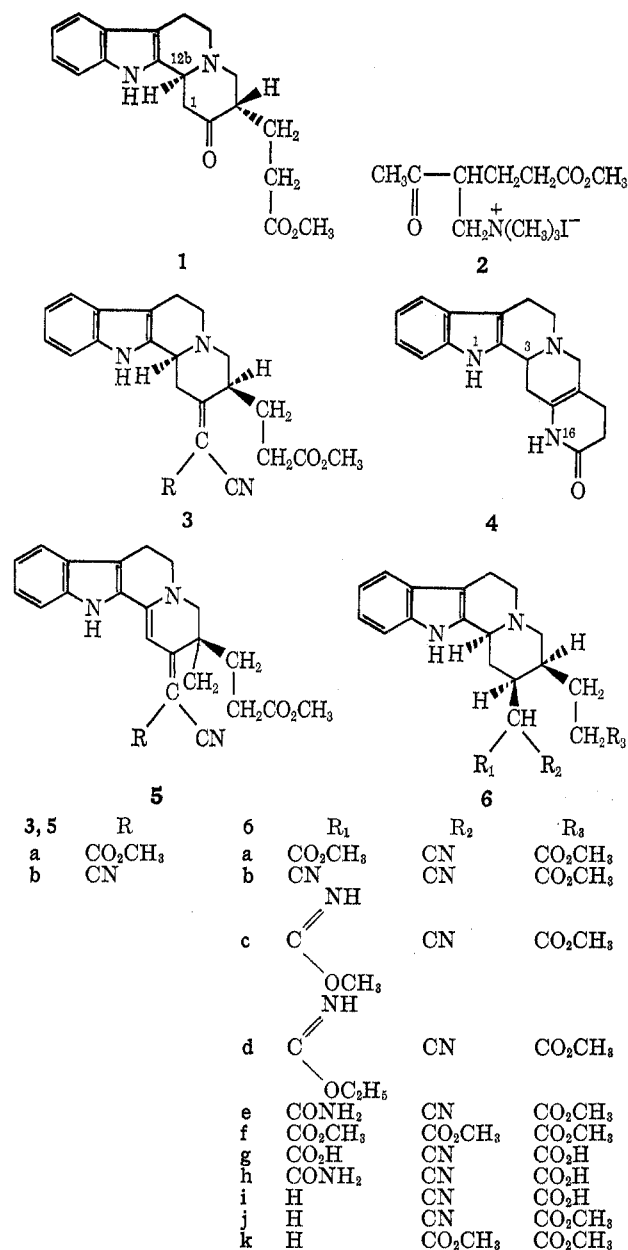
Reduction of **3a** with sodium borohydride gives **6a** in good yield. The nmr spectrum of this product shows that the methoxyl methyl of the R<sub>1</sub> ester group is split into two peaks which are independent of temperature. This phenomenon is a consequence of the new asymmetric center formed following the reduction.<sup>4</sup> 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.<sup>6</sup> 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<sub>1</sub> 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

(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,<sup>6a</sup> 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<sub>2</sub> 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.

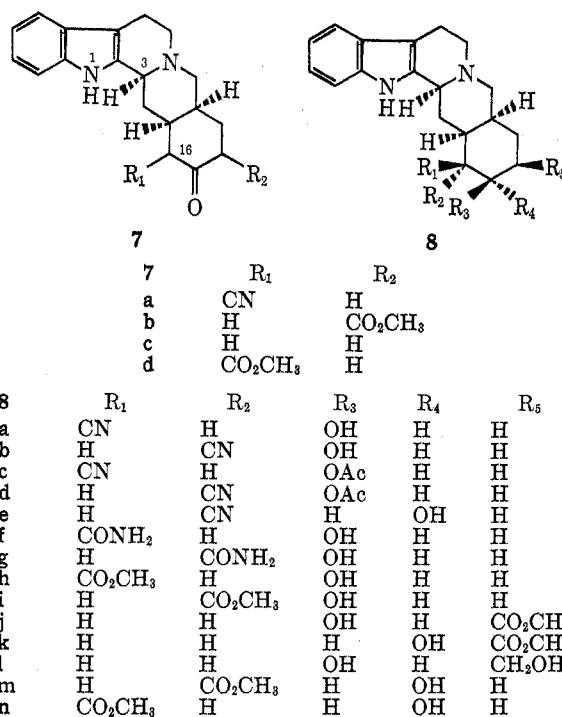


dissolving in alkali at 0° and then acidifying. The precipitate formed is diacid **6g**. This exceedingly rapid hydrolysis could be due to neighboring group participation. A similar behavior is also shown toward alkali by the dinitrile **6b**. However, in this case, the amide **6h** is also present besides 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 Alloyhimbine 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,<sup>1</sup> 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**.



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

TABLE I  
SPECTRAL VALUES

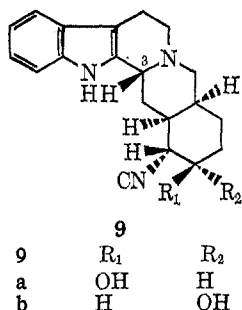
Compd	Nmr, <sup>a</sup> $\delta$		$I_r$ , <sup>b</sup> cm <sup>-1</sup> , Bohlmann bands
	$C_{17}$ proton multiplet	$C_{17}$ hydroxyl doublet	
<b>8a</b>	3.95	5.05	2815, 2765
<b>8b</b>	3.93	5.15	2810, 2770
<b>8c</b>	5.10		2810, 2760
<b>8d</b>	4.95		2805, 2760

<sup>a</sup> In DMSO- $d_6$  at 60 MHz. <sup>b</sup> 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  $\beta$ , so that attack by borohydride must occur from the convex side of the molecule and is subject to "steric approach control."

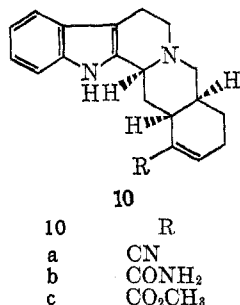
The above conclusions are also supported by the chemical behavior of the two compounds. Either isomer when dissolved in alcoholic alkali at room temperature yields a nearly 1:1 mixture of **8a** and **8b**. Under such mild conditions only the carbon atom, adjacent to the nitrile group, can be epimerized. 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



earlier.<sup>1</sup> 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<sub>17</sub> OH group must be  $\beta$ . 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 penta-cyclic indole bases could be hydrolyzed in two steps.<sup>4,7</sup> 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<sub>16</sub> isomerization. The unsaturated amide **10b**, which was formed in substan-



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 allo-cis (A<sub>c1</sub>) conformation must predominate. In the A<sub>t</sub> conformation both the carboxamide and the hydroxyl groups must be axial, while in the A<sub>c1</sub> 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- $\alpha$ -yohimbine. The chromatographic behaviors of both esters **8h** and **8i** differ from that of natural  $\alpha$ -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  $\alpha$ -yohimbine (**8n**) discussed earlier.<sup>1</sup>

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

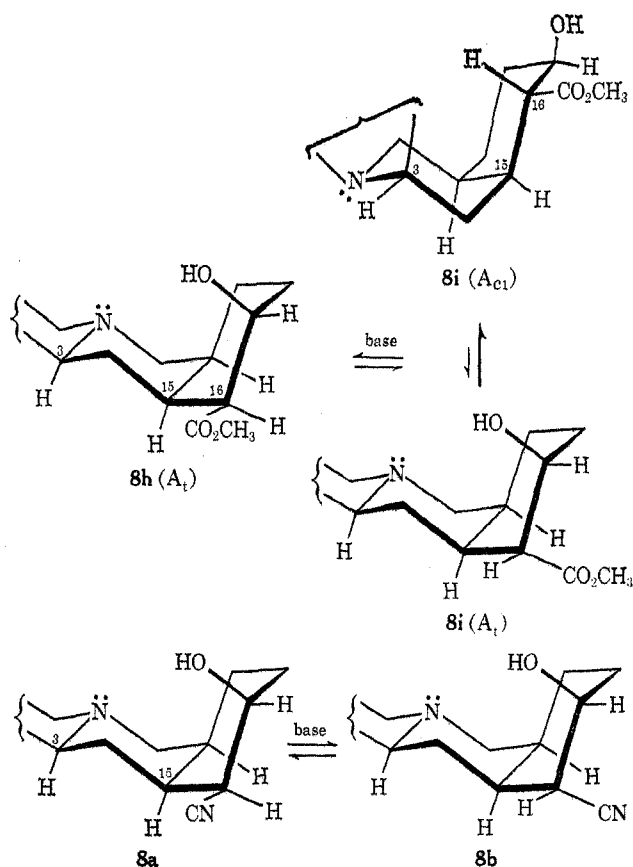
TABLE II  
SPECTRAL VALUES

Compd	Nmr, $\delta$		Ir, $^{\circ}$ cm <sup>-1</sup> , Bohlmann bands	Conformation		
	C <sub>17</sub> proton	C <sub>3</sub> proton		C <sub>17</sub> OH	C <sub>3</sub> indole ring	Skele- ton
<b>8h</b>	4.26 <sup>a</sup>	3.05	2810, 2760	ax	eq	A <sub>t</sub>
<b>8i</b>	3.75 <sup>a</sup>	3.95	Very weak	eq	ax	A <sub>c1</sub>
<b>8m</b> (alloyo- himbine)	3.80 <sup>b</sup>	3.25	2805, 2760	eq	eq	A <sub>t</sub>
<b>8n</b> ( $\alpha$ -yohim- bine)	3.99 <sup>a</sup>	3.15	2805, 2765	eq	eq	A <sub>t</sub>

<sup>a</sup> In CDCl<sub>3</sub> at 300 MHz. <sup>b</sup> In CDCl<sub>3</sub> at 60 MHz. <sup>c</sup> 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<sub>16</sub> 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**  $\rightarrow$  **8b** occurs between compounds possessing the A<sub>t</sub> conformation, and the equilibrium ( $\sim$ 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<sub>t</sub>  $\rightarrow$  A<sub>c1</sub> conformational equilibrium also plays an important role (Chart I). Species **8i** is one of those rare sub-

CHART I



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<sup>7</sup> 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<sup>8</sup> ( $\pm$ )-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<sub>18</sub>. 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**, alloyohimbione, 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 ( $\pm$ )-alloyohimbone (**7c**) upon hydrolysis and decarboxylation.

The optically active form of alloyohimbione (**7d**) is known<sup>9</sup> from the oxidation of  $\alpha$ -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<sub>t</sub> 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 ( $\pm$ )-alloyohimbine<sup>1</sup> (**8m**), while the third product was ( $\pm$ )- $\alpha$ -yohimbine (**8n**). The ratio of the alkaloids was **8h**:**8m**:**8n** = 7:3:2.

Taking into consideration our earlier investigations in the normal yohimbane,<sup>7</sup> epialloyohimbane,<sup>1</sup> and berbaine series,<sup>10</sup> it can be stated that the structures and relative quantities of the stereoisomeric alcohols obtained from the sodium borohydride reduction of yohimbiones 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  $\delta$  units downfield from internal tetramethylsilane. Mass spectra were recorded at 70 eV on a AEL-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<sub>254+366</sub>

and Al<sub>2</sub>O<sub>3</sub> PF<sub>254+366</sub>, 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.**<sup>2</sup>—A suspension of 138 g (0.6 mol) of diethyl  $\alpha$ -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  $\times$  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  $\times$  50 ml). The combined alcoholic solution was dehydrated by azeotrope 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  $\times$  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).<sup>2</sup>

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  $\times$  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°.<sup>2</sup>

**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<sub>18</sub>H<sub>19</sub>N<sub>3</sub>O: 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<sup>-1</sup> (C=C); nmr (DMSO-*d*<sub>6</sub>)  $\delta$  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  $\times$  10<sup>-5</sup> 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 azeotrope 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.<sup>2</sup>

Anal. Calcd for C<sub>19</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>: 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<sub>2</sub>CH<sub>3</sub>), 1710 cm<sup>-1</sup> (C=O).

**Methyl 3 $\beta$ -(2-Methoxycarbonyl)ethyl-1,3,4,7,12,12 $\beta$ -hexahydro-2H,6H-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 recovered from the mother liquor with methanolic oxalic acid. A recrystallized sample of 3a exhibited mp 173–174°.

*Anal.* Calcd for  $C_{22}H_{25}N_3O_4$ : 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<sub>2</sub>CH<sub>3</sub>), 1600 cm<sup>-1</sup> (C=C); nmr (CDCl<sub>3</sub>) δ 8.58 (s, 1, NH), 7.60–7.00 (m, 4, aromatic protons), 4.08 (m, 1, C<sub>1</sub>H<sub>eq</sub>), 3.85 (s, 3, CO<sub>2</sub>CH<sub>3</sub> conj), 3.65 (s, 3, CO<sub>2</sub>CH<sub>3</sub>).

**3β-(2-Methoxycarbonyl-ethyl)-1,3,4,7,12,12α-hexahydro-2H,6H-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<sub>2</sub>CH<sub>3</sub>), 1605 cm<sup>-1</sup> (C=C); nmr (CDCl<sub>3</sub>) δ 8.35 (s, 1, NH), 7.6–7.1 (m, 4, aromatic protons), 3.70 (s, 3, CO<sub>2</sub>CH<sub>3</sub>).

**(E,Z)-Methyl 3β-(2-Methoxycarbonyl-ethyl)-3,4,7,12-tetrahydro-2H,6H-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 mercuric(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% 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°.

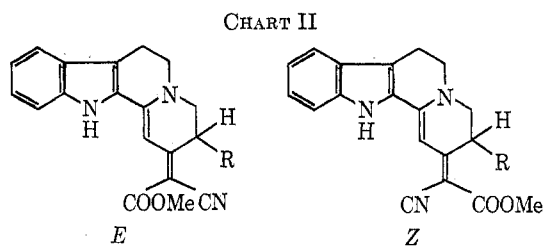
*Anal.* Calcd for  $C_{23}H_{28}N_3O_4$ : C, 68.13; H, 5.72; N, 10.36. Found: C, 68.16; H, 5.94; N, 10.45.

Ir (KBr) 3255 (NH), 2200 (C≡N conj), 1740, 1730 (CO<sub>2</sub>CH<sub>3</sub>), 1690, 1680 (CO<sub>2</sub>CH<sub>3</sub> conj), 1582 cm<sup>-1</sup> (C=C); nmr (CDCl<sub>3</sub>) δ 10.27, 9.03 (s, 1, NH), 7.8–7.1 (m, 4, aromatic protons), 6.27 (s, 0.6, C<sub>1</sub>H), 3.82 (s, 3, CO<sub>2</sub>CH<sub>3</sub> conj), 3.71 (s, 3, CO<sub>2</sub>CH<sub>3</sub>); nmr (C<sub>6</sub>D<sub>6</sub>NO<sub>2</sub>, 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<sub>1</sub>H (E)], 3.84 [s, 0.57, CO<sub>2</sub>CH<sub>3</sub> conj (Z)], 3.71 [s, broad, 5.43 (0.43, CO<sub>2</sub>CH<sub>3</sub> conj (E), 3, CO<sub>2</sub>CH<sub>3</sub>, 2, C<sub>6</sub>H)] (see Chart II); uv (MeOH) λ<sub>max</sub> 222 nm (log ε 4.54), 254 (4.06), 346 (4.04), 455 (4.66) 481 (4.76).

**3β-(2-Methoxycarbonyl-ethyl)-3,4,7,12-tetrahydro-2H,6H-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<sub>2</sub>CH<sub>3</sub>), 1580 cm<sup>-1</sup> (C=C); nmr (DMSO-*d*<sub>6</sub>) δ 11.9 (s, 1, NH), 7.6–7.1 (m, 4, aromatic protons), 6.15 (s, 1, C<sub>1</sub>H), 3.55 (s, 3, CO<sub>2</sub>CH<sub>3</sub>); nmr (C<sub>6</sub>D<sub>6</sub>NO<sub>2</sub>) δ 10.07 (s, 1, NH), 7.5–7.0 (m, 4, aromatic protons), 6.32 (s, 1, C<sub>1</sub>H), 3.73 (s, 3, CO<sub>2</sub>CH<sub>3</sub>); uv (MeOH) λ<sub>max</sub> 221 nm (log ε 4.27), 246 (3.88), 348 (3.98), 448 (4.57), 475 (4.64).



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	
	E	Z		E	Z
36 <sup>a</sup>	10.6		119	4.8	
63	8.6		138	4.0	
82	7.9		155	2.7	
100	7.1		$T_c = 183$		

<sup>a</sup> Determined with a Varian A-60 instrument operated at 60 MHz in C<sub>6</sub>D<sub>6</sub>NO<sub>2</sub>.

**Methyl 3β-(2-Methoxycarbonyl-ethyl)-1,3,4,7,12,12α-hexahydro-2H,6H-indolo[2,3-a]quinolizin-2-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<sup>-1</sup> (CO<sub>2</sub>CH<sub>3</sub>); nmr (CDCl<sub>3</sub>) δ 8.15, 7.94 (s, 1, NH), 7.45–6.96 (m, 4, aromatic protons), 3.92, 3.87 (s, 3, CO<sub>2</sub>CH<sub>3</sub>), 3.68 (s, 3, CO<sub>2</sub>CH<sub>3</sub>); nmr (DMSO-*d*<sub>6</sub>) 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<sub>2</sub>CH<sub>3</sub>), 3.66 (s, 3, CO<sub>2</sub>CH<sub>3</sub>).

**3β-(2-Methoxycarbonyl-ethyl)-1,3,4,7,12,12α-hexahydro-2H,6H-indolo[2,3-a]quinolizin-2-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  $C_{22}H_{22}N_4O_2$ : 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<sup>-1</sup> (CO<sub>2</sub>CH<sub>3</sub>); nmr (DMSO-*d*<sub>6</sub>) δ 10.5 (s, 1, NH), 7.5–6.9 (m, 4, aromatic protons), 3.58 (s, 3, CO<sub>2</sub>CH<sub>3</sub>).

**Methyl Cyano-3β-(2-methoxycarbonyl-ethyl)-1,3,4,7,12,12α-hexahydro-2H,6H-indolo[2,3-a]quinolizin-2-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  $C_{23}H_{28}N_4O_3$ : 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<sub>2</sub>CH<sub>3</sub>), 1670 cm<sup>-1</sup> (C=N); ir (DMSO) 2190 (C≡N), 1740 (CO<sub>2</sub>CH<sub>3</sub>), 1675 (C=N), 1660–1630 (NH def), 1600 cm<sup>-1</sup> (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<sup>+</sup>), 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<sub>2</sub>CH<sub>3</sub>), 1660 cm<sup>-1</sup> (C=N); ir (DMSO) 2190 (C≡N), 1735 (CO<sub>2</sub>CH<sub>3</sub>), 1665–1580 cm<sup>-1</sup> (C=C and C=NH); nmr, see Table IV.

TABLE III

Solvent	Nmr, $\delta$				
	Indole NH	NH <sub>2</sub> <sup>b</sup>	OCH <sub>3</sub>	C=NH <sup>b</sup>	Aromatic protons
DMF-d <sub>7</sub>	10.73 (0.36) <sup>a</sup>	6.65 (0.36)	3.90, 3.95	8.8 (0.72)	7.55-6.95 (4)
	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 <sub>6</sub>	11.16	6.54	3.78		
	11.21		3.65		

<sup>a</sup> The sign intensities in parentheses are given in proton units. <sup>b</sup> Assignments for NH<sub>2</sub> and C=NH groups differ from those given in the preliminary communication (ref 6).

TABLE IV

Solvent	Nmr, $\delta$					
	Indole NH	NH <sub>2</sub> <sup>b</sup>	CO <sub>2</sub> CH <sub>3</sub>	OCH <sub>2</sub> CH <sub>3</sub>	C=NH <sup>b</sup>	Aromatic protons
DMSO-d <sub>6</sub>	10.60	6.41	3.48	3.99 (q, $J = 6$ Hz)	8.6 (0.30) <sup>a</sup>	7.55-6.95 (m, 4)
	10.65	6.30		4.05 (q, $J = 6$ Hz)		
	10.80					

<sup>a</sup> The sign intensity in parentheses is given in proton units. <sup>b</sup> Assignments for NH<sub>2</sub> 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<sub>22</sub>H<sub>22</sub>N<sub>4</sub>O<sub>3</sub>: 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<sub>2</sub>CH<sub>3</sub>), 1695, 1620 cm<sup>-1</sup> (CONH<sub>2</sub>); nmr (DMSO-d<sub>6</sub>)  $\delta$  11.5 (s, 1, NH), 8.25 (s, 2, NH<sub>2</sub>), 7.8–7.1 (m, 4, aromatic protons), 3.67 (s, 3, CO<sub>2</sub>CH<sub>3</sub>); mass spectrum (70 eV) *m/e* (rel intensity) 394 (85.8, M<sup>+</sup>), 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<sub>f</sub>* 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 3 $\beta$ -(2-Methoxycarbonyl)ethyl-1,3,4,7,12,12b $\alpha$ -hexahydro-2H,6H-indolo[2,3-*a*]quinolizin-2 $\beta$ -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<sub>f</sub>* 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<sub>24</sub>H<sub>31</sub>ClN<sub>4</sub>O<sub>6</sub>: 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<sup>-1</sup> (CO<sub>2</sub>CH<sub>3</sub>).

**3 $\beta$ -(2-Carboxyethyl)-1,3,4,7,12,12b $\alpha$ -hexahydro-2H,6H-indolo[2,3-*a*]quinolizin-2 $\beta$ -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<sub>f</sub>* 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<sub>2</sub>H), 1650, 1620 cm<sup>-1</sup> (CO<sub>2</sub><sup>-</sup>).

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.

**2 $\beta$ -(Cyanocarbamoylmethyl)-1,3,4,7,12,12b $\alpha$ -hexahydro-2H,6H-indolo[2,3-*a*]quinolizin-3 $\beta$ -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<sup>-1</sup> (CONH<sub>2</sub>, CO<sub>2</sub>H).

**2 $\beta$ -Cyanomethyl-1,3,4,7,12,12b $\alpha$ -hexahydro-2H,6H-indolo[2,3-*a*]quinolizin-3 $\beta$ -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<sub>f</sub>* 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<sub>2</sub>H), 1630–1550 cm<sup>-1</sup> (CO<sub>2</sub><sup>-</sup>); mass spectrum (70 eV) *m/e* (rel intensity) 337 (95, M<sup>+</sup>), 336 (100), 319 (8), 318 (8.4), 297 (27), 269 (18), 211 (9.5), 184 (20), 170 (33), 169 (24), 156 (18).

**Methyl 2 $\beta$ -Cyanomethyl-1,3,4,7,12,12b $\alpha$ -hexahydro-2H,6H-indolo[2,3-*a*]quinolizin-3 $\beta$ -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<sub>f</sub>* 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<sup>-1</sup> (CO<sub>2</sub>CH<sub>3</sub>); mass spectrum (70 eV) *m/e* (rel intensity) 351 (99.4 M<sup>+</sup>), 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 2 $\beta$ -Methoxycarbonylmethyl-1,3,4,7,12,12 $\beta$ -hexahydro-2H,6H-indolo[2,3-a]quinolizin-3 $\beta$ -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  $\times$  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<sub>22</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>: 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<sup>-1</sup> (CO<sub>2</sub>CH<sub>3</sub>); mass spectrum (70 eV) *m/e* (rel intensity) 384 (100, M<sup>+</sup>), 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<sub>22</sub>H<sub>29</sub>ClN<sub>2</sub>O<sub>4</sub>: 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<sup>+</sup>), 1745 cm<sup>-1</sup> (CO<sub>2</sub>CH<sub>3</sub>).

**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<sub>f</sub>* 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  $\times$  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 $\equiv$ N), 2210 (C $\equiv$ N conj), 1735 (C=O), 1665 cm<sup>-1</sup> (C=C); ir (pyridine) 2810, 2760 (Bohlmann bands), 2210 (C $\equiv$ N), 1730 cm<sup>-1</sup> (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 319 (91, M<sup>+</sup>), 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).

**17 $\beta$ -Hydroxyalloyohimban-16 $\beta$ -carbonitrile (8a) and 17 $\beta$ -Hydroxyalloyohimban-16 $\alpha$ -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<sub>f</sub>* 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<sub>254+366</sub>, chloroform–methanol (100:14), *R<sub>f</sub>* 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<sub>20</sub>H<sub>23</sub>N<sub>3</sub>O: 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 $\equiv$ N), 1000 cm<sup>-1</sup> (COH); ir (pyridine or acetone) 2815, 2765 cm<sup>-1</sup> (Bohlmann bands); nmr (DMSO-*d*<sub>6</sub>)  $\delta$  10.90 (s, 1, NH), 7.60–6.90 (m, 4, aromatic protons), 5.05 (d, 1, *J* = 4.0 Hz, C<sub>17</sub>OH), 3.95 (m, 1, C<sub>17</sub>H); mass spectrum (70 eV) *m/e* (rel intensity) 321 (73.3, M<sup>+</sup>), 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<sub>20</sub>H<sub>23</sub>N<sub>3</sub>O: 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 $\equiv$ N), 1015 cm<sup>-1</sup> (COH); ir (pyridine) 2810, 2770 cm<sup>-1</sup> (Bohlmann bands, w); nmr (DMSO-*d*<sub>6</sub>)  $\delta$  10.91 (s, 1, NH), 7.60–6.80 (m, 4, aromatic protons), 5.15 (d, broad, 1, C<sub>17</sub>OH), 3.93 (m, 1, C<sub>17</sub>H); mass spectrum (70 eV) *m/e* (rel

intensity) 321 (87.8, M<sup>+</sup>), 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<sub>f</sub>* 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  $\times$  50 ml), and the combined extracts were washed with water (3  $\times$  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 $\equiv$ N conj), 1630 cm<sup>-1</sup> (C=C); mass spectrum (70 eV) *m/e* (rel intensity) 303 (100, M<sup>+</sup>), 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).

**17 $\beta$ -Hydroxyalloyohimban-16 $\beta$ -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  $\times$  10 ml). The combined extracts were washed with water (3  $\times$  5 ml) and dried. After the solvents were evaporated, the product was separated by preparative tlc [silica gel PF<sub>254+366</sub>, methylene chloride–methanol (100:14), *R<sub>f</sub>* 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 $\equiv$ N), 1745, 1230 cm<sup>-1</sup> (OCOCH<sub>3</sub>); ir (pyridine) 2810, 2760 (Bohlmann bands, s); nmr (DMSO-*d*<sub>6</sub>)  $\delta$  10.90 (s, 1, NH), 7.40–6.70 (m, 4, aromatic protons), 5.10 (m, 1, C<sub>17</sub>H), 1.87 (s, 3, OCOCH<sub>3</sub>); mass spectrum (70 eV) *m/e* (rel intensity) 363 (100, M<sup>+</sup>), 362 (108), 320 (5.7), 304 (30), 303 (42), 302 (50), 277 (9.9), 184 (13), 170 (22), 169 (28), 156 (28).

**17 $\beta$ -Hydroxyalloyohimban-16 $\alpha$ -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 $\equiv$ N), 1725, 1250 cm<sup>-1</sup> (OCOCH<sub>3</sub>); ir (pyridine) 2805, 2760 cm<sup>-1</sup> (Bohlmann bands, w); nmr (DMSO-*d*<sub>6</sub>)  $\delta$  10.80 (s, 1, NH), 7.50–6.90 (m, 4, aromatic protons), 4.95 (m, 1, C<sub>17</sub>H), 2.00 (s, 3, OCOCH<sub>3</sub>); mass spectrum (70 eV) *m/e* (rel intensity) 363 (100, M<sup>+</sup>), 362 (83), 320 (4.7), 304 (32), 303 (24), 302 (33), 184 (9.7), 170 (15.3), 169 (17), 156 (15).

**17 $\beta$ -Hydroxyalloyohimban-17 $\beta$ -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<sub>f</sub>* 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<sub>2</sub>O<sub>3</sub>, PF<sub>254+366</sub>, 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<sub>2</sub>), 1010 cm<sup>-1</sup> (COH); mass spectrum (70 eV) *m/e* (rel intensity) 339 (100, M<sup>+</sup>), 338 (70), 337 (15), 321 (79), 320 (53), 295 (14), 277 (15), 271 (13), 221 (13), 209 (20), 197 (16), 195 (12), 184 (53), 170 (24), 169 (34), 156 (34).

**17 $\beta$ -Hydroxyalloyohimban-16 $\alpha$ -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<sub>2</sub>O<sub>3</sub>, 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 [ $\text{Al}_2\text{O}_3$  PF<sub>254+366</sub>, 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<sub>2</sub>), 1015 cm<sup>-1</sup> (COH); ir (pyridine) 2800, 2750 cm<sup>-1</sup> (Bohlmann bands, w); mass spectrum (70 eV) *m/e* (rel intensity) 339 (100, M<sup>+</sup>), 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**<sup>1</sup> (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<sub>254+366</sub>, 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 [ $\text{Al}_2\text{O}_3$  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<sub>254+366</sub>, 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<sup>-1</sup> (C≡N); ir (pyridine) 2805, 2760 (Bohlmann bands), 2245 cm<sup>-1</sup> (C≡N); mass spectrum (70 eV) *m/e* (rel intensity) 321 (90, M<sup>+</sup>), 320 (100), 306 (1.6), 293 (2.2), 292 (3.0), 184 (5), 170 (22), 169 (14), 156 (8).

**Alloyhimb-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,  $\text{Al}_2\text{O}_3$  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<sup>+</sup>), 320 (65), 277 (9.4), 197 (9.4), 184 (34), 170 (8), 169 (18), 156 (30).

**Methyl 17 $\beta$ -Hydroxyalloyohimban-16 $\beta$ -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<sub>254+366</sub>, 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<sub>2</sub>CH<sub>3</sub>), 1020 cm<sup>-1</sup> (COH); ir (CHCl<sub>3</sub>) 3550–3460 (OH, NH), 3480 (NH), 2810, 2760 (Bohlmann bands, s), 1020 cm<sup>-1</sup> (COH); nmr (CDCl<sub>3</sub>, 300 MHz)  $\delta$  7.76 (s, 1, NH), 7.42 (d, 1, C<sub>9</sub>H),<sup>11</sup> 7.27 (d, 1, C<sub>12</sub>H), 7.12–7.01 (m, 2, C<sub>16</sub> and C<sub>11</sub>H), 4.26 (s, 1, C<sub>17</sub>H), 3.82 (s, 3, CO<sub>2</sub>CH<sub>3</sub>), 3.05 (m, 1, C<sub>8</sub>H);<sup>12</sup> mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M<sup>+</sup>), 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 17 $\beta$ -Hydroxyalloyohimban-16 $\alpha$ -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<sub>3</sub>) 3480–3350 (OH, NH), 3480 (NH), 2760, 2801

(Bohlmann bands, very weak), 1725 (CO<sub>2</sub>CH<sub>3</sub>), 1025 cm<sup>-1</sup> (COH); mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M<sup>+</sup>), 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*<sub>6</sub>) 10.65 (s, 1, NH), 7.4–6.8 (m, 4, aromatic protons), 4.61 (s, 1, OH), 3.97 (m, 1, C<sub>17</sub>H), 3.60 (s, 3, CO<sub>2</sub>CH<sub>3</sub>).

**Methyl 17-Oxoalloyohimban-16-carboxylate (7d) [(±)-Alloyohimbionone], 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<sub>254+366</sub>, 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<sub>2</sub>CH<sub>3</sub>), 1720 cm<sup>-1</sup> (C=O); ir (CHCl<sub>3</sub>) 3400 (NH), 2820, 2770 (Bohlmann bands), 1740 (CO<sub>2</sub>CH<sub>3</sub>, s), 1720 (C=O, s), 1670, 1630 cm<sup>-1</sup> (enolic  $\beta$ -keto ester, m); ir (pyridine) 1750 (CO<sub>2</sub>CH<sub>3</sub>, w), 1720 (C=O, w), 1680–1620 cm<sup>-1</sup> (enolic  $\beta$ -keto ester, s); mass spectrum (70 eV) *m/e* (rel intensity) 352 (100, M<sup>+</sup>), 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<sup>+</sup>), 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<sub>3</sub>) 3480 (NH), 2810, 2770, 2760 (Bohlmann bands), 1750 (CO<sub>2</sub>CH<sub>3</sub>, shoulder), 1720 (C=O, m), 1660, 1620 cm<sup>-1</sup> (enolic  $\beta$ -keto ester, m); mass spectrum (70 eV) *m/e* (rel intensity) 352 (100, M<sup>+</sup>), 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°.<sup>8</sup>

**Methyl 17 $\beta$ -Hydroxyalloyohimban-18 $\beta$ -carboxylate (8j), Methyl 17 $\alpha$ -Hydroxyalloyohimban-18 $\beta$ -carboxylate (8k), and 17 $\beta$ -Hydroxy-18 $\beta$ -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<sub>254+366</sub>, 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<sup>+</sup>), 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<sub>2</sub>CH<sub>3</sub>), 1045 cm<sup>-1</sup> (COH).

**8k** had mp 164–167°; mass spectrum (70 eV) *m/e* (rel intensity) 354 (100, M<sup>+</sup>), 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<sup>-1</sup> (COH); nmr (DMSO-*d*<sub>6</sub>)  $\delta$  10.65 (s, 1, NH), 7.40–6.80 (m, 4, aromatic protons), 4.11 (d, 2, CH<sub>2</sub>OH), 3.86 (m, 1, C<sub>17</sub>OH); mass spectrum (70 eV) *m/e* (rel intensity) 326 (91, M<sup>+</sup>), 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 17 $\beta$ -Hydroxyalloyohimban-16 $\beta$ -carboxylate (8h), ( $\pm$ )-Alloyohimbine (8m) and ( $\pm$ )- $\alpha$ -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  $\times$  50 ml). The extracts were combined, washed with water (2  $\times$  10 ml), dried, and evaporated and the resulting mixture of isomers (96 mg, 90%) was separated by (1) preparative tlc [Al<sub>2</sub>O<sub>3</sub> G (type E), hexane-ethyl methyl ketone (60:40),  $R_f$  8h > 8n  $\sim$  8m, and then silica gel PF<sub>254+366</sub>, 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 ( $\pm$ )-alloyohimbine obtained from 9b.<sup>1</sup>

8n had ir (CHCl<sub>3</sub>) identical with that of natural  $\alpha$ -yohimbine, 3570 (OH), 3480 (NH), 2805, 2765 (Bohlmann bands), 1730 (CO<sub>2</sub>CH<sub>3</sub>), 1055 cm<sup>-1</sup> (COH); nmr (CDCl<sub>3</sub> at 300 M-z)  $\delta$  7.75 (s, 1, NH), 7.44 (d, 1, C<sub>9</sub> H),<sup>11</sup> 7.28 (d, 1, C<sub>12</sub> H), 7.15-7.02 (m, 2, C<sub>10</sub>, C<sub>11</sub> H), 3.99 (d of t, 1, C<sub>17</sub> H,  $J$  = 26 Hz), 3.84 (s, 3, CO<sub>2</sub>CH<sub>3</sub>), 3.15 (m, 1, C<sub>3</sub> H);<sup>12</sup> mass spectrum (70 eV)  $m/e$  (rel intensity) 354 (100, M<sup>+</sup>), 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 Alloyohimbine Isomers. Preparation of 8i (and 10c) from 8h.**—8h (28 mg, 7.9  $\times$  10<sup>-4</sup> 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<sub>2</sub>O<sub>3</sub> 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<sub>2</sub>CH<sub>3</sub> conj), 1640 cm<sup>-1</sup> (C=C); mass spectrum (70 eV)  $m/e$  (rel intensity) 336 (100, M<sup>+</sup>), 335 (99), 321 (23), 206 (15), 197 (11), 191 (12), 184 (17), 169 (14), 165 (26).<sup>12</sup>

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

**Preparation of ( $\pm$ )- $\alpha$ -Yohimbine (8n) from ( $\pm$ )-Alloyohimbine (8m).**—8m (30 mg, 8.1  $\times$  10<sup>-2</sup> 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  $\times$  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<sub>2</sub>O<sub>3</sub> 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  $\alpha$ -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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## Heterocyclic Amino Sugar Derivatives. VI. Stabilization of a Reactive Intermediate by Steric Hindrance. Mechanism of 3,6-Anhydro Sugar Formation<sup>1</sup>

CURTIS A. JOHNSON AND PAUL H. GROSS\*

Department of Chemistry, University of the Pacific, Stockton, California 95204

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Circumstantial evidence was obtained that 3,6-anhydro-2-benzamido-2-deoxy- $\beta$ -D-glucopyranosides are formed from 2-benzamido-2-deoxy-3-*O*-mesyl- $\beta$ -D-glucopyranosides via the 3,4 epoxide, and *not via* an oxazoline intermediate. For the synthesis of benzyl 2-amino-3,6-anhydro-2-*N*,4-*O*-carbonyl-2-deoxy- $\beta$ -D-glucopyranoside from benzyl 2-benzoyloxycarbonylamino-2-deoxy-6-*O*-*p*-toluenesulfonyl- $\beta$ -D-glucopyranoside the order of ring closures of the carbonyl and anhydro rings was determined. An intermediate with the 3,6-anhydro structure was isolated. This intermediate was then changed to the 2-*N*,4-*O*-carbonyl compound.

Two procedures are currently available for the synthesis of 3,6-anhydro derivatives of 2-amino-2-deoxy- $\beta$ -D-glucopyranosides.

Foster, Stacey, and Vardheim<sup>2</sup> used methyl 2-benzoyloxycarbonylamino-2-deoxy-6-*O*-tosyl- $\beta$ -D-glucopy-

ranoside (I) in reaction with base to form methyl 2-amino-3,6-anhydro-2-*N*,4-*O*-carbonyl-2-deoxy- $\beta$ -D-glucopyranoside (II).<sup>2</sup> Under these conditions no inversion occurred at C<sub>3</sub>. The tosyl group at C<sub>6</sub> was readily displaced and the 3,6-anhydro ring was unequivocally formed, the formation of other rings being sterically impossible. In the second procedure, Reckendorf and Bonner used methyl 2-benzamido-2-

(1) A preliminary communication was presented at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, Abstract Carb 000. Taken from the doctoral thesis of C. A. Johnson, University of the Pacific, 1971. This work was partially supported by Grant No. GP 12222 of the National Science Foundation. Part V: F. R. Seymour and P. H. Gross, *J. Org. Chem.*, **36**, 1085 (1971).

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