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The Alkaloids of *Hunteria eburnea* Pichon. II. The Quaternary Bases

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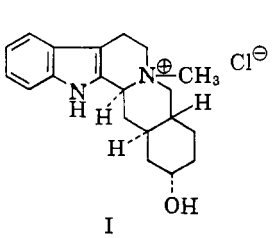
The isolation of one tertiary and thirteen quaternary alkaloids from *Hunteria eburnea* is described. Three of these are identified as yohimbol methochloride (I), dihydrocorynantheol methochloride (II), and akuammicine methochloride (III). The first example of a new class of alkaloids is given which occurs in the form of its diastereoisomeric quaternary N_b salts, hunterburnine α- and β-methochlorides (IV and V). The structure of a third 5-hydroxyindole, huntrabrine methochloride (VI), is proposed from degradative work.

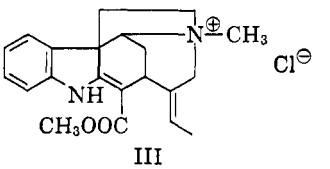
As part of a program to identify the hypotensive principles of *Hunteria eburnea* Pichon,[1,2] we have isolated nine inactive or weakly effective tertiary bases.[3a,b] Further work showed that methanolic extracts of the bark from which the majority of the tertiary bases had been removed with methylene chloride contained most of the activity. This extract again was separated into water insoluble residual tertiary bases and water soluble quaternary bases, the latter possessing most of the activity.[4] The quaternary alkaloids were removed from the water at pH 5 as their insoluble picrates which for subsequent work were transformed into the chloride salts. In all, fourteen crystalline alkaloids were separated from this mixture by processes (see Experimental and Fig. 1) which had as their end chromatography on cellulose powder.[5]

Six of these alkaloids were isolated in quantities insufficient for complete or accurate characterization and are referred to by the suffixes F, H, I, J, K, and N.[6]

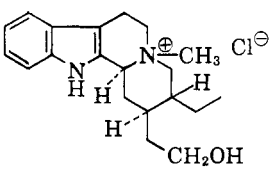
Yohimbol methochloride (I),[7] dihydrocorynantheol methochloride (II),[8,9] and akuammicine methochloride (III) were recognized, and the structures of the 5-hydroxyindoles hunterburnine α- and β-methochlorides (IV and V, respectively)[10-12] were elucidated by the X-ray crystallographic technique. The absolute stereochemistry depicted for the latter two alkaloids is based



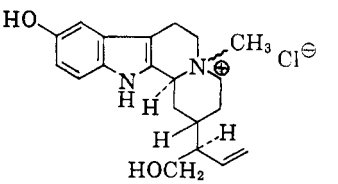
I



III



II



IV. $\alpha = -CH_3$ V. $\beta = -CH_3$

upon biogenetic considerations[13] and the validity of the C_{15} rule[14] for these molecules. In agreement with Katritzky's findings,[15] the chemical shift attributed to the quaternary methyl of the *cis*-quinolizidine (IV) is found at lower field (δ = 3.47) than in the case of *trans*-

(1) Raymond-Hamet, *Compt. rend.*, **240**, 1470 (1955); A. Engelhardt and H. Gelbrecht, *Naturwissenschaften*, **45**, 547 (1958); A. Engelhardt and H. Gelbrecht, *Arzneimittel Forsch.*, **11**, 414 (1961).

(2) The activity referred to throughout this paper means the blood pressure lowering response observed in anesthetized dogs by Drs. A. J. Plummer and W. A. Barrett of our pharmacology department.

(3) (a) Unpublished work from these laboratories; (b) For structures of four of the tertiary bases see M. F. Bartlett and W. I. Taylor, *J. Am. Chem. Soc.*, **82**, 5941 (1960).

(4) The weak hypotensive activity found in the residual tertiary bases could be enhanced by quaternization, however, no crystalline compounds were isolable even after extensive processing.

(5) The isolation of the alkaloids of calabash curare is a classical example of complex mixtures of quaternary alkaloids being separated by cellulose powder chromatography; H. Schmid, J. Kebrle, and P. Karrer, *Helv. Chim. Acta*, **35**, 1864 (1952).

(6) The possibility that some of these compounds were different crystalline forms of already isolated material was not investigated. In one case another unknown was identified as hunterburnine β-methochloride by seeding a methanolic solution of the former with crystals of the latter.

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

(8) C. Vamvacas, W. v. Philipsborn, E. Schlittler, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, **40**, 1793 (1957).

(9) Dihydrocorynantheol has now been isolated from *Aspidosperma* species; B. Gilbert, L. D. Antonaccio, and C. Djerassi, *J. Org. Chem.*, **27**, 4702 (1962).

(10) J. D. M. Asher, J. Monteath Robertson, G. A. Sim, M. F. Bartlett, R. Sklar, and W. I. Taylor, *Proc. Chem. Soc.*, 72 (1962).

(11) C. C. Scott, G. A. Sim, and J. Monteath Robertson, *ibid.*, 355 (1962).

(12) The tertiary base hunterburnine has yet to be recognized and isolated.

(13) E. Schlittler and W. I. Taylor, *Experientia*, **16**, 244 (1960).

(14) E. Wenkert and N. V. Bringi, *J. Am. Chem. Soc.*, **81**, 1474, 6535 (1959).

(15) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962).

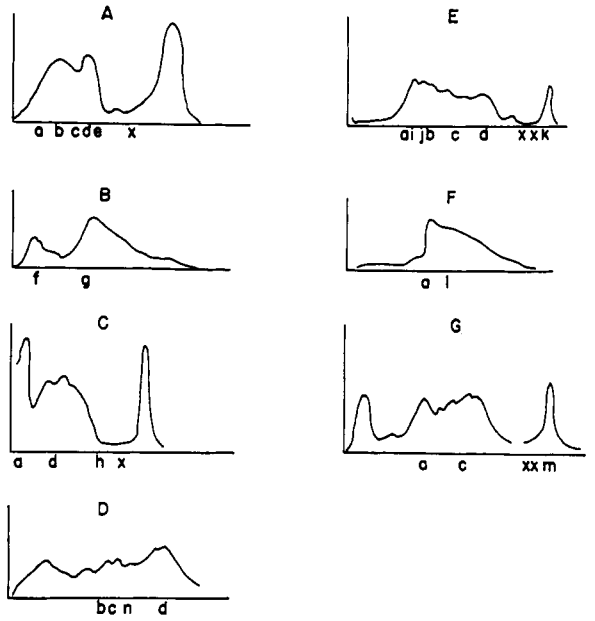
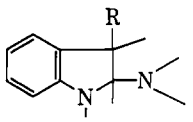


Fig. 1.—Diagrammatic eluate patterns of chromatograms A–G. The weights of alkaloids eluted are plotted as a function of the volume of eluent (see Table I for actual weights and volumes used), with the alkaloids isolated at: a, huntracine chloride; b, yohimbol methochloride; c, hunterburnine β-methochloride; d, huntrabrine methochloride; e, hunterburnine α-methochloride; f, hunteria alkaloid-F; g, akuammicine methochloride; h, hunteria alkaloid-H; i, hunteria alkaloid-I; j, hunteria alkaloid-J; k, hunteria alkaloid-K; l, dihydrocorynantheol methochloride; m, hunteramine; n, hunteria alkaloid-N; X, solvent change.

(V) (δ = 3.31).[16] Although this is the first recognized example of the occurrence in nature[17] of such N_b diastereoisomers, we predict that this will be found to be quite common in quaternary bases where the possibility exists,[18] and, since they have been found together, it suggests that the biological methylation step may parallel the specificity of the analogous laboratory operation.

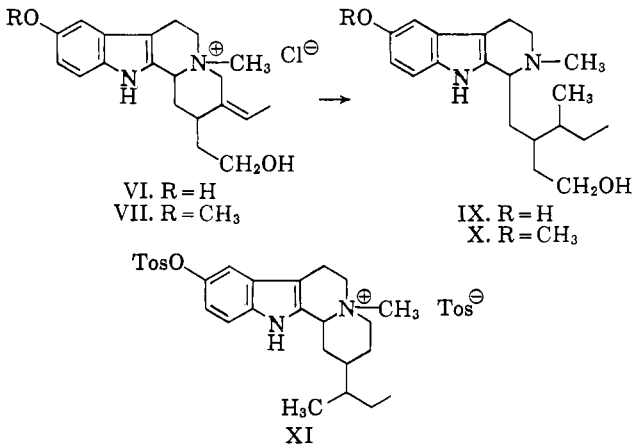
A third 5-hydroxyindole, huntrabine methochloride (VI), was available in sufficient amounts for degradative work (*vide infra*). Of the remaining two alkaloids, hunteramine (possibly $C_{26}H_{34}N_2O_{10}$) was a water soluble tertiary base. The final one, huntracine chloride ($C_{20}H_{25}N_2OCl$), has a chromophore similar to echitamine, suggesting the partial structure VIII.



VIII

There was no methoxyl or N-methyl group (confirmed by p.m.r. spectroscopy)[19]; the compound was unaffected under acetylation conditions and had a reducible double bond shown to be an ethylidine by p.m.r. spectroscopy. Sublimation of the quaternary hydroxide gave a crystalline tertiary pseudoindoxyl along with a water soluble quaternary compound with the same chromophore as the starting material. Upon attempted pyrolysis or selenium dehydrogenation, hunteracine chloride was recovered unchanged. Lack of material precluded substantiation of these intriguing results, in which R in VIII may be hydroxyl.

Huntrabrine methochloride, $C_{20}H_{27}N_2O_2Cl$, in agreement with its proposed structure VI, gave on acetylation a mixture of O-mono-, O,O-di-, and O,O,N-triacetates. The p.m.r. spectrum[19] of the alkaloid revealed the presence of an ethylidene, a quaternary N-methyl, and confirmed the distribution of protons on the aromatic nucleus. Reaction with either diazomethane or dimethyl sulfate gave the phenolic methyl ether (VII). Upon hydrogenation, either huntrabrine methochloride or the methyl ether underwent a facile Emde degradation yielding the tertiary bases (IX and X), respectively. The Emde product (IX) upon



tosylation gave a phenolic O-tosyl quaternary tosylate (XI)[20] which was converted readily to the phenolic-O-tosyl quaternary chloride (XI. tosyl$^-$ = Cl$^-$), and which upon selenium dehydrogenation afforded a product with a sempervirine-like ultraviolet absorption spectrum as well as a 2-pyridyl indole. The Emde base (IX) itself upon dehydrogenation also gave products with 2-pyridylindole ultraviolet absorption spectra which we suggest is the result of a cyclization under the reaction conditions.[21]

Interestingly, none of the quaternary bases so far isolated are quaternary salts of the known co-occurring tertiary bases. In fact, the quaternary alkaloids whose structures were determined were derived from yohimbinoid precursors, whereas the tertiary bases[3b] belong to the *aspidosperma-eburnea* type. Whether this means that the quaternary compounds are not derived from their immediate tertiary precursors is a question which cannot be settled from our work, but may be answerable if suitable studies with labeled compounds were carried out.

Experimental

The melting points were taken in evacuated capillaries and are uncorrected. Unless noted otherwise, analytical samples were routinely dried at 80–100° for 12–24 hr. *in vacuo*, the ultraviolet

(16) The spectra were run on the Varian Model A-60 spectrometer in trifluoroacetic acid by Misses N. Cahoon and J. A. Siragusa using tetramethylsilane as a reference.

(17) The epimeric methiodides of yohimban have been reported in the literature; B. Witkop, *J. Am. Chem. Soc.*, **71**, 2559 (1949); B. Witkop and S. M. Goodwin, *ibid.*, **75**, 3371 (1953).

(18) The difficulty which we have experienced in the isolation of the pure quaternary bases from the crude mixture may be due to the presence of further examples of this type of isomerism.

(19) Run by Dr. A. F. Zürcher in deuterium oxide with tetramethylsilane as standard.

(20) This is more facile that the analogous quaternization of dihydrocorynantheol; E. Wenkert and N. V. Bringi, *J. Am. Chem. Soc.*, **80**, 3484 (1958); ref. 14.

(21) Cyclizations during dehydrogenation reactions are known; for example, the dehydrogenation of melinonine B (ref. 8).

TABLE I

SUMMARY OF THE CHROMATOGRAPHIC RESULTS

Chromatogram	Column size, cm.	Solvent	Vol., l.	Added[a] wt., g.	Eluted wt., g.	Alkaloids isolated[b]
A	15 × 40	Water–acetone (8%)	15	26	14	a (1.05 g.), b (0.41 g.), c (0.12 g.), d (0.30 g.), e (1.41 g.)
		Water–acetone (20%)	9		10	.....
B	9.5 × 40	Ethyl Acetate–acetone–water (50:45:17)	3	3.9	3.7	f (0.34 g.), g (0.11 g.)
C	15 × 40	Water–acetone (10%)	15	33	21	a (0.20 g.), d (5.10 g.), h (0.20 g.)
		Water–acetone (20%)	14		9	.....
D[c]	8 × 110	Water–acetone (8%)	16	4.5	4.2	b (0.09 g.), c (0.009 g.), d (0.65 g.), n (0.033 g.)
E	8 × 110	Water–acetone (10%)	15	5	3.4	a (0.01 g.), b (0.01 g.), c (0.08 g.), d (0.10 g.), i (0.02 g.), j (0.02 g.)
		Water–acetone (15%)	4		0.1	.....
		Water–acetone (20%)	4		.1	k (0.014 g.)
F[d]	8 × 110	Water–acetone (10%)	8	6.4	5.0	a (0.28 g.), l (0.15 g.)
G	10 × 40	Water–acetone (8%)	8	3.5	2.5	a (0.02 g.), c (0.08 g.)
		Water–acetone (15%)	1.5		0.17	.....
		Water–acetone (20%)	4		.70	m (0.20 g.)

[a] See Experimental section for description of material used. [b] Letters correspond to names of alkaloids shown in Fig. 1. [c] Rechromatography of the mother liquors of huntrabrine methochloride. [d] Rechromatography of the first peak of chromatogram A.

absorption spectra were run in ethanol and expressed as mμ (ε), and the infrared absorption spectra were run in Nujol.

Isolation of the Alkaloids. Extraction of the Bark.—The root and stem bark which had previously been extracted with methylene chloride were reprocessed with recycling methanol at 40°, yielding 8 kg. of extractables from 60 kg. of bark.[22] A portion (300 g.) was dissolved in 10% acetic acid, filtered, and shaken with three portions of methylene chloride which removed 3.4 g. of material. The pH was brought to 8–9 with lithium hydroxide, generating a precipitate (112 g.) which was removed by filtration.

The filtrate was extracted with methylene chloride, brought to pH 6 (acetic acid), and all traces of methylene chloride were removed by bubbling nitrogen through the solution. This procedure led to a filterable precipitate (40 g.) upon addition of lithium picrate solution (30 g. of picric acid in 300 ml. of water with sufficient added lithium hydroxide to give a clear solution). The picrate salts were converted to the chloride salts by stirring with Amberlite IRA 400 (Cl^-) (360 g.) in acetone–methanol–water (900 ml., 6:2:1) for 18 hr. yielding the crude chloride salts (16.5 g.) after lyophilization (chromatogram A).

A portion of the filtrate of the picrate precipitation was evaporated to a small volume *in vacuo*. The precipitate was washed with water and converted to its chloride salts [Amberlite IRA 400 (Cl^-)]. After removing inorganic salts by partial precipitation from methanol, the chlorides (24 g.) were precipitated by addition of acetone and shaken with Darco decolorizing charcoal (*ca.* 50 g.) in hot water. The material (3.5 g.) adsorbed on the charcoal was eluted with hot methanol and used in chromatogram G.

A sample of the crude chloride salts (40 g.), used for chromatogram A, was dissolved in water and extracted continuously with methylene chloride for 24 hr., yielding 1.9 g. of residue. After a second extraction with methylene chloride for 4 days, a further 1.4 g. was extracted which was combined with similar material (2.5 g.) and used in chromatogram B. The aqueous phase of this extraction was heated on a steam bath with Darco decolorizing charcoal (35 g.), filtered and concentrated *in vacuo*, and finally freeze dried (yield 33 g., chromatogram C). Material (5 g.) was eluted from the charcoal with hot methanol (chromatogram E).

Chromatography.—The following solvent systems for chromatography on paper strips gave separations of the crude chloride mixture: methyl ethyl ketone–methanol–water (12:4:1), *t*-butyl alcohol–benzene–water (3.1:1:2), ethyl acetate–*t*-butyl alcohol–water (4:2:1), *t*-butyl alcohol–toluene–water (3.1:1:1). Upon application of these systems to columns, little separation was achieved. The completely homogeneous system acetone–water and later ethylacetate–acetone–water which gave poor separations on paper because of streaking were the solvents of choice for the columns.

(22) Carried out by J. Drew and L. Blodgett in pilot plant equipment.

Preparation of the Cellulose Columns.—A glass column (120 cm. by 8 cm.) was half-filled with acetone. A flat bed for the cellulose was made of glass wool and Berkshire sand. Cellulose powder (Whatman ashless standard grade, *ca.* 2 kg.) was placed in a vacuum desiccator, covered with acetone, and the air removed by repeated suction.[23] A portion (*ca.* 400 ml.) of this slurry was poured into the column, stirred to break up lumps, allowed to settle, and compressed tightly with a tamping rod using leverage. Repetition of this procedure resulted in a column 110 cm. long, which upon washing with 8% water–acetone caused the cellulose to expand, the top few segments rising slightly in the column. After washing with 8-hydroxyquinoline (1 g.) and testing the uniformity of the packing with Calco oil red or blue H 1700 (American Cyanamid Co., Boundbrook, New Jersey), the column was ready for use. The sample was placed on the column in water–acetone (usually 13% water) and immediately the chosen eluent added and the flow rate adjusted to 3–6 ml./min. All chromatograms were carried out at 25 ± 0.5°, streaking being pronounced whenever the temperature fluctuated. The elution pattern of a number of the chromatograms are shown in Fig. 1 and the results are summarized in Table I.

Hunteracine Chloride.—A sample from chromatogram A was recrystallized from ethanol for analysis, m.p. 343–344° dec., $[\alpha]_D$ −91° (27.5% H_2O–MeOH); λ_{max} 234 (7900), 291 (2200); λ_{min} 218 (4200), 256 (200), with no shift observed in acid or base.

Anal. Calcd. for $C_{20}H_{25}N_2OCl$: C, 69.60; H, 7.30; N, 8.12; Cl, 10.28; CCH_3, 4.06. Found: C, 69.87; H, 7.47; N, 8.17; Cl, 10.94; OCH_3, 0.0; CCH_3, 6.9.

Hydrogenation of Hunteracine Chloride.—Hunteracine chloride (19 mg.) in water (1.4 ml.) was hydrogenated in the presence of prereduced platinum catalyst with the uptake stopping at 1 mole equivalent. After filtration and evaporation, the residue crystallized from methanol–acetone, m.p. >320°.

Anal. Calcd. for $C_{20}H_{27}N_2OCl \cdot H_2O$: C, 65.81; H, 8.01. Found: C, 66.38; H, 7.83.

Hofmann Degradation of Hunteracine Chloride.—Hunteracine chloride (200 mg.) was converted to the methohydroxide with Amberlite CG 45 (OH) in methanol (10 ml.). After concentration the hydroxide (210 mg.) was sublimed at 150–180° under high vacuum yielding a sublimate (190 mg.) purified by chromatography on alumina. The methylene chloride eluate furnished a residue (20 mg.) crystallized from methanol–ether and recrystallized from benzene–ethyl acetate yielding a product (8 mg.), m.p. 183–185°; λ_{max} ($\epsilon_{1\,cm}^{1\%}$) 231 (900), 390 (120); λ_{sh} 250 (240), 263 (130), 343 (37); λ_{min} 285–295 (15) showing no change in acid or base.

Anal. Found: C, 75.59; H, 8.18.

The 10 and 20% methanol–methylene chloride eluates of the above chromatogram gave a residue crystallizing from ethanol–

(23) This is a modification of a procedure recommended by S. Gardell, *Acta Chem. Scand.* **11**, 668 (1957).

ethyl acetate to afford a neutral compound (20 mg.), m.p. 159–160°; λ_{max} ($\epsilon^{1\%}_{1cm}$) 234 (250), 290 (70); λ_{min} 219 (140), 256 (10).

Anal. Found: C, 65.98; H, 7.31; N, 10.99.

Yohimbol Methochloride.—A sample from chromatogram A was crystallized from acetone–water for analysis, m.p. 264–265°.

Anal. Calcd. for $C_{20}H_{27}N_2OCl \cdot {}^1/_2H_2O$: C, 67.47; H, 7.93; N, 7.87. Found: C, 67.40; H, 8.16; N, 7.52.

Yohimbol from Yohimbol Methochloride.—Yohimbol methochloride (100 mg.) after drying at 100° *in vacuo* was heated in two 50-mg. portions at 340° under high vacuum. The sublimate was dissolved in methylene chloride and washed with dilute sodium carbonate. Evaporation yielded a solid (62 mg.) purified by chromatography on alumina with the 0.5% methanol–methylene chloride eluate affording yohimbol (55 mg.), m.p. 249–251°, from methanol–water; $[\alpha]_D$ −49° (methanol). It was found to be identical in all respects with yohimbol prepared from epiyohimbol by the route given below.

Yohimbol from Epiyohimbol.—Epiyohimbol (1.9 g.), mesyl chloride (1.1 mole equivalents), and pyridine (10 ml.) were allowed to stand overnight at 0°. The crystals were removed by filtration, taken up in water, made basic with sodium hydroxide, extracted with methylene chloride, which was dried and evaporated, and the mesylate was crystallized from methanol–methylene chloride (m.p. 180°, yield 1.3 g.).

The mesylate (430 mg.) was heated overnight on a steam bath with acetic acid (10 ml.) and sodium acetate (450 mg.). Upon diluting with water, making basic (sodium hydroxide), extracting with methylene chloride, and evaporating, the residue was chromatographed on alumina yielding a yohimbene (290 mg.) from the methylene chloride eluate, m.p. 215–216°, from methanol–water; $[\alpha]_D$ −180° (ethanol).

Anal. Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97. Found: C, 81.94; H, 8.03. From the 2% methanol–methylene chloride eluate yohimbol O-acetate (43 mg.) crystallized from methanol–water, m.p. 251°. It was sublimed for analysis.

Anal. Calcd. for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74. Found: C, 74.7; H, 7.9.

Alkaline hydrolysis of the acetate furnished yohimbol,[24] m.p. 251–253°, $[\alpha]_D$ −38° (methanol).

Yohimbol Methochloride from Yohimbol.—The above prepared yohimbol was quaternized with methyl chloride in a sealed tube at 100°, yielding yohimbol methochloride, m.p. 263° dec., $[\alpha]_D$ +53° (methanol).[25]

Dihydrocorynantheol Methochloride.—A sample from chromatogram F was recrystallized from ethanol for analysis, m.p. 296–297°, $[\alpha]_D$ +101°, and was identical in all respects with an authentic sample.[26]

Anal. Calcd. for $C_{20}H_{29}N_2OCl$: C, 68.85; H, 8.36; N, 8.01. Found: C, 68.51; H, 8.40; N, 7.78.

Hunteramine.—This water-soluble base was recrystallized twice from ethanol, m.p. 206–208°, pK_a' 4.6; λ_{max} ($\epsilon^{1\%}_{1cm}$) 221 (800), 271 (150), 278 (150); λ_{sh} 282 (140), 289 (120); λ_{min} 253 (120), 276 (150), 287 (103); ν_{max} 3350–3170, 1160, 1075, 745 cm.$^{-1}$.

Anal. Found: C, 58.60; H, 6.73; N, 5.31.

Akuammicine Methochloride. (a).—A sample from chromatogram B was recrystallized from methanol and then from *t*-butyl alcohol for analysis, m.p. 271–272°, $[\alpha]_D$ −567° (3:1 methanol–water).

Anal. Calcd. for $C_{21}H_{25}N_2O_2Cl$: C, 67.62; H, 6.76; N, 7.51; Cl, 9.51. Found: C, 67.56; H, 6.76; N, 7.77; Cl, 10.79.

(b).—Akuammicine[27] (20 mg.) was heated with excess methyl chloride in methanol in a sealed tube for 4.5 hr. at 100°. The product crystallized from ethanol–water, m.p. 265–276° dec., was identical to the compound isolated previously.

Hunterburnine α-Methochloride.—For analysis it was recrystallized four times from water, m.p. 335°, λ^{EtOH}_{max} 273 (8700), 300 (4300); λ_{sh} 311 (3700); λ_{min} 244 (6500), 294 (3700).

Anal. Calcd. for $C_{20}H_{27}N_2O_2Cl$: C, 66.17; H, 7.50; N, 7.72. Found: C, 66.10; H, 7.53; N, 7.76; NCH_3, 3.83.

A sample of hunterburnine α-methochloride was converted into the iodide with Amberlite CG 45 (I) in aqueous methanol. The product, crystallized from water, melted at 294–295°.

Hunterburnine β-Methochloride.—The salt was crystallized from acetone–water, m.p. 307–308°, $[\alpha]_D$ +105° (27.5% water–methanol).

Anal. Calcd. for $C_{20}H_{27}N_2O_2Cl$: C, 66.17; H, 7.50; N, 7.72. Found: C, 66.31; H, 7.58; N, 7.61.

Hunterburnine β-Methiodide.—A sample of the methochloride was filtered through a column of Amberlite CG 45 (I) in methanol, and the product from the eluate was crystallized from ethanol–ethyl acetate, m.p. 277–280°.

Anal. Calcd. for $C_{20}H_{27}N_2O_2I$: C, 52.86; H, 5.99. Found: C, 52.87; H, 6.04.

Huntrabrine Methochloride.—This alkaloid was recrystallized from ethanol–water for analysis, m.p. 285–287°, $[\alpha]_D$ +54° (water), λ^{EtOH}_{max} 271 (8800), 300 (4300); λ_{sh} 310 (3800); ν_{max} 3120, 1220, 1135, 1031, 923, 913, 839, 814 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{27}N_2O_2Cl$: C, 66.31; H, 7.58; N, 7.61. Found: C, 65.88; H, 7.77; N, 7.81; CCH_3, 4.24.

The alkaloid took up one mole equivalent upon hydrogenation in water using Adam's catalyst and gave acetaldehyde (characterized as its dinitrophenylhydrazone derivative) upon ozonolysis. Methylation using either diazomethane or dimethyl sulfate gave the same amorphous O-methyl ether.

Acetylation of Huntrabrine Methochloride.—Huntrabrine methochloride (31 mg.) in acetic anhydride (0.5 ml.) and pyridine (1 ml.) was heated *in vacuo* for 4 hr. After concentration, the residue was crystallized from methanol–acetone to furnish the O,N-diacetate; melting commenced at 160° (evolution of water) and was complete at 195°; when inserted at 170° it softened slightly and melted at 200°; ν_{max} 1740 (weak shoulder at 1760), 1700 cm.$^{-1}$; λ_{max} 239–41 (17,100), 287 (5350), 299 (4150); λ_{sh} 230 (15,200), 265 (10,600), 292 (5060).

Anal. Calcd. for $C_{24}H_{31}N_2O_4Cl \cdot H_2O$: C, 61.99; H, 7.15. Found: C, 61.47; H, 7.09.

Emde Reduction of Huntrabrine Methochloride.—Huntrabrine methochloride (500 mg.) in 80% aqueous ethanol (50 ml.) was added to platinum oxide catalyst (100 mg.) prereduced in 95% ethanol (25 ml.), and stirred in a hydrogen atmosphere. The uptake of hydrogen was complete (67 ml., 2 mole equivalents) in 2 hr. After removal of the catalyst and evaporation, the residue (504 mg.) in methylene chloride was washed with dilute sodium bicarbonate and potassium hydroxide, dried, and evaporated to dryness. The crude Emde product (380 mg.) was sublimed in high vacuum at 190–220° for analysis, pK_a' 6.94.

Anal. Calcd. for $C_{20}H_{30}N_2O_2$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.35; H, 9.09; N, 8.55.

On chromatography the Emde product was eluted with 2% methanol–methylene chloride. It also gave an amorphous monoacetate ester ($\nu_{C=O}$ 1738 cm.$^{-1}$) with acetic anhydride in pyridine.

Tosylation of the Emde Product.—The Emde product (360 mg.) was treated with *p*-tosyl chloride (500 mg.) in pyridine (5 ml.) at 0° for 4 days. Upon evaporating to dryness under reduced pressure (bath temperature 30–40°), the residue (860 mg.) crystallized from acetone–ether to furnish the quaternary phenolic O-tosyl tosylate (180 mg.), m.p. 281–282°, λ_{max} 223 (60,000), 273 (8200), 282 (8100), 291 (6200); λ_{min} 247 (5600), 278 (8000), 290 (6100).

Anal. Calcd. for $C_{34}H_{42}N_2O_6S_2$: C, 63.91; H, 6.63; N, 4.38. Found: C, 64.03; H, 6.65; N, 4.08.

The ditosyl derivative upon refluxing in collidine for 1 hr. was recovered unaltered.

The quaternary salt was filtered through Amberlite CG 45 (Cl^-) in methanol to give the crystalline phenolic O-tosyl quaternary chloride, m.p. 225–226° (m.m.p. with the starting material was 225–245°).

Anal. Calcd. for $C_{27}H_{35}N_2O_3SCl$: Cl, 7.0. Found: Cl, 6.1.

Selenium Dehydrogenation of the Ditosylate.—The above ditosylate (120 mg.) and selenium (1.1 g.) were heated at 365°

(24) Yohimbol, along with epiyohimbol, has previously been prepared by the Meerwein-Pondorff-Verley reduction of yohimbone (ref. 7); A. Le Hir and R. Goutarel, *Bull. soc. chim. France*, 1023 (1953); but this was unsatisfactory in our hands, the epi compound being the major product. In agreement with E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **80**, 1613 (1958), and in contrast to Z. J. Vejdelek and R. Macek, *Chem. Listy*, **52**, 2140 (1958), we find that sodium borohydride reduction of yohimbone gives the epi alcohol as the sole product.

(25) The rotation found for the yohimbol methochloride from *H. eburnea* was −16° (27.5% water–methanol), indicating that this compound was contaminated with a trace of a highly levorotatory substance, perhaps akuammicine methochloride ($[\alpha]_D$ −567°). It is also possible that the rotations of other alkaloids which we describe may be influenced in a similar fashion.

(26) Prepared from corynanetheine furnished by Dr. M.-M. Janot, according to published procedures [M.-M. Janot and R. Goutarel, *Bull soc. chim. France*, 588 (1951)].

(27) Kindly supplied by G. F. Smith, Manchester, England.

for 8 min. in a sealed evacuated tube. The contents were dissolved in methylene chloride and chromatographed on alumina.

The methylene chloride eluate gave a fraction (15 mg.) with ultraviolet (λ_{max} 330; 2-pyridylindole), and the 1% methanol in methylene chloride eluate afforded a sempervirine-like substance (2 mg.), $\lambda_{max}^{neutral}$ 385, 340, 286; λ_{max}^{base} 354, 286.

Emde Reduction of Phenolic O-Methylhuntrabrine Chloride.—The crude methyl ether (600 mg.) was dissolved in 80% ethanol (40 ml.), added to prereduced platinum oxide (200 mg.) in alcohol (25 ml.), and stirred in a hydrogen atmosphere for 18 hr. After removal of the catalyst and evaporation, the residue (600 mg.) was shaken with dilute potassium hydroxide and methylene chloride, yielding the crude Emde base (290 mg.) to the organic phase. Chromatography on basic alumina gave from the benzene–ether (2:1) eluate the Emde base (230 mg.) which gave crystals (150 mg.) from ether–hexane, m.p. 107–108°.

Anal. Calcd. for $C_{21}H_{32}N_2O_2$: C, 73.21; H, 9.36; N, 8.13. Found: C, 73.24; H, 9.50; N, 8.06.

Partially Characterized Bases.—All the following bases described contained halide as determined by precipitation with silver nitrate, and the ultraviolet absorption spectra are recorded as λ ($\epsilon_{1\,cm}^{1\%}$).

Alkaloid-F.—It was recrystallized from *t*-butyl alcohol–water (20:1), m.p. 242–243°, λ_{max} 222 (860), 275 (230); λ_{sh} 283 (200), 292 (150); λ_{min} 246 (75); ν_{max} 3460, 3410, 1737, 1211 and 750 cm.$^{-1}$.

Anal. Found: C, 64.70; H, 6.81.

Alkaloid-H.—This yellow compound crystallized from ethanol–ethyl acetate, m.p. 300°; $\lambda_{max}^{EtOH\ or\ acid}$ 312–315 (420), 403 (630); λ_{sh} 245 (341); λ_{min} 274 (126), 345 (189); λ_{max}^{base} 227–232 (590), 323 (370), 418–423 (460); λ_{min} 283 (150), 360 (240); ν_{max} 3535, 3175, 1640, 1573, 1203, 1062, 853 and 810 cm.$^{-1}$.

Alkaloid-I.—Crystallized from ethanol, it had m.p. 278–280°, λ_{max} 219 (1200), 273 (240), 279 (250), 289 (210); λ_{min} 240 (60), 276 (240), 286 (180) with no change in base; ν_{max} 3300, 3150, 750 cm.$^{-1}$.

Alkaloid-J.—A sample crystallized from ethanol had m.p. 291–293°, λ_{max} 272 (230), 279 (230), 289 (200); λ_{min} 240 (51), 276 (220), 286 (160) with no shift in acid or base; ν_{max} 3437, 3149, 1631, 1245, 1050, 752 cm.$^{-1}$.

Alkaloid-K.—It was obtained crystalline from ethanol, m.p. 207–208°; λ_{max} 222 (840), 272 (150), 279 (150), 289 (120); λ_{min} 253 (120), 277 (140), 287 (110).

Alkaloid-N.—It was crystallized from ethanol, m.p. 263–266°, λ_{max} 266 (210), 270 (220), 277 (210), 280 (160); λ_{sh} 280 (210), 310 (20); λ_{min} 240 (56), 274 (210), 285 (140), with no shift in acid or base; ν_{max} 3330, 3140, 1308, 1226, 1110, 1076, 1060, 1048, 903, 758, 740 cm.$^{-1}$.

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Reactions of Metal Chelates. V.[1,2] Substitution of Metal Acetylacetonates with Friedel-Crafts Acylating Reagents and Sulfur Electrophiles

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The inert trisacetylacetonates of chromium(III), cobalt(III), and rhodium(III) have been acylated with acid chlorides in the presence of Lewis acids. Mono-, di-, and triacyl chelates have been characterized. Thiocyanogen, sulfur dichloride, and arenesulfenyl chlorides substitute the chelate rings without catalysis. The reactions of a chelate sulfenyl chloride have been studied.

During a general study of reactions of coordinated ligands we have sought to demonstrate quasi-aromatic chemical properties of metal acetylacetonates.[1-10] Electrophilic substitution at the central carbon of these chelate rings has been illustrated with a variety of reagents. Through such reactions iodo,[5] bromo,[5,11] chloro,[5] thiocyanato,[1,12] nitro,[4] acetyl,[4] formyl,[8] chloromethyl,[13] and aminomethyl[13] groups have been substituted directly into the relatively inert trisacetylacetonates of rhodium(III), chromium(III), and cobalt(III).

Since the Friedel and Crafts synthesis of aryl ketones is one of the best-known classical aromatic reactions it was of interest to see if this method could be applied to the acylation of stable metal chelate rings. Furthermore, in certain cases it seemed possible to prepare the anticipated products independently by chelation of triacylamethanes.

The first attempted acylations of chromium(III) acetylacetonate failed, largely because of acid-catalyzed degradation of the chelate ring. Although chromium acetylacetonate is fairly stable in the presence of aluminum chloride, treatment of this chelate with a mixture of aluminum chloride and acetyl chloride led to extensive decomposition. Less powerful acids such as stannic chloride and zinc chloride were not effective in catalyzing this reaction. A mixture of pyridine and acetic anhydride or acetyl chloride also failed to react with this chelate. However, the acetylation was successful when chromium acetylacetonate was allowed to react with acetic anhydride and boron trifluoride etherate in methylene chloride. Under these conditions a complex mixture of acetylated chelates was formed. Careful recrystallization afforded a sample which seemed to be pure triacetylated chelate A.[4]

(1) Previous paper, J. P. Collman, R. P. Blair, R. L. Marshall, and L. Slade, *Inorg. Chem.*, in press.

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