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Oxidative Transformations of Indole Alkaloids. II. The Preparation of Oxindoles from *cis*-DE-Yohimbinoid Alkaloids. The Partial Synthesis of Carapanaubine[1]

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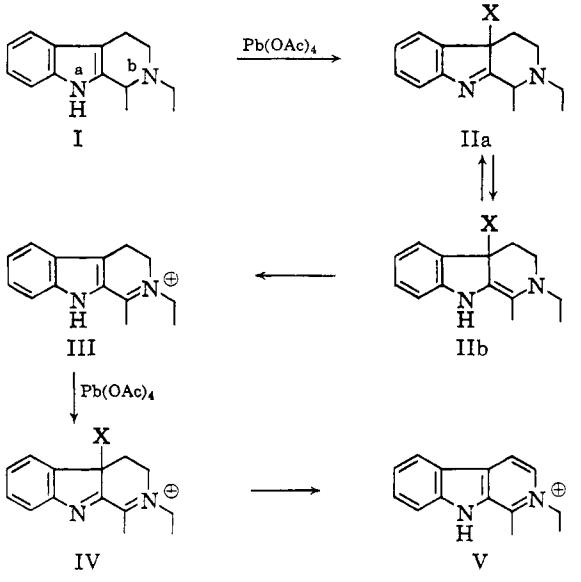
The reaction of lead tetracarboxylates with yohimbine, methyl reserpate and related alkaloids affords acyloxyindolenines. These compounds on reflux in methanolic acetic acid yield the corresponding oxindoles. Use of this observation has been made to transform reserpiline into carapanaubine, thereby defining the complete stereochemistry of this new alkaloid. The mechanism by which the acyloxyindolenines are formed and the mechanism of the rearrangement step are discussed.

Our previously published method[1,2] for the conversion of yohimbinoid alkaloids into oxindoles was of practical utility only for the *trans*-DE-indole alkaloids. Therefore, only those oxindole alkaloids with a *trans*-DE ring fusion, *e.g.*, mitraphylline, rhyncophylline and corynoxeine, could be prepared. There are, however, several oxindole alkaloids known or believed to have *cis*-DE stereochemistry, *viz.*, uncarine B (formosanine),[3] corynoxine[4] and carapanaubine, recently isolated from *Aspidosperma carapanauba*.[5] We wished, therefore, to develop a new method for the preparation of these compounds from their indole equivalents.

Our continued interest in the reactivity of indoles toward electrophilic reagents caused us to re-examine the reaction of indole alkaloids (I) with lead tetraacetate. In acetic acid solution this reagent has often been used for obtaining the tetradehydro compounds V.[6] Based on our previous observations of the reaction of *t*-butyl hypochlorite with indoles,[1,2] it was considered that lead tetraacetate would react according to the scheme I → V(X = $Pb(OAc)_3$ and/or OAc).[7]



When the reaction was carried out in methylene chloride with one molar equivalent of lead tetraacetate at room temperature, acetoxyindolenines (IIa, X = OAc) were obtained, which could be easily isolated and characterized.[8]

By this procedure the corresponding acetoxyindolenines of yohimbine, pseudoyohimbine, isoreserpiline, tetrahydroalstonine, reserpine, methyl reserpate and and methyl isoreserpate were prepared. Other lead[IV] salts (*e.g.*, lead tetrabenzoate and tetra *m*-bromobenzoate) could be used to furnish the analogous acyloxyindolenines.

On treatment with acetic or dilute mineral acid, these compounds (IIa, X = O-acyl) eliminated the acyloxy group and gave rise to dehydro compounds (III). If, however, the acetoxyindolenines derived from the *cis*-DE-yohimbinoid alkaloids were refluxed in methanol containing a few drops of acetic acid, a rearrangement occurred. The product isolated was the oxindole. Both procedures, *viz.*, methanolysis of the chloroindolenine and rearrangement of the acetoxyindolenine, were employed on methyl isoreserpate. The latter process gave a much higher yield of methyl isoreserpate oxindole B. Quite generally, rearrangement of the acetoxyindolenine with dilute methanolic acetic acid proved to be a superior procedure for the preparation of oxindoles from the *cis*-DE-yohimbinoid alkaloids.

The yield of oxindole by this method was insensitive to the stereochemistry at C_3, so that either methyl reserpate or methyl isoreserpate gave methyl isoreserpate oxindole B in fair yield. Epimerization at C_3 can occur subsequent to the rearrangement step, as oxindoles are known to equilibrate in dilute acetic acid,[1,2,9] or it can occur prior to the rearrangement step, as must be the case when the chloroindolenine of methyl reserpate is transformed by sodium methoxide into a small yield of the imido ether of methyl isoreserpate oxindole A. Epimerization prior to rearrangement can be more extensive with the acyloxyindolenines, as the imino–enamine (IIa ⇄ IIb) tautomerism is more susceptible to acid than base catalysis. There must be a delicate balance, however, between tautomerism and the irreversible formation of the dehydro compound III which is quantitative under more acidic conditions. We envis-

(1) (a) Part I, N. Finch and W. I. Taylor, *J. Am. Chem. Soc.*, **84**, 3871 (1962). (b) Presented at the International Symposia on the Chemistry of Natural Products, Brussels, June 12, 1962, and Prague, August 31, 1962.

(2) N. Finch and W. I. Taylor, *J. Am. Chem. Soc.*, **84**, 1318 (1962); see also J. Shavel and H. Zinnes, *ibid.*, **84**, 1320 (1962).

(3) E. Wenkert, B. Wickberg and C. Leicht, *Tetrahedron Letters*, 822 (1961).

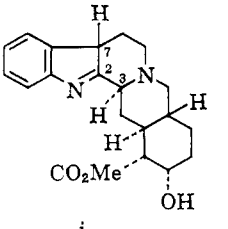
(4) N. AnCu, R. Goutarel and M.-M. Janot, *Bull. soc. chim. France*, 1292 (1957).

(5) B. Gilbert, J. A. Brissolese, N. Finch, W. I. Taylor, H. Budzikiewicz, J. M. Wilson and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 1523 (1963).

(6) G. Hahn, E. Kappes and H. Ludewig, *Ber.*, **67**, 686 (1934).

(7) W. I. Taylor, *Proc. Chem. Soc.*, 247 (1962).

(8) These derivatives are systematically named as substitution products of the hypothetical 7H-tautomers, *e.g.* the acetoxyindolenine (7-acetoxy-7H-yohimbine) derived from yohimbine is regarded as a derivative of 7H-yohimbine (i).

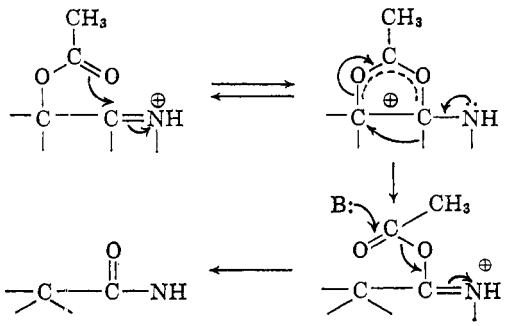


i

The nomenclature for the chloroindolenines[1,2] can also be systematized in this way.

(9) J. Seaton, M. D. Nair, O. E. Edwards and L. Marion, *Can. J. Chem.*, **38**, 1035 (1960).

age rearrangement of the acetoxyindolenines as proceeding *via* protonation of the indolenine nitrogen and participation of the neighboring acetoxy group with the resulting carbonium ion (Scheme I).



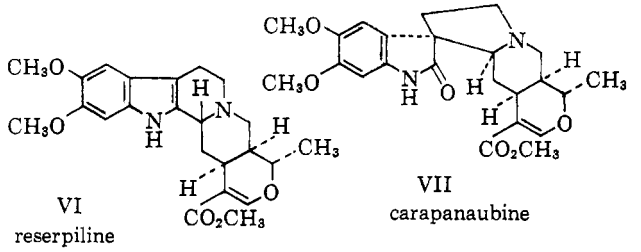
SCHEME I

The different behavior of the acyloxy indolenines of *cis*-DE series and the *trans*-DE series (*cf.* Table I) may be a reflection of the very small amount of N_a protonation, which can occur in the *trans*-DE case because of the stronger N_b. On the other hand, the presence of a 1:3 diaxial interaction with the lone pair of N_b, which is inherent in the *cis*-DE stereochemistry, so reduces the basicity of N_b that in these cases N_a can be more readily protonated (*e.g.*, 7-acetoxy 7H-(iso)reserpine has a $pK_a' < 4$ in 80% methyl Cellosolve–water). This may not be the only effect, as the conformational mobility of ring E, possible with the *cis*-DE ring fusion, can make N_a more accessible to protonation.

If one could establish whether oxindole A or oxindole B was the primary product of the rearrangement, then the stereochemistry of the acetoxy group could be deduced. This information would shed light on the stereochemistry of lead tetraacetate reaction with indoles.

We attempted to make use of these observations to obtain the *cis*-DE–oxindole alkaloids which were not accessible by the previous method.[1,2] Tetrahydroalstonine[10] was treated with lead tetraacetate and the product subjected to the rearrangement conditions. An amorphous compound was obtained which had the correct spectral properties for an oxindole but which was clearly not uncarine B (formosanine). Recent work[3] has indicated that mayumbine (the C_{19}-epimer of tetrahydroalstonine) would have been the correct starting material.

Greater success attended the conversion of reserpiline (VI)[11,12] into its oxindole. The B stereochemistry was assigned to the crystalline compound which was isolated, because of its reduced mobility upon paper chromatography as compared with that of the amorphous oxindole which accompanied it in the reaction mixture.[1,2] Isoreserpiline oxindole B was identical in all respects with carapanaubine (VII).[13]



VI
reserpiline

VII
carapanaubine

(10) We are indebted to Dr. Price (C.S.I.R.O., Melbourne) and Professor Elderfield (University of Michigan) for gifts of this valuable alkaloid.

(11) For proof of stereochemistry, *cf.* M. Shamma and J. B. Moss, *J. Am. Chem. Soc.*, **83**, 5038 (1961).

(12) Sample kindly provided by Dr. P. R. Ulshafer.

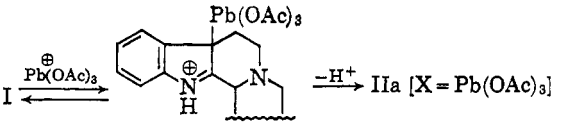
(13) We are grateful to Professor Djerassi for direct comparison of the natural and synthetic materials.

TABLE I

OXIDATION OF YOHIMBINOID ALKALOIDS WITH $Pb(OAc)_4$

Stereochemistry	Rate of oxidation	MeOH–HOAc on product
cis-DE, $C_3H\alpha$	Rapid	Oxindole
cis-DE, $C_3H\beta$	Rapid	Oxindole
trans-DE, $C_3H\alpha$	Rapid	Unchanged
trans-DE, $C_3H\beta$	Very slow	Unchanged

As the attack of electrophilic reagents on indoles takes place at the β-position,[14,15] and the reactions of lead tetraacetate have been successfully interpreted as proceeding *via* the lead triacetate cation,[16,17] we favor initial formation of an intermediate (VIII) from the indole and lead tetraacetate.



VIII

This compound can undergo elimination or substitution reactions, as $Pb(OAc)_3$ is a good leaving group. Elimination proceeds as shown previously (IIa → III), substitution (by OAc^- the only nucleophile available) leads to the isolable product IIa (X = OAc). If we assume these reactions occur on the unprotonated indolenine (which is reasonable; if there were any amount of IIa, X = OAc, in its N_a protonated form present, one might expect to obtain oxindole products directly) and also that they are rapid (as judged by the color change, colorless → yellow; the elimination of acetoxy indolenines to give dehydro compounds IIa → III is instantaneous in acetic acid), then the rate-determining step may be proton loss from VIII. This may be the explanation for the sluggish formation of 7-acetoxy-7H-pseudoyohimbine, because in pseudoyohimbine N_a is quite crowded by the carbomethoxy group and ring E is conformationally rigid, as it is *trans* fused to ring D.

The existence of an intermediate such as VIII receives some support from the observation that if the reaction is conducted in the presence of other nucleophilic reagents, other products can be obtained. Thus the reaction of isoreserpine with lead tetraacetate in methanol yields 7 methoxy-7H-isoreserpine.

Further work on the chemistry of these indolenines will be reported, and experiments are in progress which may solve the stereochemistry of these interesting substances.

Experimental

All melting points are uncorrected. Unless stated, optical rotations were measured in chloroform at 25 ± 2° ($c \approx 1$), ultraviolet spectra recorded as $m\mu$ (log ϵ) in ethanol, infrared spectra in chloroform, proton magnetic spectra (Varian A60 instrument) in deuteriochloroform and dissociation constants in 80% methyl Cellosolve–water. Woelm activity III neutral alumina was used for column chromatography. Silica gel G (Merck, Darmstadt) was used for thin-layer chromatography, and the results are reported as distance run from the origin in cm. Magnesium sulfate was used as the drying agent.

7-Acetoxy-7H-pseudoyohimbine.—Pseudoyohimbine (4.14 g.) and lead tetraacetate (5.32 g.) in methylene chloride (1200 ml.) were stirred at room temperature until the solution no longer gave a positive reaction with starch–iodide paper (*ca.* 1.5 hr.). The organic phase was washed with water, dried ($MgSO_4$), the solvent removed, and the residue (3.14 g.) was chromatographed over alumina. The methylene chloride eluates gave several fractions which yielded, from methylene chloride–isopropyl ether, the 7-acetoxy-7H-pseudoyohimbine (1.69 g.), m.p. 190–192°,

(14) T. S. Stevens, in "Chemistry of Carbon Compounds," Ed. E. H Rodd, Vol. IVa, Elsevier Press, New York, N. Y., 1957, p. 78.

(15) R. L. Hinman and E. P. Whipple, *J. Am. Chem. Soc.*, **84**, 2534 (1962).

(16) R. Criegee, *Angew. Chem.*, **70**, 173 (1958).

(17) Fr. R. Preuss and I. Janshen, *Arch. Pharm.*, **295**, 284 (1962).

raised after several crystallizations to 196–197°, $[\alpha]_D$ −208°; ν_{max} 1762, 1730, 1610 cm.$^{-1}$; λ_{max} 219 (4.33), 259 (3.70); pK_a' 3.90. Upon reflux for 1.5 hr. in methanol (5 ml.) and acetic acid (3 drops), it was recovered unaltered in high yield.

Anal. Calcd. for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84. Found: C, 66.74; H, 6.94.

Isoreserpiline Oxindole B (Carapanaubine).—Reserpiline (3.58 g.) in methylene chloride (60 ml.) was treated with lead tetraacetate (3.83 g.). After 10 minutes the solution was poured into ice-cold 10% potassium bicarbonate, shaken, and the organic phase removed and concentrated. The residue (3.05 g.) in methylene chloride was passed through alumina (200 g.) to furnish from the eluate the crude acetoxy compound (1.1 g.). The acetoxy derivative (900 mg.) was refluxed for 1.5 hr. in methanol (10 ml.), water (2 ml.) and acetic acid (10 drops), poured into ice-cold 10% potassium bicarbonate and extracted with methylene chloride. The solid (770 mg.) was chromatographed on alumina; the methylene chloride eluate furnished a glass (260 mg.), and the methylene chloride–0.5% methanol eluate furnished carapanaubine[18] (237 mg.), which crystallized from ether (160 mg.); m.p. 217–218°, $[\alpha]_D$ −97°; λ_{max} 244 (4.11), shoulders 285 (3.72) and 304 (3.62). For analysis it was recrystallized from methanol–water.

Anal. Calcd. for $C_{23}H_{28}N_2O_6 \cdot 0.5\ H_2O$: C, 63.14; H, 6.68; N, 6.41. Found: C, 63.42; H, 6.48; N, 6.30.

Attempt to Convert Tetrahydroalstonine into its Oxindole.—Tetrahydroalstonine (208 mg.) in methylene chloride (50 ml.) was stirred at 0° for 20 minutes with lead tetraacetate (264 mg.). The solution was washed with water, dried ($MgSO_4$) and concentrated to afford a foam (150 mg.) which after filtration in methylene chloride through alumina gave a glass (80 mg.), λ_{max} 240 and 220. The crude acetoxy compound was dissolved in methanol (5 ml.), water (1 ml.) and acetic acid (5 drops), refluxed for 1.5 hours and poured into 10% potassium bicarbonate. The methylene chloride extract yielded a glass (80 mg.) which was not successfully characterized either by chromatography or attempted salt formation.

The Imido Ether from Methyl Isoreserpate.—Methyl isoreserpate (200 mg.) in methylene chloride (20 ml.) containing triethylamine (0.1 ml.) was cooled in an acetone–Dry Ice-bath. To the well-stirred solution, 0.0975 *M tert*-butyl hypochlorite (5 ml. in CCl_4) was added dropwise. After 30 minutes the solution was washed with water, dried and taken to dryness to yield the crude chloroindolenine, a brown foam (223 mg.). The crude chloro compound (350 mg.) was refluxed for 5 minutes in methanolic sodium methoxide [25 ml. from sodium (500 mg.)]. The reaction mixture was poured into ice and extracted with methylene chloride which furnished a residue (270 mg.) which was chromatographed. The benzene and benzene–methylene chloride eluated gave traces of non-crystalline material, whereas with methylene chloride the imido ether (57 mg.) was obtained. It gave crystals from ether, m.p. 168°, $[\alpha]_D$ +64°; ν_{max} 1740, 1590 cm.$^{-1}$; λ_{max} 224–226 (4.45), 266–270 (3.54) with shoulders at 284 (3.51) and 294 (3.40).

Anal. Calcd. for $C_{24}H_{32}N_2O_6$: C, 64.84; H, 7.25; N, 6.30. Found: C, 65.05; H, 7.46; N, 6.13.

Methyl Isoreserpate Oxindole B.—The above imido ether (300 mg.) was refluxed for 15 minutes in 10% aqueous acetic acid. The isolated base (230 mg.) was chromatographed on alumina; elution with methylene chloride–0.5% methanol gave oxindole A, a foam (147 mg.), homogeneous as judged by thin-layer chromatography.

Further elution with methylene chloride–10% methanol gave oxindole B (33 mg.), m.p. 240–242° from ether, $[\alpha]_D$ −110°; λ_{max} 259 (3.59) with shoulders at 273 (3.54), 283 (3.52) and 293 (3.41); ν_{max}^{Nujol} 3420, 3220, 1710 and 1626 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}N_2O_6$: C, 64.17; H, 7.02. Found: C, 64.14; H, 7.13.

When methyl isoreserpate oxindole B was refluxed in 10% aqueous acetic acid for 8 hours, it gave rise to an equilibrium mixture of oxindoles A and B (predominating) according to thin-layer chromatographic assay.

Methyl Isoreserpate Imido Ether from Methyl Reserpate.—Methyl reserpate (1 g.) was stirred in ice-cold methylene chloride containing triethylamine (0.5 ml.) and 0.14 *M tert*-butyl hypochloride (17 ml. in CCl_4) was added. After 5 minutes the reaction mixture was poured into ice and the organic layer dried and reduced to dryness. The resultant crude chloro methyl reserpate (530 mg., λ_{max} 296) was refluxed in methanol (30 ml.) containing dissolved sodium (1 g.), poured onto ice and extracted with methylene chloride. Removal of the solvent gave a residue (305 mg.) which after chromatography furnished, from one of the methylene chloride eluates, methyl isoreserpate imido ether (10 mg.), m.p. 167–168°, after crystallization of the crude product (30 mg.) from ether.

(18) Carapanaubine from *Aspidosperma carapanauba* has m.p. 218°, $[\alpha]_D$ −101°; Drs. Djerassi and Gilbert, personal communication.

Methyl 7-chloro-7H-reserpate (1.1 g.) was refluxed in methanol (10 ml.) and water (2 ml.) containing acetic acid (10 drops). Even after careful chromatography, no methyl isoreserpate oxindole B could be isolated.

7-Acetoxy Methyl 7H-Reserpate.—Methyl reserpate (7.6 g.) in methylene chloride (400 ml.) was stirred at 10° for 3 minutes with lead tetraacetate (8.5 g.). The precipitate was removed by filtration and the residue (10.3 g.) from the organic phase was placed on an alumina column in benzene and eluted with methylene chloride. The eluted material (3.3 g.) crystallized from aqueous methanol to furnish acetoxy methyl reserpate (980 mg.), m.p. 152–153°, $[\alpha]_D$ −225°; ν_{max}^{Nujol} 3400, 1730, 1630, 1594 cm.$^{-1}$; λ_{max} 230–232 (4.39), 292–297 (3.57); pK_a' 4.45.

Anal. Calcd. for $C_{25}H_{32}N_2O_7 \cdot 0.5\ H_2O$: C, 62.30; H, 6.90. Found: C, 62.14; H, 6.88.

7-Benzoyloxy Methyl 7H-Reserpate.—Methyl reserpate (830 mg.) in methylene chloride (150 ml.) was cooled in an ice-bath and stirred with lead tetrabenzoate (1.52 g.) for 5 minutes. The mixture was poured into ice-cold 5% potassium bicarbonate, shaken, and the organic layer was removed, dried and taken to dryness. The residue (700 mg.) was chromatographed over alumina; the methylene chloride–0.5% methanol eluate furnished the crude benzoyloxy methyl reserpate (517 mg.) which was crystallized from hexane to m.p. 134°, $[\alpha]_D$ −202°; ν_{max} 3580, 1726, 1627, 1595 cm.$^{-1}$; λ_{max} 234 (4.50), plateau 269–279 (3.61).

Anal. Calcd. for $C_{30}H_{34}N_2O_7$: C, 67.40; H, 6.41; N, 5.24. Found: C, 66.78; H, 6.68; H, 5.34.

7-Acetoxy Methyl 7H-Isoreserpate.—Methyl isoreserpate (2.34 g.) in methylene chloride (60 ml.) was stirred with lead tetraacetate (2.50 g.) for 10 minutes at 0°. The product (2.27 g.) of the reaction was clarified by filtration in benzene through Darco activated charcoal. The pale yellow filtrate was diluted with cyclohexane to yield the amorphous acetoxy compound (1.21 g.).

Methyl Isoreserpate Oxindole B from 7-Acetoxy Methyl 7H-Isoreserpate.—(a) Acetoxy methyl isoreserpate (170 mg.) was refluxed in methanol (5 ml.), water (1 ml.) and acetic acid (3 drops), and poured into 10% potassium bicarbonate. Extraction with methylene chloride gave the crude oxindole (132 mg.) which crystallized on contact with ether. Thin-layer chromatography showed it to be the oxindole B along with a little oxindole A.

(b) 7-Acetoxy methyl 7H-reserpate (1 g.) was refluxed in methanol (10 ml.) containing water (2 ml.) and a few drops of acetic acid. The isolated base, after recrystallization (380 mg.), m.p. 234–236°, $[\alpha]_D$ −110°, was identical in all respects with methyl isoreserpate oxindole B prepared by the other methods above.

Anal. Calcd. for $C_{23}H_{30}N_2O_6$: C, 64.17; H, 7.02. Found: C, 64.26; H, 6.86.

7-Benzoyloxy Methyl 7H-Isoreserpate.—Lead tetrabenzoate (0.102 *M*; 23.5 ml. of CH_2Cl_2) was added over half an hour to methyl isoreserpate (1 g.) in ice-cold methylene chloride (75 ml.). The reaction mixture was poured into ice-cold 10% potassium bicarbonate, shaken and the organic layer was dried ($MgSO_4$) and reduced to dryness. The product (932 mg.) was clarified by filtration through Darco activated charcoal in benzene solution. Addition of cyclohexane and scratching afforded the benzoyloxy derivative (388 mg.), m.p. 130–140°, $[\alpha]_D$ +103°; ν_{max} 3580, 1720, 1590 cm.$^{-1}$; λ_{max} 232 (4.55), shoulders 274 (3.63) and 283 (3.57).

Anal. Calcd. for $C_{30}H_{28}N_2O_7$: C, 67.40; H, 6.41; N, 5.24. Found: C, 67.21; H, 6.84; N, 5.00.

7-*m*-Bromobenzoyloxy Methyl 7H-Isoreserpate.—By a method analogous to that used for the preparation of benzoyloxy methyl isoreserpate, the *m*-bromobenzoyloxy methyl isoreserpate was obtained as microcrystals from benzene–cyclohexane; m.p. 130° dec., $[\alpha]_D$ +108°; λ_{max} 231 (4.52), plateau 275–183 (4.34) and shoulder 293 (4.30).

Anal. Calcd. for $C_{30}H_{33}N_2O_7Br$: C, 58.73; H, 5.43; N, 4.58. Found: C, 58.71; H, 5.85; N, 4.12.

7-Acetoxy-7H-yohimbine.—Yohimbine (1 g.) dissolved in benzene (75 ml.) was stirred for 5 minutes with lead tetraacetate (1.26 g.), filtered and concentrated to dryness. The residue (1.06 g.) was chromatographed over alumina to furnish from one of the methylene chloride eluates the acetoxyyohimbine (400 mg.), m.p. 123–124° from aqueous ethanol, $[\alpha]_D$ +198°; λ_{max} 219 (4.32), 264 (3.63); pK_a' 5.20.

Anal. Calcd. for $C_{23}H_{28}N_2O_5 \cdot 2H_2O$: C, 61.59; H, 7.9. Found: C, 61.37, 61.22; H, 7.28, 7.24.

Upon reflux for 1.5 hours in methanol containing a trace of acetic acid it was recovered unchanged. Treatment of the acetoxy compound with sodium borohydride regenerated yohimbine in quantitative yield.

7-Acetoxy-7H-reserpine.—Reserpine (0.5 g.) in methylene chloride (25 ml.) was stirred for 2 minutes with lead tetraacetate

(0.37 g.), filtered and passed through alumina. The eluate and the methylene chloride washings gave the crude acetoxy compound (392 mg.) which was crystallized from methanol–water; m.p. 200°, $[\alpha]_D$ −195°; λ_{max} 233 (4.43), 267 (3.16), shoulder 296 (3.89); pK_a' K 4.0.

Anal. Calcd. for $C_{35}H_{42}N_2O_{11}$: C, 63.06; H, 6.36. Found: C, 62.95; H, 6.42.

Isoreserpine Oxindole B.—(a) Acetoxyreserpine (0.5 g.) was refluxed for 1.5 hours in methanol (5 ml.), water (2 ml.) and acetic acid (7 drops). The product from methanol gave isoreserpine oxindole B (300 mg.), m.p. 253°, $[\alpha]_D$ −192°.

Anal. Calcd. for $C_{33}H_{40}N_2O_{10}$: C, 63.5; H, 6.46. Found: C, 63.63; H, 6.56.

(b) Methyl isoreserpate oxindole B (300 mg.) was mixed with 3,4,5-trimethoxybenzoyl chloride (192 mg., 1.2 molar equivalents) and freshly distilled dry pyridine (3 ml.) was added. The mixture stood at room temperature for 4 days. The pyridine was removed *in vacuo*, and the residue dissolved in methylene chloride and filtered through alumina, the eluate being discarded. Further elution by 1–2% methanol in methylene chloride yielded material which crystallized from ether (166 mg.); m.p. 245–246°, identical with that from preparation (a).

7-Methoxy 7H-Isoreserpine.—Lead tetraacetate (2.9 g., dried over KOH) was added to isoreserpine (4 g.) in methanol (500 ml.) and stirred for 5 minutes at 15°. The mixture was poured into ice and extracted into methylene chloride, dried ($MgSO_4$) and concentrated. The residue (4.30 g.) was chromatographed over alumina (200 g.). Elution with benzene yielded an oil (280 mg.), followed by a solid (527 mg.). Elution with methylene chloride furnished isoreserpine (1.03 g.), and finally a resin (1.4 g.). The solid eluted by benzene was recrystallized several times from cyclohexane; m.p. 120–130°, $[\alpha]_D$ −28°; ν_{max} 1716, 1704, 1590 cm.$^{-1}$; λ_{max} 230 (4.49), 266–269 (4.13), shoulder 239 (4.37). This compound was recovered unaltered after reflux in methanol containing a trace of acetic acid.

Anal. Calcd. for $C_{34}H_{42}N_2O_{10}$: C, 63.93; H, 6.63; N, 4.39. Found: C, 63.86; H, 6.74; N, 4.29.

7-Methoxy-7H-reserpine.—Reserpine (4 g.) oxidized in an analogous manner yielded after chromatography a solid (435 mg.) which could be recrystallized from ether–methylene chloride; m.p. 233–235°, $[\alpha]_D$ −190°; ν_{max} 1718, 1596 cm.$^{-1}$; λ_{max} 230 (4.47), 263–266 (4.18), shoulder 236 (4.41).

Anal. Calcd. for $C_{34}H_{42}N_2O_{10}$: C, 63.93; H, 6.63; N, 4.39. Found: C, 64.23; H, 6.56; N, 4.36.

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Mass Spectrometry in Structural and Stereochemical Problems. XX.[1] Carapanaubine, a New Alkaloid from *Aspidosperma carapanauba* and Some Observations on Mass Spectra of Oxindole Alkaloids[2]

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The mass spectra of a number of naturally occurring, as well as recently synthesized, oxindole alkaloids have been investigated. By the use of deuterium labeling, as well as variations in substitution in the aromatic and alicyclic portions of the molecule, the principal mass spectral fragmentation processes have been elucidated. Some of these processes are uniquely different from those observed with other indole alkaloids, and mass spectrometry can thus be used as an excellent criterion for establishing membership in this class of alkaloids. As an illustration, there is reported the first isolation of a new oxindole alkaloid, carapanaubine, from an *Aspidosperma* species—mass spectrometry pointing toward an oxindole structure, which was subsequently confirmed by synthesis.

Our studies[3] of the alkaloids of Brazilian Aspidosperma species have led to a remarkable variety of structural types ranging in complexity from hexacyclic N-acyldihydroindoles such as pyrifoline,[4] refractine[5] and aspidoalbine[6] to the relatively simple dihydrocorynantheol[7] and even harman-3-carboxylic acid.[8]

From the bark of another Amazonian species, *Aspidosperma carapanauba* M. Pichon, we have isolated a new base to which the empirical formula $C_{23}H_{28}N_2O_6$ could be attributed with certainty on the basis of elementary analysis and mass spectrometrically determined molecular weight. As noted in Table I, the n.m.r. spectrum of this new alkaloid, now named carapanaubine, showed remarkable similarities to that of isoreserpiline ($C_{23}H_{28}N_2O_5$) IIb originally isolated[9] from *Rauwolfia canescens* L. and recently encountered[10] in *Aspidosperma discolor* A. DC. The similarity of these spectra indicated that the main portion of the carapanaubine (Ic) structure might be identical with that of isoreserpiline (IIb).[9]

The non-indolic ultraviolet spectrum and the presence of an additional carbonyl band in the infrared spectrum of carapanaubine, coupled with the downfield shift of the N–H proton signal in the n.m.r. spectrum (Table I) and the presence of a sixth oxygen atom in the molecule, suggested the possibility of an oxindole structure. Since such alkaloids have hitherto not been encountered in this genus, it was decided to examine the mass spectra of known oxindoles, which have recently become readily available[11–13] by partial synthesis, in order to determine whether some correlation could be made between mass spectral fragmentation patterns and the structures of these alkaloids.

(1) For paper XIX see H. Budzikiewicz, J. M. Wilson, C. Djerassi, J. Levy, J. Le Men and M.-M. Janot, *Tetrahedron*, in press.

(2) (a) This work represents part of a joint program, supported by the Rockefeller Foundation, between the Instituto de Quimica Agricola and Stanford University on the chemistry of Brazilian plant products. Additional financial support was provided by the National Institutes of Health of the United States Public Health Service through Grants No. A-4257 and 29-682. (b) First presented at the second I.U.P.A.C. International Symposium on the Chemistry of Natural Products, Prague, August, 1962.

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