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Rauwolfia Alkaloids. XVII. 3-Epi-α-yohimbine

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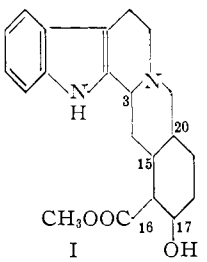
The isolation from *Rauwolfia serpentina* of a new alkaloid isomeric with yohimbine and identified as 3-epi-α-yohimbine is reported. Degradative and synthetic evidence demonstrates the presence of the 3-epialloyohimbane ring system. This is confirmed by isomerization of 3-epi-α-yohimbine to α-yohimbine. Neither the alkaloid nor its synthetic esters possess reserpine-like activity.

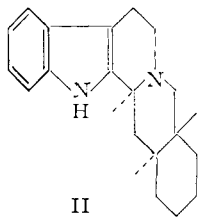
Interest in the Rauwolfia species aroused by the unique activity of reserpine led to the isolation of many alkaloids from these plants. Among these alkaloids are several isomers of yohimbine. Yohimbine[1,2] itself, corynanthine,[2] isorauhimbine[3] and serpine[4] were isolated from *Rauwolfia serpentina*. α-Yohimbine (rauwolscine)[5] and yohimbine[6] were found in *Rauwolfia canescens*. The occurrence of a new isomer, provisionally called "alkaloid 3078," was announced recently.[7] Elucidation of its structure, now complete with the exception of the configuration of two asymmetric centers, shows that "alkaloid 3078" is 3-epi-α-yohimbine (3-epirauwolscine).

Yohimbine and its isomers correspond to the structure I, differing from each other in the con-

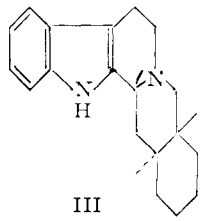


I

figurations of the five asymmetric centers. Both yohimbine and corynanthine have the yohimbane configuration (II),[8,9] but differ in the configuration of carbon 16. Serpine is reported to have the ψ-yohimbane configuration (III)[4] and α-yohimbine, the alloyohimbane configuration (IV).[5,10] No structure has been assigned as yet to isorauhimbine. It now is established that 3-epi-α-yohimbine has the 3-epialloyohimbane configuration (V) and represents the first recognition of this ring system in a natural product. It is to be understood that IV and V do not represent absolute configuration.



II



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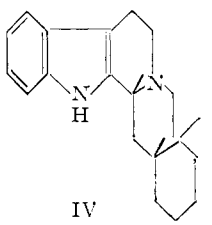

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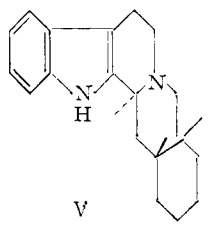


V

3-Epi-α-yohimbine was isolated from the mother liquors encountered in the preparation of large quantities of ajmaline. As obtained at first it melted at 125–128°. Subsequent purification through chromatography induced the crystallization of a polymorphic form melting at 181–183°. The two forms are readily interconvertible and have identical infrared and ultraviolet absorption. The base was characterized further by the preparation of its hydrochloride, methiodide and hydrazide. Saponification of 3-epi-α-yohimbine readily afforded the corresponding acid which on treatment with diazomethane reformed the original alkaloid.

The isolation of yobyrine and tetrabyrine from selenium dehydrogenation of 3-epi-α-yohimbine (VI) is positive evidence for the presence of the pentacyclic ring system common to the yohimbine isomers. Proof that the carbomethoxy group is attached to carbon 16 is afforded by selenium dehydrogenation of 3-epi-α-yohimbyl alcohol (VII) to methylyobyrine (VIII) identical with that formed from yohimbyl alcohol.[11] The position of the hydroxyl group adjacent to the carbomethoxy group is evident from the formation of 3-epialloyohimbone (IX) as the product of Oppenauer oxidation. Reduction of the ketone by the Huang-Minlon method yielded a mixture of alloyohimbane (IV) and 3-epialloyohimbane (V). One of these apparently arises from isomerization under the alkaline conditions of the reduction. To resolve this question, the ethylene mercaptal derivative of the ketone IX was desulfurized with Raney nickel. Only one product, 3-epialloyohimbane (V) was formed. This clearly demonstrates that the ketone IX is indeed 3-epialloyohimbane. The identification of 3-epialloyohimbane was based on a

(1) F. E. Bader, D. F. Dickel and E. Schlittler, THIS JOURNAL, **76**, 1695 (1954).

(2) A. Hofmann, *Helv. Chim. Acta*, **37**, 849 (1954).

(3) A. Hofmann, *ibid.*, **37**, 314 (1954).

(4) A. Chatterjee and S. Bose, *Science and Culture (India)*, **19**, 512 (1954); A. Chatterjee and S. Bose, *Experientia*, **10**, 246 (1954).

(5) A. Chatterjee, A. K. Bose and S. Pakrashi, *Chemistry & Industry*, 491 (1954); A. Chatterjee and S. Pakrashi, *Naturwissenschaften*, **41**, 215 (1954).

(6) E. Haack, A. Popelak, H. Spingler and F. Kaiser, *ibid.*, **41**, 479 (1954).

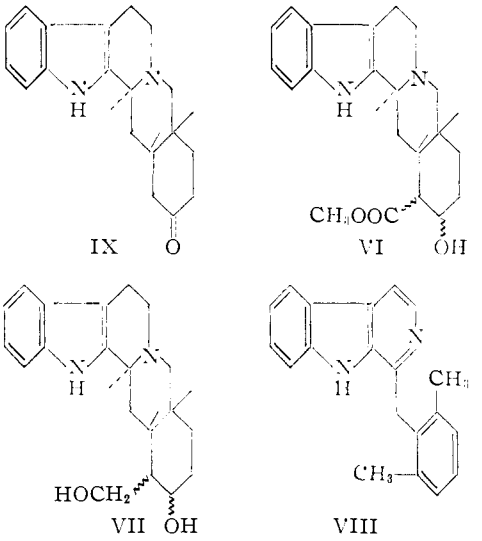
(7) F. E. Bader, D. F. Dickel, R. A. Lucas and E. Schlittler, *Experientia*, **10**, 298 (1954).

(8) M. M. Janot, R. Goutarel, A. Le Hir, M. Amin and V. Prelog, *Bull. soc. chim. France*, 1085 (1952).

(9) R. C. Cookson, *Chemistry & Industry*, 337 (1953).

(10) A. Le Hir, M. M. Janot and R. Goutarel, *Bull. soc. chim. France*, 1027 (1953).

(11) P. Karrer, R. Schwyzer, A. Flam and R. Saemann, *Helv. Chim. Acta*, **35**, 865 (1952).



comparison of its infrared absorption spectrum with that of synthetic *dl*-3-epialloyohimbane.[12] Identification of alloyohimbane was based primarily on a similar comparison with *dl*-alloyohimbane prepared by reduction of sempervirine.[13]

That 3-epi-α-yohimbine and α-yohimbine differ only in the configuration of carbon 3 was proved by conversion of the former compound to α-yohimbine. Oxidation of 3-epi-α-yohimbine with lead tetraacetate afforded the corresponding anhydronium compound which on reduction with sodium borohydride gave a product shown to be identical with α-yohimbine. Since this oxidation is known to involve only ring C, no asymmetric center other than carbon 3 would be affected.[8,10,14,15] Two proposals have been made concerning the stereochemistry of the substituent groups in α-yohimbine. In one of these the hydroxyl group is assigned the axial and the carbomethoxy the equatorial conformation.[5] In the other, the equatorial conformation is advanced for the hydroxyl group while the carbomethoxy group is not defined.[10] The evidence does not appear conclusive in either case.

A number of esters of 3-epi-α-yohimbine were prepared for biological testing. However, neither the alkaloid itself nor any of its esters resembled reserpine in general pharmacological activity. Acetylation of 3-epi-α-yohimbine with acetic anhydride in pyridine gave only the monoacetyl derivative, while boiling acetic anhydride and sodium acetate yielded a small amount of the diacetyl derivative along with a large amount of the monoacetate. Esterification with benzoyl chloride in pyridine led exclusively to the dibenzoyl derivative. On the other hand, only monoacylated compounds were obtained by reaction of the alkaloid with either 3,4,5-trimethoxybenzoyl chloride or *p*-toluenesulfonyl chloride. Although the physical constants of 3-epi-α-yohimbine show many similarities with those published for ajmalinine,[16] the two alkaloids may be distinguished readily by the dissimilarity of their ultraviolet absorption spectra.[17]

Experimental

Isolation of 3-Epi-α-yohimbine.—The alkaloid was isolated from "Solution A" described previously[18] by extraction of 20-liter batches (equivalent to 40 kg. *R. serpentina* roots). Twenty liters of ethyl ether containing 10% methanol were added to each batch and the *p*H adjusted to 7. After stirring for 10 minutes the organic layer containing weak bases was separated. The aqueous solution was again covered with 20 l. of ether–10% methanol and the *p*H brought to 9.2. After stirring for 10 minutes, the aqueous layer containing the strong bases was removed. The organic layer was clarified by filtration and then stirred for 30 seconds with 350 ml. of 2 *N* hydrochloric acid. The aqueous layer was separated quickly and the organic layer extracted four times with 150-ml. portions of 2 *N* hydrochloric acid, stirring for two minutes each time. The first two acid extracts were combined (ext. I) as were the last three (ext. II). On standing for three hours at 5°, ext. I yielded 35 g. and ext. II, 3.5 g. of ajmaline hydrochloride. An additional 20 g. crystallized from the filtrate after 18 hours. The mother liquors were combined and the bases precipitated by addition of excess ammonia. The mixture was stirred a few hours and allowed to stand overnight at 5° to convert the gummy precipitate to a granular form. The light brown precipitate was filtered, washed with water and dried *in vacuo* at 40°; yield 150 g. Seven grams of this material in 50 ml. of benzene was chromatographed on 200 g. of acid-washed alumina, activity II–III, starting with benzene, followed by benzene with increasing amounts of acetone and then with 50-ml. portions of methanol. 3-Epi-α-yohimbine was present in the first three methanol extracts. The fourth contained ajmaline (dark red color with nitric acid). The first three extracts were combined (4.9 g.) and yielded 1.5 g. of 3-epi-α-yohimbine by crystallization from methanol–water (1:1), m.p. 124–128°, $[\alpha]^{26}D$ −96° (1%, pyridine), −88° (1%, chloroform). The melting point was not raised by repeated crystallization from methanol–water. Rechromatography of 2.5 g. of 3-epi-α-yohimbine on 75 g. of alumina (activity III) and elution with chloroform containing increasing amounts of methanol gave a series of fractions containing two crystalline forms, one melting at 124–125° and the other at 179–180°. The two forms are readily interconvertible by recrystallization from methanol–water and seeding with the desired form.

A sample of the high melting form was recrystallized repeatedly from methanol–water; m.p. 181–183°, $[\alpha]^{26}D$ −90° (1%, pyridine).

Anal. Calcd. for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90; OCH_3, 9.75. Found (high melting form): C, 71.06; H, 7.65; N, 7.77. Found (low melting form): C, 70.94; H, 7.39; N, 7.96; OCH_3, 8.51.

3-Epi-α-yohimbine Hydrochloride.—A slight excess of methanolic hydrogen chloride was added to a solution of 3-epi-α-yohimbine in methanol. Addition of an equal volume of ether afforded the hydrochloride as colorless prisms. The hygroscopic salt was recrystallized twice from methanol-ether and dried for 10 hours at 100° *in vacuo;* m.p. 235–240°, $[\alpha]^{26}D$ −75° (1%, water).

Anal. Calcd. for $C_{21}H_{26}N_2O_3 \cdot HCl$: C, 64.52; H, 6.96; N, 7.17; Cl, 9.07. Found: C, 64.11; H, 6.71; N, 6.88; Cl, 9.05.

3-Epi-α-yohimbine Methiodide.—3-Epi-α-yohimbine (0.5 g.) and 0.5 ml. of methyl iodide were dissolved in 10 ml. of acetone and allowed to stand at room temperature for one hour. The methiodide separated as a tan powder; yield 0.4 g. Recrystallization from ethanol afforded colorless crystals of 3-epi-α-yohimbine methiodide, m.p. 234–238° dec., $[\alpha]^{25}D$ −28° (1%, ethanol).

(12) G. Stork and R. K. Hill, THIS JOURNAL, **76**, 949 (1954). We are very grateful to Dr. Gilbert Stork for making this comparison.

(13) A. Le Hir, R. Goutarel and M. M. Janot, *Bull. soc. chim. France*, 1091 (1952).

(14) H. Schwarz, *Experientia*, **6**, 330 (1950).

(15) F. L. Weisenborn, M. Moore and P. A. Diassi, *Chemistry & Industry*, 375 (1954).

(16) S. Siddiqui and R. H. Siddiqui, *J. Indian Chem. Soc.*, **8**, 667 (1931); **12**, 37 (1935).

(17) The ultraviolet absorption spectrum of ajmalinine was given by M. Raymond-Hamet, *Compt. rend.*, **237**, 1435 (1953).

(18) L. Dorfman, A. Furlenmeier, C. F. Huebner, R. A. Lucas, H. B. MacPhillamy, J. M. Mueller, E. Schlittler, R. Schwyzer and A. F. St. Andre, *Helv. Chim. Acta*, **37**, 59 (1954).

Anal. Calcd. for $C_{22}H_{29}IN_2O_3$: C, 53.23; H, 5.89; N, 5.64. Found: C, 53.14; H, 5.82; N, 5.63.

3-Epi-α-yohimbic Acid Hydrazide.—Anhydrous hydrazine (5 g.) was added to a solution of 4.0 g. of 3-epi-α-yohimbine in 25 ml. of anhydrous ethanol and the mixture refluxed for four hours. Crystallization of 3-epi-α-yohimbic acid hydrazide began after the first hour; yield 3.7 g. The hydrazide was purified by precipitation from dilute acetic acid with sodium hydroxide. After recrystallization from methanol it melted at 288–295° dec., $[\alpha]^{26}D$ −93° (0.5%, pyridine).

Anal. Calcd. for $C_{20}H_{26}N_4O_2$: N, 15.29. Found: N, 15.59.

3-Epi-α-yohimbic Acid Hydrochloride.—3-Epi-α-yohimbine (5 g.) was refluxed for two hours with 200 ml. of 1 *N* methanolic potassium hydroxide, the solution cooled, and the equivalent amount of methanolic hydrogen chloride added. The precipitate of potassium chloride was removed and the filtrate evaporated to dryness. Extraction by trituration with a total of 400 ml. of chloroform–methanol (4:3) yielded an amorphous product. It was dissolved in ethanol, treated with excess alcoholic hydrogen chloride and the solution evaporated to dryness. Repeated crystallization from ethanol yielded 1.6 g. of 3-epi-α-yohimbic acid hydrochloride, m.p. 255–258°, $[\alpha]^{26}D$ −89 (1%, water).

Anal. Calcd. for $C_{20}H_{24}N_2O_3 \cdot HCl \cdot H_2O$: N, 7.09; Cl, 8.98. Found: N, 6.98; Cl, 8.53.

Reconstitution of 3-Epi-α-yohimbine.—Excess diazomethane was distilled into a suspension of 0.3 g. of 3-epi-α-yohimbic acid hydrochloride in 25 ml. of ether and 10 ml. of methanol. After standing overnight the solution was evaporated to dryness and the residue crystallized from 4 ml. of ethanol–water (1:1) yielding 0.2 g. of 3-epi-α-yohimbine, m.p. 123–130°. Recrystallization from the same solvent yielded the polymorph melting at 185–187°. Its infrared absorption was identical with that of the original alkaloid.

3-Epi-α-yohimbyl Alcohol.—Solid lithium aluminum hydride (2 g.) was added in small portions to a stirred suspension of 2 g. of 3-epi-α-yohimbine in 150 ml. of ether. The excess reagent was decomposed with 20 ml. of water, and 88 ml. of 20% sodium potassium tartrate added. After evaporation of the ether, the aqueous suspension was extracted 10 times with 150-ml. portions of chloroform. The extracts were washed three times with water, combined, dried with sodium sulfate, and evaporated *in vacuo*. Crystallization of the residue from acetone yielded 1.2 g. of 3-epi-α-yohimbyl alcohol, which on further recrystallization melted at 239–242°, $[\alpha]^{26}D$ −9° (1%, ethanol).

Anal. Calcd. for $C_{20}H_{26}N_2O_2$: C, 73.58; H, 8.03; N, 8.58. Found C, 73.57; H, 7.94; N, 8.60.

Selenium Dehydrogenation of 3-Epi-α-yohimbine.—An intimate mixture of 0.3 g. of 3-epi-α-yohimbine and 0.3 g. of red selenium was heated in an open glass tube for 10 minutes at 245°. The fused product was ground with sand and extracted with 500 ml. of boiling benzene. The extract was evaporated to dryness and the residue chromatographed on alumina, activity I, using benzene followed by ether. Ether eluted 74 mg. of oily crystals which were rechromatographed in benzene on alumina, activity I. The first of a series of 10-ml. fractions yielded approximately 13 mg. of tetrabyrine which melted at 166–168° after recrystallization from benzene; ultraviolet absorption (ethanol): plateau at 234–242 mμ (18,400); maxima at 318–324 mμ (23,000); minima at 273 mμ (4,670). Crystallization of the material from fraction three yielded 3 mg. of yobyrine, m.p. 212–212.5°; ultraviolet absorption (ethanol): maxima at 236 mμ (33,500), 289 (16,900), 338 (4,590), 351 (4490); minima 222 mμ (21,500), 270 (4980), 301–2 (730), 345 (4,200). An additional 5 mg. of yobyrine was isolated from fractions two, four and five.

Selenium Dehydrogenation of 3-Epi-α-yohimbyl Alcohol.—An intimate mixture of 1 g. of 3-epi-α-yohimbyl alcohol and 1 g. red selenium was heated for 10 minutes at 250–260° in three separate portions. The reaction product was ground with sand and extracted for four hours with benzene in a Soxhlet apparatus. The benzene solution was stirred with an equal volume of 2 *N* hydrochloric acid, the mixture filtered and the filtrate made alkaline with concentrated aqueous ammonia. The aqueous layer was extracted three times with benzene. The combined benzene layers were dried with sodium sulfate concentrated to a small volume and chromatographed over 30 g. of alumina, activity I. Fractions of 20 ml. were collected. Fractions 1 to 50 were eluted with benzene, 51 to 79 with 50% benzene–ether and 80 to 107 with ether. Fractions 65 to 75 were combined and crystallized from benzene yielding approximately 10 mg. of methylyobyrine (1-(2,6-dimethylbenzyl)-9H-pyrid[3,4-b]indole). After sublimation at 0.05 mm. and 150–160°, it melted at 225–226°, and was identical by infrared absorption analysis with authentic methylyobyrine.[11]

3-Epialloyohimbone.—3-Epi-α-yohimbine (4 g.) was dried by azeotroping with 200 ml. of xylene and then mixed with 20 g. of aluminum phenoxide and 100 ml. of cyclohexanone. After refluxing for 18 hours, the mixture was poured into 400 ml. of 2 *N* sulfuric acid. The xylene was separated and extracted with a further 100 ml. of 2 *N* sulfuric acid. The combined acid solution was washed with small portions of ether totaling 200 ml. and made alkaline with 10% sodium hydroxide. The resulting precipitate was crystallized from ethanol yielding 0.7 g. of 3-epialloyohimbone. A sample was sublimed at 0.002 mm. and 150–160°, m.p. 247–250°, $[\alpha]^{26}D$ +163° (1%, pyridine).

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.52. Found: C, 77.71; H, 7.63; N, 9.66.

3-Epialloyohimbane and Alloyohimbane (Wolff–Kishner Reduction of 3-Epialloyohimbone).—A mixture of 0.54 g. of 3-epialloyohimbone, 5 ml. of diethylene glycol, 0.5 ml. of hydrazine (100%) and 0.70 g. of potassium hydroxide was warmed over a free flame, after which the flask was heated for two hours at 210°. The reaction mixture was allowed to cool to room temperature and diluted with 100 ml. of water. The pale yellow solid which precipitated was washed with 20 ml. of methanol, dissolved in benzene–acetone (1:1) and decolorized by filtration through a 20-g. alumina column, activity I. Crystallization from methanol gave 0.14 g. of 3-epialloyohimbane, m.p. 205–207°. After recrystallization from a small volume of acetone it melted at 216–218°, $[\alpha]^{22}D$ +90° (1%, ethanol). The infrared absorption was identical with that of *dl*-3-epialloyohimbane.

Anal. Calcd. for $C_{19}H_{24}N_2$: N, 9.99. Found: N, 9.63.

Concentration of the methanol mother liquor yielded 0.17 g. of alloyohimbane, which after recrystallization from acetone melted 154–156°, $[\alpha]^{26}D$ −162° (1%, pyridine). The infrared absorption was identical with that of *dl*-alloyohimbane.

Anal. Calcd. for $C_{19}H_{24}N_2$: N, 9.99. Found: N, 10.08.

***dl*-Alloyohimbane.**—Reduction of 1.3 g. of sempervirine according to the published procedure yielded crude *dl*-alloyohimbane.[13] It was chromatographed in benzene on 10 g. of alumina, activity I. The first 200 ml. of benzene eluted *dl*-alloyohimbane, which after crystallization from methanol melted at 149–150°.

Anal. Calcd. for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.24; H, 8.50; N, 10.08.

3-Epialloyohimbone Ethylene Mercaptal.—A cold solution of 0.50 g. of 3-epialloyohimbone and 2.5 ml. of ethanedithiol in 20 ml. of glacial acetic acid was treated with a moderate stream of hydrogen chloride for 15 minutes. The mixture was allowed to stand at room temperature overnight. The white crystalline thioketal hydrochloride was filtered and washed with ether; yield 0.49 g., m.p. 318–320°. The hydrochloride (0.3 g.) was dissolved in 15 ml. of water and 30 ml. of methanol and converted to the free base by treatment with excess aqueous ammonia. 3-Epialloyohimbone ethylene mercaptal (0.17 g.) crystallized from the solution as fine needles, m.p. 155–158°.

Anal. Calcd. for $C_{21}H_{26}N_2S_2$: N, 7.56; S, 17.30. Found: N, 7.44; S, 17.42.

3-Epialloyohimbane (Desulfurization of 3-Epialloyohimbone Ethylene Mercaptal).—The thioketal (0.20 g.) derived from 3-epialloyohimbone was dissolved in 50 ml. of 95% ethanol and refluxed with 1.5 g. of pyrophoric Raney nickel for four hours. After removing the nickel, the filtrate was evaporated to a film from which 17 mg. of 3-epialloyohimbane crystallized on addition of methanol, m.p. 207–209°, $[\alpha]^{26}D$ +88° (1%, ethanol); +105° (1%, chloroform). The infrared absorption was identical with that of 3-epialloyohimbane prepare by the Wolff–Kishner reduction.

***py*-Tetradehydro-α-yohimbine Hydrochloride.**—A solution of lead tetraacetate in acetic acid (120 ml. of 0.051 *M*, 2.08 molar equivalents) was added dropwise over a 2-hour

period to a stirred solution of 1 g. of 3-epi-α-yohimbine in 25 ml. of acetic acid at 60°. The addition was controlled so that only a slight excess of oxidant was present at any time as determined by the action of a test drop on starch–potassium iodide paper. Most of the acetic acid was removed *in vacuo*, 150 ml. of chloroform and 25 ml. of water were added, and the mixture made just alkaline (*p*H 9) by the slow addition of 50% sodium hydroxide. The chloroform solution was dried over sodium sulfate and made acid by the addition of ethanolic hydrogen chloride. Upon evaporation *in vacuo* the *py*-tetradehydro-α-yohimbine hydrochloride (0.7 g.) was obtained as an orange glass; ultraviolet absorption (ethanol): maxima at 253 mμ (20,800), 308 (14,900) and 361 (6910); minima at 228 mμ (13,700), 280 (4,730) and 324 (4040).

The crystalline reineckate was prepared by addition of aqueous ammonium reineckate to an aqueous solution of the base hydrochloride. After recrystallization from acetone–water it melted at 230–235° dec.

Anal. Calcd. for $C_{26}H_{29}CrN_8O_5S_4 \cdot H_2O$: N, 15.02. Found: N, 15.05.

α-Yohimbine.—Sodium borohydride (0.30 g.) was added to a solution of 0.30 g. of *py*-tetrahydro-α-yohimbine hydrochloride in 20 ml. of methanol. The solution was refluxed for one hour, concentrated *in vacuo*, 5 ml. of water added and the mixture extracted with 25 ml. of chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo* to a brown glass. Crystallization from ethanol–water yielded 0.15 g. of crude α-yohimbine which on recrystallization from ethanol melted at 238–239°, $[\alpha]^{25}D$ −12 (1%, chloroform). Identity with α-yohimbine (rauwolscine isolated from *R. canescens*) was established by mixed melting point determination and comparison of the infrared spectra in nujol mull.

Anal. Calcd. for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.29; H, 7.14; N, 7.93.

O,N-Diacetyl-3-epi-α-yohimbine.—A mixture of 3 g. of 3-epi-α-yohimbine, 3 g. of sodium acetate and 30 ml. of acetic anhydride was refluxed for three hours. After cooling the reaction mixture was poured into 200 ml. of cold water. Aqueous ammonia was added carefully in just sufficient quantity to precipitate a small amount of a brown resinous material. The mixture was filtered and a further quantity of aqueous ammonia added to the filtrate to completely precipitate 3.5 g. of a nearly white product. The crude material was dissolved in the minimum amount of methanol and, after cooling overnight, yielded 270 mg. of white needles. Concentration of the mother liquor failed to give additional material. After recrystallization from methanol the O,N-diacetyl-3-epi-α-yohimbine melted at 194–196°, $[\alpha]^{26}D$ −102° (1%, pyridine).

Anal. Calcd. for $C_{25}H_{30}N_2O_5$: C, 68.47; H, 6.90; N, 6.39. Found: C, 68.45; H, 6.83; N, 6.65.

O-Acetyl-3-epi-α-yohimbine.—(A) The mother liquor from O,N-diacetyl-3-epi-α-yohimbine was evaporated to dryness and the residue crystallized from benzene affording 1.3 g. of O-acetyl-3-epi-α-yohimbine. After recrystallization from benzene it melted at 179.5–181°, $[\alpha]^{26}D$ −124° (1%, pyridine). After extended drying the compound still contained one-half mole of benzene of crystallization.

Anal. Calcd. for $C_{23}H_{28}N_2O_4 \cdot {}^1/_2C_6H_6$: C, 71.70; H, 7.17; N, 6.43. Found: C, 71.58; H, 6.96; N, 6.50.

(B) 3-Epi-α-yohimbine (5 g.), 10 ml. of acetic anhydride and 40 ml. of pyridine were allowed to stand for three weeks at 5°. The solution was concentrated, 100 ml. of water added, the solution filtered, and aqueous ammonia added to precipitate 5.3 g. of crude O-acetyl-3-epi-α-yohimbine. It crystallized from benzene with one mole of solvent, m.p. 179–180°, $[\alpha]^{24}D$ −116° (0.5%, pyridine), −110° (0.6%, chloroform).

Anal. Calcd. for $C_{23}H_{28}N_2O_4 \cdot C_6H_6$: C, 73.39; H, 7.22; N, 5.90. Found: C, 73.61; H, 7.00; N, 5.97.

O,N-Dibenzoyl-3-epi-α-yohimbine.—3-Epi-α-yohimbine (5 g.), 40 ml. of pyridine and 10 ml. of benzoyl chloride were allowed to stand for six weeks at 5°. The reaction mixture was poured into 200 ml. of cold water and evaporated almost to dryness *in vacuo*. The residue was dissolved in 200 ml. of chloroform and washed three times with 150-ml. portions of 2% potassium hydroxide and three times with 250-ml. portions of water. The combined chloroform extracts were dried with sodium sulfate and evaporated. Crystallization from 25 ml. of acetone yielded 3.4 g. of bright yellow O,N-dibenzoyl-3-epi-α-yohimbine, m.p. 225–226°. To a suspension of 2.2 g. of the base in 25 ml. of acetone, a slight excess of aqueous hydrochloric acid (1:1) was added forming 2.4 g. of the colorless hydrochloride, m.p. 246–248°.

Excess aqueous ammonia was added to a suspension of 1.9 g. of the hydrochloride in acetone; yield 1.7 g. of the regenerated base. It was recrystallized from acetone–water (5:2), m.p. 230–231°, $[\alpha]^{25}D$ +63° (1%, chloroform).

Anal. Calcd. for $C_{35}H_{34}N_2O_5$: C, 74.71; H, 6.09; N, 4.98. Found: C, 74.93; H, 6.04; N, 5.03.

O-3,4,5-Trimethoxybenzoyl-3-epi-α-yohimbine.—A mixture of 5 g. of 3-epi-α-yohimbine, 40 ml. of pyridine and 10 g. of 3,4,5-trimethoxybenzoyl chloride was allowed to stand for eight days at 5°. After removal of trimethoxybenzoic acid anhydride, the filtrate was diluted with twice its volume of water and then concentrated *in vacuo*. The residue was dissolved in 100 ml. of chloroform, the solution washed three times with 100-ml. portions of 2% sodium hydroxide, 100 ml. of water, dried with sodium sulfate and the solvent evaporated *in vacuo*. The residue in 25 ml. of benzene was chromatographed over 50 g. of alumina, activity II–III, using benzene and benzene with increasing amounts of acetone. The product crystallized readily on addition of a small amount of acetone; yield 2.3 g. of crude 3,4,5-trimethoxybenzoyl-3-epi-α-yohimbine. After recrystallization from ethanol it melted at 222–226°, $[\alpha]^{26}D$ −53° (1%, ethanol).

Anal. Calcd. for $C_{31}H_{36}N_2O_7$: C, 67.86; H, 6.62; N, 5.11. Found: C, 68.16; H, 6.40; N, 5.23.

O-*p*-Toluenesulfonyl-3-epi-α-yohimbine.—3-Epi-α-yohimbine (5 g.), 40 ml. of pyridine and 10 g. of *p*-toluenesulfonyl chloride were allowed to stand for two weeks at 5°. The reaction mixture was poured on 150 g. of ice and then extracted twice with 200-ml. portions of chloroform. The chloroform extracts were washed twice with 200 ml. of 2% sodium hydroxide and twice with 250 ml. of water. The combined chloroform extracts were dried with sodium sulfate and evaporated. Final traces of pyridine were removed from the residue by repeated evaporation with benzene. Crystallization from acetone yielded 3.4 g. of *O*-*p*-toluenesulfonyl-3-epi-α-yohimbine, m.p. 167–172°, $[\alpha]^{24}D$ +178° (1%, pyridine), +182° (1%, chloroform).

Anal. Calcd. for $C_{28}H_{32}N_2O_5S$: N, 5.51; S, 6.30. Found: N, 5.62; S, 6.47.

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