Yohimbane Derivatives. III. The Oxidative Rearrangement of Indole Alkaloids to Their Spirooxindole Analogs[1]

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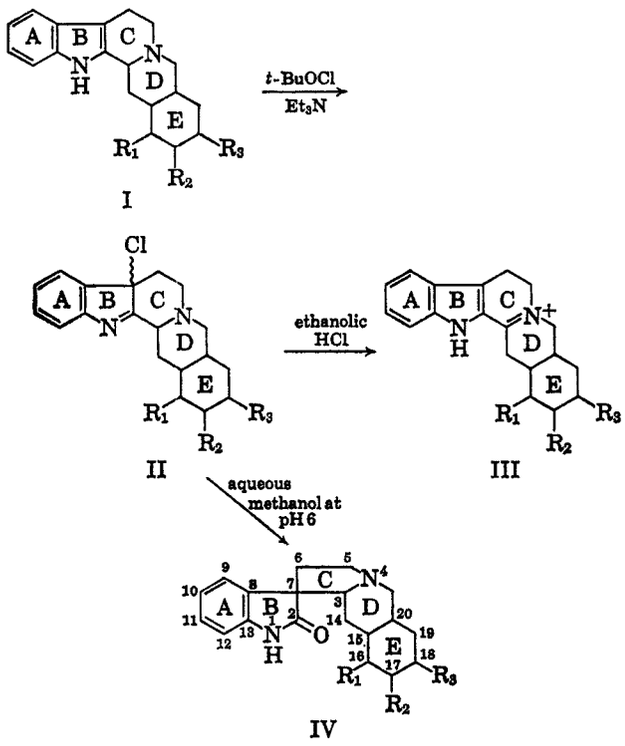
Received January 11, 1966

The hydrolytic rearrangement of 7-chloro-7H-yohimbane derivatives II under acidic conditions to give epimeric mixtures of oxindole analogs IV of the parent alkaloids I is described. 7-Chloro-7H-yohimbine and 7-chloro-7H-pseudoyohimbine gave the same yields of the same products. The epimers obtained from ajmalicine were shown to be identical with mitraphylline and isomitraphylline derived from natural sources. Crystalline chloro derivatives IIa and d were isolated and the former was fractionated into its two epimers. The chloro derivatives were established as common intermediates which could be converted to 3-dehydro derivatives III or oxindole analogs IV by employing the appropriate conditions. Some chemical transformations of the oxindole analogs are described.

Godtfredsen and Vangedal[2] have shown that ethanolic hydrogen chloride treatment of the chloro derivative II arising from *t*-butyl hypochlorite oxidation of indole alkaloids I (Chart I) is a high yielding procedure for the preparation of the corresponding 3-dehydro salts III. We have observed that hydrolysis of the same oxidation product by refluxing in aqueous methanol, which had been adjusted to pH 6 by the addition of acetic acid, resulted in rearrangement to give a completely different class of compounds.

CHART I

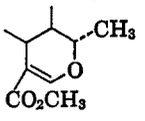


I-IVa, $R_1=R_2=R_3=H$

b, $R_1=\alpha$-CO_2CH_3; $R_2=\alpha$-OH; $R_3=H$

c, $R_1=\alpha$-CH_3; $R_2=\alpha$-OH; $R_3=H$

d, $R_1=H$; $R_2=\beta$-OH; $R_3=\equiv CHC_6H_5$

e, Ring E = 

Employing this procedure, yohimbane Ia,[3] yohimbine Ib,[4] 16α-methylyohimbol Ic,[5] 18-benzylidene-17β-hydroxyyohimbane Id,[6] and ajmalicine Ie[4] were converted to their corresponding oxindole analogs having the structure IV. Pseudoyohimbine Ib,[2] which differs from the aforementioned alkaloids in its configuration at C-3, afforded a product which was identical, with respect to both composition and yield, with that obtained with yohimbine.[7] In all cases the product was found to consist predominantly of a mixture of two components which could be differentiated by the use of paper chromatography. These were separated and shown to be isomeric substances having the same ultraviolet spectrum. Of each pair, the slower-moving compound had the greater basicity and as such was designated as a derivative of "spiroxyane B."[8] It was apparent that the two isomers were epimeric about carbon 3 and/or carbon 7 since refluxing one of them with pyridine gave a mixture of both.[9,10] The epimers could be differentiated further by a test based on their relative rates of oxidation by mercuric acetate; only

(1) (a) For a preliminary report of some of this work, see J. Shavel, Jr., and H. Zinnes, *J. Am. Chem. Soc.*, **84**, 1320 (1962). (b) Previous papers in this series: H. Zinnes, R. A. Comes, and J. Shavel, Jr., *J. Org. Chem.*, **30**, 105 (1965); M. von Strandtmann, G. Bobowski, and J. Shavel, Jr., *J. Med. Chem.*, **8**, 338 (1965).

(2) W. O. Godtfredsen and S. Vangedal, *Acta Chem. Scand.*, **10**, 1414 (1956).

(3) J. Jost, *Helv. Chim. Acta*, **32**, 1297 (1949).

(4) R. E. Woodson, Jr., H. W. Youngken, E. Schlittler, and J. A. Schneider, "Rauwolfia," Little, Brown, and Co., Boston, Mass., 1957, Chapter 3, and references contained therein.

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

(6) J. Shavel, Jr., G. Bobowski, and M. von Strandtmann, U. S. Patent 3,139,428, (June 30, 1964).

(7) N. Finch and W. I. Taylor [*J. Am. Chem. Soc.*, **84**, 1318, 3871 (1962)] have achieved the transformation of IIb and e to IVb and e, respectively, by a related two-step procedure. Their method consisted of treatment of the chloro derivative with methanolic alkali to give the corresponding imido ethers of IVb and e which were hydrolyzed to IVb and e, respectively, by refluxing with dilute acid. In contrast with the method used in the present investigation, this procedure yielded only trace amounts of the imido ether of IVb when employed with the chloro derivative of pseudoyohimbine.

(8) For the unsubstituted nucleus, IVa, we propose the trivial name spiroxyane with the numbering as shown to maintain the relationship with yohimbane. The suffix A or B follows the convention used by T. Nozoye [*Chem. Pharm. Bull.* (Tokyo), **6**, 300 (1958)] who observed that uncarine B was more basic than uncarine A. The more basic epimer of structure IVb is thus named 16α-carbomethoxy-17α-hydroxyspiroxyane B. It is identical with the "yohimbine oxindole B" that was reported by Finch and Taylor.[7]

(9) J. C. Seaton, M. D. Nair, O. E. Edwards, and L. Marion [*Can. J. Chem.*, **38**, 1035 (1960)] have shown that the naturally occurring oxindole alkaloids are one of a pair of epimers which can be interconverted by refluxing in pyridine or acetic anhydride.

(10) Finch and Taylor[7] have since reported that equilibration of IVb with pyridine gives a mixture in which the least basic epimer A is the major component whereas, with dilute acetic acid, the more basic epimer B predominates.

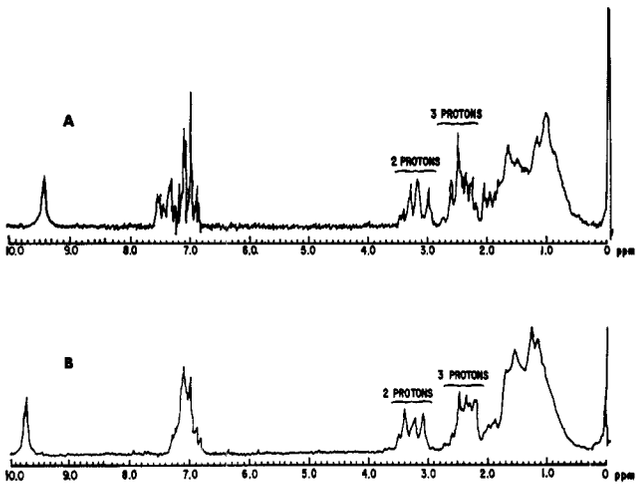


Figure 1.—Pmr spectra of spiroxyane A (A) and spiroxyane B (B)

the spiroxyanes A cause precipitation of mercurous acetate under the conditions used.[11]

Hendrickson[12] has postulated that both of the epimers of IVe have the same configuration at C-7 and that they differ only in the configuration at C-3, the hydrogen being α in the less basic compound and β in its epimer. On the other hand, Finch and Taylor[7] have concluded that the 3-hydrogen is α in both epimers with the configuration of C-7 in the spiroxyane A such that the lactam carbonyl points away from the basic nitrogen and is below the plane of rings C–E; in the spiroxyane B, the carbonyl is above this plane and is pointed toward the basic nitrogen. Support for the latter stereochemical assignment is given by our observation that the infrared spectra of chloroform solutions of both epimers of IVa[13] show a sharp band of medium intensity at 2800 and weaker bands at 2740 and 2690 cm^{-1}.[14,15] Furthermore, the pmr spectra of both epimers (Figure 1) are similar in the 2.1–3.6-ppm region in that they show a 2-proton multiplet at lower field which is quite well separated from a 3-proton multiplet at higher field. Thus, it is apparent that two of the five hydrogens adjacent to the nitrogen are equatorial and three are axial.[16] If this stereochemistry is correct, both epimers have the *trans*-diaxial arrangement of the hydrogen and lone electron pair required for reaction with mercuric acetate.[17] The relative inertness of the spiroxyanes B toward this reagent would then appear to be the result of interference on the part of the lactam carbonyl toward attack on the nitrogen by the bulky reagent. This might be in the form of steric hinderance by the oxygen itself or by a complex formed by interaction of the oxygen with mercuric acetate.

In the preparation of IVb, c, and e, the rearrangement was carried out on the crude amorphous *t*-butyl hypochlorite oxidation product. With yohimbane Ia and 18-benzylidene-17β-hydroxyyohimbane (Id), *t*-butyl hypochlorite oxidation gave a crystalline product which analyzed correctly for IIa and d, respectively. In the case of IIa the material was fractionated into two epimers, which could be distinguished by their optical rotations (+82 and −72° in dichloromethane).[18,19] Since the crystalline chloro derivative II could be converted to dehydro salts III or epimeric oxindoles IV, depending on the conditions used,[20] compounds such as II are thus established as common intermediates for their preparation from the indole alkaloids I.

The synthesis of 3-dehydro salts is favored by anhydrous conditions and has been postulated[7] to proceed as depicted in Chart II. It would appear that the selective formation of the oxindole in aqueous methanol involves reaction with water to give intermediates such as V or VI. While the mechanism for the conversion of the chloro derivatives II to oxoindoles IV has not been established, two possible pathways are given in Chart II. Mechanism A is analogous to that proposed by Finch and Taylor[7] for the alkaline methanolysis of the same chloro derivatives which results in rearrangement to oxindole imido ethers. The mechanism was presented by these workers to explain the formation of a single imido ether (retention rather than racemization) from 7-chloro-7H-yohimbine (IIb) under conditions which left the corresponding pseudoyohimbine derivative practically unaffected. Our observation, that under the conditions employed in the present investigation yohimbine and pseudoyohimbine give the same product, could be the result of prior acid-catalyzed epimerization of 7-chloro-7H-pseudoyohimbine to 7-chloro-7H-yohimbine by means of an intermediate such as VII. On the other hand, the experimental data can also be accounted for by mechanism B which involves ring opening followed by closure to give the more stable *trans*-indolizidine.[21]

Lithium aluminum hydride reduction of the B epimers of IVb and c gave, respectively, the indolines VIII and IX. Treatment of epimer B of IVb with acetic anhydride in pyridine at room temperature gave rise to the expected ester Xa which gave a negative mercuric acetate test indicating that its stereochemistry was still that of the B series. When epimer B of IVb was refluxed with acetic anhydride, the diacetyl deriva-

(11) F. L. Weisenborn and P. A. Diassi [*J. Am. Chem. Soc.*, **78**, 2022 (1956)] have shown that differences in rate of oxidation by mercuric acetate in dilute acetic acid can be used to distinguish yohimbane alkaloids having the *normal* C-3 configuration from those of the epimeric pseudo series. While Seaton, *et al.*,[9] have shown that isomitraphylline (A series) is oxidized by mercuric acetate under conditions which leave mitraphylline unaffected, we have found that general application of this reaction to the differentiation of the epimeric oxindole alkaloids requires careful regulation of both temperature and time of reaction. Unless these conditions are controlled the B epimer will often give a false positive test since it is epimerized to the A isomer by prolonged heating in the dilute acid used as the solvent. Conditions for successfully carrying out the test are given in the Experimental Section.

(12) J. B. Hendrickson, *J. Am. Chem. Soc.*, **84**, 650 (1962).

(13) This was the only crystalline pair of bases which was sufficiently soluble for this determination. The epimers B or IVb and c also give the same absorption in this region.

(14) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958); E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956).

(15) Y. Ban and T. Oishi [*Chem. Pharm. Bull.* (Tokyo), **11**, 446, 451 (1963)] have made the same observation with similarly constituted pairs of oxindoles in which ring E is missing.

(16) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Ltd., London, 1959, p 116.

(17) N. J. Leonard and D. F. Morrow, *J. Am. Chem. Soc.*, **80**, 371 (1958).

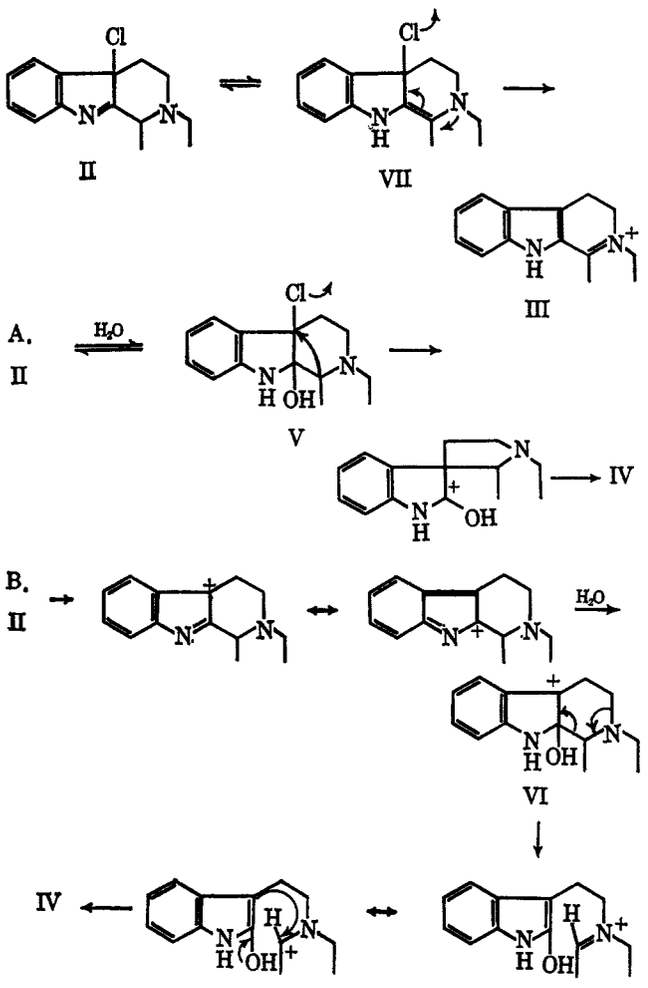
(18) This fractionation was carried out by Mr. R. Comes.

(19) N. Finch, C. W. Gemenden, I. H.-C. Hsu, A. Kerr, G. A. Sim, and W. I. Taylor [*J. Am. Chem. Soc.*, **87**, 2229 (1965)] have recently reported that the two epimers give mirror image optical rotatory dispersion curves. They have used these data to show that the positively rotating epimer has the same stereochemistry as 7α-acetoxy-7H-yohimbine whose absolute configuration was established by X-ray crystallographic analysis.

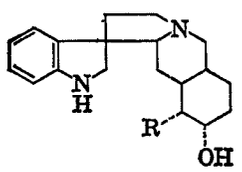
(20) The unfractionated crystalline mixture of epimers was used.

(21) A mechanism involving prior hydrolysis of II to the corresponding 7-hydroxy derivative appears to be less likely in view of the finding by B. Witkop and J. B. Patrick [*J. Am. Chem. Soc.*, **73**, 2188 (1951)] that 11-hydroxytetrahydrocarbazolenine is rearranged by acid to the indoxyl rather than the oxindole.

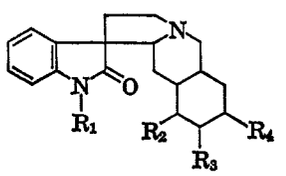
CHART II



tive Xb was obtained. This now gave a positive mercuric acetate test which suggested that it had epimerized to become one of the A series.[22] Simi-



VIII, R = CH_2OH
IX, R = CH_3



Xa, $R_1 = R_4 = H$; $R_2 = \alpha\text{-}CO_2CH_3$; $R_3 = \alpha\text{-}OCOCH_3$
b, $R_1 = COCH_3$; $R_2 = \alpha\text{-}CO_2CH_3$; $R_3 = \alpha\text{-}OCOCH_3$; $R_4 = H$
c, $R_1 = R_2 = R_4 = H$; $R_3 = =O$
d, $R_1 = R_2 = R_4 = H$; $R_3 = \beta\text{-}OH$
e, $R_1 = R_2 = R_4 = H$; $R_3 = =O$
$R_4 = =CHC_6H_5$

larly, the only product, Xc,[22] isolated from the Oppenauer oxidation of epimer B of IVb as well as its potassium borohydride reduction product, Xd, was found to give positive mercuric acetate tests. Base-catalyzed condensation of Xc with benzaldehyde gave Xe which on potassium borohydride reduction afforded epimer A of IVd.

The B epimer of IVe, obtained from ajmalicine, was found to be identical with a sample of mitraphylline[23] isolated from natural sources whereas its epimer was isolated as the picrate which was shown to be identical with a sample of isomitraphylline picrate;[23] we also obtained isomitraphylline picrate by refluxing our "synthetic" mitraphylline with pyridine as described by Seaton, *et al.*[9] The conversion of ajmalicine Ie to mitraphylline IVe confirms the structural assignment[24] of the latter since the structure of the former has been established by total synthesis.[25] The stereochemistry of rings D and E are thus also established since this has been determined for ajmalicine.[26-28]

(22) Paper chromatographic analysis of the crude reaction product revealed the presence of a slower-moving component which could have been the other epimer. We were unable to isolate this material.

Experimental Section

Melting points were taken on a Mel-Temp hot stage in open capillaries and are uncorrected. Since most of the compounds studied decompose at a temperature considerably below the melting point, the products from successive recrystallizations were compared directly, the capillaries being placed in the apparatus about 10° below the melting point. Criteria for homogeneity of the analytical samples were recrystallization to constant optical rotation and a single spot on paper chromatography.

Rotations were all taken in a 1-dm tube, using a Rudolph Model 800 photoelectric polarimeter. The solvents and concentrations (per cent, weight/volume) are given in parentheses.

Paper chromatographic analysis was carried out using the "Chromatobox"[29] technique. The compounds were spotted (as solutions in glacial acetic acid, aqueous acetic acid, chloroform or methanol) on Whatman No. 1 paper; the paper was then impregnated by spraying with 10% formamide in acetone solution and allowed to air dry for about 2 min; it was then placed in the "Chromatobox" and eluted while maintaining an ammonia atmosphere by placing a vial of concentrated aqueous ammonium hydroxide in the box. The eluents were a mixture of acetone, heptane, and benzene, in proportions of 1:2:1. Running time for the chromatograms was about 90 min. The spots were observed using an ultraviolet light ("Mineralight") with phosphor plate background.

While the reported R_f values represent typical results, they are given merely to give some idea of their order of magnitude and to give a semiquantitative expression of the differences in mobility of the substances discussed. Although the values varied somewhat from run to run, no attempt was made to improve on their precision (by more careful standardization of external conditions, etc.) since materials run on the same paper could readily and reproducibly be distinguished from one another. The procedure was used as a convenient method to rapidly differentiate between two or more materials and to establish purity. All conclusions resulting from chromatography were, therefore, based on chromatograms in which the substances to be compared were spotted together on the same paper.

The mercuric acetate test for the differentiation of epimeric spiroxyanes was carried out as follows. A solution of 50 mg of the compound to be tested in 2 ml of 5% acetic acid containing 200 mg of mercuric acetate was heated at 45-55° while stirring and scratching with a glass rod. If precipitation of crystalline mercurous acetate took place within 5 min, the compound was considered to give a "positive mercuric acetate test."

Ultraviolet spectra were determined using a Beckman DK-1 spectrophotometer and, unless otherwise stated, were taken in 95% ethanol.

Infrared spectra were recorded with a Baird Model 455 double-beam instrument; the per cent absorption is given in parenthesis. In recording the latter values, the base line varied between 5-15% absorption. The values for per cent absorption are not

(23) Samples were graciously supplied to us by Dr. L. Marion.

(24) J. C. Seaton, R. Tondeur, and L. Marion, *Can. J. Chem.*, **36**, 1031 (1958).

(25) E. E. van Tamelen and C. Placeway, *J. Am. Chem. Soc.*, **82**, 2594 (1961).

(26) E. Wenkert, B. Wickberg, and C. Leight, *ibid.*, **83**, 5037 (1961); *Tetrahedron Letters*, 822 (1961).

(27) M. Shamma and J. M. Richey, *J. Am. Chem. Soc.*, **83**, 5038 (1961); **85**, 2507 (1963).

(28) See also ref 7.

(29) J. Barrollier, *Naturwissenschaften*, **42**, 786 (1955).

to be construed as absolute measures of extinction but are given merely to call the reader's attention to the relative size of the peaks in a given spectrum without actually reproducing the curve.[30] Pmr spectra were determined in deuterated chloroform using the Varian Model A-60 spectrometer with tetramethylsilane as an internal standard.

pK_a values were determined by dissolving 0.03–0.05 mmoles of compound in a mixture of 5.0 ml of dimethylformamide and 2.0 ml of 0.025 *N* HCl and back-titrating with 0.0996 *N* NaOH. The drying agent used throughout was sodium sulfate and the petroleum ether used had bp 30–60°.

Preparation of 7-Chloro-7H-yohimbane Derivatives (II).—A mixture of 0.05 mole of the indole alkaloid I, 9 ml of triethylamine, and 300 ml of dichloromethane was cooled to −20° and a solution of 9 g of *t*-butyl hypochlorite in 18 ml of dichloromethane was added dropwise with stirring over a period of 15 min, the materials being protected from light. After stirring for an additional 30 min, the reaction mixture was stirred with 100 ml of water and the layers were separated. The organic layer was washed with an additional 100 ml of water, dried, and distilled *in vacuo* to give the crude 7-chloro derivative as a gummy residue. In the case of yohimbine Ib, pseudoyohimbine Ib, 17α-hydroxy-16α-methylyohimbane Ic, and ajmalicine Ie, the residue was rearranged to the oxindole without purification. The crude products from yohimbane Ia and 18-benzylidene-17β-hydroxyyohimbane Id were purified as described below.

7-Chloro-7H-yohimbane (IIa).—The crude product was crystallized by trituration at room temperature with 50 ml of absolute ethanol. The solid was collected, washed by stirring with 25 ml more of ethanol, and dissolved in 500 ml of refluxing petroleum ether. The solution was filtered to remove a small amount of dark insolubles and was evaporated *in vacuo* to dryness to yield (after drying *in vacuo* at 40° for 4 hr) 9.5 g of product: mp 256–270° dec; $[\alpha]_D$ +27° (*c* 0.54, CH_2Cl_2); λ_{max} 225 mμ (ε 21,200), 260 (sh) (2200), 285–295 (2400), 246 (min) (1800); $\lambda_{max}^{CH_2Cl_2}$ 275–291 mμ (ε 3000), 246–255 (min) (2100); ν_{max}^{Nujol} 1592 (80), 778 (80), 754 (68), 746 (71) cm^{-1}.

Anal. Calcd for $C_{19}H_{23}ClN_2$: C, 72.48; H, 7.36; Cl, 11.26; N, 8.90. Found: C, 72.17; H, 7.37; Cl, 11.30; N, 8.78.

A portion of this material was recrystallized from petroleum ether and the first crop was recrystallized several times from the same solvent to give material: mp 256–268 dec (darkened at 130-140°); $[\alpha]_D$ −72° (*c* 0.54, CH_2Cl_2); λ_{max} 226 mμ (ε 21,400), 260 (sh) (2200), 292-296 (2800), 247 (min) (1900); $\lambda_{max}^{CH_2Cl_2}$ 297 mμ (br) (ε 3000), 249 (min) (1500); ν_{max}^{Nujol} 1592 (50), 774 (77), 758 (25), 748 (44), 738 (20) cm^{-1}.

Anal. Found: C, 72.69; H, 7.42; Cl, 11.37; N, 8.96.

Concentration gave additional crops having higher positive rotations. Fractional crystallization of the latter from petroleum ether gave material: mp 256-268 dec (darkened at 130–140°); $[\alpha]_D$ +84° (*c* 0.50, CH_2Cl_2); $\lambda_{max}^{CH_2Cl_2}$ 276–296 mμ (ε 3100), 248 (min) (2250); λ_{max} 224 mμ (ε 21,800), 260 (sh) (2400), 285–293 (2600), 244 (min) (1800); ν_{max}^{Nujol} 1592 (87), 746 (83), 756 (82), 772 (91), 779 (71) cm^{-1}.

Anal. Found: C, 72.52; H, 7.14; Cl, 11.53; N, 9.00.

18-Benzylidene-7-chloro-18β-hydroxy-7H-yohimbane (IId).—The dried dichloromethane solution of the product was distilled *in vacuo* until crystals separated and the mixture began to bump. On standing at room temperature there was obtained 5.0 g of crystals: mp 188-191° dec (started to darken at 141°), $[\alpha]_D$ −236° (*c* 0.65, pyridine), $[\alpha]_D$ −200° (*c* 0.50, CH_2Cl_2). Recrystallization from dichloromethane gave material: mp 188–191° dec (started to darken at 141°); $[\alpha]_D$ −255° (*c* 0.6, pyridine), $[\alpha]_D$ −188° (*c* 0.60, $CHCl_3$), $[\alpha]_D$ −210° (*c* 0.50, CH_2Cl_2); ν_{max}^{Nujol} 3360 (73), 1654 (22), 1592 (55), 784 (79), 752 (78), 705 (73) cm^{-1}; $\lambda_{max}^{CH_2Cl_2}$ 252 mμ (sh) (ε 15,500), 287–290 (infl) (2500).

Anal. Calcd for $C_{26}H_{27}ClN_2O$: C, 74.53; H, 6.50; Cl, 8.46; N, 6.69. Found: C, 74.48; H, 6.61; Cl, 8.58; N, 6.79.

Preparation of Spiroxyane Derivatives IV. General Procedure.—The crude (IIb, c, and e) or crystalline (IIa and d) 7-chloro derivative obtained from 0.05 mole of indole alkaloid I was dissolved in 200 ml of methanol and 100 ml of water was added. After the addition of 1.0 ml of glacial acetic acid, the mixture was refluxed for 45 min during which time the pH changed from 6.0 to 4.4. The methanol was distilled off, 200 ml of water was added, and the solution was filtered to remove a small amount of insoluble gum. The filtrate was made basic by the addition of ammonium hydroxide and extracted with chloroform. The dried chloroform solution was evaporated to give, after trituration with petroleum ether, an amorphous solid which was purified as described for the individual examples.

Spiroxyanes IVa.—The crude product obtained from the rearrangement of 9.5 g of crystalline 7-chloro-7H-yohimbane was triturated with acetonitrile and the resulting crystals were recrystallized from the same solvent to give 5.8 g. of material: mp 184–190° dec; $[\alpha]_D$ −30° (*c* 0.64, pyridine), $[\alpha]_D$ −34° (*c* 0.58, MeOH); a paper chromatogram showed two spots, R_f 0.55 and 0.71, of *ca.* equal size; λ_{max} 251 mμ (ε 6750), 280 (sh) (1700), 230–231 (min) (3750).

Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.07; H, 8.18; N, 9.27.

A solution of 5.0 g of this material in 1000 ml of boiling absolute ether was filtered, distilled at atmospheric pressure to a volume of 300 ml, allowed to stand overnight at room temperature, and the resulting crystals were collected. There was obtained 1.4 g of material, $[\alpha]_D$ −2° (*c* 0.65, pyridine), $[\alpha]_D$ −42° (*c* 0.71, MeOH), whose chromatogram consisted almost entirely of the slowest moving spot with only a trace of the faster spot. Recrystallization from acetonitrile gave 0.75 g of chromatographically pure spiroxyane B: mp 189–192° dec, $[\alpha]_D$ −3° (*c* 0.70, pyridine), $[\alpha]_D$ −44° (*c* 0.65, MeOH), $[\alpha]_D$ −39° (*c* 0.70, 0.1 *N* HCl); pK_a' = 7.12; λ_{max} 251–252 mμ (ε 7350), 283 (sh) (1650), 226-227 (min) (2850); ν_{max}^{Nujol} 3400 (43), 1728 (84), 1710 (81), 1621 (54), 748 (80) cm^{-1}; $\nu_{max}^{CH_2Cl_2}$ 3420 (35), 3180 (33), 1720 (92), 1706 (93), 1618 (63) cm^{-1}. It gave a negative mercuric acetate test.

Anal. Found: C, 77.13; H, 8.21; N, 9.23.

The ether filtrate was evaporated to dryness and was chromatographed over florisil using 50:50 benzene–chloroform as the eluent. The first 1000 ml of eluate was collected and evaporated to dryness to give 2.2 g of material, $[\alpha]_D$ −58° (*c* 0.74, pyridine), $[\alpha]_D$ −26° (*c* 0.68, MeOH), whose chromatogram showed only the faster spot. Recrystallization from acetonitrile gave 1.5 g of spiroxyane A: mp 199–202° dec; $[\alpha]_D$ −60° (*c* 0.55, pyridine), $[\alpha]_D$ −30° (*c* 0.70, MeOH), $[\alpha]_D$ +12° (*c* 0.58, 0.1 N HCl); pK_a' = 5.92; λ_{max} 251–252 mμ (ε 7000), 282 (sh) (1500), 227 (min (3000); ν_{max}^{Nujol} 3230 (74), 1710 (88), 1678 (73), 1617 (52), 758 (82), 744 (45), 717 (br) (53) cm^{-1}; $\nu_{max}^{CH_2Cl_2}$ 3420 (31), 3180 (32), 1720 (88), 1706 (91), 1618 (62) cm^{-1}. It gave a positive mercuric acetate test.

Anal. Found: C, 77.20; H, 8.35; N, 9.31.

16α-Carbomethoxy-17α-hydroxyspiroxyanes (IVb).—The crude product obtained from the rearrangement of crude 7-chloro-7H-yohimbine or 7-chloro-7H-pseudoyohimbine was dissolved in 40 ml of methanol and 10 ml of 6 *N* methanolic hydrogen chloride was added slowly with stirring and cooling. Addition of 50 ml of ether and scratching induced crystals to form. After refrigeration there was collected 5.2 g of the epimer B hydrochloride hemihydrate: mp 230–234° dec, $[\alpha]_D$ +23° (*c* 1.0, water). Recrystallization from methanol gave an analytical sample: mp 231–235° dec, $[\alpha]_D$ +25° (*c* 0.95, water), $[\alpha]_D$ +130° (*c* 0.64, pyridine), $[\alpha]_D$ +16° (*c* 1.0, 95% EtOH).

Anal Calcd for $C_{21}H_{26}N_2O_4 \cdot HCl \cdot 0.5H_2O$: C, 60.64; H, 6.79; Cl, 8.53; N, 6.74; OCH_3, 7.44. Found: C, 60.88; H, 6.98; Cl, 8.60; N, 6.66; OCH_3, 7.08.

To a solution of 2 g of the hemihydrate in 200 ml of hot absolute ethanol was added 200 ml of dry benzene. The mixture was distilled at atmospheric pressure to near dryness and the last traces of solvent were removed *in vacuo*. The residue was recrystallized twice from methanol to give the unhydrated epimer B hydrochloride: mp 231–235° dec; $[\alpha]_D$ +25° (*c* 0.65, water), $[\alpha]_D$ +137° (*c* 0.63, pyridine), $[\alpha]_D$ +17° (*c* 0.64, 95% EtOH); ν_{max}^{Nujol} 3320 (60), 3190 (49), 2700 (32), 2600 (35), 1733 (77), 1705 (87), 1618 (41), 770 (44), 724 (27) cm^{-1}; λ_{max} 251–252 mμ (ε 6320), 279–285 (1370), 227 (min) (2745), 275 (min) (1290).

Anal. Calcd for $C_{21}H_{26}N_2O_4 \cdot HCl$: C, 61.98; H, 6.69; Cl, 8.71; N, 6.89. Found: C, 61.92; H, 6.86; Cl, 8.91; N, 7.05.

The epimer B base was obtained by basification of an aqueous solution of the hydrochloride with ammonium hydroxide and extracting with chloroform. Evaporation of the chloroform solution gave a solid residue which was recrystallized from acetone to give material: mp 214–216° dec; $[\alpha]_D$ +155° (*c* 0.55, pyridine), $[\alpha]_D$ +17° (*c* 1.0, 95% EtOH), $[\alpha]_D$ −14°

(30) This method of presenting infrared spectra has been used by Seaton, *et al.*[9]

(*c* 0.61, $CHCl_3$); pK_a' = 6.64;[31] ν_{max}^{Nujol} 3530 (45), 3210 (32), 1725 (84), 1702 (61), 1610 (33), 748 (56) cm^{-1}; $\nu_{max}^{CHCl_3}$ 3460 (35), 3210 (31), 2900 (61), 2743 (46), 1723 (86), 1710 (90), 1624 (55) cm^{-1}; λ_{max} 251–252 mμ (ε 7220), 277–282 (sh) (1440), 227 (min) (2590); $\lambda_{max}^{0.1\ N\ NaOH\ in\ EtOH}$ 222 mμ (ε 7030), 265 (7500), 232 (min) (2400). Neutralization of the latter solution with dilute HCl gave a solution having the original spectrum.[32]

Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.08; H, 7.08; N, 7.56. Found: C, 68.02; H, 7.21; N, 7.43.

Both the free base and hydrochloride gave negative mercuric acetate tests. The acidic ethereal methanol filtrate from the hydrochloride was distilled *in vacuo* to dryness, the residue was dissolved in 100 ml of water, and 10 ml of 70% perchloric acid was added. The precipitate which formed was filtered off, dried, and recrystallized from methanol–ether to give 1.7 g of 3-dehydroyohimbine perchlorate which melted at 204–206°, resolidified and remelted at 258–265°;[33] λ_{max} 246 mμ (ε 10,500), 352 mμ (ε 22,000).

The aqueous filtrate from the precipitation of 3-dehydroyohimbine perchlorate was made basic with ammonium hyroxide and extracted with chloroform. Evaporation of the dried chloroform solution gave a residue which on trituration with petroleum ether yielded 3.5 g of amorphous epimer A: $[\alpha]_D$ +56° (*c* 0.53, 95% EtOH); $\lambda_{max}^{1\ N\ HCl}$ 251–252 mμ (ε 6400), 281–283 mμ (ε 1480), no absorption at 352 mμ. On chromatography, it gave a single spot, R_f 0.41, compared with R_f 0.16 given by the corresponding epimer B. A slight excess of ethereal hydrogen chloride was added to a solution of 2 g of the amorphous solid in 150 ml of anhydrous ether while stirring and cooling on an ice bath. The gummy precipitate, thus obtained, was triturated with dry ether and then refluxed with 200 ml of methyl ethyl ketone. A small amount of insoluble material was filtered off and the filtrate was concentrated by distillation at atmospheric pressure. The initial crops of reddish gummy material, which separated out, were filtered off and the filtrate was concentrated further until white crystals began to separate. After standing at room temperature overnight, the crystals were collected and recrystallized from methyl ethyl ketone to give 550 mg of epimer A hydrochloride: mp 231–235° dec; $[\alpha]_D$ +101° (*c* 0.86, water); pK_a' = 5.60; ν_{max}^{Nujol} 3380 (60), 3130 (53), 2600 (47), 1727 (br) (83), 1622 (55), 760 (58) cm^{-1}; λ_{max} 251 mμ (ε 6800), 282 (1400), 226–227 (min) (2950), 274 (min) (1300). It gave a positive mercuric acetate test.

Anal. Calcd for $C_{21}H_{26}N_2O_4 \cdot HCl$: C, 61.98; H, 6.69; Cl, 8.71; N, 6.89. Found: C, 61.80; H, 6.88; Cl, 8.86; N, 6.64.

17α-Hydroxy-16α-methylspiroxyanes (IVc).—Paper chromatography of the crude rearrangement product derived from crude 7-chloro-17α-hydroxy-16α-methyl-7H-yohimbane showed two spots of *ca.* equal size having R_f 0.66 and 0.35, respectively. The solid was refluxed with 70 ml of acetone for 15 min and the mixture allowed to stand overnight at room temperature. The resulting crystals were then refluxed with a mixture of 80 ml of acetone and 10 ml of methanol to yield, after standing at room temperature, 5.4 g of the epimer B: mp 248–254° dec, $[\alpha]_D$ +126° (*c* 0.69, pyridine). Paper chromatography showed only a single spot corresponding to the slower moving component of the crude mixture. Recrystallization of a portion from methanol gave an analytical sample: mp 246–249° dec; $[\alpha]_D$ +131° (*c* 0.68, pyridine), $[\alpha]_D$ −10° (*c* 0.27, $CHCl_3$); pK_a' = 6.92; mercuric acetate test was negative; ν_{max}^{Nujol} 3420 (66), 3280 (58), 1740 (90), 1685 (92), 1620 (57), 974 (49), 766 (69) cm^{-1}; $\nu_{max}^{CHCl_3}$ 3420 (37), 3200 (20), 1723 (87), 1710 (85), 1620 (57), 970 (41) cm^{-1}; λ_{max} 252 mμ (ε 7550), 280 (1500), 228 (min) (2950).

Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.58; H, 8.03; N, 8.58. Found: C, 73.35; H, 7.96; N, 8.48.

The hydrochloride, recrystallized from isopropyl alcohol, had mp 273–285° dec (sintered at 225°), $[\alpha]_D$ +10° (*c* 0.60, water); mercuric acetate test was negative.

Anal. Calcd for $C_{20}H_{26}N_2O_2 \cdot HCl \cdot C_3H_7OH$: C, 65.30; H, 8.34; Cl, 8.38; N, 6.62. Found: C, 65.48; H, 8.41; Cl, 8.13; N, 6.63.

(31) Finch and Taylor[7] reported mp 222–224°, $[\alpha]_D$ −9° ($CHCl_3$), and pK_a = 6.4 for "yohimbine oxindole B."

(32) J. W. Cornforth, C. E. Dalgeish, and A. Neuberger [*Biochem. J.*, **48**, 598 (1951)] reported a bathochromic shift in the spectrum of 3,3-dimethyloxindole in changing the solvent from water to 0.1 *N* NaOH.

(33) Weisenborn and Diassi[11] reported mp 205–206°.

The mother liquor from the first refluxing with acetone was distilled to dryness, the residue was dissolved in 175 ml of ether, the solution was filtered to remove insoluble material, and the filtrate was treated with a slight excess of methanolic hydrogen chloride. The yellow gum, thus obtained, was solidified by trituration with ether and was dissolved in 30 ml of methanol. The solution was heated to boiling, 100 ml of methyl ethyl ketone was added, and distillation at atmospheric pressure was carried out until crystals started to separate; the resulting mixture was allowed to stand at room temperature. The combined first three crops of slightly off white crystals weighed 3.2 g: mp 288–296° dec, $[\alpha]_D$ +102° (*c* 0.68, pyridine), $[\alpha]_D$ +71° (*c* 0.62, water). Recrystallization by the same procedure gave 2.3 g of white crystals, mp 300–302° dec, $[\alpha]_D$ +86° (*c* 0.5, pyridine), $[\alpha]^{25}D$ +65° (*c* 0.68, water). Paper chromatography showed only a single spot corresponding to the faster moving component of the crude mixture. A portion was recrystallized again by the same procedure to give pure epimer A hydrochloride: mp 301–303° dec; $[\alpha]_D$ +83° (*c* 0.60, pyridine), $[\alpha]_D$ +63° (*c* 0.62, water); pK_a' = 5.92; ν_{max}^{Nujol} 3400 (58), 3100 (58), 1700 (79), 1618 (47), 759 (28) cm^{-1}; λ_{max} 252 mμ (ε 7125), 282–283 (1450), 227 (min) (3000), 275 (min) (1300). The mercuric acetate test was positive.

Anal. Calcd. for $C_{20}H_{26}N_2O_2 \cdot HCl$: C, 66.19; H, 7.50; Cl, 9.77; N, 7.72. Found: C, 66.09; H, 7.32; Cl, 9.96; N, 8.00.

18-Benzylidene-17β-hydroxyspiroxyanes (IVd).—The crude product obtained from the rearrangement of 8.4 g of crystalline 18-benzylidene-7-chloro-17β-hydroxy-7H-yohimbane was recrystallized from acetone to yield 3.2 g of epimer B: mp 226–229° dec; $[\alpha]_D$ −236° (*c* 0.58, pyridine), $[\alpha]_D$ −188° (*c* 0.64, $CHCl_3$). Another recrystallization gave an analytical sample: mp 228–230° dec; $[\alpha]_D$ −257° (*c* 0.60, pyridine), $[\alpha]_D$ −191° (*c* 0.51, $CHCl_3$); pK_a' = 6.48; negative mercuric acetate test; ν_{max}^{Nujol} 3520 (25), 3210 (58), 1716 (92), 1690 (91), 1650 (30), 1618 (60), 754 (82), 742 (sh) (72), 705 (69) cm^{-1}; λ_{max} 245 mμ (ε 21,000), 280 (infl) (2250), 224 (min) (11,700).

Anal. Calcd for $C_{26}H_{28}N_2O_2$: C, 77.97; H, 7.05; N, 7.00. Found: C, 78.13; H, 7.31; N, 7.01.

The acetone filtrate was evaporated to dryness and the residue was crystallized from methanol to yield 3.7 g of epimer A: mp 152–155° dec; $[\alpha]_D$ −324° (*c* 0.63, pyridine), $[\alpha]_D$ −242° (*c* 0.58, $CHCl_3$); pK_a' 5.40; positive mercuric acetate test; ν_{max}^{Nujol} 3440–3200 (br) (57), 1708 (91), 1688 sh (81), 1652 (41), 1618 (62), 1598 (37), 766, 756, 750, 745 (quartet 64, 62, 60, 59, respectively), 702 (64) cm^{-1}; λ_{max} 244 mμ (ε 20,500), 280 (infl) (2000), 224 (min) (11,750).

Anal. Calcd for $C_{26}H_{28}N_2O_2$: C, 77.97; H, 7.05; N, 7.00. Found: C, 78.11; H, 7.29; N, 7.05.

The epimer A had R_f 0.60 compared with 0.36 for the epimer B.

Mitraphylline and Isomitraphylline IVe.—The crude rearrangement product from crude 7-chloro-7H-ajmalicine was triturated with 50 ml of methanol to yield 4.5 g of crystalline mitraphylline, mp 260–263° dec, $[\alpha]_D$ −10° (*c* 0.75, $CHCl_3$), which showed a single spot, R_f 0.62, on paper chromatography. Recrystallization from methanol gave 3.8 g of material: mp 265–266° dec; $[\alpha]_D$ −9° (*c* 0.94, $CHCl_3$), $[\alpha]_D$ +11° (*c* 0.65, pyridine), $[\alpha]_D$ −38° (*c* 0.63, 0.1 *N* HCl), $[\alpha]_D$ −10° (*c* 0.25, 95% EtOH); ν_{max}^{Nujol} 3620 (23), 3220 (35), 1722 (89), 1703 (86), 1622 (80), 1292 (77), 1272 (63), 1190 (79), 1173 (66), 1102 (79), 1091 (65) cm^{-1}; λ_{max} 243 mμ (ε 34,240), 280 (sh) (1760), 224 (min) (9960).[34]

Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.56; N, 7.60. Found: C, 68.20; H, 6.72; N, 7.63.

The perchlorate, recrystallized from ethanol had mp 213–215°, $[\alpha]_D$ +27° (*c* 1.0, 95% EtOH).[35]

Anal. Calcd for $C_{21}H_{25}ClN_2O_8$: C, 53.79; H, 5.37; Cl, 7.56; N, 5.98. Found: C, 53.84; H, 5.54; Cl, 7.35; N, 5.74.

The picrate, recrystallized from methanol, had mp 159–165° dec (softened at 146°).

(34) Seaton, *et al.*,[24] reported mp 275–276°; $[\alpha]_D$ −3° ($CHCl_3$), $[\alpha]_D$ −39° (0.1 *N* HCl), λ_{max}^{EtOH} 243 mμ (ε 34,240), 280 (sh) (1760), 224 (min) (9996), for naturally occurring mitraphylline. A sample of this material, supplied to us by Dr. Marion had mp 265–266° dec in our apparatus and there was no melting point depression when mixed with our product. The infrared spectra of the two materials were superimposable in every detail.

(35) Seaton, *et al.*,[24] reported mp 240° after softening at 214° and $[\alpha]_D$ −26° (95% EtOH).

Anal. Calcd for $C_{27}H_{27}N_5O_{11}.CH_3OH$: C, 53.41; H, 4.96; N, 11.12. Found: C, 53.11; H, 4.83; N, 11.34.

The dark red filtrate from the methanol trituration was distilled *in vacuo* to dryness. The residue was dissolved in 600 ml of ether, filtered to remove a small amount of insolubles, and treated with an excess of ethereal picric acid solution. The resulting precipitate was collected, washed with ether, and recrystallized from methanol to yield 1.4 g of material, mp 165–188° dec. Two more recrystallizations from methanol gave 1.1 g of chromatography pure (R_f 0.85) isomitraphylline picrate: mp 207–209° dec; ν_{max}^{Nujol} 3320 (33), 1724 (63), 1702 (74), 1694 (72), 1638 (75), 1628 (78), 1619 (83), 1614 (81), 1112 (48), 1094 (53), 1086 (45), 912 (24), 792 (30), 764 (44), 748 (41), 710 (45).[36]

Anal. Calcd for $C_{27}H_{27}N_5O_{11}$: C, 54.27; H, 4.56; N, 11.72. Found: C, 54.54; H, 4.58; N, 11.48.

Equilibration of 16α-Carbomethoxy-17α-hydroxyspiroxyane B.—A solution of 15.9 g of 16α-carbomethoxy-17α-hydroxyspiroxyane B in 150 ml of pyridine was refluxed for 24 hr.[37] Most of the solvent was removed by distillation *in vacuo*, and the residue was triturated with petroleum ether. The insoluble gum was triturated with ether to yield 0.95 g of a very dark insoluble amorphous residue and a light yellow solution. The solution was distilled to dryness to yield 14.3 g of light cream amorphous solid which was shown by paper chromatography to consist of about 30% epimer B, R_f 0.15, and 70% of a component, R_f 0.43, which corresponded with epimer A. This solid was dissolved in 30 ml of methanol and 10 ml of 6 *N* methanolic hydrogen chloride followed by 40 ml of anhydrous ether was added. After refrigeration there was obtained 2.4 g of epimer B hydrochloride, $[\alpha]_D$ +23° (*c* 0.75, water). The mother liquor was distilled to dryness, the residue was dissolved in 25 ml of isopropyl alcohol, and 100 ml of ether was added. The resulting white solid was refluxed with 500 ml of methyl ethyl ketone and the filtered solution was concentrated by distillation at atmospheric pressure. The red-orange precipitate which initially separated was filtered off and further concentration yielded 2.75 g of white crystals, $[\alpha]_D$ +88° (*c* 0.75, water), which could be shown by paper chromatography to consist predominately of the oxindole A but which contained a small amount of the slower moving oxindole B. Further concentration to a volume of about 50 ml followed by refrigeration gave 4.5 g of chromatographically pure epimer A hydrochloride: mp 231–235° dec, $[\alpha]_D$ +99° (*c* 0.65, water).

Equilibration of "Synthetic" Mitraphylline.—A solution of 325 mg of "synthetic" mitraphylline in 25 ml of pyridine was refluxed for 20 hr[37] and the solvent was removed by distillation *in vacuo*. Paper chromatography showed the residue to contain about 30% mitraphylline (R_f 0.62) and 70% of a faster moving material (R_f 0.85) corresponding to isomitraphylline. Trituration of the residue with ether gave 90 mg of mitraphylline. The filtrate was treated with an excess of picric acid and the resulting precipitate was recrystallized from methanol. The first material to separate consisted of yellow needles, mp 152–153°, which was shown to be nonalkaloidal.[38] Further concentration of the methanol solution gave 350 mg of yellow prisms, mp 178–190° dec. Two more recrystallizations from methanol gave 170 mg of material, mp 208–210° dec, which was shown by mixture melting point, chromatography, and comparison of infrared spectra, to be identical with isomitraphylline picrate, described above.

3-Dehydroyohimbane Chloride (IIIa) from Crystalline 7-Chloro-7H-yohimbane.—To a suspension of 4.75 g of crystalline 7-chloro-7H-yohimbane ($[\alpha]_D$ +27° in CH_2Cl_2) was added 10 ml of 4.5 *N* ethanolic hydrogen chloride. The resulting clear yellow solution was treated with 50 ml of absolute ether to induce crystallization. There was obtained 3.3 g of material: mp 265–271° dec; $[\alpha]_D$ +99° (*c* 0.57, water);[39] λ_{max} 246 mμ (ε 10,100), 251 (sh) (9500), 350 (22,300). Treatment of the filtrate with a large excess of ether gave 1.0 g of additional material: mp 265–274° dec, $[\alpha]_D$ +92 (*c* 0.52, water).

18-Benzylidene-17β-hydroxy-3-dehydroyohimbane (IIId).—To a suspension of 500 mg of crystalline 18-benzylidene-7-chloro-17β-hydroxy-7H-yohimbane in 25 ml of absolute ethanol was added, at room temperature, 2 ml of 6 *N* ethanolic hydrogen chloride. The material initially dissolved and then yellow crystals separated from the solution. Recrystallization from absolute ethanol gave 300 mg of product: mp 269–275° dec (started to turn red at 200°); $[\alpha]_D$ −140° (*c* 0.4, 95% MeOH); λ_{max} 245 mμ (ε 23,000), 350 mμ (ε 23,500).

Anal. Calcd for $C_{26}H_{28}ClN_2O$: C, 74.36; H, 6.72; Cl, 8.44; N, 6.67. Found: C, 74.09; H, 6.73; Cl, 8.19; N, 6.53.

2-Desoxy-17α-hydroxy-16α-hydroxymethylspiroxyane (IXa).—A mixture of 5 g of 16α-carbomethoxy-17α-hydroxyspiroxyane B and 5 g of lithium aluminum hydride in 300 ml of dioxane was refluxed for 6 hr, diluted with 1000 ml of tetrahydrofuran, hydrolyzed in the usual manner, and filtered. The solid residue was extracted by refluxing with several portions of chloroform and the combined chloroform and dioxane–tetrahydrofuran solutions were distilled *in vacuo* to dryness. The residue was dissolved in methanol, acidified by the addition of methanolic hydrogen chloride, and treated with ether. The resulting oil solidified on trituration with several fresh portions of ether. The solid was recrystallized from methanol to give 3.2 g of the dihydrochloride: mp 275–285° dec, $[\alpha]_D$ +83° (*c* 0.80, 95% pyridine). Half of this was recrystallized once more from methanol to give 1.2 g of material: mp 275–285° dec (started to darken at 250°); $[\alpha]_D$ +86° (*c* 0.83, 95% pyridine), $[\alpha]_D$ +41° (*c* 0.61, water); ν_{max}^{Nujol} 3520 (80), 3440 (82), 2640 (90), 2620 (90), 2400 (82), 1600 (28), 1572 (39), 1022 (68), 778 (66), 760 (59) cm^{-1}.

Anal. Calcd for $C_{20}H_{28}N_2O_2 \cdot 2HCl \cdot 0.5CH_3OH$: C, 58.99; H, 7.73; Cl, 16.99; N, 6.71. Found: C, 59.00; H, 7.71; Cl, 16.52; N, 7.01.

The remainder of the once recrystallized dihydrochloride was dissolved in 25 ml of water, made basic with ammonium hydroxide, and extracted with chloroform. The dried chloroform solution was evaporated to a residue which was recrystallized twice from acetone to give 900 mg of the free base: mp 215–218° dec (started to darken at 196°); $[\alpha]_D$ +133° (*c* 1.00, pyridine); ν_{max}^{Nujol} 3420 (74), 3320 (91), 1610 (76), 1100 (85), 743 (91), 716 (69) cm^{-1}; λ_{max} 243 mμ (ε 6730), 296 (2630), 223 (min) (3035), 269 (min), (820).

Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53. Found: C, 72.85; H, 8.63; N, 8.32.

2-Desoxy-17α-hydroxy-16α-methylspiroxyane (IXb).—A mixture of 9.8 g of 17α-hydroxy-16α-methylspiroxyane B and 10 g of lithium aluminum hydride in 750 ml of dioxan was refluxed for 12 hr, hydrolyzed in the usual manner, and filtered. The solid residue was extracted by refluxing with portions of tetrahydrofuran and the combined dioxane and tetrahydrofuran filtrates were distilled *in vacuo* to dryness. The residue was dissolved in 30 ml of isopropyl alcohol and 15 ml of 6 *N* methanolic hydrogen chloride was added. Addition of 150 ml of ether followed by refrigeration gave 6.5 g of material: mp 288–295° dec, $[\alpha]_D$ +40° (*c* 0.65, water).

Recrystallization from isopropyl alcohol gave analytically pure dihydrochloride: mp 290–297° dec (started to decompose at 260°); $[\alpha]_D$ +41° (*c* 0.6, water), $[\alpha]_D$ +98° (*c* 0.60, 95% pyridine), $[\alpha]_D$ +62° (*c* 0.6, MeOH).

Anal. Calcd for: $C_{20}H_{28}N_2O \cdot 2HCl$: C, 62.33; H, 7.85; Cl, 18.40. N, 7.27. Found: C, 62.05; H, 8.08; Cl, 18.28; N, 7.07.

An aqueous solution of 500 mg of the dihydrochloride was made basic with ammonium hydroxide and extracted with dichloromethane. The dried dichloromethane solution was evaporated to a residue which was recrystallized twice from acetone to give 280 mg of the base: mp 178–180° dec; $[\alpha]_D$ +104° (*c* 0.61, pyridine), $[\alpha]_D$ +42° (*c* 0.51, $CHCl_3$); ν_{max}^{Nujol} 3620 (63), 3320 (78), 1612 (75), 754 (84), 748 (88), 740 (73) cm^{-1}; $\nu_{max}^{CHCl_3}$ 3610 (20), 3416 (30), 1606 (64) cm^{-1}; λ_{max} 243 mμ (ε 6750), 296 (2900), 223 (min) (3450), 269 (min) (1100).

Anal. Calcd for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97. Found: C, 76.73; H, 9.01; N, 9.03.

17α-Acetoxy-16α-carbomethoxyspiroxyane B (Xa).—A solution of 3.0 g of 16α-carbomethoxy-17α-hydroxyspiroxyane B in a mixture of 30 ml of dry pyridine and 15 ml of acetic anhydride was allowed to stand at room temperature for 30 hr. Most of

(36) Seaton, *et al.*,[9] reported mp 223° for isomitraphylline picrate. A sample of this material, supplied by Dr. Marion, had mp 209–211° dec in our apparatus and there was no melting point depression when mixed with our product. The infrared spectra were practically identical.

(37) This is essentially the procedure given in ref 9 for the equilibration of naturally occurring mitraphylline.

(38) "Dictionary of Organic Compounds," Vol. IV, I. Heilbron and H. M. Bunbury Ed., Eyre and Spottiswoode, London, 1953, p 205, lists an addition compound of 1 mole of picric acid with 2 moles of pyridine having mp 144–145°.

(39) H. Zinnes, R. A. Comes, and J. Shavel, Jr. [*J. Org. Chem.*, **30**, 105 (1965)] reported mp 265–270° dec, $[\alpha]_D$ +101° (water).

the solvent was removed by distillation *in vacuo*, the residue was mixed with 40 ml of water; and 20 ml of aqueous ammonium hydroxide was added. The mixture was extracted with chloroform and the dried chloroform solution was evaporated to a residue which was recrystallized from acetone to give 1.6 g of product: mp 228–231° dec, $[\alpha]_D$ +75° (*c* 0.78 pyridine).

Recrystallization from acetone gave material: mp 230–233° dec; $[\alpha]_D$ +73° (*c* 0.82, pyridine); ν_{max}^{Nujol} 3200 (47), 1730 (83), 1720 (81), 1619 (51), 1168 (80), 1228 (69),1246 (69), 740 (75) cm^{-1}; $\nu_{max}^{CHCl_3}$ 3200 (25), 1730 (90), 1770 (90), 1700 (87), 1618 (53), 1248 (84), 1160 (68) cm^{-1}; λ_{max} 251–252 mμ (ε 7400), 283 (sh) (1500), 227 min) (2800); R_f 0.45; pK_a' = 6.24.

Anal. Calcd for $C_{28}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 67.07; H, 6.69; N, 6.69.

Since the base was too insoluble to carry out the mercuric acetate test, a small portion was converted to the hydrochloride by dissolving in ether and adding HCl. The precipitated hydrochloride which was filtered off and washed with ether gave a negative mercuric acetate test.

17α-Acetoxy-1-acetyl-16α-carbomethoxyspiroxyane A (Xb).—A mixture of 25 g of 16α-carbomethoxy-17α-hydroxyspiroxyane B and 150 ml of acetic anhydride was heated on a steam bath (temperature 90–95°) for 6 hr and then distilled *in vacuo* to give a syrup which was dissolved in 300 ml of water. The solution was made basic with ammonium hydroxide and the precipitated solid was collected, washed with water, and dried over sulfuric acid in a vacuum dessicator. The solid was refluxed with 2500 ml of Skellysolve C and filtered while hot. The filtrate was evaporated to a residue which was crystallized from 50 ml of acetonitrile to give 12.5 g of product: mp 191–193° dec, $[\alpha]_D$ +79° (*c* 0.91, pyridine). Recrystallization from acetonitrile gave material: mp 190–193° dec; $[\alpha]_D$ +77° (*c* 0.70, pyridine), $[\alpha]_D$ +43° (*c* 0.62, $CHCl_3$); pK_a' = 4.6; R_f 0.74; ν_{max}^{Nujol} 1758 (75), 1732 (89), 1693 (82), 1620 (23), 1604 (27), 1260 (90), 1176 (88), 1016 (71), 777 (55), 740 (45) cm^{-1}; $\nu_{max}^{CHCl_3}$ 1734 (85), 1702 (71), 1604 (23), 1279 (78), 1248 (77), 1015 (55); λ_{max} 228–230 mμ (ε 9860), 269–271 (1250), 222–234 (min) (9540).[40]

Anal. Calcd for $C_{25}H_{30}N_2O_6$: C, 66.06; H, 6.65; N, 6.16. Found: C, 66.02; H, 6.70; N, 6.06.

Since the base was too insoluble to carry out the mercuric acetate test, a small portion was converted to the hydrochloride by dissolving in ether and adding HCl. The precipitated hydrochloride which was filtered off and washed with ether gave a positive mercuric acetate test.

Concentration of the acetonitrile mother liquor to a volume of 20 ml gave 4.5 g of a second crop: mp 190–193° dec, $[\alpha]_D$ +80° (*c* 0.63, pyridine).

17-Ketospiroxyane A (Xc).—A mixture of 37 g of 16α-carbomethoxy-17α-hydroxyspiroxyane B and 1500 ml of xylene was distilled at atmospheric pressure until about 500 ml of distillate was collected, 750 ml of cyclohexanone (dried over sodium sulfate) and 135 g aluminum phenoxide were successively added, and the mixture was refluxed with stirring for 40 hr. The mixture was extracted with five 400-ml portions of 10% HCl and the combined aqueous layers were washed with ether. The aqueous solution was made basic with ammonium hydroxide and extracted with chloroform. The dried chloroform solution was evaporated to a residue which was crystallized from acetone to give 9.5 g of product: mp 228–230° dec, $[\alpha]_D$ +53° (*c* 1.0, pyridine). Recrystallization from acetone gave material: mp 228–230° dec; $[\alpha]_D$ +55° (*c* 1.0, pyridine); $[\alpha]_D$ −19° (*c* 0.54, $CHCl_3$); pK_a' = 5.28; R_f 0.46; mercuric acetate test was positive; ν_{max}^{Nujol} 3300 (65), 1726 (94), 1690 (75), 1624 (62), 756 (57), 742 (54) cm^{-1}; λ_{max} 251–252 mμ (ε 6820), 282 (sh) (1800), 228 (min) (3720).

Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.15; N, 9.03. Found: C, 73.24; H, 7.26; N, 9.21.

17β-Hydroxyspiroxyane A (Xd).—A solution of 2.0 g of 17-ketospiroxyane A (Xc) in 100 ml of methanol was stirred with 1 g of potassium borohydride at room temperature for 24 hr. The methanol was distilled *in vacuo*, 500 ml of water was added, and the mixture was extracted with chloroform. The dried chloroform solution was evaporated to a residue which was recrystallized from acetone to give 1.4 g of product: mp 235–242° dec, $[\alpha]_D$ +52° (*c* 1.25, pyridine). Further recrystallization gave material: mp 238–245° dec (started to darken at 226°); $[\alpha]_D$ +57° (*c* 1.12, pyridine), $[\alpha]_D$ −10° (*c* 0.58, $CHCl_3$); pK_a' = 5.68; R_f 0.19; mercuric acetate test was positive; ν_{max}^{Nujol} 3440 (65), 3180 (64), 1711 (81), 1692 (75), 1619 (54), 752 (63) cm^{-1}; λ_{max} 251 mμ (ε 7180), 282 (1800), 228 (min) (3900).

Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 72.95; H, 7.70; N, 8.87.

18-Benzylidene-17-ketospiroxyane A (Xe).—A solution of 1.0 g of 17-ketospiroxyane A (Xc), 1 ml of benzaldehyde, and 0.5 ml of 10% aqueous sodium hydroxide in 50 ml of methanol was refluxed for 16 hr; after the addition of 2 ml more benzaldehyde and 0.5 ml more 10% sodium hydroxide, the refluxing was continued for an additional 8 hr. The solvent was removed by distillation *in vacuo* and the resulting oil was dissolved in diluted acetic acid. The solution was made basic by the addition of ammonium hydroxide, and the mixture was extracted with chloroform. The chloroform solution was charcoaled, dried, and distilled *in vacuo* to dryness. The residue was dissolved in absolute ether, a slight excess of methanolic hydrogen chloride was added, and the crude hydrochloride was filtered off and washed with ether. It was refluxed with 300 ml of acetone, filtered off, and dissolved in water. The aqueous solution was made basic with ammonium hydroxide. The resulting precipitate was filtered off, washed with water, dried, and recrystallized from methanol to give 0.55 g of product: mp 238–241° dec; $[\alpha]_D$ −25° (*c* 0.50, pyridine); ν_{max}^{Nujol} 3220 (56), 1710 (84), 1675 (76), 1618 (49), 1593 (59), 755 (60), 695 (50) cm^{-1}; λ_{max} 265 mμ (ε 13,000), 288 (17,500), 236 (min) (8000), 268 (12,500).

Anal. Calcd for $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.20; H, 6.54; N, 7.23.

18-Benzylidene-17β-hydroxyspiroxyane A (IVd) from 18-Benzylidene-17-ketospiroxyane A (Xe).—A mixture of 1.0 g of Xe, 1 g of potassium borohydride, and 25 ml of methanol was stirred at room temperature for 3 hr and then 75 ml of water was added. The resulting white precipitate was filtered off, washed with water, dried, and recrystallized from methanol to give 0.3 g of product: mp 161–168° dec, $[\alpha]_D$ −187° (*c* 0.50, pyridine), $[\alpha]_D$ −215° (*c* 0.56, $CHCl_3$). It was shown to be identical with 18-benzylidene-17β-hydroxyspiroxyane A, prepared as described above.

Acknowledgment.—We wish to thank Professor E. L. Eliel for helpful discussions. The authors are indebted to the Analytical and Physical Chemistry Department under the supervision of Mr. A. D. Lewis. In particular we wish to thank Mr. T. Wildeman and Mrs. U. Zeek for the microanalyses, Mrs. M. Goodenough for determination of the p*K* values, and Mrs. B. Kane and Mr. R. Puchalski for the spectra. Special thanks are due to Miss R. Eilersten, Mr. R. A. Comes, and Mr. O. Zafiriou who assisted in the synthetic work.

(40) The ultraviolet and infrared spectra are in accord with values reported by E. E. van Tamelen, K. V. Siebrasse, and J. B. Hester [*Chem. Ind.* (London), 1145 (1956)] for simpler N-acetyl oxindoles.