Oxidative Transformations of Indole Alkaloids. III. Pseudoindoxyls from Yohimbinoid Alkaloids and Their Conversion to "Invert" Alkaloids[1,2]

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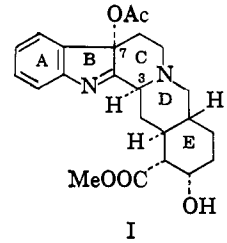
Several tetrahydro-β-carboline alkaloids have been converted to their pseudoindoxyl analogs by treatment of the derived acyloxyindolenines with base. By use of such a transformation the yellow alkaloid of Rauwolfia vomitoria Afzel. has been identified as isoreserpiline pseudoindoxyl. Optical rotatory dispersion measurements have been employed to make tentative assignments of stereochemistry for some of the acyloxyindolenines. Borohydride reduction of the pseudoindoxyls and treatment of the product with acid transforms them into their ring AB inverted indole equivalents.

In our previous work with the acyloxyindolenines[1] their stereochemistries were not defined and in view of their further synthetic utility[3] this point has now been investigated. The methiodide of acetoxyyohimbine proved to be suitable for X-ray crystallographic analysis. The quaternary salt crystallized in the orthorhombic system, space group $P_{2_12_12_1}$ with cell dimensions $a = 13.16$, $b = 26.82$, $c = 7.33$ Å. The measured crystal density was 1.44 g. cm.$^{-3}$, while with four molecules of $C_{24}H_{31}O_5N_2I$ in the unit cell the calculated density was 1.42 g. cm.$^{-3}$. From equi-inclination Weissenberg photographs taken with Cu Kα radiation 1127 independent $|F_o|$ values were derived. The coordinates of the iodide ion were determined from Patterson syntheses and the remaining atoms were then located by calculating three-dimensional electron-density distributions. Subsequent refinement of atomic coordinates by the method of least squares has reduced the average discrepancy between measured and calculated structure amplitudes to 17%. Further refinement is in progress. A view of the atomic arrangement in the molecule as seen in projection along the *c*-axis is shown in Figure 1. The results unambiguously define the structure and stereochemistry[4] of 7α-acetoxy-7H-yohimbine (I)[5] which have previously been tentatively proposed.[6] Using this compound as a known standard, the optical rotatory dispersion curves were obtained in the hope that such data would yield stereochemically useful information.[7] This was based upon the premise that C-7, being more closely involved with the chromophore than any other center, would



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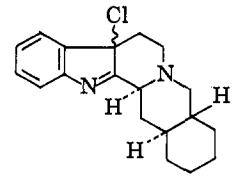

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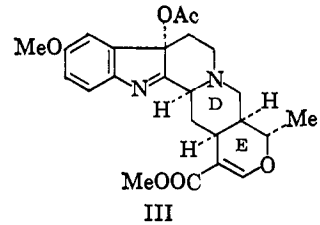

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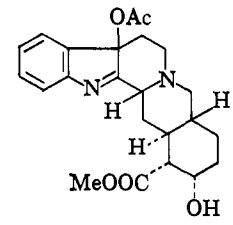

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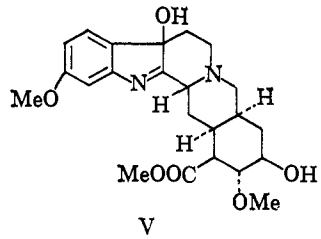

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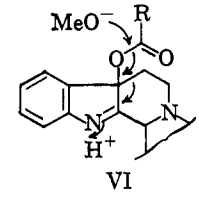


VI

have the greatest effect on the rotatory dispersion curve. This was substantiated by comparison of the curves for the pair of epimeric 7-chloro-7H-yohimbans (II)[8] which bore a virtual mirror image relationship to each other (Figure 2). It should be noted that the fusion of the indolenine moiety (rings AB) to ring C requires that the C-7 to C-8 bond be equatorial or pseudo-equatorial which requires, as a consequence, different conformations of the CDE ring for the 7-chloro-7H-yohimban epimers, with the chlorine pseudo-axial in both.

With the above considerations in mind an α-orientation was assigned to the 7-substituent of 7-acetoxy-7H-aricine (III) since its rotatory dispersion curve (Figure 3) closely resembled that of 7α-acetoxy-7H-yohimbine. It might seem surprising that the same stereochemistry has been assigned to the acyloxyindolenines of the *cis*-DE and *trans*-DE yohimbinoid-type bases in view

(1) Part II: N. Finch, C. W. Gemenden, I. H-C. Hsu, and W. I. Taylor, *J. Am. Chem. Soc.*, **85**, 1520 (1963).

(2) Some of this work has appeared in a preliminary communication: N. Finch, W. I. Taylor, and P. R. Ulshafer, *Experientia*, **19**, 296 (1963).

(3) See also L. Dolby and S. Sakai, *J. Am. Chem. Soc.*, **86**, 5362 (1964).

(4) This determination is, incidentally, a new proof of the structure and stereochemistry of yohimbine itself.

(5) For an explanation of this nomenclature see ref. 1.

(6) Lecture given by one of us (N. F.) at the IUPAC Symposium on the Chemistry of Natural Products, Prague, Aug. 1962.

(7) We wish to express our gratitude to Professor W. Klyne for obtaining the O.R.D. curves for us.

(8) J. Shavel and H. Zinnes, *J. Am. Chem. Soc.*, **84**, 1318 (1962). If -Cl can be equated with -OAc, then the stereochemistries of these two chloro-7H-yohimbans are established but the important conclusion for our work was the mirror image relationship.

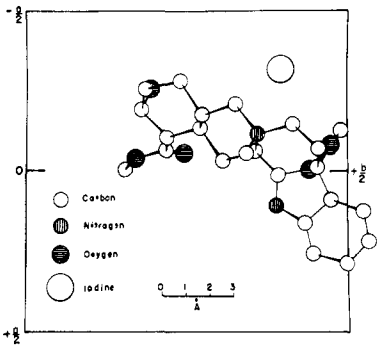


Figure 1. View of atomic arrangement of 7α-acetoxy-7H-yohimbine methiodide seen in projection along the *c*-axis.

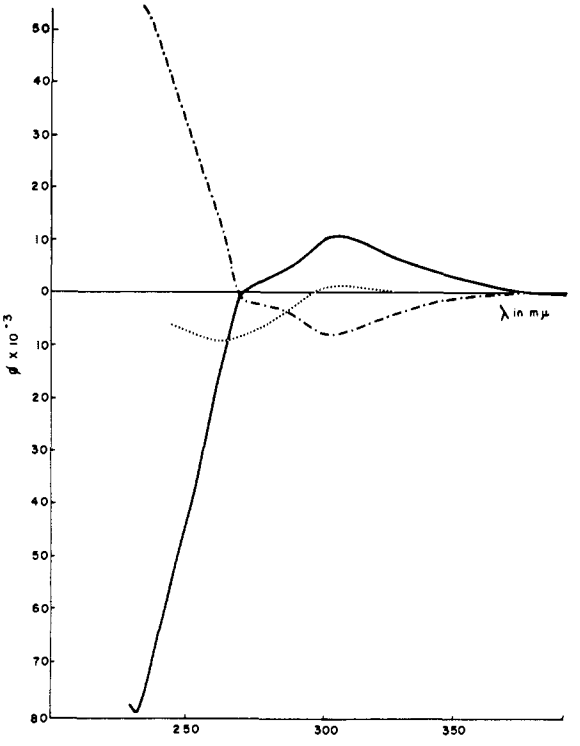


Figure 2. O.R.D. curves for yohimban, ...; epimeric 7-chloro-7H-yohimbans: faster moving, ———; slower moving, -·-·-·-.

of their differing reactivities[1] especially the conversion of the former to oxindoles by dilute acid. It should be remembered however that the explanation already advanced[1] was independent of the C-7 stereochemistry. Provided that stereochemistry at C-7 has the greatest effect on the optical rotatory dispersion curve, it might be expected that epimerization at C-3 of 7α-acetoxy-7H-yohimbine would produce a compound whose dispersion curve may show substantial changes in its amplitude but not of its sign. When pseudoyohimbine was reacted with lead tetraacetate a derivative was obtained whose optical rotatory dispersion curve (Figure 4) approximated to the mirror image of the α-acetoxy compounds, and it is concluded that this derivative is 7β-acetoxy-7H-pseudoyohimbine. Methyl 7β-hydroxy-7H-reserpate (V) showed the same type of curve (Figure 4) and it would seem that the stereochemistry of the acyloxyindolenines of the yohimbinoid alkaloids can be predicted from a knowledge of the configuration of the CD ring junction.

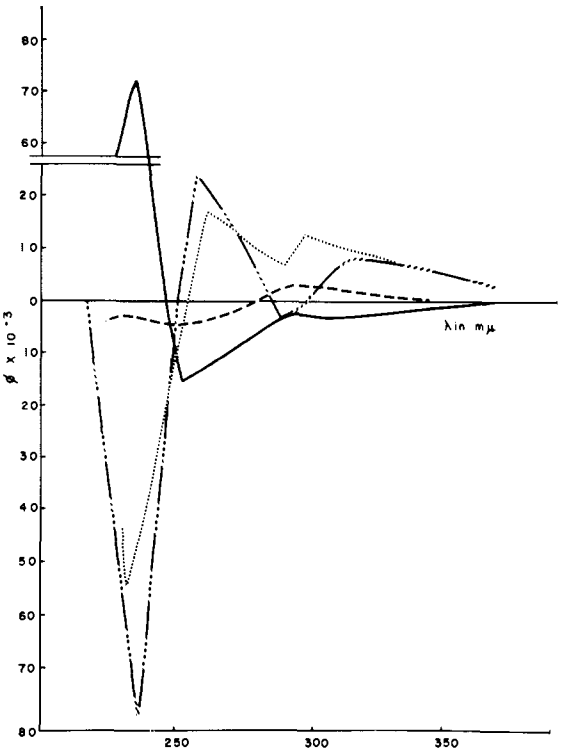


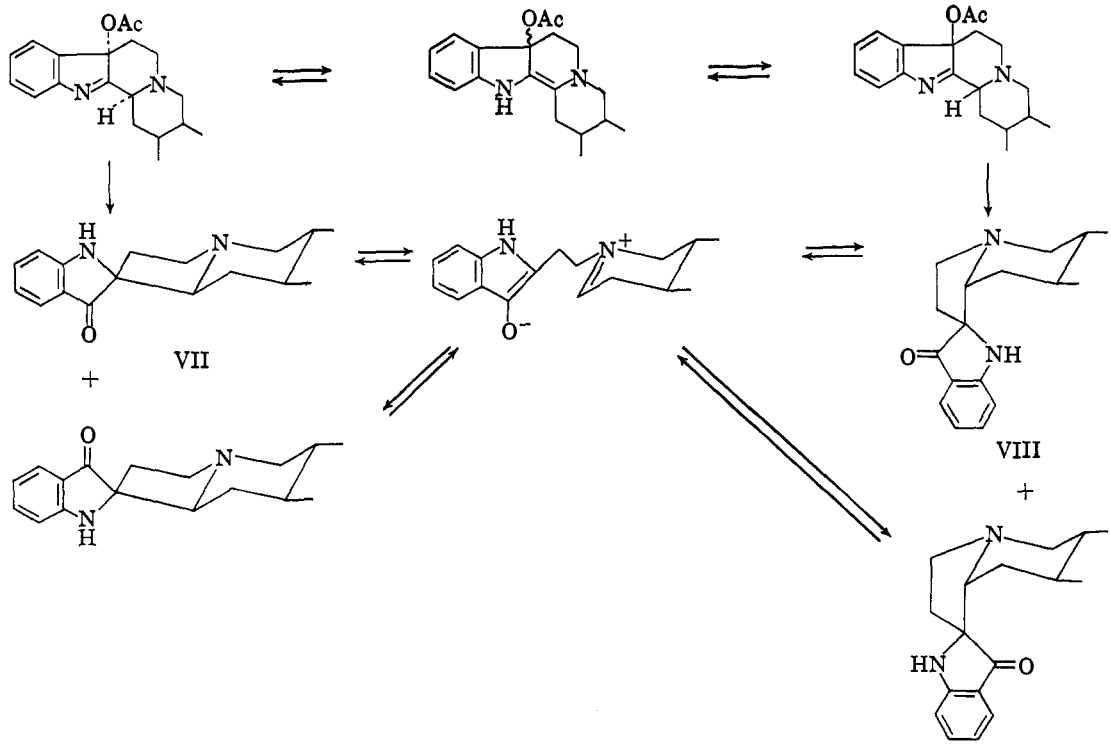
Figure 3. O.R.D. curves for aricine, ———; 7α-acetoxy-7H-aricine, —·—·—; yohimbine, --------; 7α-acetoxy-7H-yohimbine, ...

Acyloxyindolenines (VI) like their hydroxyindolenine counterparts[9,10] rearrange under basic conditions to form pseudoindoxyls. Impetus to explore this reaction in more detail came with the isolation of a new yellow alkaloid from *R. vomitoria* Afzel.[2] This compound was also isolated from *Aspidosperma discolor* A. DC.[11] and *Rauwolfia ligustrina* Roem.[12] *et* Schult. The empirical formula and ultraviolet spectrum of this substance suggested it might be isoreserpiline pseudoindoxyl, VII (partial formula), and the mass spectrum supported this structural assignment.[13] In an endeavor to improve the yield of pseudoindoxyl the effect of changing R in VI was investigated. It was hoped that electron-withdrawing groups might speed the methanolysis at the expense of side reactions and give larger yields of the pseudoindoxyl, but there were difficulties in preparing Pb^{IV} salts of strong carboxylic acids. Nevertheless use of lead tetra-*m*-bromobenzoate did lead to slightly better yields of pseudoindoxyls and the methanolysis of 7-*m*-bromobenzyloxy-7H-isoreserpiline gave a pseudoindoxyl identical in all respects with the yellow alkaloid of *R. vomitoria* Afzel.

Similar to the formation of yohimbinoid-derived oxindoles[1] up to four diastereoisomeric pseudoindoxyls could have been generated from the 7-acyloxyindolenines as indicated in Chart I. Whereas the oxindoles are known to exist in at least two forms[1,14] we have

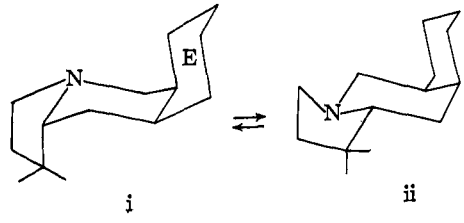
(9) B. Witkop, *Bull. soc. chim. France*, 423 (1954).
(10) M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Am. Chem. Soc.*, 80, 126 (1958).
(11) N. Dastoor and H. Schmid, *Experientia*, 19, 297 (1963).
(12) J. M. Müller, private communication.
(13) N. Finch, I. H.-C. Hsu, W. I. Taylor, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, 86, 2620 (1964).
(14) The recent work of J.-L. Pousset and J. Poisson, *Compt. rend.*, 259, 597 (1964), indicates that at least three of the four oxindoles are possible from reserpiline.

Chart I. Theoretical Equilibria and Pathways in the Conversion of 7-Acyloxy-7H-indolenines to Pseudoindoxyls



been able to detect only one pseudoindoxyl irrespective of the C-3 and C-7 stereochemistry of the starting indolenine although the rate of the conversion may differ.

In the case of the methyl 7-acetoxy-7H-reserpates, the 3αH-indolenine rearranged much faster than the 3βH-isomer. After a 30-min. reflux the former is completely transformed into the pseudoindoxyl whereas the latter has largely been converted into the 7-hydroxyindolenine (assay by thin layer chromatography). Because of this hydrolysis, the slow rearrangement cannot be due to hindrance to attack of the 7-acyloxy carbonyl by methoxide ion, nor can the stereochemistry of the transformation step be crucial since the C-7 substituent is axial (or at least pseudoaxial) to ring C in both possible C-3 epimers. It is suggested that the formation of the *cis*-pyrrolizidine VIII is thermodynamically much less favored than the *trans* system VII[15] but whether the reaction proceeds *via* VIII or by



prior rearrangement of the indolenine at C-3 is not known.

In the case of yohimbine pseudoindoxyl the hydrogen at C-3 is given an α-orientation because the strong bands at *ca.* 2800 cm.$^{-1}$ are considered to be characteristic of a nitrogen heterocycle with hydrogens

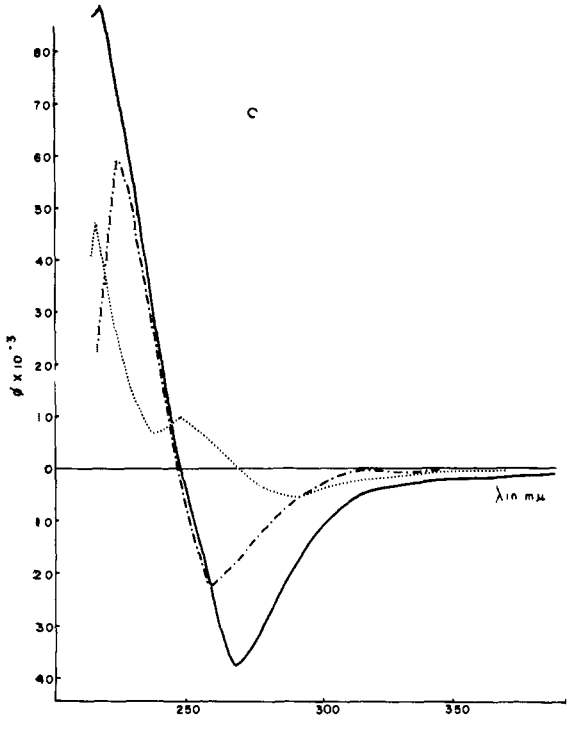


Figure 4. O.R.D. curves for pseudoyohimbine. .....; 7β-acetoxy-7H-pseudoyohimbine, ———; methyl 7β-hydroxy-7H-reserpate, ·-·-·-.

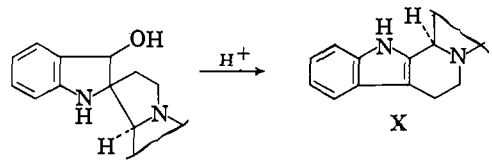
trans and axial to the lone-pair orbital.[16] A tentative assignment of the stereochemistry at C-2 is based on

(15) It should be remembered that in the *cis*-DE ring alkaloids a conformational change is possible, *viz.*, i $\rightleftarrows$ ii. In the case of methyl reserpate i is unlikely since all the ring E substituents would end up axially oriented. However, in the case of reserpiline only the methyl group would become pseudoaxial on a dihydropyran ring E.

(16) F. Bohlmann, *Chem. Ber.*, 91, 2157 (1958).

the observation that 1-methylyohimbine pseudoindoxyl (pK_a' 5.30) is a weaker base than yohimbine pseudoindoxyl[17] (pK_a' 5.76).[18] This is taken to mean that N-1 is on the same side of the molecule as the N-4 lone-pair orbital and the effect of methylation is to increase the steric effect on the conjugate acid. As a working hypothesis therefore the yohimbine pseudoindoxyl is regarded as yohimbine pseudoindoxyl A[17,19] and the other compounds in this paper are also regarded as A epimers.

Sodium borohydride reduction of the pseudoindoxyls gave the corresponding dihydropseudoindoxyls IX which upon reflux in methanolic acid rearranged not to the parent alkaloids but to ring AB "inverted" bases (X).[20] An interesting feature of their chemistry emerged from an examination of the products of the



IX X

reaction with DE *cis* ring compounds. Two indoles were obtained which could be interconverted with acid. They are thought to be epimeric at C-3[21] by a process similar to that believed to operate for yohimbinoid alkaloids.[22] The mass spectra of these inverted bases were identical with the respective parent alkaloids.[23]

Experimental

All melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations, unless stated, were measured in chloroform at 25 ± 2° ($c \approx 1$) and the optical rotatory dispersion curves were obtained in methanol. Ultraviolet spectra were recorded as mμ (ε) in ethanol, infrared spectra in chloroform unless otherwise stated and dissociation constants in 80% Methyl Cellosolve–water. The alumina used in chromatography was Woelm, neutral, activity III.

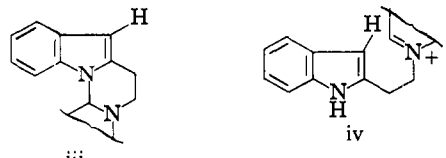
(17) The same convention as previously used to describe the configuration of oxindoles[1] is used for the pseudoindoxyls; *viz.*, the suffix A denotes the carbonyl group below the plane of the CDE rings and B the alternate isomer. The parent name is that of the base with the same stereochemistry at C-3 as the pseudoindoxyl.

(18) N-1 methylation of yohimbine gives a product, pK_a' 7.07, essentially the same as the parent base, pK_a' 6.95.

(19) The existence of the B isomer of yohimbine oxindole, stabilized in acidic solution, is due at least in part to hydrogen bonding (N. Finch and W. I. Taylor, *J. Am. Chem. Soc.*, **84**, 3871 (1962)) of the conjugate acid with the amide carbonyl group. The keto function of a pseudoindoxyl even thought of as a vinylogous amide is much less effective in this respect so that this particular isomer of yohimbine pseudoindoxyl is not especially favored over the other possibilities.

(20) *Cf.* ibogaine to "invert" ibogaine: M. F. Bartlett, D. F. Dickel, R. C. Maxfield, L. E. Paszek, and A. F. Smith, *ibid.*, **81**, 1932 (1959).

(21) The data exclude the possibility of one of the isomers being iii if iv is an intermediate in the equilibration below.



iii iv

(22) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kiersted, *Tetrahedron*, 2, 19, footnote† (1957).

(23) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 1, Holden-Day Inc., San Francisco, Calif., 1964, p. 48.

7-Chloro-7H-yohimbans (II). The crude chloroyohimbans[8] were separated by the use of thin layer chromatography using silica gel G[24] and a mixture of chloroform–tetrahydrofuran (4:6) as developing agent. The faster moving isomer (traveled 11 cm.) was readily separated from the slower which travelled 9 cm. The optical rotatory dispersion curves are shown in Figure 2: slower: $[\alpha]_{394}$ −390, $[\alpha]_{301}$ −6400 (trough), $[\alpha]_{286}$ −2850 (inflection), $[\alpha]_{272}$ −2150 (inflection), and $[\alpha]_{235}$ −50,000; and faster: $[\alpha]_{385}$ +975, $[\alpha]_{303}$ +9950 (peak), $[\alpha]_{286}$ +3390, $[\alpha]_{270}$ −1200 (inflection), and $[\alpha]_{227}$ −83,500.

7α-Acetoxy-7H-yohimbine Methiodide. 7α-Acetoxy-7H-yohimbine was dissolved in methyl iodide and deposited shortly afterwards the methiodide. The salt recrystallized from methanol in a form suitable for X-ray crystallography, m.p. 225–227°, $[\alpha]_D$ +202° (*c* 1.5, MeOH).

Anal. Calcd. for $C_{24}H_{31}IN_2O_5$: C, 52.03; H, 5.64. Found: C, 52.10; H, 6.27.

Lead Tetraanisate. Lead tetraacetate (1 g.) in dry dioxane (10 ml.) was added to a solution of anisic acid (3.1 g.) in dry dioxane (40 ml.). The mixture was allowed to stand at room temperature for 30 min., and the solvent was removed *in vacuo* without heating above 50°. The residue stood overnight in a desiccator under a high vacuum over sodium hydroxide pellets and was slurried with dry methanol and collected. The solid was washed with dry methanol, dried, and recrystallized from dry benzene to give material; m.p. 185–186°; λ_{max} 256 mμ (ε 28,800); ν_{max} 1610, 1520, 1420, and 1220 cm.$^{-1}$.

Anal. Calcd. for $C_{32}H_{28}O_{12}Pb$: C, 47.34; H, 3.48. Found: C, 46.91; H, 3.48.

Lead Tetra-m-bromobenzoate. This was prepared as above from lead tetraacetate (1 g.) and *m*-bromobenzoic acid (4.1 g.) and recrystallized from benzene, m.p. 178–180° dec., λ_{max} 283 mμ (ε 8000). Satisfactory analyses could not be obtained on this compound, but the purity was better than 97% by iodometric assay.

Lead Diphthalate. On mixing the dioxane solutions of phthalic acid (2 g.) and lead tetraacetate (1 g.), lead diphthalate precipitated (1.8 g.). This was washed with dioxane and dried, m.p. 150° dec.

Anal. Calcd. for $C_{16}H_8O_8Pb$: C, 35.89; H, 1.51. Found: C, 35.31; H, 1.82.

Reaction of Pb^{IV} Acylates with Methyl Isoreserpate. Standard solutions of the Pb^{IV} salts were prepared in methylene chloride (lead tetra-*m*-bromobenzoate 0.028 *M*, lead tetraanisate 0.030 *M*, and lead tetrabenzoate 0.099 *M*) and were estimated iodometrically. Portions of methyl isoreserpate (300, 304, and 344 mg., respectively) were dissolved in methylene chloride (50 ml.), cooled in ice, and treated with 1 mole equiv. of each reagent. When the oxidation was completed (starch–iodide paper) water was added, and the organic layer was separated, dried, and taken to dryness. The residues (392, 340, and 298 mg., respectively) were dissolved in dry methanol (30 ml.) and refluxed under nitrogen for 30 min. with 1 molar equiv. of sodium methoxide, poured into water, and extracted (methylene chloride). The residues (200, 163, and 270 mg.,

(24) Silica gel G according to Stahl, E. Merk A.-G., Darmstadt.

respectively) were estimated by their ultraviolet spectra, λ_{max} 383 [$E^{1\%}_{1\,cm}$ 57.2, 38.4, and 39.5, respectively (based on ϵ 5000)]. The yields of pseudoindoxyl were 47, 24, and 34%, respectively (there was no appreciable change in $E^{1\%}_{1\,cm}$ on addition of 0.1 *N* KOH).

7-m-Bromobenzoyloxy-7H-isoreserpiline. Isoreserpiline (4 g.) was dissolved in methylene chloride (250 ml.) and cooled in ice to below 5°. Lead tetra-*m*-bromobenzoate (9.80 g., 1 mole equiv.) was added in one portion with rapid stirring. After 5 min. the oxidizing power had faded. The reaction was stirred for an additional 3 min., poured onto ice, and extracted (methylene chloride). The extract was washed (10% $KHCO_3$) and dried ($MgSO_4$). Removal of the solvent gave a residue (4.76 g.), which was chromatographed on alumina. The main band (1.7 g.) eluted by methylene chloride crystallized. Recrystallization from ether gave needles; m.p. 164–165°; $[\alpha]_D$ +135°; γ_{max} 239 mμ (ϵ 48,000) and 294 mμ (ϵ 5740); ν_{max} 1730, 1700, and 1635 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{31}BrN_2O_7$: C, 58.93; H, 5.11; Br, 13.08; N, 4.58. Found: C, 58.77; H, 5.06; Br, 12.79; N, 4.42.

Isoreserpiline Pseudoindoxyl. 7-m-Bromobenzoyl-7H-isoreserpiline (770 mg.) was dissolved in dry methanol (40 ml.), sodium methoxide (1.1 mole equiv.) in methanol was added, and the mixture was refluxed under nitrogen for 0.5 hr. The reaction was poured onto ice and extracted (methylene chloride). Removal of the solvent gave a foam (717 mg.) which was chromatographed on alumina. Elution by benzene yielded methyl *m*-bromobenzoate, m.p. 31° (185 mg.), and by methylene chloride, isoreserpiline pseudoindoxyl (294 mg.), m.p. 237–239°. Recrystallization from methanol gave bright yellow needles: m.p. 249–250° dec.; $[\alpha]_D$ −240°; λ_{max} 224 mμ (ϵ 22,900), 283 (11,750), and 405 (5600).

Anal. Calcd. for $C_{23}H_{28}N_2O_6$: C, 64.47; H, 6.59; N, 6.54. Found: C, 64.48; H, 6.58; N, 6.63.

Tetrahydroalstonine Pseudoindoxyl. Tetrahydroalstonine (290 mg.) was dissolved in methylene chloride and cooled to 5°. Lead tetraacetate (665 mg.) was added with stirring which was continued until oxidant was consumed (15 min.). The methylene chloride solution was washed (10% $KHCO_3$) and dried ($MgSO_4$) and the solvent was removed. The residue (273 mg.) was filtered through alumina in methylene chloride. Concentration of the eluates gave a foam, 140 mg. The bulk (130 mg.) of this material was dissolved in methanol and refluxed with 1 mole equiv. of sodium methoxide under nitrogen for 30 min. The product was chromatographed on alumina. Elution by 20% methylene chloride in benzene gave the main band (81 mg.). This material was recrystallized from ether to give yellow needles; m.p. 203–205°; $[\alpha]_D$ −337°; ν_{max} 2800, 1690, and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.13; H, 6.52; N, 7.42.

Aricine Pseudoindoxyl. Aricine (200 mg.) was oxidized in a manner analogous to the above experiments. The crude product (213 mg.) was methanolized, and the product (153 mg.) was chromatographed on alumina. The main crystalline fraction (65 mg.) was recrystallized from methanol to give the pseudoindoxyl (28 mg.): m.p. 212–218° dec.; $[\alpha]_D$ −370°; λ_{max} 228 mμ (ϵ 35,200) and 428 mμ (ϵ 3940); ν_{max} 2800, 1690, and 1630 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{26}N_2O_5$: C, 66.31; H, 6.58; N, 7.03. Found: C, 66.33; H, 6.48; N, 7.00.

Methyl Isoreserpate Pseudoindoxyl. Methyl 7-benzoyloxy-7H-isoreserpate (4.1 g.) was refluxed in dry methanol (50 ml.) containing dissolved sodium (256 mg.). Crude product (2.5 g.) was chromatographed on alumina and yielded after elution by 1% methanol in methylene chloride the main band (1.7 g.) obtained as an amorphous solid by precipitation from benzene with hexane. It had $[\alpha]_D$ −93°; λ_{max} 228 mμ (ϵ 20,200), 248 (18,000), 280 (10,400), and 380 (4100); ν_{max} 2800, 1730, 1675, and 1615 cm.$^{-1}$. Satisfactory analyses could not be obtained. The compound was acylated with 3,4,5-trimethoxybenzoyl chloride in pyridine to yield the ester, m.p. 211–212°, from aqueous methanol; $[\alpha]_D$ −272°; λ_{max} 232 mμ (ϵ 21,500), 249 (27,600), 276 (19,600), and 381 (4300); ν_{max} 2820, 1730, 1710, 1680, and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{33}H_{40}N_2O_{10}$: C, 63.44; H, 6.45; N, 4.48. Found: C, 63.54; H, 6.61; N, 4.52.

Yohimbine Pseudoindoxyl. 7-Acetoxy-7H-yohimbine (1.0 g.) and potassium hydroxide (1 mole equiv.) in methanol (10 ml.) were allowed to stand overnight at room temperature. The reaction mixture was diluted with water and extracted (methylene chloride). The residue (0.7 g.) was crystallized from ethyl acetate to yield *7-hydroxy-7H-yohimbine:* m.p. 187–190°; $[\alpha]_D$ +234°; λ_{max} 218 mμ (ϵ 21,200) and 262 mμ (ϵ 4200); ν^{Nujol}_{max} 3600, 3520, 3350, 1715, and 1596 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{26}N_2O_4 \cdot H_2O$: C, 64.93; H, 7.27. Found: C, 65.42; H, 7.01.

Treatment of this compound with methanolic hydrochloric acid yielded Δ^8-dehydroyohimbine hydrochloride. The hydroxy compound (1.0 g.) was refluxed for 1 hr. in methanol containing several drops of 2 *N* potassium hydroxide. The solution was concentrated and cooled. The product was collected and recrystallized from methanol: m.p. 218°; $[\alpha]_D$ −192°; λ_{max} 234 mμ (ϵ 23,800) and 400 mμ (ϵ 3800); pK_a' 5.4; ν_{max} 2800, 1700, and 1625 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07. Found: C, 68.21; H, 7.20.

1-Methylyohimbine Pseudoindoxyl. Yohimbine pseudoindoxyl (500 mg.) was added to liquid ammonia (25 ml.) containing dissolved sodium (40 mg.). Methyl iodide (0.1 ml.) was added to the red solution which changed to yellow. After evaporation of the ammonia the residue was washed with water and recrystallized from benzene–cyclohexane: m.p. 187–189°; $[\alpha]_D$ −292°; λ_{max} 232 mμ (ϵ 25,600), 260 (7130), and 419 (4200); ν_{max} 2820, 1710, 1700, and 1625 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{28}N_2O_4$: C, 68.72; H, 8.34; N, 7.29. Found: C, 68.51; H, 7.43; N, 7.02.

Ajmalicine Pseudoindoxyl. Oxidation of ajmalicine with lead tetraacetate as described above gave *7-acetoxy-7H-ajmalicine:* m.p. 198–199°; $[\alpha]_D$ +256°; λ_{max} 219 mμ (ϵ 28,600), 237 (13,600), and 248 (11,560); ν^{Nujol}_{max} 3370, 1700, 1620, and 1595 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.39. Found: C, 67.68; H, 6.55.

The acetoxyindolenine (2.15 g.) was methanolized to furnish ajmalicine pseudoindoxyl (880 mg.): m.p. 223–225°; $[\alpha]D$ −203°; λ_{max} 234 mμ (ε 23,430) and 398 mμ (ε 4050); ν_{max}^{Nujol} 1690 and 1615 cm.$^{-1}$.

7-Hydroxy-7H-pseudoyohimbine.[25] 7-Acetoxy-7H-pseudoyohimbine (642 mg.) in hot methanol (12 ml.) was treated with 1 equiv. of sodium methoxide. It was worked up after standing overnight to give a solid (545 mg.) which crystallized from methylene chloride–isopropyl ether and finally with moist ethyl acetate to afford crystals: m.p. 136–138°; $[\alpha]D$ −228°; λ_{max} 245 mμ (ε 4900) and 297 mμ (ε 2810); ν_{max} 3520, 3350, 1715, and 1695 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}N_2O_5$: C, 64.93; H, 7.27; N, 7.21. Found: C, 64.63; H, 7.38; N, 7.08.

If in the above experiment the solution was refluxed for 2 hr., yohimbine pseudoindoxyl was the principal product.

Methyl 7-Hydroxy-7H-reserpate. Methyl 7-benzoyloxy-7H-reserpate (3.21 g.) was refluxed for 15 min. in dry methanol with 1 mole equiv. of sodium methoxide. After working up it gave a solid (2.60 g.). A portion (1 g.) was separated by preparative thin layer chromatography on silica gel and the main band (720 mg.) was eluted. It was an amorphous solid which had $[\alpha]D$ −211°; λ_{max} 233 mμ (ε 16,700) shoulder and 283 mμ (ε 2800); ν_{max} 3320, 1725, 1620, and 1590 cm.$^{-1}$; $[\alpha]_{345}$ −1170, $[\alpha]_{333}$ −1220 (trough), $[\alpha]_{318}$ −930 (peak), $[\alpha]_{257}$ −23,000 (trough), $[\alpha]_{228}$ +59,000 (peak), and $[\alpha]_{217}$ +22,000.

Anal. Calcd. for $C_{23}H_{30}N_2O_6$: C, 64.17; H, 7.02; N, 6.51. Found: C, 63.43; H, 7.29; N, 6.25.

A minor band (50 mg.) from the thin layer chromatogram was identified with methyl isoreserpate pseudoindoxyl by thin layer chromatography and infrared and ultraviolet spectroscopy.

Borohydride Reductions of the Pseudoindoxyls. The reductions were conducted in methanol (no reduction occurred in ethanol) with excess sodium borohydride. The completion of the reaction was determined by the absence of the long wave length band in the ultraviolet and the yields were quantitative.

Yohimbine dihydropseudoindoxyl had m.p. 230–232° from methylene chloride: $[\alpha]D$ +90° (ethanol); ν_{max}^{Nujol} 3500, 3365, 1710, and 1610 cm.$^{-1}$; λ_{max} 246 mμ (ε 9550) and 301 mμ (ε 2240).

Anal. Calcd. for $C_{21}H_{28}N_2O_4$: C, 67.72; H, 7.58. Found: C, 67.43; H, 7.55.

This compound was also prepared by hydrogenation of the pseudoindoxyl in ethanol over Adams catalyst.

Ajmalicine dihydropseudoindoxyl had m.p. 219–221° from methylene chloride: $[\alpha]D$ +50°, ν_{max}^{Nujol} 3300, 1700, and 1618 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.09. Found: C, 68.17; H, 7.12.

Isoreserpine dihydropseudoindoxyl had m.p. 115–125° from benzene–cyclohexane, λ_{max} 258–262 mμ (ε 12,700).

Anal. Calcd. for $C_{33}H_{42}N_2O_{10}$: C, 63.24; H, 6.75; N, 4.47. Found: C, 63.01; H, 6.83; N, 4.49.

(25) According to the ultraviolet absorption spectrum (dihydroindole) and analytical data this compound is really the addition product of water to the imino group of the indolenine moiety.

Invert Yohimbine. Yohimbine dihydropseudoindoxyl (1.66 g.) was refluxed in methanol (150 ml.) containing 2 *N* hydrochloric acid (5 ml.) for 0.5 hr. The solution was concentrated, diluted with water, made basic (2 *N* NaOH), and extracted (methylene chloride). Removal of the solvent gave a residue which was recrystallized from ethanol to furnish the indole (1.01 g.): m.p. 250–252°; $[\alpha]D$ −90°; λ_{max} 224 mμ (ε 37,100), 282 (7060), and 289 (6010); ν_{max}^{Nujol} 3300, 1710, 1625, and 1590 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39. Found: C, 70.73; H, 7.54.

The methiodide had m.p. 265–268° from ethanol and the O acetate had m.p. 159–161° from ether.

Invert ajmalicine, prepared as for invert yohimbine, had m.p. 220–224° from ethanol with $[\alpha]D$ −135°; ν_{max}^{Nujol} 3340, 1690, and 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86. Found: C, 71.22; H, 7.07.

Methyl Invert Isoreserpate. Methyl isoreserpate dihydropseudoindoxyl (5.5 g.) was rearranged as above. The product isolated was not homogeneous. Chromatography on alumina and elution by 2% methanol in methylene chloride yielded the main band (2.0 g.) which was recrystallized from methanol to give methyl invert isoreserpate (1.23 g.): m.p. 240–242°; $[\alpha]D$ −158°; λ_{max} 227 mμ (ε 35,500), 267 (4380), and 297 (5110); ν_{max} 2800, 2750, 1730, and 1630 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}N_2O_5$: C, 66.64; H, 7.30; N, 6.76. Found: C, 66.84; H, 8.39; N, 6.93.

Acylation with trimethoxybenzoyl chloride in pyridine yielded invert isoreserpine: m.p. 139–144° (from ethanol); $[\alpha]D$ −254°; λ_{max} 266 mμ (ε 15,900); ν_{max} 2850, 2750, 1730, 1710, 1630, and 1595 cm.$^{-1}$.

Anal. Calcd. for $C_{33}H_{40}N_2O_9$: C, 65.11; H, 6.62; N, 4.80. Found: C, 64.93; H, 6.64; N, 4.48.

Elution by 5% methanol in methylene chloride yielded a second compound (1.1 g.). Recrystallization from methylene chloride–isopropyl ether yielded methyl invert reserpate: m.p. 210–215°; $[\alpha]D$ +5.5°; λ_{max} 223 mμ (ε 27,800), 268 (4300), and 293 (5080); ν_{max}^{Nujol} 1730 and 1630 cm.$^{-1}$. Satisfactory analyses could not be obtained for this compound. Acylation with 3,4,5-trimethoxybenzoyl chloride yielded invert reserpine: m.p. 224–225° (from methanol); $[\alpha]D$ −79°; λ_{max} 267 mμ (ε 15,500); ν_{max} 1725, 1710, 1630, and 1595 cm.$^{-1}$.

Anal. Calcd. for $C_{33}H_{40}N_2O_9$: C, 65.11; H, 6.61; N, 4.60. Found: C, 65.02; H, 6.55; N, 4.45.

Invert Tetrahydroalstonine. The crude borohydride product from tetrahydroalstonine pseudoindoxyl (1.88 g.) was rearranged as above. The product (1.80 g.) was chromatographed on alumina. The first major band (0.72 g.) was eluted by 20% methylene chloride in benzene. This material was recrystallized from ether–petroleum ether (b.p. 30–60°) to give invert tetrahydroalstonine: m.p. 195–196°; $[\alpha]D$ −134°; λ_{max} 225 mμ (ε 39,000) and 289 mμ (ε 5600), ν_{max} 2800, 2750, 1700, and 1635 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.98; H, 7.20; N, 7.96.

A second band (0.49 g.) was eluted by methylene chloride. This material was crystallized from cyclohexane to yield invert akuammigine: m.p. 110–117°

dec.; $[\alpha]D$ +11°; λ_{max} 225 mμ (ε 55,800) and 289 mμ (ε 7800); ν_{max} 1700 and 1625 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{24}N_2O_3 \cdot H_2O$: C, 68.09; H, 7.07; N, 7.56. Found: C, 68.00; H, 7.03; N, 7.21.

Invert Isoreserpiline. Isoreserpiline dihydropseudoindoxyl (266 mg.) was rearranged and the product was chromatographed on alumina. The first band (68 mg.) was eluted by methylene chloride. This was treated in methanol with 1 mole equiv. of nitric acid. Invert isoreserpiline nitrate was obtained and recrystallized from methanol: m.p. 200°; ν_{max}^{Nujol} 3300, 1720, and 1645 cm.$^{-1}$; free base ν_{max} 2840, 2780, 1700, and 1630 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{29}N_3O_8 \cdot CH_3OH$: C, 56.79; H, 6.55. Found: C, 56.43; H, 6.70.

The second band (89 mg.), eluted by 0.5% methanol in methylene chloride, was treated with nitric acid to give invert reserpiline nitrate, m.p. 194–196° (free base), ν_{max} 1700 and 1625 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{29}N_3O_8 \cdot CH_3OH$: C, 56.79; H, 6.55; N, 8.28. *Found:* C, 56.98; H, 6.47; N, 8.60.

Equilibration of Methyl Invert Isoreserpate and Methyl Invert Reserpate. Samples of methyl invert isoreserpate (10 mg.) and methyl invert reserpate (10 mg.) were refluxed for 1 hr. in methanolic HCl (1 ml.). The products were spotted on Whatman No. 1 paper, impregnated with formamide, using the starting materials as standards. The eluent was xylene–methyl ethyl ketone (3:1) in an ammonia atmosphere. The mixtures showed 80% methyl invert isoreserpate and 20% methyl invert reserpate.

Optical rotatory dispersion showed yohimbane $[\alpha]_{361}$ −460, $[\alpha]_{310}$ +1070 (peak), $[\alpha]_{266}$ −9400, and $[\alpha]_{244}$ −5660; aricine $[\alpha]_{345}$ −1220, $[\alpha]_{308}$ −3240 (trough), $[\alpha]_{204}$ −1770 (peak), $[\alpha]_{253}$ −15,100 (trough), $[\alpha]_{233}$ +72,500, and $[\alpha]_{226}$ +44,000; 7α-acetoxy-7H-aricine $[\alpha]_{370}$ +2940, $[\alpha]_{318}$ +8130 (peak), $[\alpha]_{290}$ −3180 (trough), $[\alpha]_{260}$ +24,200 (peak), $[\alpha]_{233}$ −80,000 (trough), and $[\alpha]_{208}$ +40,000; yohimbine $[\alpha]_{333}$ +1030, $[\alpha]_{296}$ +3600 (peak), $[\alpha]_{250}$ −4620 (trough), $[\alpha]_{236}$ −3500 (peak), and $[\alpha]_{233}$ −4240; 7α-acetoxy-7H-yohimbine $[\alpha]_{300}$ +12,950 (peak), $[\alpha]_{282}$ +7250 (trough), $[\alpha]_{264}$ +16,900 (peak), $[\alpha]_{230}$ −54,200 (trough), and $[\alpha]_{227}$ −43,700; pseudoyohimbine $[\alpha]_{370}$ −800, $[\alpha]_{288}$ −5150 (trough), $[\alpha]_{248}$ +9450 (peak), $[\alpha]_{238}$ −6450 (trough), $[\alpha]_{213}$ −47,000 (peak), and $[\alpha]_{210}$ +40,000; 7β-acetoxy-7H-pseudoyohimbine $[\alpha]_{385}$ −2080, $[\alpha]_{266}$ −38,900 (trough), $[\alpha]_{219}$ +88,000 (peak), and $[\alpha]_{217}$ +86,400.

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(26) "Computing Methods and the Phase Problem in X-Ray Crystal Analysis," R. Pepinsky, J. M. Robertson, and J. C. Speakman, Ed., Pergamon Press Ltd., London, 1961: (a) J. S. Rollett, p. 87; (b) J. G. Sime, p. 301.