

New Quaternary *Corynanthé* Alkaloid from *Lerchea bracteata*

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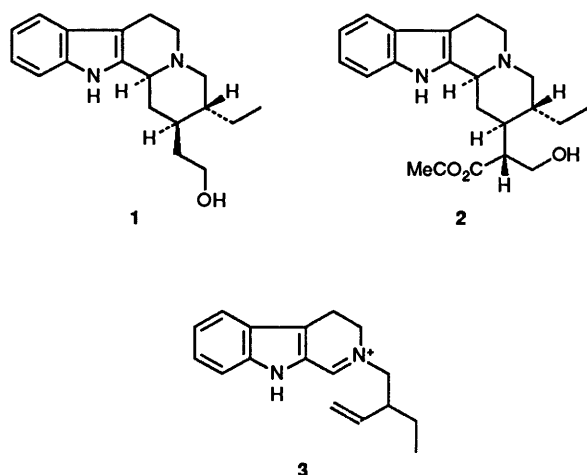
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Extraction of the leaves of *Lerchea bracteata* Val. (Rubiaceae) has yielded a quaternary *Corynanthé* alkaloid, dihydro-3-*epi*-corynantheol methochloride (lercheine) **4** the structure of which followed from analysis of its spectral data and by X-ray crystal structure determination of the corresponding bromide.

In continuation of our phytochemical survey of West Sumatra, we have examined *Lerchea bracteata* Val. (Rubiaceae) a small tree, attaining a height of ca. 2 m, the leaves of which gave a positive Mayer's test. The young leaves of this plant are used by traditional healers in Sumatra for a poultice as treatment of skin infections.

A methanolic extract of the leaves was fractionated in the usual way and the butanolic fraction furnished a crystalline quaternary alkaloid, m.p. 289–291 °C, which analysed for C₂₀H₂₉ClN₂O and for which we suggest the trivial name lercheine. The EIMS exhibited a peak at *m/z* 312 (C₂₀H₂₈N₂O, by high resolution) corresponding to the loss of HCl by thermal Hofmann elimination from C₂₀H₂₉ClN₂O.² A peak at *m/z* 298 could be attributed to the loss of methyl chloride (identified by peaks at *m/z* 50 and 52) by attack of chloride on an *N*-methyl group at the quaternary centre, yielding the molecular ion of the tertiary base.² The rest of the spectrum could be ascribed to the fragmentation of the tertiary base. The peaks at *m/z* 297 (*M* – 1), 184, 170, 169 and 156 were characteristic of a yohimbinoïd alkaloid with no substituent on the homocycle or the indolic nitrogen.³ The methyl group is therefore located on the piperidine nitrogen. A peak at *m/z* 253, present also in the mass spectra of dihydrocorynantheol **1**⁴ and dihydrositsirikine **2**⁵ can be ascribed to the ion **3**. The electronic spectrum was also in accord with the presence of a tetrahydro-β-carboline moiety.



The ¹H and ¹³C spectra of the alkaloid (see Table 1) were highly informative and their analysis was aided by proton–proton decoupling, double quantum-filtered COSY, ¹H, ¹³C

Table 1 ¹³C (75.5 MHz) and ¹H (500 MHz) NMR data for dihydro-3-*epi*-corynantheol methochloride **4** in deuteriomethanol

Carbon ^a	δ _C	δ _H [multiplicity, coupling constants (Hz)]
2	128.18	
3	65.88	4.90 (br, <i>W</i> _β 9.5)
5	64.26	3.77 (m), 3.81 (m)
6	19.32	3.02 (br d, <i>J</i> _{6β,6α} 16.0), 3.16 (m)
7	106.30	
8	127.31	
9	119.22	7.41 (dd, <i>J</i> _{9,0} 8.4, <i>J</i> _{9,11} 2.0)
10	123.79	7.08 (ddd, <i>J</i> _{10,9} 8.4, <i>J</i> _{10,11} 7.5, <i>J</i> _{10,12} 1.2)
11	120.87	6.98 (ddd, <i>J</i> _{11,12} 8.1, <i>J</i> _{11,10} 7.5, <i>J</i> _{11,9} 2.0)
12	112.67	7.30 (dd, <i>J</i> _{12,11} 8.1, <i>J</i> _{12,10} 1.2)
13	138.77	
14	29.39	2.23 (ddd, <i>J</i> _{14α,14β} 16.0, <i>J</i> _{14α,15α} 12.5, <i>J</i> _{4α,3α} 5.5) 2.56 (br d, <i>J</i> _{14β,14α} 16.0)
15	32.12	1.17 (dddd, <i>J</i> _{15α,14α} = <i>J</i> _{15α,20α} = <i>J</i> _{15α,16} = 12.5, <i>J</i> _{15α,16} 4.0)
16	35.07	1.81 (m), 1.35 (m)
17	58.51	3.57 (m), 3.64 (m)
18	10.60	0.74 (t, <i>J</i> _{18,19} 7.5)
19	23.70	0.97 (ddd, <i>J</i> _{19,19'} = <i>J</i> _{19,18} = <i>J</i> _{19,20β} = 7.5), 1.58 (ddd, <i>J</i> _{19',19} = <i>J</i> _{19',18} = 7.5, <i>J</i> _{19',20β} 3.5)
20	37.43	1.80 (dddd, <i>J</i> _{20β,15α} = <i>J</i> _{20β,21α} = 12.5, <i>J</i> _{20β,19} 7.5, <i>J</i> _{20β,19'} = <i>J</i> _{20β,21β} = 3.5)
21	60.04	3.26 (dd, <i>J</i> _{21β,21α} 13.0, <i>J</i> _{21β,20β} 3.5), 3.18 (m)
NMe	50.82	3.34

^a This biogenetic numbering system is that of ref. 25.

heteronuclear correlation, and the DEPT techniques. The presence of an ethyl group attached to a methine carbon was confirmed by signals at δ_H 0.74 (3 H, t) and 0.97 and 1.58 (both: 1 H, dd) in its ¹H spectrum with corresponding signals at δ_C 10.60 and 23.70. The presence of a hydroxyethyl group attached to a methine carbon could also be discerned since there were signals at δ_H 3.57 and 3.64 (CH₂OH), and 1.35 and 1.81 (CH₂CH₂OH) in the ¹H spectrum, with corresponding signals at δ_C 58.71 and 35.07 in the ¹³C spectrum. The ¹³C spectrum was generally similar to that of the *Corynanthé* alkaloid dihydrocorynantheol **1**⁶ except that there was an *N*-methyl signal at δ_C 50.82 and there were significant differences in the chemical shifts for C-3, C-5, C-6 and C-14. The chemical shifts for C-3 (δ_C 65.88) and the *N*-methyl group (δ_C 50.82) were very similar to those reported for *cis-N*-methylquinolizidinium chloride, δ_C 67.65 and 51.02, and different from those for the *trans*-isomer, δ_C 71.24 and 38.63.⁷ The proton chemical shift of the *N*-methyl group was also in accord with a *cis*-C/D ring junction.^{8–10}

The stereochemistry at C-3 in alkaloids containing the

Table 2 Ring torsion angles for the non-aromatic fragment^a

Ring C		Ring D	
Atoms	Angle (°)	Atoms	Angle (°)
7-2-3-4	-14.4 (13)	14-3-4-21	47.6 (9)
2-3-4-5	43.0 (9)	3-4-21-20	-52.3 (10)
3-4-5-6	-62.9 (9)	4-21-20-15	57.3 (10)
4-5-6-7	47.4 (10)	21-20-15-14	-57.7 (10)
5-6-7-2	-17.4 (12)	20-15-14-3	56.5 (10)
6-7-2-3	1.7 (16)	15-14-3-4	-50.6 (10)

^a Atoms are denoted by number only, *N*-italicized.

Table 3 Non-hydrogen positional parameters

Atom	x	y	z
Br	0.516 85(6)	0.434 70(8)	1.202 0(2)
N(1)	0.413 7(4)	0.766 6(5)	1.063(1)
C(2)	0.432 1(5)	0.703 8(7)	0.918 (1)
C(3)	0.482 4(5)	0.724 2(5)	0.755(1)
N(4)	0.497 3(4)	0.637 4(5)	0.642(1)
C(4)	0.525 1(6)	0.660 8(7)	0.437(1)
C(5)	0.431 8(5)	0.584 4(7)	0.606(1)
C(6)	0.396 9(4)	0.554 5(6)	0.802(2)
C(7)	0.391 6(5)	0.629 4(6)	0.946(2)
C(8)	0.349 0(5)	0.644 0(6)	1.118(1)
C(9)	0.300 8(5)	0.592 6(6)	1.220(2)
C(10)	0.268 1(5)	0.629 0(7)	1.383(2)
C(11)	0.282 9(5)	0.713 4(8)	1.448(2)
C(12)	0.331 0(5)	0.766 6(6)	1.350(2)
C(13)	0.363 5(5)	0.731 4(6)	1.186(2)
C(14)	0.549 6(5)	0.769 8(6)	0.822(2)
C(15)	0.599 4(5)	0.707 8(7)	0.936(1)
C(16)	0.665 3(5)	0.758 7(8)	0.997(2)
C(17)	0.656 5(6)	0.843 7(8)	1.118(2)
O(17)	0.627 1(4)	0.827 3(5)	1.306(1)
C(18)	0.683 2(7)	0.481 1(9)	0.780(2)
C(19)	0.666 3(5)	0.561 8(8)	0.907(2)
C(20)	0.616 6(5)	0.627 2(6)	0.805(2)
C(21)	0.548 6(4)	0.579 3(6)	0.749(1)

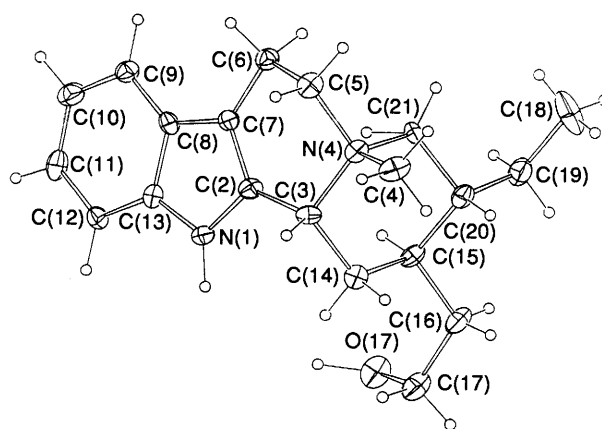
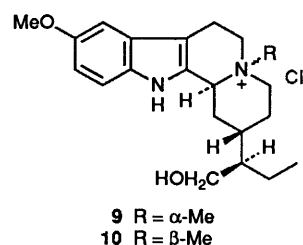


Fig. 1 Projection of the cation of **4** in its methobromide. 20% Thermal ellipsoids are shown for the non-hydrogen atoms; hydrogen atoms have arbitrary radii of 0.1 Å.

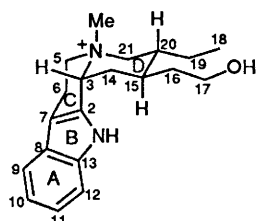
with the hydrogen atoms being diaxial so that the pseudo stereochemistry is indicated. These deductions concerning the absolute configuration of the alkaloid were confirmed by the determination of the X-ray crystal structure of the corresponding bromide (Tables 2 and 3, Fig. 1) so that absolute structure **4** follows.

Quaternization of the piperidine nitrogen in *Corynanthe* yohimbinoïd alkaloids by methylation produces a new stereogenic centre. Those alkaloids with a *trans* C/D ring junction can give a mixture of both α - and β -*N*-methyl salts but it appears that those compounds with a *cis* C/D junction only give one diastereoisomer.^{9,10,12,14} In no case has the absolute configuration at nitrogen been defined by the X-ray method. The *Hunteria* alkaloids, with the unusual 15 β -H configuration, α - and β -hunterburnine methochlorides (**9** and **10**, respectively)¹⁵

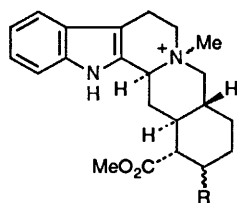


9 R = α -Me
10 R = β -Me

corynane and yohimbane skeleta can be defined by the sign of the Cotton effect between 270 and 300 nm in their ORD and CD spectra.¹¹ The new alkaloid exhibited a negative Cotton effect at 270 nm in its CD spectrum so that the 3 β -H configuration is deduced if the usual rules can be extended to quaternary alkaloids. This appears to be the case since the yohimbine methiodides **5–8** which all possess the 3 α -H con-



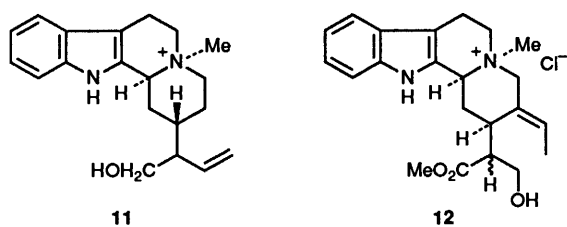
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5 4 α -Me; R = α -OH
6 4 β -Me; R = α -OH
7 4 α -Me; R = β -OH
8 4 β -Me; R = β -OH

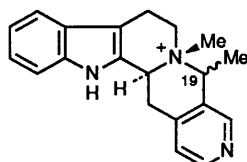
figuration exhibit a positive Cotton effect near 270 nm.¹² If the alkaloid is of the usual *Corynanthe* type then the configuration at C-15 is *S* (α -H) and must, therefore, belong to the pseudo (3 β -H, 20 β -H) or *epi-allo*-(3 β -H, 20 α -H) series.¹³ It follows that for a 3 β -H and a *cis*-C/D ring junction that the *N*-methyl group must adopt a β -configuration and if ring D is in a chair conformation the magnitude of $J_{1,5,20}$ (see Table 1) is consistent

have been obtained by partial synthesis from quinine and the chemical shifts of the *N*-methyl signals in their ¹H NMR spectra have been used to define their stereochemistry at nitrogen,⁹ and their relative stereochemistry has been established by X-ray crystal structure determination.¹⁶ 4-Methylantirrhine,^{17,18} diploceline,¹⁹ malindine,^{18,20} and isomalindine¹⁸ have been assigned structures **11–14** respectively, on spectroscopic grounds. Melinonine **B**, isolated from *Strychnos melinoniana*, has been assigned structure **15** with the configuration at C-20 undefined.²¹ Its hydrogenation product **16** was different from dihydrocorynantheol methochloride **17** (which occurs in *Hunteria eburnia*)¹⁵ and corynantheidol methochloride **18**, both prepared from the tertiary alkaloids by methylation with methyl iodide, followed by ion exchange. The 3 β -H configuration for melinonine **B** was therefore assumed. Since only one product, of undefined configuration at nitrogen was isolated from each of the quaternization reactions this assumption is not valid. The configuration of dihydrocorynantheol methochloride **17** is thus not known but that of the 10-hydroxy compound, ochrosandwine **19**, isolated from *Ochrosia sandwicensis*,²² has been defined by similar methods to those



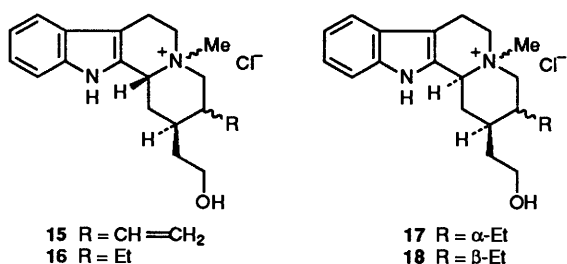
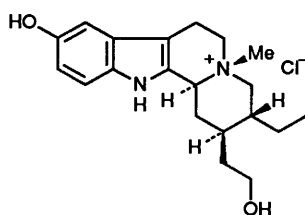
11

12



13 19β-Me

14 19α-Me

15 R = CH=CH₂
16 R = Et17 R = α-Et
18 R = β-Et

19

used for the hunterburnines.¹⁰ The stereochemistry of melinonine B is therefore worthy of reinvestigation.

Preliminary results indicate that lerceine 4 inhibits the growth of *Streptococcus aureus* using the paper disc technique.

Experimental

General details have been given previously.²³

Extraction of *Lerchea bracteata*.—The botanical material was collected in Anai Reserved Forest, West Sumatra in July 1991. Herbarium specimens (DA900) are deposited in the Herbarium Bogoriense (BO) and the Herbarium Biology, Universitas Andalas (AND). Finely chopped fresh leaves (2.5 kg) were extracted for five days with methanol (3 × 5 dm³). The combined extracts were evaporated under diminished pressure to a small volume (500 cm³) and next diluted with sulfuric acid (5%; 250 cm³) and set aside overnight. Next day the aqueous layer was decanted, extracted with light petroleum (4 × 250 cm³), basified with ammonia and then extracted with chloroform (6 × 250 cm³). The combined chloroform extracts were washed with saturated brine, dried (Na₂SO₄) and evaporated to yield a brown gum (0.9 g). The aqueous layer was neutralised by the addition of dilute sulfuric acid and then extracted with

butanol (6 × 250 cm³). Work-up of the butanolic extract gave a brown gum (5.25 g) which was crystallized from methanol thereby affording plates (250 mg). The mother liquors were evaporated and combined with the chloroform fraction and next chromatographed over silica gel with increasing amounts of methanol in chloroform as eluent. Those fractions which gave a positive Dragendorff test and exhibited the same *R_F* on TLC were combined and crystallized from methanol thereby yielding plates (550 mg).

Dihydro-3-epi-corynantheol methochloride (Lerceine) 4 had m.p. 289–291 °C (Found: C, 68.65; H, 8.7; Cl, 10.1; N, 7.8. C₂₀H₂₉N₂ClO requires C, 68.8; H, 8.35; Cl, 10.15; N, 8.0%); [α]_D²³ +100 (c 0.2, MeOH); CD λ_{max} 270 nm (Δε, −4.8); *m/z* 312 (13%), 299 (11), 298 (75), 297 (100), 267 (22), 253 (11), 251 (12), 225 (22), 184 (13), 182 (10), 171 (11), 170 (53), 169 (43), 168 (26), 167 (10), 156 (20), 154 (11), 144 (10), 143 (15) and 142 (13); λ_{max}/nm 218, 270, 282 and 290 (ε 32 000, 7200, 7100 and 6000).

The sample of the bromide for X-ray analysis was obtained by allowing a solution of lerceine 4 (20 mg) in methanol containing concentrated hydrobromic acid (1 drop) to evaporate slowly. It was then crystallized twice from methanol.

Structure Determination of 4 (as Methobromide).—A diffractometer data set (*hk* ± *l*) was recorded at ~295 K (2θ/θ scan, monochromatic Mo-Kα radiation [λ = 0.7107(3) Å] to 2θ_{max} = 50°; out of 1955 (*hk*l) and 1954 (*hkl*) reflections, 1279 and 1249 reflections with *I* > 3σ(*I*) were considered 'observed' and used in independent full matrix least squares refinements after gaussian absorption correction (data for *hk*l is recorded in the archive). Anisotropic thermal parameters were refined for the non-hydrogen atoms; (*x*, *y*, *z*, *U*_{iso})_H were included constrained at estimated values. At convergence, residuals on |*F*| for the chirality given were *R* = 0.053, *R_w* = 0.052, and 0.069, 0.069 for the opposite chirality, similar differentials being observed for the *hkl* set; for the total data a refinement of 'Flack *x*' yielded *x* = 0.006 (25). Neutral atom complex scattering factors were employed, computation using the XTAL 3.2 program system²⁴ implemented by S. R. Hall. Material deposited comprises thermal and hydrogen atom parameters, cation geometry and structure factor amplitudes.*

Crystal data. C₂₀H₂₉N₂O⁺Br[−], *M* = 393.4. Orthorhombic, space group *P*2₁2₁2₁ (*D*₂⁴, No. 19), *a* = 19.210(4), *b* = 15.038(3), *c* = 6.656(1) Å, *U* = 1922.6(6) Å³. *D_c* (*Z* = 4) = 1.36 g cm^{−3}; *F*(000) = 824. μ_{Mo} = 22.8 cm^{−1}; specimen: 0.07 × 0.18 × 0.45 mm; *A**_{min,max} = 1.11, 1.47.

Acknowledgements

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* For details of the Cambridge Crystallographic Data deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1992, issue 1.

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