solution was heated under reflux for 3 hr. while 52.5 g. (0.495 mole) of Na_2CO_3 was added in small portions whereby vigorous foaming occurs. The reflux temperature was maintained for an additional 2 hr. and then the reaction mixture cooled to room temperature. The mixture was filtered, and the filtrate was evaporated to dryness. Aqueous acid was added to the residue and the resulting solution was extracted several times with chloroform. The acidic solution was then basified to pH 10 with 5 *N* NaOH solution and extracted well with ether. The ether extract was dried over Na_2SO_4. The drying salt was then filtered off, and the ether was removed on the steam bath. The oily residue was distilled *in vacuo* and the product was collected at 110–113° (0.15 mm.). The yield was 82%.

Anal. Calcd. for $C_{12}H_{18}N_2$: C, 75.74; H, 9.54; N, 14.72. Found: C, 75.61; H, 9.48; N, 14.34.

Acknowledgment.—We are indebted to Dr. Plummer and his colleagues, Drs. Barrett and Renzi, for the biological data reported herein. We wish to thank Mr. Louis Dorfman and his microanalytical staff for the analytical data.

Yohimbane Derivatives. II. The Synthesis and Psychopharmacological Properties of Yohimbane Derivatives with Halogen Substituents in Ring E

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17α-Fluoro-, -chloro-, and -bromoyohimbanes, 17β-fluoro- and 17β-chloro-16α-methylyohimbanes, 17β-chloro-16α-chloromethylyohimbane, and 16β-chloroyohimbane were prepared. On pharmacological evaluation, most of these compounds produced significant tranquilizing effects in untamed monkeys. The clinical evaluation of the 17α-haloyohimbanes, the most active of this series, was precluded by strong adrenolytic effects in dogs. A convenient n.m.r. method for conformational assignments of some cyclic alcohols is described.

The tranquilizing and hypotensive properties of reserpine have inspired considerable effort by various research groups to investigate the activity of other compounds having the pentacyclic yohimbanoid skeleton.[1] The resulting studies have centered mainly on the cardiovascular area leaving the pharmacology of the central nervous system largely unexplored. The scarce data available create the impression that *trans* C/D ring junction, opposite configuration at C-3, and other differences, as compared with reserpine, render derivatives of yohimbane devoid of sedative activity.[1a]

Our interest in this field arose from the observation[2] of significant analgesic and sedative properties in a group of previously described compounds, such as yohimbane (I), 16α-methylyohimbane (II),[3] epiyohimbol (III),[4] and 16α-methylyohimbol (IV).[3] This finding suggested the synthesis of a wide variety of compounds based on the yohimbane nucleus for evaluation of their central nervous system effects. The present study is concerned with the preparation of 16- and 17-haloyohimbanes and their pharmacological properties.

Two of the starting materials for this work, 17β-hydroxyyohimbane (III) and 17α-hydroxy-16α-methylyohimbane (IV), were readily accessible by procedures described in the literature.[3,4] The third, 16α-hydroxyyohimbane (XIX), was prepared by the KBH_4 reduction of 16-ketoyohimbane.[5] The ratio of the resulting epimers (XIX and XX), which was close to 1:1, did not permit any conclusions as to the configuration of the hydroxyl groups. The low solubility of one of the isomers (XX) in chloroform, pyridine, dimethyl sulfoxide, and other common solvents precluded steric studies by conventional infrared and n.m.r. methods. Configurational assignments were finally made on the basis of the observation that on warming in trifluoroacetic acid for 15–30 min. at 50° only epimer XX eliminated water. The dehydration reaction was most conveniently carried out in the n.m.r. sample tube, the formation of the olefin being detected by the appearance of a signal at 5.5 p.p.m. Application of this technique to model compounds with known configuration, showed definite stereochemical specificity. For example, in the case of 17α-hydroxy-16α-methylyohimbane and 17β-hydroxy-16α-methylyohimbane[6] only the former compound, in which the hydroxyl is axial, eliminated water to give rise to an olefinic signal at 5.25 p.p.m. This analogy, as well as the established concept that 1,2-elimination reactions are particularly facile if the two substituents are in a *trans* coplanar (diaxial) arrangement, led to the assignment of the 16β-OH (axial) configuration for the epimer XX which is easily dehydrated.

The tosylation of the alcohols III, IV, and XIX gave 17β-(*p*-toluenesulfonyloxy)yohimbane (V), 16α-methyl-17α-(*p*-toluenesulfonyloxy)yohimbane (VI), and 16α-(*p*-toluenesulfonyloxy)yohimbane (VII). When these compounds were allowed to react with a saturated solution of dry hydrogen halide in pyridine, substitution with inversion[7] took place to give 17α-fluoro-, 17α-chloro-,[8] and 17α-bromoyohimbane (VIII–X), 17β-fluoro-16α-methylyohimbane (XI), 17β-chloro-16α-methylyohimbane (XII), and 16β-chloroyohimbane (XIII) (see Table I).

The reactions involving hydrogen bromide were accompanied by partial elimination in the case of 17β-

(1) The subject was reviewed by: J. Kerwin, C. P. Balant, and G. E. Ullyot in "Medicinal Chemistry," A. Burger, Ed., 2nd. Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 565; (b) R. A. Lucas, "Progress in Medicinal Chemistry," Butterworths, London, 1963, p. 149.

(2) We thank Mr. M. Chessin, Dr. J. F. Emele, and Dr. J. Gylys for their pharmacological studies.

(3) P. Karrer and R. Seamann, *Helv. Chim. Acta*, **35**, 1932 (1952).

(4) B. Witkop, *Ann.*, **554**, 83 (1943).

(5) R. K. Hill and K. Muench, *J. Org. Chem.*, **22**, 1276 (1957).

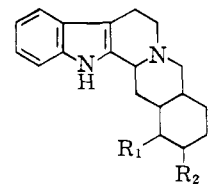
(6) J. Shavel, Jr., and M. von Strandtmann, U. S. Patent 3,096,245 (1963).

(7) Nucleophilic substitution of the *p*-toluenesulfonyloxy group has been shown by H. Phillips [*J. Chem. Soc.*, **123**, 44 (1923)] to proceed with inversion and very little racemization.

(8) After completion of this work, the conversion of epiyohimbol to IX with $POCl_3$ was described by Y. Ban and O. Yonemitsu, *Tetrahedron Letters*, No. **5**, 181 (1962).

TABLE I

ANALYTICAL AND PHYSICAL DATA



Compd.	R_1	R_2	M.p., °C.	$[\alpha]^{25}D$, deg. (c)[a]	% yield	Formula	Calcd., % C	H	N	X[b]	Found, % C	H	N	X[b]
V	H	β-OTs[c]	285–293	−17 (0.7)	37	$C_{26}H_{30}N_2O_3S$	69.30	6.71	6.22	7.12	69.07	6.62	6.23	6.94
VI	α-CH_3	α-OTs	290–295	−50 (0.7)	75	$C_{27}H_{32}N_2O_3S\cdot0.5H_2O$	68.46	7.02	5.92	6.77	68.36	6.82	5.65	6.48
VII	α-OTs	H	268–271	−131 (0.5)	80	$C_{26}H_{30}N_2O_3S$	69.30	6.71	6.22	7.12	69.03	6.80	6.31	6.91
VIII	H	α-F	203–220	−108 (0.9)	80	$C_{19}H_{23}FN_2$	76.47	7.77	9.39	6.37	76.67	7.85	9.44	6.40
IX	H	α-Cl	195–200[d]	−49 (0.9)	80	$C_{19}H_{23}ClN_2$	72.48	7.36	8.90	11.26	72.55	7.49	9.10	11.03
X	H	α-Br	292–297	−83 (0.8)	50	$C_{19}H_{23}BrN_2$	63.51	6.45	7.80	22.24	63.73	6.50	7.63	22.24
XI	α-CH_3	β-F	195–200	−145 (0.3)	10	$C_{20}H_{25}FN_2\cdot C_2H_5OH$	73.71	8.72	7.81		73.96	8.91	7.85	
XII	α-CH_3	β-Cl	310–313	−188 (0.5)	63	$C_{20}H_{25}ClN_2$	73.04	7.66	8.52	10.78	73.05	7.81	8.59	10.43
XIII	β-Cl	H	265–268	−161 (0.6)	43	$C_{19}H_{23}ClN_2$	72.48	7.36	8.90	11.26	72.35	7.44	9.09	11.15
XVI	α-$ClCH_2$	α-OH	230–232	−49 (0.8)	58	$C_{20}H_{25}ClN_2O$	69.65	7.31	8.12	10.28	69.41	7.23	8.29	10.34
XVII	α-$ClCH_2$	β-Cl	259–263	+11 (0.6)[e]	44	$C_{20}H_{24}Cl_2N_2$	66.11	6.66	7.71	19.52	65.82	6.92	7.80	19.52
XVIII	CH_2OSO_2		220–221	−20 (0.6)	35	$C_{20}H_{24}N_2O_3S\cdot0.5H_2O$	62.96	6.61	7.34	8.39	63.23	6.64	7.09	8.56
XIX	α-OH	H	275–276	+22 (0.5)	40	$C_{19}H_{24}N_2O$	76.99	8.16	9.45		77.20	8.26	9.41	
XX	β-OH	H	294–297	−102 (0.5)[f]	36	$C_{19}H_{24}N_2O$	76.99	8.16	9.45		76.86	8.04	9.23	

[a] Concentration in pyridine. [b] Sulfur or halogen. [c] Ts = p-$CH_3C_6H_4SO_2$. [d] Resolidifies at 215° and remelts at 299–304°. [e] In chloroform. [f] In 5 N acetic acid.

hydroxyyohimbane p-toluenesulfonate and by complete elimination in the case of 17α-hydroxy-16α-methylyohimbane p-toluenesulfonate. The identity of the resulting 17-yohimbene (XIV) was established by comparison of its physical constants with those reported in the literature.[8] The position of the double bond in 16α-methylyohimbene (XV) was assigned, in agreement with the Saytzeff rule, to be at C-16,17. This assignment was based on the n.m.r. spectrum in $CDCl_3$ which showed only one band, integrating for a single proton, in the olefinic region at 5.38 p.p.m. and an unsplit methyl group signal at 1.8 p.p.m.

Treatment of yohimbyl alcohol mono-p-toluenesulfonate[3] with HCl in pyridine gave 16α-chloromethyl-17α-hydroxyyohimbane (XVI), which was converted to 17β-chloro-16α-chloromethylyohimbane (XVII) by $POCl_3$ in pyridine. The latter deviation from the usual method of synthesis was necessary since we were not successful in our attempts to tosylate XVI.

Other approaches to the introduction of halogen into ring E were found to be less feasible than the route described above. Treatment of epiyohimbol (III) with $SOCl_2$ or $POCl_3$ yielded 17α-chloroyohimbane (IX), but the yields were unsatisfactory due to extensive decomposition. Interaction of yohimbyl alcohol with thionyl chloride gave the yohimbyl alcohol cyclic sulfite ester (XVII)[9] instead of the desired chloroyohimbane.

Summary of Pharmacological Data.—The psychopharmacological effects of the compounds described were evaluated in untamed Rhesus monkeys by a technique similar to that used by Plummer, *et al.*,[10] in the study of reserpine. The drugs were administered by stomach tube to animals which had been fasted overnight. Scoring was based on the changes produced in hostility, locomotor activity, and response to food stimulus. In grading hostility, emphasis was placed on behavioral components such as mouth opening, teeth baring, facial expressions, lunging, and reaction to chain pulling. The objective of this procedure was to determine the minimal effective dose (MED) of the drug which would induce an alteration of the behavioral responses as was generally reflected by a reduction of activity, refusal of food, and submission of the animal to handling and petting.

The evaluation of the analgesic activity was based on the ability of the compound to antagonize phenylquinone-induced "writhing syndrome" in mice.[11] The results are summarized in Table II.

Most of the compounds elicited a significant tranquilizing response in monkeys which usually was noticeable 40–60 min. after administration and lasted on the average for 4–7 hr.

Examination of the test data shows that the psychopharmacological properties of yohimbane and 16α-methylyohimbane were increased by the introduction of α-fluoro and α-chloro substituents at C-17. The fact that such an increase was not effected by the corresponding α-bromo and β-chloro substituents and that the introduction of the halogen atoms into ring E abolished the analgesic activity of the parent compounds (I and II) renders untenable the assumption of a simple correlation of lipid solubility and central nervous system activity in this series. The finding that 17β-chloro-16α-methylyohimbane was less active than 17α-chloroyohimbane points to the significance of the spatial arrangement at C-17 and is in agreement with the trend shown by the corresponding 17-hydroxy compounds, namely, the lower activity of 17β-hydroxyyohimbane (III), as compared with 17α-hydroxy-16α-methylyohimbane (IV).

On cardiovascular evaluation in anesthetized dogs[12] 17α-fluoroyohimbane and 17α-chloroyohimbane at 7 mg./kg. i.v. produced marked adrenolytic effects manifested in reversal of epinephrine, block of norepi-

(9) For analogous reactions of steroidal diols see: (a) B. R. Brown, P. W. Trown, and J. M. Woodhouse, *J. Chem. Soc.*, 2478 (1961); (b) J. Fried, M. A. Guiducci, P. A. Diassi, E. F. Sabo, I. Bacso, and P. Grabowich, *Chem. Ind.* (London), 466 (1961).

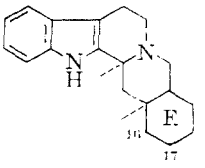
(10) A. J. Plummer, A. Earl, J. A. Schneider, J. Trapold, and W. Barret, *Ann. N. Y. Acad. Sci.*, **59**, 8 (1954).

(11) E. A. Siegmund, A. Cadmus, and G. Lu, *J. Pharmacol. Exptl. Therap.*, **119**, 184 (1957).

(12) For a detailed description of the test method see M. von Strandtmann, M. Cohen, and J. Shavel, Jr., *J. Med. Chem.*, **6**, 719 (1963).

TABLE II

PHARMACOLOGICAL ACTIVITIES OF YOHIMBANES



Compd.	Ring E	ALD_{50}, mg./kg. *p.o.*	Effect on monkey behavior, MED, mg./kg. *p.o.*	Analgesic effect on phenylquinone writhing syndrome, ED_{50}, mg./kg. *p.o.*
I		300	10–25	50
II		850	10	85
III		400	50–75	61
IV		250	10–20	7.5
VIII		200	5	Not tested
IX		>1000	4–5	Not tested
X		>1000	5–10	>1000
XII		1000	10	>400
XVI		400	25–50	45
XVIII		1500	>50	Not tested
Chlorpromazine			5	
Reserpine			5	
Codeine				10

nephrine, and strong depressor response. On evaluation of psychopharmacological activity in dogs and rats, 17α-bromoyohimbane caused no significant behavioral changes at 20 mg./kg. *p.o.* and 50 mg./kg. *p.o.*, respectively. This pronounced species variation in pharmacological responses as well as the undesirable cardiovascular effects precluded the 17α-haloyohimbanes from clinical evaluation. Compounds not included in Table II received no pharmacological testing.

Experimental[13]

Physical constants, yields, and analytical values for the compounds below are reported in Table I. Melting points were taken on a Mel-Temp aluminum block apparatus and are uncorrected. Infrared spectra were determined on a Baird Model 455 spectrograph as Nujol mulls. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer with tetramethylsilane as an internal reference. The isomeric purity was established by spiral paper chromatography in a Chromatobox according to the procedure reported by Barrolier[14] on Whatman No. 1 paper which was impregnated by spraying with 10% formamide in acetone and allowed to air dry for about 2 min. The solvent systems used were ethyl methyl ketone–heptane (1:3), heptane–benzene–acetone (1:1:1), both in NH_3 atmosphere. The chromatograms were developed with aqueous potassium iodoplatinate. Rotations were taken in a 1-dm. tube, using a Rudolph photoelectric polarimeter (Model 800).

17β-Hydroxyyohimbane *p*-Toluenesulfonate (V).—*p*-Toluenesulfonyl chloride (6.0 g.) in 5 ml. of dry pyridine was added dropwise to a solution of 8.0 g. of epiyohimbol in 25 ml. of pyridine over a period of 15 min. with stirring at 0°. After standing at room temperature for 4 hr., the solution was treated with ether (200 ml.). The precipitate was filtered off and partitioned between dilute NH_4OH and $CHCl_3$. The $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was crystallized from methanol–tetrahydrofuran (1:1); ν_{max} 3470 (s), 1345 (vs), 1173 (vs), 955 (w), 918 (vs), 871 (vs), 839 (m), 816 (m), 663 (m) cm.$^{-1}$.

17α-Hydroxy-16α-methylyohimbane *p*-Toluenesulfonate (VI).—*p*-Toluenesulfonyl chloride (18.6 g.) in dry pyridine (20 ml.) was added with stirring to a chilled solution of 17α-hydroxy-16α-methylyohimbane (9.3 g.) in pyridine (50 ml.). The reaction mixture was stirred for 30 min., allowed to stand overnight at room temperature, and poured into ice-cold 1% NaOH solution (*ca.* 250 ml.). The precipitate was filtered off, washed with water, suspended in 200 ml. of 5% NH_4OH and 200 ml. of $CHCl_3$, and stirred for 1 hr. The solids were collected on a filter, dried in a vacuum dessicator, and recrystallized from acetonitrile; ν_{max} 675 (s), 1010 (ms), 1030 (ms), 1120 (ms), 1170 (s), 3200 (m), 3550 (mw) cm.$^{-1}$.

16α-Hydroxyyohimbane *p*-Toluenesulfonate (VII).—*p*-Toluenesulfonyl chloride (1.8 g.) in dry pyridine (10 ml.) was added dropwise with stirring at 0° to a solution of 16α-hydroxyyohimbane (2.3 g.) in pyridine (30 ml.). After stirring for 20 hr. at 0–5°, *p*-toluenesulfonyl chloride (0.3 g.) in pyridine (40 ml.) was added, and the stirring was continued for 2 hr. Ether (250 ml.) was added and the resulting precipitate was filtered off. The solids were treated with excess dilute NH_4OH and the resulting suspension was extracted with methylene chloride. The extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was crystallized from methanol; ν_{max} 3360 (s), 1598 (w), 1493 (w), 1340 (vs), 1191 (w), 1177 (vs), 1098 (s), 916–908 (vs), 882 (s), 840 (m), 815 (s), 783 (m) cm.$^{-1}$.

17α-Fluoroyohimbane (VIII).—A solution of 3.0 g. of 17β-hydroxyyohimbane *p*-toluenesulfonate in 25 ml. of dry pyridine was placed in a polyethylene container, protected from moisture by a $CaCl_2$ tube, and treated with 25 ml. of liquid HF while keeping the temperature at 20° by means of a water bath. After the reaction was allowed to proceed at room temperature for 8 days, the reaction mixture was poured onto 400 g. of crushed ice and made basic with ammonia. The solid was filtered off and dissolved in 200 ml. of CH_2Cl_2, and the solution was treated with charcoal, dried (Na_2SO_4), and evaporated *in vacuo*. The brown-green solid residue was crystallized from methanol; ν_{max} 1263 (m), 1119 (vs), 961 (vs), 897 (vs), 835 (s) cm.$^{-1}$.

17α-Chloroyohimbane (IX). A.—Hydrogen chloride was introduced into a heated solution (steam bath) of 0.8 g. of 17β-hydroxyyohimbane *p*-toluenesulfonate in 20 ml. of anhydrous pyridine over a period of 15 min. After the heating was maintained for another 30 min., the hot solution was poured onto 120 g. of crushed ice, made basic with ammonia, and filtered. The collected tan-colored solid was redissolved in CH_2Cl_2. The solution was dried (Na_2SO_4) and evaporated *in vacuo*. The brown residue was crystallized from methanol; yield 80%, ν_{max} 1253 (m), 729 (vs), 717 (s) cm.$^{-1}$.

B.—*p*-Toluenesulfonyl chloride (4.2 g.) in 15 ml. of dry pyridine was added, with stirring, at 0° to a solution of 6.0 g. of 17β-

(13) The authors are indebted to the Chemical Development Department under the supervision of Dr. A. W. Ruddy and to the Analytical and Physical Chemistry Section under the supervision of Mr. A. D. Lewis. In particular we wish to thank Mr. G. Conrad for large-scale preparation of intermediates, Mr. T. Wilkeman and Mrs. U. Zeek for microanalyses, and Mrs. B. Kane and Mr. R. Pachalski for spectral data.

(14) J. Barrolier, *Naturwiss.*, **42**, 186 (1955).

hydroxyyohimbane in 25 ml. of pyridine over a period of 30 min. and was allowed to stand at room temperature for 30 min. The mixture was heated on a steam bath ($CaCl_2$ tube!), and HCl was introduced for 20 min. After heating for 5 hr., the dark brown solution was poured onto 300 g. of crushed ice and filtered. The collected dark solid was stirred with a mixture of 25 ml. of 5% aqueous NaOH and 150 ml. of $CHCl_3$. The chloroform phase was dried (Na_2SO_4) and evaporated *in vacuo*. Trituration of the residue with 10 ml. of hot methanol and cooling gave a tan solid which was decolorized with charcoal and crystallized from acetone–methanol (2:1); yield 65%.

C.—To a chilled solution of 4 g. of 17β-hydroxyyohimbane in 20 ml. of dry pyridine was added with stirring and protection from moisture a solution of 7 ml. of $POCl_3$ in 20 ml. of pyridine. After heating on the steam bath for 90 min., the black reaction mixture was poured into 300 ml. of ether. The oily precipitate was triturated with two 100-ml. portions of ether and dissolved in 300 ml. of water. The solution was made basic with ammonia. The precipitated product was dissolved in the minimum amount of acetic acid, and the resulting solution was diluted with 600 ml. of water. After adjusting the pH to 5 by addition of NH_4OH the mixture was filtered through Supercel. The filtrate was made basic with ammonia, and the resulting precipitate was dried and dissolved in acetone. This solution was decolorized with charcoal and concentrated *in vacuo* until the onset of crystallization; yield 30%.

17α-Bromoyohimbane (X).—A vigorous stream of HBr was introduced into a stirred solution of 8 g. of 17β-hydroxyyohimbane *p*-toluenesulfonate in 150 ml. of dry pyridine over a period of 45 min. After heating for 5 hr., the reaction mixture was cooled to 5°, poured onto 2 l. of ice–water, made basic with ammonia, and filtered. The solution of the solids in 200 ml. of $CHCl_3$ was dried (Na_2SO_4), and evaporated *in vacuo*. Trituration of the brown residue with 20 ml. of hot methanol gave tan crystals which were recrystallized successively from methanol and from methanol–acetone; ν_{max} 1261 (m), 1224 (m), 1171 (m), 797 (w), 708 (s) cm.$^{-1}$.

Chromatography of the mother liquors over magnesium silicate (Florosil) gave 0.55 g. of 17-yohimbene, m.p. 206–211° (lit.[8] m.p. 201–203°).

17β-Fluoro-16α-methylyohimbane (XI).—A solution of 3 g. of 16α-methylyohimbol *p*-toluenesulfonate in 40 ml. of dry pyridine was placed in a polyethylene flask and treated with anhydrous HF under protection from moisture and with external cooling until the volume was doubled. The reaction mixture was heated at 60–70° for 4 hr., allowed to stand over the weekend, poured with stirring onto 600 ml. of crushed ice, and made basic with 10% NaOH. The precipitate was collected on a filter, washed with water, and extracted with five 100-ml. portions of $CHCl_3$. The combined chloroform extracts were dried (Na_2SO_4), filtered through Supercel, and evaporated to dryness. The residue was crystallized from ethanol–ethyl acetate; ν_{max} 720 (m), 960 (mw), 1040 (m), 1090 (m), 1155 (m), 3100 (ms), 3350 (m) cm.$^{-1}$.

17β-Chloro-16α-methylyohimbane (XII).—A stream of dry HCl was introduced without cooling into a solution of 3 g. of 16α-methylyohimbol *p*-toluenesulfonate in 20 ml. of dry pyridine. After 30 min. the initially hot solution began to cool and solidify to a crystalline mass. The addition of HCl was discontinued and the reaction mixture was heated on a steam bath for 4 hr., allowed to cool, poured into 600 ml. of ice water, and made basic with 2% NaOH. The precipitate was collected on a filter and dried in a vacuum dessicator over H_2SO_4. The analytical sample was obtained by recrystallizations from ethanol–ethyl acetate (1:1); ν_{max} 815 (m), 965 (m), 1265 (m) cm.$^{-1}$.

16β-Chloroyohimbane (XIII).—Hydrogen chloride was introduced over a period of 2 hr. into a solution of 1.65 g. of 16α-hydroxyyohimbane *p*-toluenesulfonate in 70 ml. of dry pyridine. The reaction mixture was heated on a steam bath and protected from moisture by a $CaCl_2$ tube. After heating for an additional 2 hr. the contents of the flask were poured onto 300 g. of crushed ice, made basic with aqueous NH_3, and filtered. The solid was taken up with $CHCl_3$ and dried (Na_2SO_4), and the solution was evaporated *in vacuo*. The residue was crystallized from methanol; ν_{max} 3410 (s), 3175 (w), 1263 (s), 1028 (m), 820 (m), 775 (m), 749 (vs) cm.$^{-1}$.

16α-Methyl-16-yohimbene (XV).—Gaseous HBr was introduced into a solution of 3 g. of 17α-hydroxy-16α-methylyohimbane *p*-toluenesulfonate in 20 ml. of dry pyridine until the mixture solidified. After heating for 4 hr. on steam bath ($CaCl_2$ tube!) and allowing to stand overnight at room temperature, the contents were poured into ice–water. The reaction mixture was made basic with *ca.* 600 ml. of 2% NaOH, triturated, and filtered. The collected material, freed of remaining pyridine by storing in a vacuum dessicator over H_2SO_4, was dissolved with stirring in 300 ml. of chloroform and 100 ml. of 2% NaOH solution. The $CHCl_3$ layer was dried (Na_2SO_4) and evaporated *in vacuo*. The residue crystallized from methanol after purification over charcoal; m.p. 195–200°; $[\alpha]^{25}D$ −168° (*c* 0.6, pyridine); yield 1.5 g.; ν_{max} 793 (m), 973 (m), 3200 (w), 3450 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{24}N_2 \cdot 0.5H_2O$: C, 79.69; H, 8.36; N, 9.29. Found: C, 79.78; H, 8.36; N, 9.20.

16α-Chloromethylyohimbol (XVI).—A cooled solution of 0.5 g. of yohimbyl alcohol monotosylate in 15 ml. of dry pyridine was saturated with dry HCl for 10 min. The thick mass was concentrated to dryness *in vacuo* on steam bath and triturated with 5% KOH solution. The solution of the residue in glacial acetic acid was diluted with water and made basic with concentrated NH_4OH. The precipitate was filtered off, washed with water, and recrystallized from acetone; ν_{max} 1106 (s), 1164 (s), 3320 (s), 3580 (m) cm.$^{-1}$.

17β-Chloro-16α-chloromethylyohimbane (XVII).—Phosphorus oxychloride (20 ml.) was added dropwise with stirring to a solution of 6.0 g. of 16α-chloromethyl-17α-hydroxyyohimbane in 50 ml. of dry pyridine over a period of 40 min. at 0°. After standing at room temperature for 3 hr., the reaction mixture was heated at 65–75° for 3 hr., cooled to 5°, and poured onto 500 g. of ice water. The solid was filtered off and stirred with 10 ml. of 10% aqueous NaOH and 150 ml. of $CHCl_3$. The $CHCl_3$ extract was dried (Na_2SO_4) and evaporated *in vacuo*. Trituration of the residue with 15 ml. of hot methanol and cooling gave crystals, which were recrystallized from methanol–acetone with the aid of charcoal; ν_{max} 1335 (w), 1285 (w), 1100 (w) cm.$^{-1}$.

Yohimbyl Alcohol Cyclic Sulfite Ester (XVIII).—To the solution of 25 g. of azeotropically dried yohimbyl alcohol in 100 ml. of dry pyridine, a solution of 6 ml. of thionyl chloride in 50 ml. of dry pyridine was added dropwise with stirring and protection from moisture at 0–5°. After allowing to stand overnight in the cold, the mixture was diluted with several volumes of water, neutralized with $NaHCO_3$, and filtered. The solids were stirred for 30 min. with 2.5% aqueous NaOH at 0°, collected on a filter, washed with water, dried in a vacuum dessicator over H_2SO_4, and recrystallized several times from acetone using charcoal for decolorization; ν_{max} 892 (s), 942 (s), 976 (s), 1160 (s), 1210-1230 (m) cm.$^{-1}$.

16-Hydroxyyohimbanes (XIX and XX).—A mixture of 5 g. of 16-ketoyohimbane and 2 g. of KBH_4 was stirred at 35° for 1 hr. After evaporation of the solvent, the residue was triturated with water, filtered, and washed until no alkaline material was detectable in the washings. The product was extracted with refluxing acetone for 1 hr. and filtered to give 1.8 g. of the β-epimer XX, which was recrystallized from large amounts of ethanol; ν_{max} 3190 (s), 3030 (w), 1316 (s), 1176 (s), 1053 (s), 988 (s) cm.$^{-1}$. On concentration of the acetone solution 2 g. of the α-epimer XIX was obtained. Successive recrystallizations from acetone–methanol (1:1) and methanol gave the analytical sample: ν_{max} 3370 (s), 1323 (m), 1052 (vs), 1017 (m), 992 (s) cm.$^{-1}$.