Quaternary Bases from *Hunteria eburnea* Pichon

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A re-examination of the quaternary alkaloids of *Hunteria eburnea* has shown the presence of antirhine β-methochloride **6**, dihydroantirhine β-methochloride **7** (originally called H. alkaloid J), and pleiocarpamine methochloride **5** (H. alkaloid F). A novel structure (**1**) has been forwarded for hunteracine chloride (bromide).

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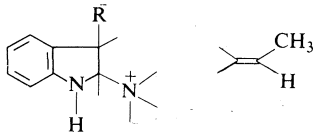
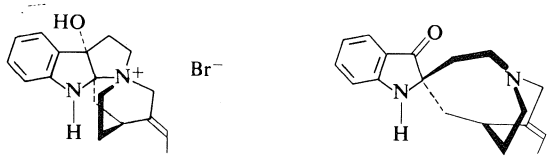
On a réexaminé les alcaloïdes quaternaires de *Hunteria eburnea*: on y retrouve le β-méthochlorure d'antirhine **6**, le β-méthochlorure de dihydroantirhine **7** (originalement appelé alcaloïde J de H.) et le méthochloride de pléiocarpamine **5** (alcaloïde F de H.). On propose une nouvelle structure (**1**) pour le chlorure (bromure) de l'huntéracine. [Traduit par le journal]

Previous workers (1) investigating the quaternary bases extracted from the bark of *Hunteria eburnea* Pichon identified (or established structures for) six alkaloids and referred to six other compounds isolated in quantities insufficient for complete characterization. One of the salts described in some detail (hunteracine) analyzed for $C_{20}H_{25}N_2OCl$ and was assumed to contain among its structural members:



with the suggestion that R might be a hydroxyl group. The promise of an original structure prompted our isolation of more of this quaternary base. Elemental analyses of both the chloride and the bromide convinced us that the original molecular formula should be changed to $C_{18}H_{23}N_2OCl$ and the 283 *m/e* molecular ion in the mass spectrum supported our findings. The u.v. absorption and n.m.r. spectrum of the base chloride confirmed the partial structure and the changes in the n.m.r. on hydrogenation (to saturate the ethylidene moiety) were as expected. Hunteracine chloride (or bromide) proved remarkably stable; for instance, it could be purified by sublimation under reduced pressure and survived a variety of conditions normally used to degrade alkaloid salts. Several reactions attempted in basic medium produced a tertiary base in varying amounts and this proved to be a pseudoindoxyl, obtained in very limited quantities by earlier workers (1). The best yields were obtained by refluxing the salt for short periods with potassium hydroxide in ethanol and elemental analysis (with mass spectral confirmation) established the molecular formula $C_{18}H_{22}N_2O$. The fragmentation of hunteracine cation and hunteracine pseudoindoxyl in the mass spectrum afforded major peaks at 122 and 108 *m/e*; numerous examples have shown these to be indicative of the presence of an ethylidene piperidine moiety (n.m.r. confirms the ethylidene side chain).

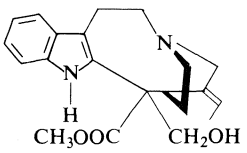


1 **2**

To eliminate the ambiguity that chemical degradation would probably engender it was decided to determine the structure by X-ray diffraction. In a preliminary report (2) the structure **1** was advanced for the hunteracine cation (discrepancy index 8.4%) and full details will be published shortly. From this structure the pseudoindoxyl must be **2**.

A plausible biogenetic origin for hunteracine would be via stemmadenine (**3**) necessitating degradative removal of the ester and carbinol functions and hydroxylation at the β-position of the indole. Transannular attack by the elec-

[1]Revision received February 28, 1974.



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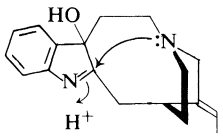
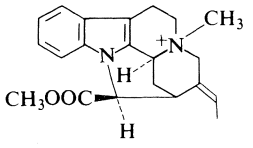


4

tron pair of the basic nitrogen on either an indolenine or indolenium double bond would afford hunteracine (as in **4**). Hunteracine chloride appears to be the first indole alkaloid wherein the C-2. of the indole moiety is incorporated in a quinuclidine system (in this case quinuclidinium).

Among the other quaternary bases incidentally isolated, we identified the alkaloid F which on demethylation afforded pleiocarpamine, identical with a sample provided by Dr. M. Hesse (Zurich). This is the first alkaloid isolated from this species as both the quaternary **5** and tertiary base (3) contrary to the suggestion (1) that yohimboid precursors afford the quaternary alkaloids of *H. eburnea* while the tertiary bases belong to the aspidosperma-eburnea type.

The properties of another quaternary chloride suggested it to be antirhine methochloride but comparison with a sample obtained from Dr. S. R. Johns (Melbourne) did not establish identity despite great simularity. This appeared to be another example of N_b diastereomers, already noted for the hunterburnines (1). In fact, demethylation of the new quaternary alkaloid with sodium thiophenoxide afforded a tertiary base showing all the properties reported for antirhine and conversion to the methochloride (via the methiodide) gave a product in all ways identical with the sample from Dr. Johns.



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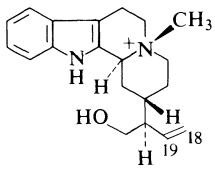

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Previous studies by Sawa and Matsumura (4) have shown that laboratory *N*-methylation of tertiary bases with the antirhine skeleton gives only one product (the α-methochloride) and since in our case the natural salt is not the same as the laboratory derivative, we feel the alkaloid is antirhine β-methochloride **6**. None of the products referred to in earlier *H. eburnea* investigations resemble antirhine β-methochloride but hydrogenation of the natural alkaloid afforded a dihydro derivative, $C_{20}H_{29}N_2OCl$ (**6**) (no 18,19 double bond) identical with the product of unknown structure called H. alkaloid J. We also isolated the latter from the plant. The *O*-acetyl derivative of natural alkaloid J proved more soluble than the alcohol and afforded a clear n.m.r. spectrum showing the *N*-methyl singlet at 3.2 δ (in CF_3COOH). After demethylation with thiophenoxide, reaction with methyl iodide, and exchanging the cation to chloride, the new methochloride showed the *N*-methyl singlet at 3.5 δ (in CF_3COOH). This agrees with earlier findings (4, 5) which show that *N*-methyl peaks in the n.m.r. spectra of *trans*-quinolizidinium salts (β-metho salts in our case) are found at higher field than the *cis*-isomers.

Experimental

The methanol extract (8 kg) of the root and stem bark of *H. eburnea* was fractionated following essentially the method given by Taylor and co-workers (1). In our hands higher concentrations of water in acetone were needed to elute the products from the cellulose columns. The various chromatograms afforded the amounts shown in Table 1.

Hunteracine Chloride (1)

Recrystallised from ethanol, m.p. 343° (dec.), $[\alpha]_D$ −90° (c 0.1, in aqueous methanol); λ_{max} (EtOH) 234 (3.95) and 289 (3.49) nm (no change in acid or base); i.r. peaks at 3440, 3150 and 1620 (C=C) cm^{-1}; n.m.r.: 1.67 (3H, d: CH_3—CH=C) and 5.20 (1H, m. C=C*H*—) δ; mass spectrum: 283 (M^+), 282 (base peak), 266, 265, 172, 159, 158, 146, 137, 130, 124, 122, 121, and 108 *m/e*.

Anal. Calcd. for $C_{18}H_{23}N_2OCl$: C, 67.8; H, 7.3; N, 8.8; O, 5.0; Cl, 11.1. Found: C, 67.8; H, 7.3; N, 8.7; O, 5.0; Cl, 11.2.

The anion was exchanged on Permatit Isopor SRA-66 bromide form resin in 50% aqueous acetone to give the *bromide*, m.p. 340° (dec.) after recrystallisation from acetone–water.

Anal. Calcd. for $C_{18}H_{23}N_2OBr$: C, 59.5; H, 6.3; N, 7.7; O, 4.4; Br, 22.0. Found: C, 59.6; H, 6.3; N, 7.9; O, 4.5; Br, 22.2.

Dihydrohunteracine Chloride

Hunteracine chloride (70 mg) was hydrogenated over Adams' catalyst in 90% ethanol. After 1 mol of hydrogen, uptake ceased and the product showed m.p. 313–315° (dec.) from ethanol. The n.m.r. spectrum now showed: 0.90 (3H, t J = 6.5 Hz) δ and lacked peaks in the vinyl region.

Anal. Calcd. for $C_{18}H_{25}N_2OCl$: C, 67.5; H, 7.8; N, 8.7; O, 5.0; Cl, 11.1. Found: C, 67.5; H, 7.9; N, 8.7; O, 5.0; Cl, 11.1.

Hunteracine Pseudoindoxyl (2)

Hunteracine chloride (220 mg) was refluxed with potassium hydroxide (250 mg) in ethanol (50 ml) for 30 min. After filtration and elimination of most of the ethanol the basic tertiary base (155 mg), as fine very pale

TABLE 1. Summary of chromatographic data

Alkaloid	Yield (mg) from chromatogram* A	B	C	D	Total	Remarks
Hunteracine chloride (1)	400	560	520	250	1730	
Yohimbol methochloride	700	—	900	400	2000	
Hunterburnine α-methochloride	100	—	30	40	170	
Huntrabrine methochloride	15	—	—	—	15	
Hunterburnine α-methochloride	20	—	—	50	70	
Pleiocarpamine methochloride (5)	—	960	—	—	960	≡ Alkaloid F
Akuammicine methochloride	—	20	—	—	20	
Antirhine α-methochloride (**6**)	—	500	900	200	1600	Not previously reported
Dihydroantirhine β-methochloride	—	—	630	350	980	≡ Alkaloid J

*Briefly, the origins of the samples are the following: A, crude chlorides; B, chlorides extracted with CH_2Cl_2; C, chlorides *not* extracted with CH_2Cl_2 or adsorbed on charcoal; D, chlorides not extracted with CH_2Cl_2, desorbed from charcoal.

yellow needles, was isolated by extraction, m.p. 235° (dec.), from ethanol, $[\alpha]_D$ −355° (c 0.1, in ethanol); λ_{max} (EtOH) 229 (4.35) and 380 (3.48) nm; i.r. spectrum: 3400, 3200, 1692, 1625 cm^{-1}; mass spectrum: 282 (M^+), 281, 238, 237, 236, 210, 201, 196, 185, 183 (base peak), 158, 130, 122, and 108 *m/e*.

Anal. Calcd. for $C_{18}H_{22}N_2O.C_2H_5OH$: C, 73.1; H, 8.6; N, 8.5; O, 9.7. Found: C, 73.5; H, 8.3; N, 8.8; O, 9.4.

Antirhine β-Methochloride (6)

From ethanol, m.p. 306° (dec.), $[\alpha]_D$ +75° (c, 0.04, in ethanol); λ_{max} (EtOH) 222 (4.84), 272 (3.85) and 289 (3.80) nm; n.m.r. spectrum (D_2O): 7.1–7.7 (4H, m aromatic protons), 5.54 (3H, m vinyl protons); mass spectrum: 311 (M^+), 310, 296, 295, 265, 239, 225 (base peak), 223, 197, 184, 169, 156, and 143 *m/e*.

Anal. Calcd. for $C_{20}H_{27}N_2OCl$: C, 69.2; H, 7.8; N, 8.1; O, 4.6; Cl, 10.2. Found: C, 69.0; H, 7.9; N, 8.1; O, 4.4; Cl, 10.2.

O-Acetylantirhine β-Methochloride

This product, m.p. 306° (dec.) was prepared from antirhine β-methochloride (130 mg) using acetic anhydride (1 ml) and pyridine (2 ml) in a sealed tube at 85° for 40 h; i.r. spectrum: 3130, 1740, 1245 cm^{-1}; n.m.r. spectrum showed the CH_3CO— resonance at 1.87 δ and a singlet at 3.305 (N—CH_3); mass spectrum gave 352 *m/e* as M^+.

Anal. Calcd. for $C_{22}H_{29}N_2OCl$: C, 67.9; H, 7.2; O, 8.2; Cl, 9.1. Found: C, 67.7; H, 7.7; O, 8.1; Cl, 9.2.

Dihydroantirhine β-Methochloride (H. alkaloid J)

Antirhine β-methochloride (100 mg) in ethanol (50 ml) was shaken under hydrogen (50 p.s.i.) in the presence of 10% palladium–charcoal (15 mg). The dihydro derivative crystallized from ethanol, m.p. 305° (dec.), $[\alpha]_D$ +71.4° (c 0.13, in water), and was identical with *H. alkaloid J* which was obtained from the extraction; λ_{max} (EtOH) 220 (4.59), 272 (3.88), 282 (sh. 3.87), and 289 nm; i.r. peaks at 3390 and 3150 cm^{-1}; n.m.r.: methyl triplet 1.2 δ (J = 7 Hz and *N*-methyl 3.20 δ; *m/e* 312 (M^+).

Anal. Calcd. for $C_{20}H_{29}N_2OCl$: C, 68.9; H, 8.3; N, 8.0; O, 4.6; Cl, 10.2. Found: C, 68.7; H, 8.1; N, 8.1; O, 4.5; Cl, 10.3.

Sealed tube acetylation afforded *O-acetyldihydroantirhine β-methochloride*, m.p. 303° (dec.), $[\alpha]_D$ +68° (c, 0.1 in aqueous methanol); i.r. 3130, 1722, 1245 cm^{-1}; *m/e* 355 (M^+); n.m.r. spectrum (CF_3COOH) showed *N*-methyl at 3.2, and CH_3CO at 2.32 δ.

Antirhine α-Methochloride (Des-N-methylation and N-Methylation)

Antirhine β-methochloride (221 mg) and sodium thiophenoxide (235 mg) were stirred together in ethanol (40 ml) for 20 min. The sodium chloride was removed by filtration and the solvent evaporated. The residue was dissolved in methyl ethyl ketone (100 ml) and refluxed under nitrogen for 36 h. Evaporation and extraction afforded the tertiary base, *antirhine* (135 mg) as pale yellow needles, m.p. 112–115°, $[\alpha]_D$ −2° (c, 0.1 in chloroform) (lit. (6) m.p. 112–114°, $[\alpha]_D$ −2° all other physical data were in agreement with those published).

Antirhine α-Methiodide, m.p. 288–290° (dec.) $[\alpha]_D$ −24.4 (c 0.1 in ethanol) formed rapidly and almost quantitatively from methanol containing methyl iodide (n.m.r.: three proton —$\overset{+}{N}$—CH_3 singlet at 3.42 δ). The methiodide was passed over a column of Permutit Isopor SRA-66 (chloride form) in 50% aqueous acetone and the product crystallized from methanol–water giving *antirhine α-methochloride*, m.p. 325–328° (dec.), $[\alpha]_D$ −17.9° (c 0.27 in aqueous methanol). Comparison with a sample kindly supplied by Dr. S. R. Johns (Melbourne) confirmed the identity of the product (i.r., t.l.c., u.v., and mass spectrum).

Dihydroantirhine α-Methochloride

Demethylation of dihydroantirhine α-methochloride (with thiophenoxide) and treatment with methyl iodide gave *dihydroantirhine α-methiodide*, m.p. 296–298° (dec.), which was converted to the α-methochloride on ion exchange resin. Recrystallization from ethanol–water, m.p. 310–312° (dec.), $[\alpha]_D$ −8° (c 0.13, in aqueous ethanol). The other physical characteristics of the α-isomer were very similar to the β-isomer except the more prominent Bohlmann bands in the i.r. (2840 cm^{-1}) and the N—CH_3 peak in the n.m.r. (now at 3.5 δ, taken in trifluoroacetic acid).

Pleiocarpamine Methochloride (≡ H, Alkaloid F) (5)

Recrystallized from ethanol–water, m.p. 242–243° (dec.), $[\alpha]_D$ +165° (c 0.5, in aqueous methanol); λ_{max} 223 (4.47), 274 (3.92), 283 (sh 3.87) and 292 (sh 3.75) nm; i.r. spectrum: 3460, 3410, and 1737 cm^{-1}; n.m.r. peaks at 6.9–8 (arom), 5.65 (1H *d*), 4.99 (1H *d*), 3.70 (CH_3OOC—),

3.18 ($\overset{+}{N}$—CH_3) and 1.58 (3H *d* CH_3—CH=) δ; mass spectrum: 375, 374, *373* (base peak), 337, *314*, 313, 283, *180*, *122*, *108* *m/e*. (Note incorporation of halide, see ref. 7.)

Anal. Calcd. for $C_{21}H_{25}N_2O_2Cl$. H_2O: C, 64.5; H, 7.2; N, 7.0; O, 12.3; Cl, 9.1. Found: C, 64.3; H, 7.0; N, 7.1; O, 12.5; Cl, 9.4.

The *methiodide* (prepared by ion exchange), m.p. 230° (dec.) showed mass spectrum peaks at 464, 405, 337, 180, 128, 122 *m/e*.

Demethylation (thiophenoxide method) gave the tertiary base, pleiocarpamine, m.p. 158°, $[\alpha]_D$ +134° (c 0.2, in chloroform). Compared with a sample kindly sent by Dr. M. Hesse (Zurich) the two products were identical (m.p., mixture m.p., t.l.c., i.r., and mass spectrum).

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