white needles, m.p. 69–70°, which was shown to be identical with the subsequently described material by a mixed melting-point determination and by comparison of infrared and ultraviolet spectra.

5-Methylindanone (5).—β-(*m*-Tolyl)propionic acid (**6**), m.p. 40.5–41.5° (lit.[4b] 42–43°), was prepared from *m*-bromotoluene *via* *m*-tolualdehyde[26] and *m*-methylcinnamic acid,[27] m.p. 115–116° (lit. 111.5°,[4b] 113–114°[27b]), as previously described. To 10 g. of polyphosphoric acid heated to 78 ± 2° was added, portionwise and with stirring over a 20-min. period, 718 mg. (4.36 mmoles) of the acid **6**. After the addition, the mixture was stirred at 78 ± 2° for 4.5 hr. and then cooled and diluted with ice water. The crude product, extracted with ether, was washed successively with aqueous sodium bicarbonate and aqueous sodium chloride, dried, and concentrated to leave 616 mg. (96.5%) of crude product as a yellow oil which crystallized on standing, m.p. 31–43°.[28] The thin-layer chromatogram[18] of the crude product indicated the presence of approximately equal amounts of two components, one of which has the same R_f value as 7-methylindanone (**7**). A 598-mg. sample of the crude product was chromatographed on 75 g. of silica gel to separate 272 mg. (43.5%) of crude 7-methylindanone (**7**) (eluted with 4:1 petroleum ether–ether), m.p. 51–53°, and 319 mg. (51.5%) of crude 5-methylindanone (**6**) (eluted with 1:1 petroleum ether–ether), m.p. 67–69°. Recrystallization from petroleum ether followed by sublimation afforded 144 mg. of pure 7-methylindanone (**7**) as white needles, m.p. 52.5–53.5°, identified with a previously described sample[23] by a mixed melting-point determination and comparison of infrared spectra.

Recrystallization from petroleum ether separated 229 mg. of the pure 5-methylindanone (**6**) as white needles, m.p. 69–70°, infrared absorption[15] at 1710 cm.$^{-1}$ (conj. C=O in a 5-membered ring), ultraviolet maxima[16] at 253 mμ (ε 15,500), 287 mμ (ε 3520), and 294 mμ (ε 3630). The sample has n.m.r. peaks[25] (60 Mc.) at 7.58 τ (3*H*, singlet, CH_3-), 7.2 to 7.5 τ (2*H*, multiplet) and 6.8 to 7.1 τ (2H multiplet), as well as peaks in the region 2.3 to 2.9 τ (3*H*, aromatic C–H).

Anal. Calcd. for $C_{10}H_{10}O$: C, 82.16; H, 6.90; mol. wt., 146. Found: C, 82.37; H, 6.95; mol. wt., 146 (mass spectrum).

(26) L. I. Smith and M. Bayliss, *J. Org. Chem.*, **6**, 437 (1941).

(27) The Doebner modification of the Knoevenagel reaction was employed. (a) J. R. Johnson, *Org. Reactions*, **1**, 248 (1942); (b) P. N. Agarval, K. C. Pandya and I. L. Tripath, *Proc. Indian Acad. Sci.*, **22A**, 400 (1945).

(28) The supposedly pure 5-methylindanone previously prepared by this method (ref. 4) was reported to melt at 59–60°[4a] and at 59°.[4b]

Indole Alkaloids. I. Base-catalyzed Condensations with Yohimbanones and Alloyohimbanones[1]

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Base-catalyzed condensations of yohimban-17-one (**1**) with magnesium methyl carbonate, ethyl formate, and ethyl oxalate afforded 17-oxoyohimban-18-carboxylic acid (**2**), 18-hydroxymethyleneyohimban-17-one (**11**), and ethyl 17-oxoyohimban-18-glyoxylate (**24**), respectively. Esterification of β-keto acid **2** gave methyl 17-oxoyohimban-18α-carboxylate (**3**) [isomeric with yohimbinone (**6**)] which on reduction with sodium borohydride afforded 17α-hydroxy ester **4** and 17β-hydroxy ester **5**. Neither **4** nor **5** corresponded to yohimbine (**7**) or β-yohimbine (**8**), the known C-16 isomers. Treatment of 18-hydroxymethylene ketone **11** with hydroxylamine gave two isomeric isoxazoles **12** and **13**. On conversion with base of isoxazole **12** to 17-oxo-18α-carbonitrile **14** and reduction of **14** with sodium borohydride, 17α-hydroxynitrile **15** and 17β-hydroxynitrile **16** were obtained. Hydrolysis of **15** followed by esterification afforded 17α-hydroxy ester **4**. Similarly, **16** was converted to 17β-hydroxy ester **5**. Collidine treatment of the *O*-tosylate of 17α-hydroxy ester **4** gave α,β-unsaturated ester **18**, isomeric with apoyohimbine (**17**). These results show that carboxylation and formylation of yohimban-17-one occurred at the C-18 position. P.m.r. spectral measurements were used to confirm assignments of structure and configuration.

The chemistry of alkaloids of the β-carboline type has been studied extensively in recent years. Reserpine, one of the more complex members of this group, has been of special interest because of its stereochemical complexity and its pharmacological properties. Reserpine has substituents at positions 16, 17 and 18 in the E ring while most of the other structurally related alkaloids lack substituents at position 18. Since the C-18 trimethoxybenzoyloxy substituent of reserpine has an important influence on its pharmacological properties,[2] and since there is little known about C-18 substituted derivatives of yohimbine or its stereoisomers,[3] we became interested in a study of the introduction of activating groups, such as carboxyl and ethoxalyl, into several yohimbanes containing a keto group in the E ring. Such activating groups were considered an essential prerequisite for the selective introduction of other functional groups (*i.e.*, bromine, methyl, etc.) into the E ring.

A number of suitable E ring ketones have been prepared by transformations of known alkaloids[4] or by total synthesis.[5] However, few reactions have been reported in which these ketones have been utilized for the introduction of functional groups into the E ring. Russian workers have reported the introduction of ethoxycarbonyl[6] and formyl[7] groups at the C-16 position of yohimban-17-one (**1**); however, the reliability

(1) A portion of this work was presented at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September 3–8, 1961.

(2) R. A. Lucas, M. E. Kuehne, M. J. Ceglowski, R. L. Dziemian, and H. B. MacPhillamy, *J. Am. Chem. Soc.*, **81**, 1928 (1959); M. M. Robison, R. A. Lucas, H. B. MacPhillamy, W. Barrett, and A. J. Plummer, *Experientia*, **17**, 14 (1961).

(3) Oxygenation at the C-18 position of certain derivatives has been reported using microbiological techniques: S. C. Pan and F. L. Weisenborn, *J. Am. Chem. Soc.*, **80**, 4749 (1958); W. O. Godtfredsen, Y. Korsby, H. Loreck, and S. Vangedal, *Experientia*, **14**, 88 (1958).

(4) (a) B. Witkop, *Ann.*, **554**, 83 (1943); (b) J. Jost, *Helv. Chim. Acta*, **32**, 1297 (1949); (c) Z. J. Vjdělek and K. Macek, *Collection Czech. Chem. Commun.*, **24**, 2493 (1959); (d) A. Le Hir and E. W. Warnhoff, *Compt. rend.*, **246**, 1564 (1958); (e) S. Kimoto, M. Okamoto, and H. Kondo, *Chem. Pharm. Bull.* (Tokyo), **7**, 650 (1959); (f) A. Le Hir, M.-M. Janot, and R. Goutarel, *Bull. soc. chim.* France, 1027 (1953); (g) R. K. Hill and K. Muench, *J. Org. Chem.*, **22**, 1276 (1957); (h) E. Wenkert, E. W. Robb, and N. V. Bringi, *J. Am. Chem. Soc.*, **79**, 6570 (1957); (i) C. F. Huebner, A. F. St. André, E. Schlittler, and A. Uffer, *ibid.*, **77**, 5725 (1955); (j) R. C. Elderfield, A. E. Hydorn, E. Schenker, and K. K. Wyckoff, *J. Org. Chem.*, **24**, 1296 (1959).

(5) (a) G. A. Swan, *J. Chem. Soc.*, 1534 (1950); (b) P. G. Philpott and A. M. Parsons, *ibid.*, 3018 (1958); (c) G. B. Kline, *J. Am. Chem. Soc.*, **81**, 2251 (1959).

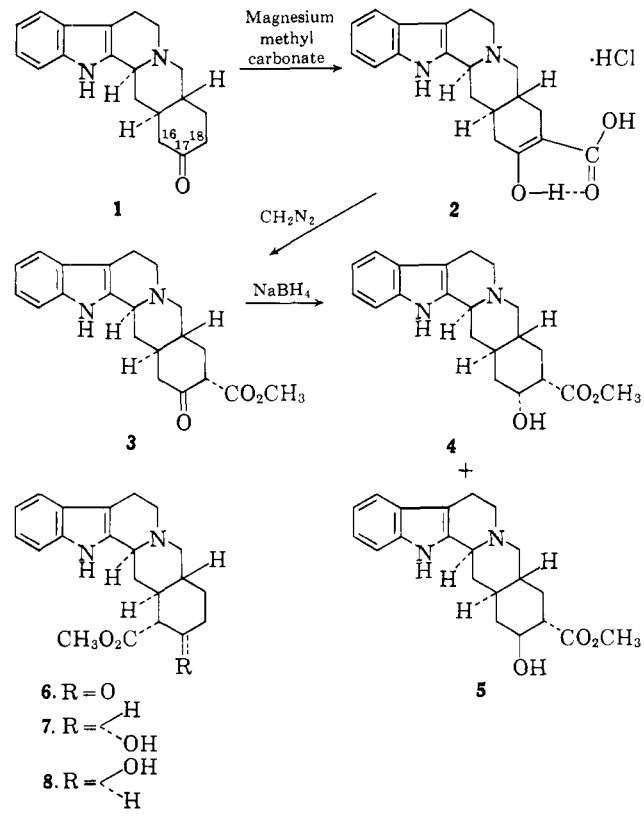
(6) L. A. Aksanova and N. A. Preobrazhenskiĭ, *Dokl. Akad. Nauk SSSR*, **117**, 81 (1957).

(7) G. S. Gusakova and N. A. Preobrazhenskiĭ, *ibid.*, **101**, 1061 (1955).

of this work has been questioned.[8,9] By analogy to results obtained with 3-keto-5α-steroids substitution at C-18 is expected, for it has been amply demonstrated that these steroids give 2-substituted derivatives in reactions (brominations, formylations, ethoxalylations) involving intermediate enol or enolate ion formation.[10] In order to ascertain the position of substitution we studied the ethoxalylation, carboxylation and formylation of yohimban-17-one.[9]

Treatment of ketone **1** with magnesium methyl carbonate (MMC)[11,12] in *N*,*N*-dimethylformamide, followed by hydrolysis with cold hydrochloric acid, afforded a good yield of a β-keto acid which, on the basis of its subsequent transformations, was shown to be 17-oxoyohimban-18-carboxylic acid hydrochloride (**2**). The β-keto acid was assigned the enolized chelate structure **2** on the basis of its infrared spectrum [ν_{max}^{Nujol} 1658 (s), 1619 cm.$^{-1}$ (m)]. Upon warming an aqueous solution, decarboxylation to yohimban-17-one (92%) readily occurred. On treatment with diazomethane (or *N*,*N*'-dicyclohexylcarbodimide and methanol[13]) methyl 17-oxoyohimban-18α-carboxylate (**3**) was formed. The infrared spectrum showed the presence of both keto and enol forms for **3** and the ultraviolet spectrum in base showed increased absorption at 289 mμ (ϵ 20,200), as anticipated for a β-keto ester which readily forms an enolate ion. Since enolization provides a convenient pathway for equilibration of the methoxycarbonyl group the more stable equatorial α-configuration was assigned. The equatorial conformation of the methoxycarbonyl group was demonstrated by the absence of change on equilibration of the ester with base. The physical properties of **3** were clearly different from those of the known non-enolic methyl 17-oxoyohimban-16α-carboxylate (**6**) (yohimbinone)[4d,e,14,15] which has an equatorial methoxycarbonyl group. The non-identity of **3** and **6** showed that substitution had indeed occurred at the C-18 position. Further proof for the position of substitution was obtained by reduction of **3** with sodium borohydride to give two epimeric 17-hydroxy esters **4** and **5**. Neither **4** nor **5** corresponded to the known C-16 isomers, yohimbine (**7**) and β-yohimbine (**8**).

The epimer **4**, m.p. 210–214° dec., was the first epimer eluted from an alumina column and was considered to have an axial C-17 hydroxyl group since axial alcohols are generally adsorbed less strongly on alumina



than equatorial alcohols. The second epimer, m.p. 142–147°, eluted from the column was assigned structure **5** with an equatorial C-17 hydroxyl group.

The p.m.r. spectra[16] (see Table I) of epimeric hydroxy esters **4** and **5**, as well as their *O*-acetates, confirmed the assignments of structure and configuration. In agreement with the general observation[17] that axial proton signals are shifted to higher field than equatorial, the equatorial C-17 proton signal of yohimbine (**7**) was observed at 5.82 τ whereas the axial C-17 proton signal of β-yohimbine (**8**) was shifted to higher field and was obscured by the methoxycarbonyl signal, thus giving a four-proton intensity peak centered at 6.27 τ. On tosylation of β-yohimbine the C-17 proton signal was shifted downfield and observed at 5.17 τ while the C-17 proton signal of yohimbine *O*-tosylate was observed at 4.78 τ. The equatorial C-17 proton signals of pseudoyohimbine and corynanthine were observed at 5.97 τ and 6.02 τ, respectively, whereas the axial C-17 proton signal of α-yohimbine (**10**) was overlapped by the methoxycarbonyl signal at 6.27 τ (four-proton intensity peak). The doublets at 5.12–5.67 τ observed in the spectra of these compounds (see Table I) measured in deuterodimethyl sulfoxide were assigned to the hydroxyl proton spin-coupled to the adjacent C-17 proton since, on addition of deuteriomethanol to solutions of yohimbine and β-yohimbine, the signals at 5.38 τ and 5.15 τ, respectively, disappeared. When dissolved in deuteriochloroform the hydroxyl signal

(8) J. E. Saxton, *Ann. Rept. Progr. Chem. (Chem. Soc. London)*, **55**, 306 (1958).

(9) After the completion of this work a report on the introduction of formyl and methoxycarbonyl groups at the C-18 position of yohimban-17-one was brought to our attention: P. D. Pacht, Ph.D. thesis, Harvard University, 1960.

(10) H. J. Ringold, E. Batres, O. Halpern, and E. Necoechea, *J. Am. Chem. Soc.*, **81**, 427 (1959); N. A. Nelson and R. N. Schut, *ibid.*, **80**, 6630 (1958), and references contained therein.

(11) (a) M. Stiles and H. L. Finkbeiner, *J. Am. Chem. Soc.*, **81**, 505 (1959); (b) M. Stiles, *ibid.*, **81**, 2598 (1959).

(12) The experimental details for the preparation of the reagent, MMC, were kindly supplied by Professor M. Stiles (University of Michigan).

(13) For similar esterifications with *N*,*N*'-dicyclohexylcarbodiimide and alcohols see L. Peyron, *Bull. soc. chim.* France, 613 (1960) and A. Brossi, M. Baumann, M. Gerecke, and E. Kyburz, *Helv. Chim. Acta*, **43**, 2071 (1960).

(14) E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, **81**, 5601 (1959), have ascribed the non-enolic properties of yohimbinone (**6**) to the steric interactions (*peri* effect) of the C-14 hydrogen atoms and the methoxycarbonyl group in the hydrogen-bonded enol.

(15) (a) Prepared according to experimental conditions kindly supplied by Professors A. Le Hir and R. Goutarel (University of Paris) prior to publication; (b) M.-M. Janot, R. Goutarel, E. W. Warnhoff, and A. Le Hir, *Bull. soc. chim.* France, 637 (1961).

(16) P.m.r. spectra were determined with a Varian Model A-60 spectrometer in deuterated dimethyl sulfoxide. This solvent was chosen for all measurements since compounds **4**, **5**, **15**, and **16** were insufficiently soluble in deuteriochloroform. τ Values were obtained in the usual manner with tetramethylsilane as internal standard.

(17) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958); R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *ibid.*, **80**, 6098 (1958); E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, No. **3**, 97 (1962); E. L. Eliel, M. H. Gianni, and Th. H. Williams, *ibid.*, No. **17**, 741 (1962).

TABLE I

PROTON MAGNETIC RESONANCE SPECTRAL MEASUREMENTS[16]

	C-17 Hydroxyl doublet (τ)	C-17 proton Multiplet (τ)	C-17 proton Conformation[a]	Methyl singlets (τ) CO_2CH_3	Methyl singlets (τ) CH_3OH solvate	Methyl singlets (τ) $OCOCH_3$
Pseudoyohimbine	5.67[b,c]	5.97	e	6.33		
Corynanthine[d]	5.12	6.02	e	6.47		
Yohimbine (7)	5.38[e]	5.82	e	6.27		
Yohimbine in $CDCl_3$[f]		5.68	e	6.10		
β-Yohimbine (8)	5.15[e]	6.27[g]	a	6.27[g]		
α-Yohimbine (10)	5.42	6.27[g]	a	6.27[g]		
Yohimbine *O*-tosylate		4.78	e	6.40		
β-Yohimbine *O*-tosylate		5.17[h]	a	6.35		
17α-Hydroxy ester 4	5.37[e]	5.75	e	6.40	6.60	
17β-Hydroxy ester 5	5.15[e]	6.38[g]	a	6.38[g]		
17α-Hydroxynitrile 15	4.68	5.95	e			
17β-Hydroxynitrile 16[f]	4.60	6.47[h]	a			
17α-Hydroxy ester *O*-acetate		4.40	e	6.38	6.42	8.05
17β-Hydroxy ester *O*-acetate		5.05[h]	a	6.38		8.05

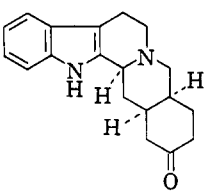
[a] a = axial, e = equatorial. [b] Multiplet of intensity equivalent to two protons; includes signal of equatorial C-3 proton. [c] After addition of CD_3OD the hydroxyl signal disappeared leaving a one-proton multiplet from the equatorial C-3 proton. [d] Measured in dimethyl sulfoxide. [e] After addition of CD_3OD this signal disappeared. [f] Determined with a Varian Model V-4300-B spectrometer operated at 56.4 Mc. [g] Axial C-17 proton signal coincident with methoxycarbonyl signal—total intensity equivalent to four protons. [h] Broad, as anticipated for an axial proton coupled with two axial and one equatorial protons.

of yohimbine was not observed. Pseudoyohimbine exhibited a two-proton multiplet centered at 5.67 τ from the coincidence of signals from the equatorial C-3 proton and the C-17 hydroxyl. On addition of deuteriomethanol the hydroxyl signal disappeared leaving a one-proton multiplet with unchanged chemical shift (equatorial C-3 proton).[18]

Hydroxy ester **4** showed a multiplet centered at 5.75 τ (equatorial C-17 proton) whereas the signal for the axial C-17 proton of hydroxy ester **5** was shifted to higher field and coincided with the methoxycarbonyl signal to produce a four-proton peak at 6.38 τ. The doublets at 5.37 τ and 5.15 τ from the hydroxyls of **4** and **5**, respectively, disappeared when the hydroxyl protons were exchanged for deuterium on addition of deuteriomethanol.

These arguments are confirmed and extended by an examination of the respective p.m.r. spectra[16] after acetylation whereupon the anticipated shifts to lower field[17,18] were observed. The *O*-acetate of **4** exhibited a signal from the equatorial C-17 proton as a multiplet centered at 4.40 τ and the *O*-acetate of **5** exhibited a signal centered at 5.05 τ from the axial C-17 proton as a broad multiplet, as anticipated for an axial proton coupled with two axial and one equatorial protons.

Carboxylation experiments with alloyohimban-17-one[4f] (**9**) using magnesium methyl carbonate were not encouraging since the isolated β-keto acid hydrochloride appeared to be unstable. Esterification with diazomethane followed by reduction with sodium borohydride gave a mixture of products which, after chromatography on alumina, afforded alloyohimban-17α-ol and a hydroxy ester fraction. The hydroxy ester fraction was a mixture of five components as shown by paper chromatography.[4c] One component had an R_f identical with that of α-yohimbine[4f,19] (**10**), suggesting that condensation occurred to some extent at C-16. Two other components had R_f's corresponding with alloyohimban-17-one and alloyohimban-17α-ol, leaving the remaining two components



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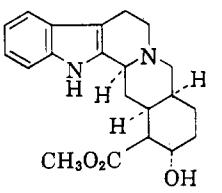

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unidentified. Carboxylation at C-18, therefore, has not been excluded. Analogies based on studies of 3-keto-5β-steroids are of little help since substitutions at C-4 and C-2 have been reported in reactions involving intermediate enol formation.[20] More definitive experiments are in progress to determine the exact nature of the substitution products.

We next directed our attention to the formylation of yohimban-17-one (**1**), where substitution at C-16 has been reported.[7] When **1** was treated with ethyl formate and sodium methoxide in either benzene or dioxane, a formylation product was obtained in 70–90% yields whose chemical properties indicated that it was 18-hydroxymethyleneyohimban-17-one (**11**) rather than the C-16 substitution product reported by the Russian workers.[7] The hydroxymethylene ketone **11** was treated with hydroxylamine hydrochloride in acetic acid to give a mixture of yohimbano[18,17*d*]isoxazole (**12**) and yohimbano[17,18*c*]-isoxazole (**13**). Treatment of the mixture with sodium methoxide in methanol at room temperature, or heating with sodium ethoxide in ethanol, afforded ketonitrile **14**,[21] along with unchanged isoxazole **13**. Conversion of hydroxymethylene ketone **11** directly to ketonitrile **14** with *O*,*N*-bis(trifluoroacetyl)hydroxylamine[22] gave a poor yield. The cyano group in **14**

(18) W. E. Rosen and J. N. Shoolery, *J. Am. Chem. Soc.*, **83**, 4816 (1961).

(19) A. Le Hir, R. Goutarel, and M.-M. Janot, *Ann. Pharm. Franc.*, **11**, 546 (1953).

(20) H. H. Inhoffen, G. Kölling, G. Koch, and I. Nebel, *Chem. Ber.*, **84**, 361 (1951); R. O. Clinton, R. L. Clark, F. W. Stoner, D. K. Phillips, K. F. Jennings, and A. J. Manson, *Chem. Ind.* (London), 2099 (1961).

(21) For similar preparations of α-ketonitriles see K. v. Auwers, T. Bahr, and E. Frese, *Ann.*, **441**, 54 (1925); W. S. Johnson, J. W. Petersen, and C. D. Gutsche, *J. Am. Chem. Soc.*, **69**, 2942 (1947); G. V. Bhide, N. L. Tikotkar, and D. D. Tilak, *Tetrahedron*, **10**, 230 (1960), and references cited therein.

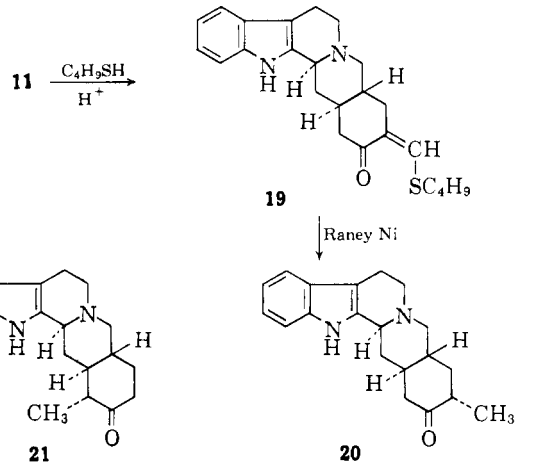
(22) J. H. Pomeroy and C. A. Craig, *J. Am. Chem. Soc.*, **81**, 6340 (1959); H. M. Kissman, A. S. Hoffman, and M. J. Weiss, *J. Org. Chem.*, **26**, 2610 (1961).

was assigned the equatorial α-configuration by virtue of its method of preparation, for the basic reaction conditions assure equilibration of the nitrile group to the more stable α-configuration.

Reduction of ketonitrile **14** with sodium borohydride and chromatography of the product over alumina afforded two epimeric 17-hydroxynitriles. The epimer, m.p. 263–265° dec., eluted first from the column, was tentatively assigned the structure **15** with an axial hydroxyl group and the second epimer from the column, m.p. 247–250° dec., was assigned the structure **16** with an equatorial hydroxyl group. In the p.m.r. spectra[16] the equatorial C-17 proton multiplet of **15** was observed at 5.95 τ while **16** showed a broad multiplet centered at 6.47 τ. These results support the assigned structures, for the axial C-17 proton signal in **16** is shifted to higher field than the equatorial as expected.[17] Doublets from the hydroxyls were observed at 4.68 τ and 4.60 τ for **15** and **16**, respectively.

Hydrolysis of 17β-hydroxynitrile **16** with sodium hydroxide afforded a crude hydroxy acid which was esterified with diazomethane to a hydroxy ester in 41% over-all yield. The ester was identical with the 17β-hydroxy ester **5** obtained on reduction of methyl 17-oxoyohimban-18α-carboxylate (**3**) (*vide supra*). Hydrolysis of 17α-hydroxynitrile **15**, followed by esterification with diazomethane and chromatography over alumina, gave methyl yohimb-17-ene-18-carboxylate (**18**) (10% yield) and a hydroxy ester (12% yield) identical with the 17α-hydroxy ester **4** obtained on reduction of the keto ester **3**. Elimination during hydrolysis of 17α-hydroxynitrile **15** with formation of α,β-unsaturated ester **18** provides further support for the axial C-17 hydroxyl group. Collidine treatment of the *O*-tosylate of **4** also afforded the α,β-unsaturated ester **18**, isomeric with apoyohimbine (**17**).[23] In apoyohimbine the aromatic and olefinic protons were found[16] in a multiplet at 2.53–3.63 τ with the extreme high field peak centered at 3.30 τ clearly identified as the C-17 olefinic proton. The C-17 olefinic proton of **15** was found to be obscured by the absorption of the aromatic protons in the multiplet at 2.55–3.22 τ of intensity equivalent to 5 protons (1 olefinic + 4 aromatic). These results establish that the nitrile groups in **15** and **16** are at the C-18 position and, as a consequence, formylation of yohimban-17-one occurred at the C-18 position.

A second proof for the position (C-18) of the formyl group in **11** was obtained by conversion of **11** to 18α-methylyohimban-17-one (**20**), which was clearly different from 16α-methylyohimban-17-one (**21**).[4j,24] The hydroxymethylene ketone **11** was converted to 18-

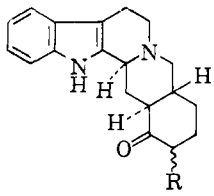


butylthiomethyleneyohimban - 17 - one (**19**) with 1-butanethiol and glacial acetic acid in the presence of anhydrous magnesium sulfate and **19** was reduced with Raney nickel[25] to give the methyl ketone **20** in good yield. Comparison of **20** with a sample of the 16α-methyl-17-ketone **21**, prepared by Oppenauer oxidation of 16-methylyohimbol,[26] served to distinguish the two compounds. Small but distinct differences were observed in the infrared spectra of the two compounds and their X-ray powder diagrams were distinctly different.

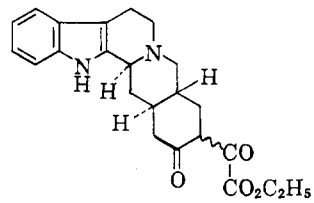
Thus base-catalyzed condensations of yohimban-17-one with magnesium methyl carbonate and ethyl formate have occurred at C-18. These results are consistent with previous work on alicyclic ketones.[10]

When yohimban-17-one (**1**), yohimban-16-one (**22**)[4g,h] or alloyohimban-17-one (**9**) were treated with ethyl oxalate in the presence of sodium methoxide, the corresponding glyoxylates were obtained. The ethoxalyl product from ketone **1** was assigned the structure ethyl 17-oxoyohimban-18-glyoxylate (**24**) by analogy with the carboxylation results where C-18 substitution was observed. The ability of the glyoxylate from ketone **22** to form an enolate ion in base supports the assigned ethyl 16-oxoyohimban-17-glyoxylate (**23**) structure for

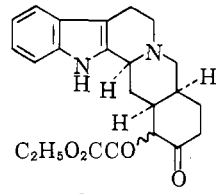
(23) C. Barger and E. Field, *J. Chem. Soc.*, **123**, 1038 (1923).
(24) Z. J. Vejdělek and K. Macek, *Chem. Listy*, **52**, 2140 (1958).
(25) R. E. Ireland and J. A. Marshall, *Chem. Ind.* (London), 1534 (1960).
(26) A sample of 16-methylyohimbol for the preparation of **21** was kindly supplied by Professor R. C. Elderfield, University of Michigan.



22. C = H
23. R = $HRCO_2C_2H_5$



24



25

this product. The ethoxalyl derivative from ketone 9 has been tentatively assigned the structure ethyl 17-oxoalloyohimban-16-glyoxylate (**25**). Definitive experiments however are needed to establish that substitution occurred at C-16.

The chemistry of the compounds reported is being studied and their use for the introduction of additional substituents into the E ring is being investigated.

Experimental

Unless otherwise noted all melting points were taken in sealed capillaries which were inserted in the bath at about 10–20° below the melting point. Unless otherwise noted samples were dried for analysis *in vacuo* over phosphorus pentoxide at 100° for 4–8 hr. Ultraviolet absorption spectra were measured on a Cary recording spectrophotometer. Infrared spectra were determined on a Perkin–Elmer spectrophotometer (Model 21).

17-Oxoyohimban-18-carboxylic Acid Hydrochloride (**2**).—A mixture of 2.0 g. (6.8 mmoles) of yohimban-17-one (**1**) and 25 ml. of a solution of magnesium methyl carbonate in *N,N*-dimethylformamide (*ca.* 2 *N*) was stirred and heated at 120–130° for 3 hr. under a slow stream of nitrogen. The mixture was cooled in an ice bath and added slowly to a stirred mixture of 50 g. of ice and 30 ml. of concentrated hydrochloric acid which was cooled in an ice–salt bath. The reaction flask was rinsed with a mixture of 2 g. of ice and 1 ml. of concentrated hydrochloric acid. The solid which separated was filtered and washed with 2 ml. of cold 6 *N* hydrochloric acid. After drying in the air for a short period of time and *in vacuo* over phosphorus pentoxide at room temperature for 6 hr., there was obtained 2.71 g. (98%) of **2** as tan crystals, m.p. 292–294° dec. Purification was accomplished by treating 1.91 g. of the crude product with 650 ml. of methanol, filtering through a coarse porosity sintered glass filter (some suspended solid passed through the filter) and diluting the filtrate with 600 ml. of ether. The mixture was cooled and filtered (medium porosity–sintered glass filter) to give 0.860 g. (45%) of white crystals, m.p. 314–317° dec.; ν_{max}^{Nujol} 3520, 3256, 3125, 1658 (s), 1619 (m), 1192 cm.$^{-1}$ (s); $\lambda_{max}^{CH_3OH}$ 221 mμ (ε 42,200), 270 (10,060), 281 (8,830), 289 (6,800). The sample for analysis was dried *in vacuo* over phosphorus pentoxide for 4 hr. at room temperature.

Anal. Calcd. for $C_{20}H_{22}N_2O_3 \cdot HCl \cdot 1/2\ H_2O$: C, 62.6; H, 6.30; N, 7.30; Cl, 9.24; H_2O, 2.34; CO_2, 11.5. Found: C, 62.4; H, 6.65; N, 7.41; Cl, 9.46; H_2O (K.F.), 2.06; CO_2, 10.9.

Methyl 17-Oxoyohimban-18α-carboxylate (**3**).—To a suspension of 0.500 g. (1.30 mmoles) of keto acid hydrochloride **2** in 50 ml. of ice-cold methanol was added 50 ml. of ice-cold ether containing diazomethane (prepared from 4.0 g. of nitrosomethylurea and 8 ml. of 40% potassium hydroxide and dried over potassium hydroxide pellets). The mixture was allowed to stand at room temperature for 10 min. and the excess diazomethane was decomposed by the dropwise addition of glacial acetic acid. The solvent was removed *in vacuo* to give 0.598 g. of a hygroscopic glass. The glass was dissolved in 15 ml. of methanol and the solution boiled while water was added dropwise until white crystals began to separate. Cooling and filtration gave 0.201 g. (42%) of white crystals, m.p. 186–188° dec. The filtrate was diluted with water to give a second crop of crystals (0.024 g., 5%). The filtrate was extracted with five 10-ml. portions of chloroform and the extracts evaporated *in vacuo* to give a glass. The glass was dissolved in 2 ml. of methanol and the solution diluted with 1 ml. of water. Cooling and filtration afforded 0.102 g. (21%) of crystals, m.p. 181–183° dec. The three crops of crystals (68%) were combined and recrystallized by dissolving in 45 ml. of methanol and diluting the solution with 3 ml. of water. Cooling and filtration gave 0.211 g. (44%) of **3** as white crystals, m.p. 186–188° dec.; $[\alpha]^{25}D$ −157° (*c* 1.00, CH_3OH), − 176° (*c* 1.10, $CHCl_3$); ν_{max}^{KBr} 3510 (w), 3379 (m), 1623 cm.$^{-1}$ (m); $\lambda_{max}^{CH_3OH}$ 225 mμ (ε 39,800), 273 (8,310), 283 (8,200), 290 (6,620); $\lambda_{max}^{0.1\ N\ NaOH}$ 225 mμ (ε 38,200), 282 (20,800), 289 (20,200); violet color with alcoholic ferric chloride.

Anal. Calcd. for $C_{21}H_{24}N_2O_3 \cdot 3/4\ H_2O$: C, 68.9; H, 7.02; N, 7.66; H_2O, 3.69. Found: C, 68.7; H, 6.52; N, 7.64; H_2O (K.F.), 4.95.

18-Hydroxymethyleneyohimban-17-one (**11**).—To a cooled mixture of 10.0 g. of yohimban-17-one (**1**), 10.0 g. of sodium methoxide (Mathieson), and 300 ml. of sodium–dried benzene was added 14 ml. of ethyl formate. After stirring under nitrogen at room temperature for 20 hr. the mixture was poured onto 300 g. of ice and 200 ml. of water. The organic layer was separated and washed with three 100-ml. portions of 0.1 *N* sodium hydroxide. The basic washings and aqueous layer were combined and neutralized in the cold with glacial acetic acid. Filtration afforded 9.4 g. (83%) of tan crystals, sinters to a glass at 140–147°. A second crop of crystals (1.8 g., 16%) was obtained from the mother liquors on cooling overnight. Recrystallization from methanol several times gave off-white needles, sinters to a glass at 139–142°. After drying over phosphorus pentoxide for 10 hr. the product **11** melted at 207–211° dec. (sinters to a glass at 145–148°); $[\alpha]^{25}D$ − 238° (*c* 1.03, dimethylformamide); ν_{max}^{KBr} 1603 (s), 1488 (s), 1470 (s), 1290 (s), 1031 cm.$^{-1}$ (m); $\lambda_{max}^{CH_3OH}$ 224 mμ (ε 35,300), 273 (sh.) (10,900), 284 (13,200), 290 (12,500), 314 (5,860); $\lambda_{max}^{0.1\ N\ NaOH}$ 218 mμ (ε 52,600), 284 (11,300), 290 (13,600).

Anal. Calcd. for $C_{20}H_{22}N_2O \cdot 1/2\ H_2O$: C, 72.5; H, 7.00; N, 8.45. Found: C, 72.3; H, 6.95; N, 8.84.

The following procedure was found to be more convenient for large scale runs: To a cooled mixture of 5.0 g. (17 mmoles) of yohimban-17-one (**1**), 5.0 g. of sodium methoxide (Mathieson), and 150 ml. of dry peroxide-free dioxane was added 7.0 ml. of ethyl formate. The mixture was stirred under nitrogen at room temperature for 21 hr. and neutralized with acetic acid. After concentration to near dryness *in vacuo*, 50 ml. of water and 25 ml. of methanol were added. Concentration and filtration gave 5.3 g. (94%) of tan crystals, m.p. 204–210° dec. (sinters to a glass at 145–154°). A 1.0-g. sample was triturated with 10 ml. of methanol to give 0.860 g. of **11** as tan crystals, m.p. 207–211° dec. (sinters to a glass at 144–148°), $[\alpha]^{25}D$ − 232° (*c* 1.3, DMF).

Yohimbano[18,17-*d*]isoxazole (**12**) **and Yohimbano[17,18-*c*]-isoxazole** (**13**) **Hydrochlorides**.—A mixture of 1.0 g. (3.0 mmoles) of hydroxymethylene ketone **11**, 0.225 g. (3.2 mmoles) of hydroxylamine hydrochloride and 15 ml. of glacial acetic acid was heated in an oil bath at 100° for 6 min. The mixture was chilled and filtered to give 0.430 g. (39%) of white needles. Recrystallization was carried out by dissolving in aqueous methanol and concentrating on a steam bath. There was obtained 0.148 g. of a mixture of **12** and **13** as white needles, m.p. 310–315° dec. (heating block), $[\alpha]^{25}D$ −132° [*c* 0.264, dimethylformamide–H_2O (1:1)].

Anal. Calcd. for $C_{20}H_{21}N_3O \cdot HCl \cdot 1/4\ H_2O$: C, 66.7; H, 6.29; N, 11.7; Cl, 9.84; H_2O, 1.25. Found: C, 66.7; H, 6.38; N, 11.9; Cl, 9.95; H_2O (K.F.), 1.96.

17-Oxoyohimban-18α-carbonitrile (**14**).—A mixture of 0.360 g. (1.0 mmole) of isoxazoles **12** and **13** was added to a solution of 0.115 g. of sodium in 10 ml. of ethanol. After being allowed to stand overnight the mixture was refluxed under nitrogen for 3 hr. The mixture was neutralized with glacial acetic acid, diluted with 30 ml. of water, and chilled to give 0.281 g. of tan crystals, m.p. 263–268° dec. A 0.225-g. sample was dissolved in chloroform:acetone (9:1) and chromatographed over silica gel. The product was eluted with chloroform:acetone (1:1) and crystallized from aqueous methanol to afford 0.100 g. of **14** as tan needles, m.p. 287–289° dec.; $[\alpha]^{25}D$ − 220° (*c* 1.09, pyridine); ν_{max}^{KBr} 2252, 2203, 1724 cm.$^{-1}$; $\lambda_{max}^{0.1\ N\ NaOH}$ 224 mμ (ε 37,250), 269 (14,740).

Anal. Calcd. for $C_{20}H_{21}N_3O \cdot 1/4\ H_2O$: C, 74.2; H, 6.69; N, 13.0; H_2O, 1.39. Found: C, 74.5; H, 6.69; N, 13.2; H_2O (K.F.), 1.27.

17α-Hydroxyyohimban-18α-carbonitrile (15) 17β-Hydroxyyohimban-18α-carbonitrile (16).—To a cold solution of 0.350 g. of sodium borohydride in 50 ml. of ethanol was added 2.00 g. of ketonitrile **14**. The mixture was stirred under nitrogen at room temperature for 4 hr. and then excess sodium borohydride was decomposed with acetic acid and the solvent removed *in vacuo*. The residual pale yellow solid was washed with two 50-ml. portions of chloroform and the extracts concentrated *in vacuo* to a glass (1.62 g.). The original solid was washed with water and there remained 0.220 g. of insoluble solid. The glass and the water-insoluble solid were combined and chromatographed over 125 g. of alumina (Woelm, activity III). Elution with chloroform:acetone (3:2) afforded 0.460 g. of 17α-hydroxynitrile **15** which, on crystallization from aqueous methanol, gave 0.320 g. of white needles. Recrystallization from aqueous methanol afforded white needles, m.p. 263–266° dec. (sinters 248°); $[\alpha]^{25}D$ − 66° (*c* 1.1, pyridine); ν_{max}^{KBr} 2252 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{23}N_3O \cdot 1/4\ H_2O$: C, 73.7; H, 7.27; N, 12.9. Found: C, 73.5; H, 7.28; N, 13.1.

Further elution of the column with chloroform:methanol (99:1) afforded 0.534 g. of 17β-hydroxynitrile **16** which, on crystallization from methanol, gave 0.360 g. of fluffy white needles, m.p. 247–250° dec. (sinters 245°); $[\alpha]^{25}D$ − 66° (*c* 0.92, pyridine); ν_{max}^{KBr} 2252 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{23}N_3O \cdot 1/4\ H_2O$: C, 73.7; H, 7.27; N, 12.9. Found: C, 73.8; H, 7.08; N, 13.1.

Methyl 17α-Hydroxyyohimban-18α-carboxylate (4) and Methyl 17β-Hydroxyyohimban-18α-carboxylate (5). Sodium Borohydride Reduction of Keto Ester 3.—To a cooled solution of 5.0 g. of sodium borohydride in 300 ml. of methanol was added 10.0 g. of keto ester **3**. The mixture was cooled and stirred under nitrogen for 1.5 hr. and carefully neutralized with acetic acid. The solvent was removed *in vacuo* and the residue partitioned between 100 ml. of chloroform and 100 ml. of 2.5% sodium bicarbonate solution. Solid separated at the interface and was removed by filtration. The organic layer was separated and the aqueous phase extracted with additional chloroform. The combined chloroform extracts were dried over magnesium sulfate and evaporated *in vacuo* to give 6.1 g. of partly crystalline yellow solid. The solid was dissolved in methanol and treated twice with Darco. Concentration of the filtrate afforded a glass which was dissolved in chloroform and chromatographed over 300 g. of neutral alumina (Woelm, activity III). Elution with chloroform, evaporation of the eluate, and crystallization of the resultant solid from methanol afforded 17α-hydroxy ester **4** as colorless needles, m.p. 210–214° dec. (sinters to a glass 132–136°); $[\alpha]^{25}D$ − 65° (*c* 1.18, pyridine); ν_{max}^{KBr} 1736 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{26}N_2O_3 \cdot CH_3OH$: C, 68.4; H, 7.82; N, 7.25; O–CH_3 7.78. Found: C, 68.5; H, 7.85; N, 7.38; O–CH_3, 7.45.

In a second run 11.6 g. of keto ester **3** in 300 ml. of methanol was treated with 2.38 g. of sodium borohydride for 1 hr. Work-up of the mixture as described above gave 13.0 g. of a glass which was chromatographed over 900 g. of alumina (Woelm, activity III). Elution with chloroform and crystallization of the solid from methanol gave 0.730 g. of 17α-hydroxy ester **4**. Elution with chloroform:methanol (99:1) afforded 2.24 g. of 17β-hydroxy ester **5** as a glass. Crystallization from aqueous methanol gave off-white needles which were recrystallized from moist ethyl acetate and gave 1.50 g. of 17β-hydroxy ester **5** as off-white broken plates, m.p. 142–147°; $[\alpha]^{25}D$ − 60° (*c* 0.90, pyridine); ν_{max}^{KBr} 1733 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{21}H_{26}N_2O_3 \cdot 1/4\ H_2O$: C, 70.3; H, 7.44 N, 7.81. Found: C, 70.6; H, 7.77, N, 7.92,

Methyl 17α-Hydroxyyohimban-18α-carboxylate (4) and Methyl Yohimb-17-ene-18-carboxylate (18) from 17α-Hydroxyyohimban-18α-carbonitrile (15).—A mixture of 0.100 g. of 17α-hydroxynitrile **15**, 4.0 ml. of ethanol, 1.0 ml. of water, and 0.250 g. of sodium hydroxide was refluxed for 21 hr. The solvent was removed *in vacuo* and the residue dissolved in 5 ml. of water and brought to pH 7 with glacial acetic acid. The solid which separated was removed by filtration and washed with 3 ml. of water. After drying, there was obtained 0.090 g. of solid (crystals and glass). The solid was suspended in 10 ml. of methanol and treated with excess of an ethereal solution of diazomethane. After 10 min. the excess diazomethane was decomposed with acetic acid and the solvent removed *in vacuo*. There remained 0.092 g. of a glass which was chromatographed over neutral alumina (Woelm, activity III). Elution with chloroform afforded 0.010 g. of Δ^{17}-ester **18** which was crystallized from methanol to give white needles, m.p. 227–230° dec.; $[\alpha]^{25}D$ − 131° (*c* 0.92, $CHCl_3$); ν_{max}^{KBr} 3424 (m), 1712 (s), 1664 cm.$^{-1}$ (m). Further elution of the column with chloroform afforded 0.012 g. of 17α-hydroxy ester **4** as white needles, m.p. 206–211° dec. (sinters 150°). By comparison of infrared spectra and X-ray powder diagrams, the product was identical with the 17α-hydroxy ester **4** obtained on reduction of keto ester **3**. A mixture melting point showed no depression.

Methyl 17β-Hydroxyyohimban-18α-carboxylate (5) from 17β-Hydroxyyohimban-18α-carbonitrile (16).—A mixture of 0.092 g. of 17β-hydroxynitrile **16**, 4.0 ml. of ethanol, 1.0 ml. of water, and 0.220 g. of sodium hydroxide was refluxed for 18 hr. The mixture was concentrated to *ca.* 1.5 ml., 4.0 ml. of water was added, and the mixture was neutralized with acetic acid. Filtration gave 0.130 g. of solid which was suspended in 10 ml. of methanol and treated with excess of an ethereal solution of diazomethane. After 10 min. the excess diazomethane was decomposed with acetic acid and the solution concentrated *in vacuo* to give 0.130 g. of a glass. The glass was crystallized from aqueous methanol to give 0.030 g. of **5** as white needles, m.p. 145–148°, $[\alpha]^{25}D$ − 54° (*c* 1.0, pyridine). By comparison of infrared spectra and X-ray powder diagrams the product was identical with the 17β-hydroxy ester **5** obtained on reduction of keto ester **3**. A mixture melting point showed no depression.

Methyl Yohimb-17-ene-18-carboxylate (18) from Methyl 17α-Hydroxyyohimban-18α-carboxylate *O*-Tosylate.—A mixture of 0.386 g. (1.0 mmole) of methyl 17α-hydroxyyohimban-18α-carboxylate (**4**), 0.517 g. (3.0 mmoles) of *p*-toluenesulfonyl chloride, and 2.0 ml. of dry pyridine was allowed to stand at room temperature for 66 hr. The dark mixture was poured into a mixture of 12 g. of ice and 15 ml. of chloroform. After being allowed to stand for 2 hr. the mixture was cooled and made basic with concentrated ammonium hydroxide. The chloroform layer was separated and the aqueous layer extracted with three 25-ml. portions of chloroform. The combined extracts were dried over sodium sulfate and concentrated to dryness *in vacuo*. The last traces of pyridine were removed by addition of toluene and concentration *in vacuo* to give 0.38 g. of brown crystals, m.p. 149–154°. From the infrared spectrum the product was shown to be a mixture of *O*-tosylate and α,β-unsaturated ester **18**.

A 0.100-g. sample of this mixture was heated with 1.5 ml. of 2,4,6-collidine at 160–170° for 2 hr. The mixture was cooled, diluted with 10 ml. of water, and extracted with four 10-ml. portions of chloroform. The extracts were combined, washed with 20 ml. of water containing 5 drops of concentrated ammonium hydroxide, dried over sodium sulfate, and concentrated *in vacuo*. The residue was crystallized from aqueous methanol to give 0.044 g. of α,β-unsaturated ester **18** as brown crystals, m.p. 223–230° dec. Chromatography over neutral alumina (Woelm, activity III) with chloroform as eluant, and crystallization from methanol, gave 0.015 g. of **18** as pale pink needles, m.p. 226–230° dec.

Compound **18** was different from apoyohimbine (**17**)[23] (m.p. 247–250°) by comparison of infrared and p.m.r. spectra[16]; **18** showed a multiplet at 2.55–3.22 τ (1 olefinic + 4 aromatic protons) while apoyohimbine showed a one-proton peak at 3.30 τ (olefinic proton) clearly defined from the multiplet from the lower field aromatic protons.

Methyl 17α-Hydroxyyohimban-18α-carboxylate *O*-Acetate.—A mixture of 0.225 g. of 17α-hydroxy ester **4**, 4.0 ml. of anhydrous pyridine and 2.0 ml. of acetic anhydride was allowed to stand at room temperature for 66 hr. The dark mixture was concentrated *in vacuo* to a viscous mass which was dissolved in 10 ml. of methanol:water (1:4). The solution was cooled and made basic with concentrated ammonium hydroxide. The mixture was filtered and the solid dissolved in methanol, treated with Darco, and filtered. The filtrate was concentrated *in vacuo* to a glass and the glass crystallized from aqueous methanol to give 0.085 g. of tan crystals, m.p. 232–234° dec. Recrystallization from aqueous methanol afforded 0.050 g. of off-white crystals, m.p. 236–238° dec.; $[\alpha]^{25}D$ + 4° (*c* 0.94, pyridine; ν_{max}^{KBr} 3436, 1757, 1739 cm.$^{-1}$ (sh).

Anal. Calcd. for $C_{23}H_{28}N_2O_4 \cdot H_2O \cdot 1/2\ CH_3OH$: C, 65.7; H, 7.49; N, 6.51. Found: C, 65.7; H, 7.21; N, 6.36.

Methyl 17β-Hydroxyyohimban-18α-carboxylate *O*-Acetate.—A mixture of 0.250 g. of 17β-hydroxy ester **5**, 4.0 ml. of anhydrous pyridine, and 2.0 ml. of acetic anhydride was allowed to stand at room temperature for 77 hr. The dark mixture was concentrated *in vacuo* to a viscous mass which was dissolved in 10 ml. of methanol:water (1:4). The cooled solution was made basic with

ammonium hydroxide and the solid which separated was removed by filtration and washed with water. The partially dried solid was dissolved in methanol, treated with Darco, filtered, and the filtrate concentrated *in vacuo* to a brown glass (0.225 g.). Crystallization of the glass from aqueous methanol gave 0.118 g. of tan crystals, m.p. 122–125°. Recrystallization from aqueous methanol afforded 0.049 g. of tan needles, sinters 125–129°, melts slowly above 130°.

Anal. Calcd. for $C_{23}H_{28}N_2O_4 \cdot 1/4\ H_2O$: C, 69.0, H, 7.24; N, 7.06. Found: C, 68.9; N, 7.17; H, 6.99.

18-Butylthiomethyleneyohimban-17-one (19).—To a mixture of 0.663 g. (2.0 mmoles) of hydroxymethylene ketone **11**, 2.0 g. of anhydrous magnesium sulfate and 5.0 ml. of 1-butanethiol was added 10 ml. of glacial acetic acid. The mixture was stirred at room temperature for 20 hr., filtered, and the filtrate poured into cold mixture of 50 ml. of chloroform and 100 ml. of 4 *N* sodium hydroxide. The chloroform layer was separated and the aqueous layer extracted with two 50 ml. portions of chloroform. The combined extracts were dried over magnesium sulfate and the solvent removed *in vacuo* to give 0.66 g. of off-white crystals. Recrystallization from acetone gave, in two crops, 0.542 g. (69%) of **19** as off-white crystals, m.p. 216–219° dec. Recrystallization from ethanol and from acetone afforded off-white crystals, m.p. 219–222° dec.; $[\alpha]^{25}D$ − 164° (*c* 1.0, pyridine); ν_{max}^{KBr} 1661, 1541 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{30}N_2OS$: C, 73.0; H, 7.66; N, 7.10; S, 8.13. Found: C, 72.6; H, 7.89; N, 7.43; S, 8.13.

18α-Methylyohimban-17-one (20).—A mixture of *ca.* 9 g. of Raney nickel, 0.80 g. of 18-butylthiomethyleneyohimban-17-one (**19**), and 80 ml. of acetone was stirred and refluxed for 7 hr. Fresh catalyst (*ca.* 1 g.) was added and the mixture refluxed for an additional 5 hr. The mixture was filtered through Celite and the filter cake washed thoroughly with acetone. Concentration of the filtrate *in vacuo* gave 0.50 g. (83%) of off-white crystals which were chromatographed over 40 g. of alumina (Woelm, activity III). Elution with chloroform afforded 0.42 g. of white crystals which were recrystallized by dissolving in methanol–chloroform and concentrating. There was obtained 0.275 g. (46%) of **20** as white needles, m.p. 292–298° dec. Recrystallization from methanol gave white needles, m.p. 290–295° dec.; $[\alpha]^{25}D$ − 109° (*c* 1.08, pyridine, ν_{max}^{KBr} 1704 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{24}N_2O \cdot 1/2\ H_2O$: C, 75.7; H, 7.94; N, 8.83; C–CH_3, 4.74. Found: C, 76.1; H, 8.08; N, 9.09; C–CH_3 4.46.

By comparison of infrared spectra and X-ray powder diffraction patterns, 18α-methyl ketone **20** was found to differ significantly from 16α-methylyohimban-17-one (**21**),[4j,24] prepared by Oppenauer oxidation of 16-methylyohimbol.[26]

Ethyl 16-Oxoyohimban-17-glyoxylate (23).—A mixture of 4.71 g. (16 mmoles) of yohimban-16-one (**22**), 0.944 g. (18 mmoles) of sodium methoxide (Mathieson), 16.0 ml. of diethyl oxalate, and 200 ml. of dry benzene was stirred under nitrogen at room temperature for 20 hr. The mixture was cooled by means of an ice bath, neutralized with glacial acetic acid, and diluted with 200 ml. of chloroform. After filtration the solvent was removed *in vacuo* to give a red-brown solid. The solid was dissolved in 200 ml. of ethanol, treated with Darco, and filtered. Chilling and filtering afforded 0.490 g. of orange crystals, m.p. 208–215° dec. The filtrate was diluted with 600 ml. of water and chilled to give 2.6 g. (40%) of **23** as orange crystals, m.p. 198–200° dec. Recrystallization of a 0.200 g. sample from ethanol afforded 0.098 g. of tan crystals, m.p. 193–198° dec.; $[\alpha]^{25}D$ − 56° (*c* 0.62, DMF); violet color with ferric chloride; $\lambda_{max}^{0.1\ N\ NaOH}$ 223 mμ (ε 40,000), 283 (10,700), 290 (12,200), 318 (18,800).

Anal. Calcd. for $C_{23}H_{26}N_2O_4 \cdot H_2O$: C, 67.0; H, 6.84; N, 6.79; H_2O, 4.37. Found: C, 67.3; H, 6.64; N, 7.15; H_2O (K.F.), 2.18.

Ethyl 17-Oxoyohimban-18-glyoxylate (24).—A mixture of 0.294 g. (1.0 mmole) of yohimban-17-one (**1**), 0.059 g. (1.1 mmoles) of sodium methoxide, and 1.0 ml. (7.4 mmoles) of freshly distilled ethyl oxalate in 20 ml. of dry benzene was stirred at room temperature for 20 hr. The red-brown suspension was diluted with 500 ml. of cold anhydrous ether and filtered to give 0.346 g. (83%) of the crude sodium salt of m.p. > 350°; λ_{max}^{MeOH} 225 mμ (ε 42,700), 280 (9,330), 290 (sh) (8,320), 315 (sh) (3,240).

The salt (7.56 g.), obtained from 5.0 g. of **1**, was dissolved in 150 ml. of cold water containing a few drops of 10 *N* sodium hydroxide solution and rapidly extracted with two 100-ml. portions of ethyl acetate. The aqueous phase was separated and brought to pH 7.0 by the dropwise addition of dilute acetic acid. A voluminous precipitate formed and was separated by filtration to give 3.41 g. (51%) of **24**, m.p. 207–209° dec. The melting point was raised to 215–216° dec. by recrystallization from methanol. The product gave a brown-purple color with an alcoholic solution of ferric chloride; λ_{max}^{MeOH} 221 mμ (ε 37,200), 283 (11,800), 290 (12,600), 312 (12,300); ν_{max}^{KBr} 1718, 1710 (sh), 1704 (sh), 1610 cm.$^{-1}$ (broad).

Anal. Calcd. for $C_{23}H_{26}N_2O_4 \cdot 3/4\ H_2O$: C, 67.7; H, 6.79; N, 6.87; H_2O, 3.31. Found: C, 68.1; H, 6.87; N, 7.17; H_2O (K.F.) 3.25.

Ethyl 17-Oxoalloyohimban-16-glyoxylate (25).—A mixture of 0.294 g. (1.0 mmole) of alloyohimban-17-one (**9**), 0.059 g. (1.1 mmoles) of sodium methoxide, and 1.0 ml. (7.4 mmoles) of freshly distilled ethyl oxalate in 20 ml. of dry benzene was stirred at room temperature for 20 hr. under nitrogen. The orange solution was dropped slowly into 200 ml. of dry ether with magnetic stirring. After 30 min. at room temperature the suspension was filtered and the bright orange-yellow powder was washed thoroughly with ether to give 0.286 g. (69%) of sodium enolate of **25**, m.p. > 350°; red-brown color with alcoholic ferric chloride solution; λ_{max}^{MeOH} 225 mμ (ε 30,200), 280 (8,320), 290 (8,710), 314 (9,950); $\lambda_{max}^{0.1\ N\ HCl}$ 221 mμ (ε 32,400), 280 (7,760), 289 (6,920); ν_{max}^{KBr} 1614, 1678, 1716 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{25}N_2O_4Na \cdot H_2O$: C, 63.6; H, 5.80; N, 6.45; H_2O, 4.14. Found: C, 58.3; H, 5.71; N, 6.08; H_2O (K.F.), 5.32; ash, 12.9.

The crude salt (1.88 g.) was dissolved in 50 ml. of 50% aqueous methanol and passed slowly over 30 g. of Amberlite IRC-50 (H^+) resin. The first 400 ml. eluted mainly alloyohimban-17-one (**9**). The next 300 ml., as well as 200 ml. of methanol used to strip the column, contained **25**. Accordingly, the latter eluate was concentrated to a low volume *in vacuo* and the resulting brown precipitate was collected by filtration and washed extensively with water to produce 0.28 g. (9%) of a brown amorphous powder, m.p. 198–200° dec. Crystallizations from methanol produced 0.030 g. of crude **25** as tan microcrystals, m.p. 207–209° dec., $[\alpha]^{25}D$ − 162° (*c* 0.553, pyridine); λ_{max}^{MeOH} 228 mμ (ε 33,100), 284 (12,000), 292 (11,800); $\lambda_{max}^{0.1\ N\ NaOH}$ 227 mμ (ε 34,700), 284 (10,500), 291 (11,800), 314 (13,500).

Anal. Calcd. for $C_{23}H_{26}N_2O_4 \cdot H_2O$: C, 67.0; H, 6.84; N, 6.79. Found: C, 61.7; H, 5.97; N, 7.52.

Carboxylation of Alloyohimban-17-one (9).—Alloyohimban-17-one (**9**) (0.589 g., 2.0 mmoles) was suspended in 8.0 ml. of a 2.8 *M* solution of magnesium methyl carbonate in dimethylformamide, heated to 120° and stirred under dry nitrogen for 3 hr. After cooling to room temperature, the viscous mixture was poured into a chilled mixture of 4.0 ml. of concentrated hydrochloric acid and 20 g. of ice and the resulting solid was removed by filtration and washed with a little cold water. After drying overnight the crude carboxylation product as the hydrochloride weighed 0.718 g., ν_{max}^{KBr} 1661, 1718 cm.$^{-1}$. To a cold solution of 0.710 g. of the crude β-keto acid hydrochloride in 10 ml. of methanol was added 5 ml. of an ethereal solution of diazomethane prepared from 1 g. of nitrosomethylurea and 3 ml. of 40% aqueous potassium hydroxide. An immediate white precipitate appeared. After 5 min. at 5°, 2 ml. of glacial acetic acid was added and the solution was concentrated to dryness *in vacuo* with a minimum of heat to give 0.629 g. of crude β-keto ester. The product gave a brown-red color with an alcoholic solution of ferric chloride and possessed infrared bands at 1661, 1718 and 1739 (sh) cm.$^{-1}$.

To a chilled 2% solution of sodium borohydride in 25 ml. of methanol was added dropwise a solution of 0.500 g. of the crude β-keto ester in 50 ml. of cold methanol. The solution was allowed to come to room temperature while being stirred for 1 hr., a few milliliters of acetic acid were added and the solution concentrated to a small volume *in vacuo*. The resulting suspension was partitioned between water and ether and the ethereal solution was evaporated to dryness to produce 0.268 g. of an amorphous white solid. This was dissolved in chloroform and chromatographed on 30 g. of neutral alumina (Woelm, activity II), 25-ml. cuts being collected. Fractions 3 and 4 (0.0576 g.) were combined and crystallized from aqueous methanol to give 0.0202 g. of crude hydroxy ester, m.p. 113–126° dec., ν_{max} 1720 cm.$^{-1}$. The majority of the material (0.287 g.) was eluted in fractions 5–7. This material was crystallized from chloroform to give 0.095 g. of colorless needles of alloyohimban-17α-ol, m.p. 206–209° dec. (reported[27] m.p. 212–214° dec.).

(27) A. Chatterjee and S. Ghosal, *J. Indian Chem. Soc.*, **36**, 545 (1959).

Anal. Calcd. for $C_{19}H_{24}N_2O \cdot 1/6\ H_2O$: C, 76.2; H, 8.18; N, 9.36; H_2O, 1.00. Found: C, 76.5; H, 8.36; N, 9.69; H_2O (K.F.), 1.00.

The crude hydroxy ester was chromatographed on Whatman #1 paper (impregnated with an ethanolic solution of formamide and ammonium formate) in the system chloroform:benzene (saturated with formamide).[4c] Ultraviolet absorbing spots were observed at R_f = 0.06, 0.32, 0.48, 0.65 and 0.80, corresponding to alloyohimban-17α-ol (R_f = 0.05), α-yohimbine (**10**) (R_f = 0.65) and alloyohimban-17-one (9) (R_f = 0.82).

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Synthesis of Isophytol

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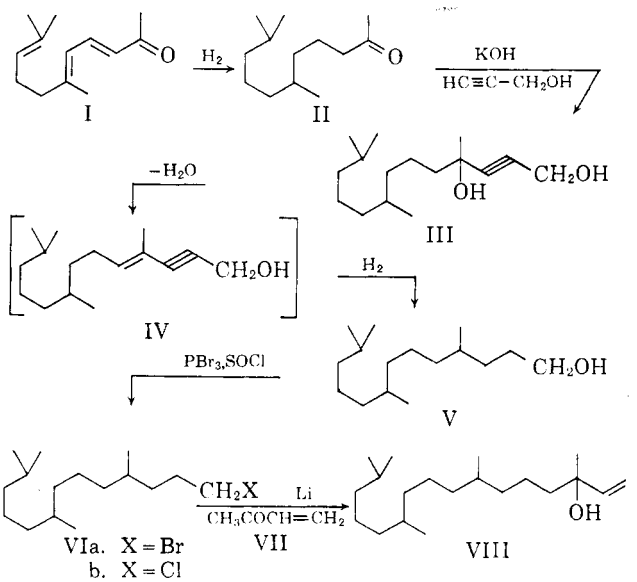
Isophytol was synthesized from pseudoionone and propargyl alcohol. The synthesis involved six steps, much fewer than the steps in other procedures. It was found in a model experiment that methyl vinyl ketone reacts with laurylmagnesium bromide to yield the 1,4-addition product, whereas the 1,2-addition product was obtained with lauryllithium. The specificity found for lauryllithium was applied for the synthesis of isophytol from 1-bromo-4,8,12-trimethyltridecane.

It has been known that tocopherols (vitamins E) are synthesized by condensation of hydroquinones with phytol[1] or its derivatives such as isophytol,[2] phytyl halides,[3,4] and phytadiene.[5] Isophytol (VIII) is a key material for the synthesis, since phytol, phytyl halides, and phytadiene can be easily derived from isophytol. A number of investigations of the synthesis of isophytol have been carried out with linalool or citral[6-14] as the starting material *via* pseudoionone. Recently, Nazarov[15] and Lukes[16] succeeded in the total synthesis of isophytol from acetylene and laevulic acid, respectively. However, these syntheses are awkward for a large scale operation, because of the many stages even from pseudoionone. A new synthesis of isophytol presented in this paper is comprised of six steps from pseudoionone (I) and propargyl alcohol. The process of the synthesis is as follows.

Hexahydropseudoionone (II) prepared from pseudoionone by hydrogenation reacted smoothly with propargyl alcohol to give 4,8,12-trimethyltridec-2-yn-1,4-diol (III) in 84% yield. The condensation was carried out in the presence of finely powdered potassium hydroxide according to Chodkiewicz.[17] 4,8,12-Trimethyltridecan-1-ol (V) was obtained in 70–75% yield from this glycol (III), by dehydration of the tertiary hydroxy group of this glycol with fused potassium hydrogen sulfate and by subsequent hydrogenation. The dehydration reaction was vigorous and completed within about ten minutes at the boiling point of xylene. The intermediate, enyne alcohol (IV), if desired, could be isolated as a pale yellow oil which, upon exposure to air, slowly polymerized to a sticky dark red material. The alcohol was highly sensitive to heat and polymerized even by careful distillation. It is, therefore, recommended that, after treating with dehydrating agent and removing the solvent, the crude product, IV, be directly hydrogenated without isolation. The reduction was smooth and quantitative in the presence of Raney nickel catalyst in ethyl alcohol to 80° under a pressure of about 140 atmospheres of hydrogen. Compound V was a colorless, stable oil, and could be converted smoothly into its bromide (VIa) and chloride (VIb) by action of phosphorus tribromide and thionyl chloride, respectively.



The final product, isophytol, may be obtained by the reaction of a metallic compound of VI with methyl

(1) P. Karrer, H. Salmon, and H. Fritzshe, *Helv. Chim. Acta.*, **21**, 309 (1938); Hoffmann-La Roche & Co., Swiss Patent 212,353 (1941); P. Karrer and O. Isler, U.S. Patent 2,411,968 (1946).

(2) P. Karrer and O. Isler, U.S. Patent 2,411,969 (1946); Hoffmann-La Roche & Co., Swiss Patent 208,446 (1940).

(3) P. Karrer, R. Escher, H. Fritzsche, H. Keller, B. Ringier, and H. Salmon, *Helv. Chim. Acta.*, **21**, 939 (1938).

(4) J. D. Surmatis and J. Weber, U.S. Patent 2,723,278 (1955); J. D. Surmatis and J. Weber, Can. Patent 530,254 (1956).

(5) L. I. Smith and H. E. Ungnale, U.S. Patent 2,421,811 (1947).

(6) F. G. Fischer and K. Löwenberg, *Ann.*, **475**, 183 (1929).

(7) P. Karrer and B. H. Ringier, *Helv. Chim. Acta*, **22**, 610 (1939).

(8) P. Karrer, A. Geiger, H. Rentschler, E. Zbinder, and A. Kugler, *ibid.*, **26**, 1741 (1943).

(9) I. K. Sarycheva, G. A. Vorobova, N. A. Kuznetsova, and N. A. Preobrazhenskii, *Zh. Obshch. Khim.*, **28**, 647 (1958).

(10) L. I. Smith and J. A. Sprung, *J. Am. Chem. Soc.*, **65**, 1276 (1943).

(11) J. Weicht and J. Hodrová, *Chem. Listy*, **51**, 568 (1957).

(12) L. I. Smith and G. Rouault, *J. Am. Chem. Soc.*, **65**, 745 (1943).

(13) J. W. K. Burrell, L. M. Jackmann, and B. C. L. Weedon, *Proc. Chem. Soc.*, 263 (1959).

(14) V. I. Gunar and S. I. Zavyalov, *Dokl. Akad. Nauk SSSR*, **132**, 829 (1960).

(15) I. N. Nazarov, B. P. Gusev, and V. I. Gunar, *Zh. Obshch. Khim.*, **28**, 1444 (1958).

(16) R. Lukes and A. Zobácová, *Chem. Listy*, **51**, 330 (1957).

(17) W. Chodkiewicz, *Compt. rend.*, **240**, 1903 (1955).