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STRUCTURE AND ABSOLUTE STEREOCHEMISTRY OF 19-EPI-(+)-ECHITOVENILINE

A NEW INDOLE ALKALOID OF THE LEAVES OF *ALSTONIA VENENATA* R.BR.

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Abstract—19-Epi-(+)-echitoveniline, a new indole alkaloid of the leaves of *Alstonia venenata* R.Br., has been shown to possess the structure and absolute stereochemistry represented by **5b** on the basis of spectral and chemical evidence. A mechanistic rationale for the dependence of the mode of LAH reduction of the δ-lactone **11** on its configuration at C-19 has been offered. The influence of the C-19 configuration on the chemical shift values of the C-16 carbomethoxy protons in the 19-aroyloxy-(+)-and (−)-vincadifformine alkaloids has been discussed.

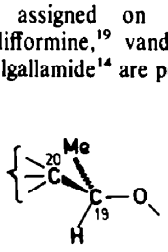
In continuation of our work[1–15] on the alkaloidal constituents of the different parts of *Alstonia venenata* R.Br., further investigation on the leaves of this plant has now resulted in the isolation of yet another new base, designated as 19-epi-(+)-echitoveniline. Spectral and chemical evidence leading to the elucidation of the structure and absolute stereochemistry of this alkaloid are summarised in this communication.

19-Epi-(+)-echitoveniline, $C_{31}H_{36}N_2O_7$($M^{\cdot+}$ 548), m.p. 168–69°, was isolated from the petrol extract of the leaves of *A. venenata* in poor yield. Its high specific rotation, $[\alpha]_D$ +462° (EtOH), and the IR absorption bands at 3410, 1675 and 1605 cm^{-1} are typical of a β-anilinomethacrylate chromophore[16] (**1**). Like its congener fruit alkaloid, (−)-echitoveniline (**2a**), it showed an additional IR band at 1710 cm^{-1} indicating the presence of an aryl ester moiety. This was also supported by the UV spectrum of the alkaloid exhibiting striking resemblance to that of **2a**. The set of three maxima at 215, 295–96 and 330 nm (log ∈ 4.58, 4.11 and 4.19) characteristic of the chromophore **1** and the additional maximum at 270 nm (log ∈ 4.09) attributed to an aryl ester moiety appeared almost at the same positions as in the case of **2a**.

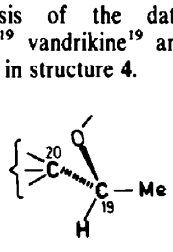
The presence of identical chromophoric systems and functionalities in both 19-epi-(+)-echitoveniline and **2a** was also revealed by the close similarity of the PMR spectra of the two alkaloids. Thus the signals of 19-epi-(+)-echitoveniline at δ 6.50–7.23 (4H, m, Ar–H), 3.81 (3H, s, CO_2CH_3) and 8.84 (1H, br.s, NH; disappearing on deuterium exchange) characteristic of the chromophore **1**, and those at δ 7.09 (2H, s, Ar–H), 3.92 (6H, s, $ArOCH_3$), 3.94 (3H, s, $ArOCH_3$), 4.69(1H, q, J 6.5 Hz) and 1.05 (3H, d, J 6.5 Hz) assigned to the system **3** appeared almost at the same value as in **2a**, except a 0.36 ppm upfield shift of the methyl ester proton of the latter. The presence of a trimethylgalloyl ester moiety in 19-epi-(+)-echitoveniline, as in **2a**, was also corroborated by the differential UV spectrum of the alkaloid against methyl trimethylgallate, which, showing complete elimination of the peak at 270 nm, is characteric of the alkaloids bearing only the chromophore **1**.

The mass spectrum of 19-epi-(+)-echitoveniline showed significant peaks at *m/e* 548 ($M^{\cdot+}$), 337 (M–211), 336 (M–212), 334, 309, 212, 195 (base peak), 124, 123 and 122, which can be rationalised[17,18] only in terms of vincadifformine-like gross structure **4** bearing a trimethylgalloyloxy function at C-19 similar to that in **2a**. This is evident from the fact that the MS of the latter showed identical peaks differing only in their relative abundance.

The ^{13}C NMR spectral data of 19-epi-(+)-echitoveniline not only confirmed the vincadifformine skeletal structure of the alkaloid and the presence in its molecule of the trimethylgalloyloxy moiety, but also pin-pointed the latter to be at its C-19 position. The carbon chemical shifts assigned on the basis of the data of vincadifformine,[19] vandrikidine,[19] vandrikine[19] and trimethylgallamide[14] are portrayed in structure **4**.

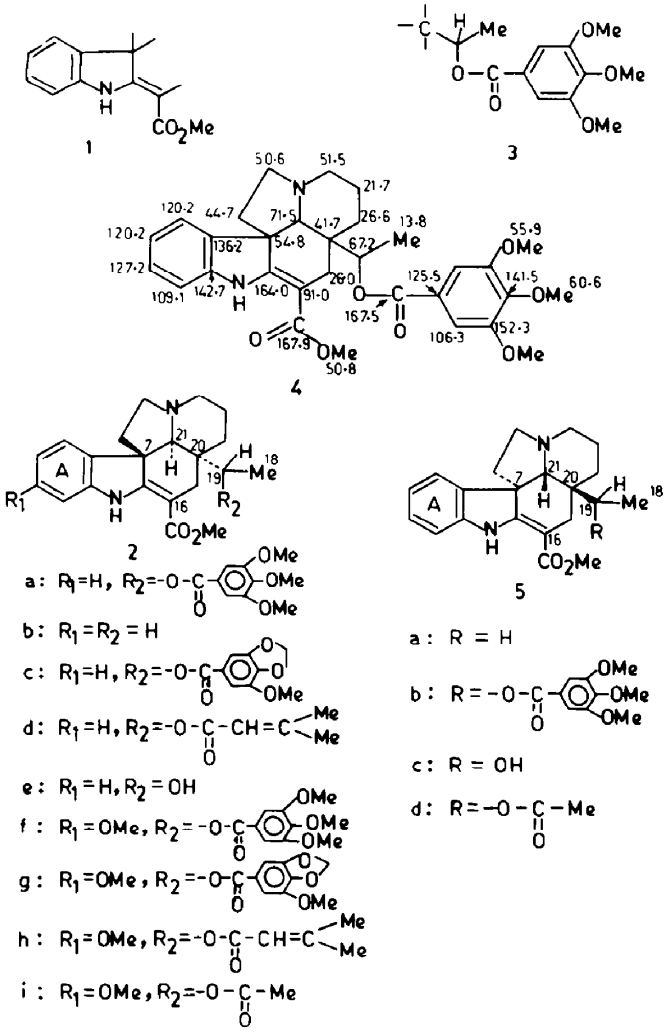


a



b

The foregoing physical and spectral data of 19-epi-(+)-echitoveniline when compared with those of its congener **2a** are only intelligible in terms of a diastereoisomeric relationship between the two alkaloids. Confirmation of this supposition was provided by the following chemical transformations characteristic[20] of the vincadifformine type of alkaloids. Thus sealed-tube acid-catalysed hydrolysis of 19-epi-(+)-echitoveniline afforded an acid identified as trimethylgallic acid (TMGA) and a base **A**, $C_{19}H_{24}N_2O$ ($M^{\cdot+}$ 296), m.p. 184°, $[\alpha]_D$ +216.7° (EtOH) showing typical indolenine UV Spectrum,[20] λ_{max} 221 and 263 nm (log ∈ 4.63 and 3.99). Its IR spectrum, ϑ_{max} 1587 (>C=N–) and 3300 (OH) cm^{-1}, coupled with its mass fragmentation pattern [significant peaks at *m/e* 251 (M–45; base peak), 194, 143, 130 and 109] exhibiting striking resemblance to that of 1,2-dehydroaspidospermidine,[21]

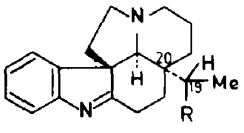


established its structure as a 19-hydroxy derivative of the same. Reduction of the indolenine **A** with $NaBH_4$ in alkaline methanolic solution gave a base **B**, $C_{19}H_{26}N_2O$ (M^{+} 298), m.p. 75°, $[\alpha]_D - 110°$ ($CHCl_3$), showing UV absorptions, λ_{max} 229, 285 and 292 nm ($\log \in$ 4.54, 3.83 and 3.80), characteristic of 2,3-disubstituted indole chromophore.[16] The IR spectrum of the compound, ϑ_{max} 3440 (OH) and 3360 (>NH) cm^{-1}, in conjunction with its PMR spectrum [δ 1.03 (3H, d, J 6.5 Hz; –CH(OH)CH_3), 4.26 (1H, br.signal; –C$\underline{H}$(OH)CH_3) and 6.8–7.45 (4H, m, Ar$\underline{H}$)] and typical quebrachamine-like[17,21] mass fragmentation established its gross structure to be 19-hydroxyquebrachamine. The formation of the latter in the above sequence of reactions is reminiscent of the derivation of (−)-quebrachamine (**9a**) from (+)-1,2-dehydroaspidospermidine[20] (**6a**) [which would be formed from (+)-vincadifformine (**5a**)], (+)-quebrachamine (**8a**) from (−)-vincadifformine[22] (**2b**) and 19R-19-hydroxy-(+)-quebrachamine (**8b**) from (−)-echitoveniline[15] (**2a**), echitoserpidine[10] (**2c**) and echitovenidine[4b] (**2d**) with the configuration at C-19 shown as in "**a**" by identical sequence of reactions. Assuming that the hydroxyl function is in no position as to completely reverse the sign of specific rotation, the above 19-hydroxy-(−)-quebrachamine obtained from 19-epi-(+)-echitoveniline should have the (−)-quebrachamine absolute stereochemistry at its C-20 position. This in turn implied the (+)-vincadifformine absolute stereochemistry at C-20, C-21 and C-7 of 19-epi-(+)-echitoveniline. It may be pointed out that although the compounds **A** and **B** exhibited striking spectral similarities with those of the indolenine[15] **7b** and quebrachamine[15] **8b**, respectively, a comparison of the respective physical constants as well as the non-superimposability of the respective pair of IR spectra not only clearly established their non-identity but also indicated that they belonged to opposite but non-antipodal stereochemical series. This view attained credibility from a comparison of the CD curves of compound **B**, $[\theta]_{295}$ −5809 and **8b**, $[\theta]_{300}$ +4398. Although the signs of the Cotton effect are opposite for the two compounds, the fact that the two curves are not mirror images of each other firmly established a diastereoisomeric relationship between the two compounds. This is possible only if compound **B** also possesses a *R* configuration at C-19. Compound **B** should therefore be represented by the 19R-19-hydroxy-(−)-quebrachamine formulation **9b** with the configuration at C-19 shown as in "**b**". This in turn also established a *R* configuration at C-19 of both compound **A** and the parent alkaloid, which should therefore be expressed as **6b** and **5b**, respectively, with figure "**b**" illustrating the C-19 configuration.

The same conclusion was also drawn from an

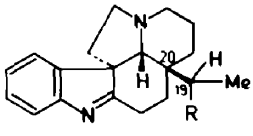
examination of the physical and spectral data of the basic constituent obtained by methanolysis of 19-epi-(+)-echitoveniline. Treatment of 19-epi-(+)-echitoveniline with NaOMe in dry methanol afforded a neutral and a basic compound. The neutral compound on alkaline hydrolysis gave TMGA, while the basic constituent (**C**), $C_{21}H_{26}N_2O_3$ $M^{\cdot+}$ 354), m.p. 148°, $[\alpha]_D + 503°$ (EtOH), exhibited spectral properties very similar to those of the isomeric alkaloid 19R-(−)-minovincinine[23] (**2e**), m.p. 135°, $[\alpha]_D$–580° (EtOH), obtained also by methanolysis of **2a**[15] and **2c**,[10] wherein the C-19 configuration in each structure is illustrated by figure "**a**". Compound **C** and its O-acetyl derivative were eventually identified as (+)-minovincinine[4b] and echitovenine,[4a] respectively, the two congener alkaloids of heretofore undefined absolute stereochemistry. Comparison of the physical constants of compound **C** with those of **2e**[23] and their non-superimposable IR spectra clearly indicated also a diastereoisomeric relationship between them. This was also evident from their CD curves, which, although displaying opposite signs of Cotton effect [**C**: $[\theta]_{350} + 16350$, **2e**: $[\theta]_{355} - 4205$], are not mirror images of each other. With the stereochemistry of the parent vincadifformine skeleton dictating the sign of the Cotton effect, opposite signs of Cotton effect definitely signified that the two compounds belong to two opposite vincadifformine stereochemical series, whereas the lack of exact mirror-image relationship between the two CD curves ruled out an antipodal relationship between the two compounds, and hence implied an identical configuration at the additional asymmetric centre C-19. An established 19R-19-hydroxy-(−)-vincadifformine absolute stereochemistry for **2e**,[23] therefore, demanded a 19R-19-hydroxy-(+)-vincadifformine formulation (**5c**) for compound **C** and hence a 19R-19-trimethylgalloyloxy-(+)-vincadifformine structure (**5b**) for 19-epi-(+)-echitoveniline itself, wherein figure "**b**" illustrates the C-19 configuration in each.

A further convincing evidence in support of the structure and absolute sterochemistry of 19-epi-(+)-echitoveniline was provided by the following chemical transformation of the alkaloid. Reduction of 19-epi-(+)-echitoveniline with zinc and 10% methanolic sulphuric acid followed by heating the resultant reaction mixture with aqueous sulphuric acid furnished, besides TMGA, a basic compound (**D**), $C_{20}H_{24}N_2O_2$ ($M^{\cdot+}$ 324), m.p. 209°, $[\alpha]_D + 35°$ (EtOH). The striking resemblance of its spectral data to those of the isomeric δ-lactone[10,15] **10** obtained from **2a**, **2c** and **2d** (Fig. "**a**" illustrating the C-19 configuration) by identical reaction is indicative of a similar δ-lactone structure for the compound **D**. Such a facile formation of a C-16–C-19 δ-lactone bridge with concomitant elimination of TMGA is yet another proof for the location of a trimethylgalloyloxy moiety at C-19 of 19-epi-(+)-echitoveniline. Here again a comparison of the spectral data and physical constants of compound **D** with those of **10** indicated a diastereoisomeric relationship between the two compounds. This view was also supported by the CD curves of the two compounds [compound **D**: $[\theta]_{229} - 32590$, $[\theta]_{255} + 44330$ and $[\theta]_{300} - 26070$; **10**: $[\theta]_{233} + 25070$, $[\theta]_{260} - 36860$ and $[\theta]_{306} + 16220$] which show unequal opposite Cotton effects. This is intelligible only in terms of the structure **11** for the



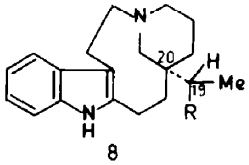
7

a : R = H
b : R = OH



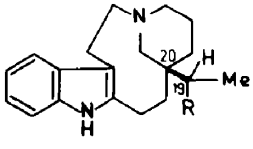
6

a : R = H
b : R = OH



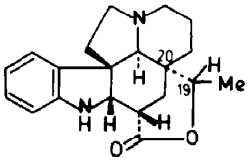
8

a : R = H
b : R = OH

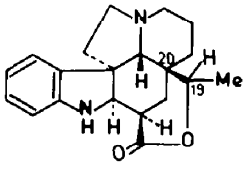


9

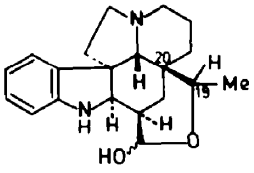
a : R = H
b : R = OH



10



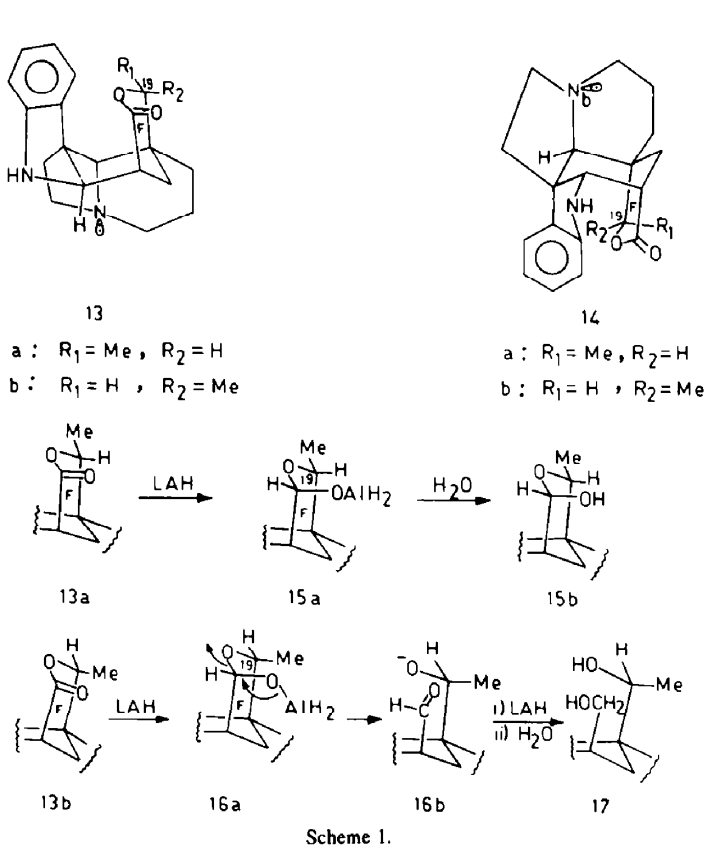
11



12

δ-lactone **D** possessing the same *R* configuration at C-19 (vide figure "**b**") as in **10** (see Fig. "**a**"). The low frequency (ϑ_{max} 1710 cm^{-1}) of the IR absorption band for the lactone carbonyl of **11** in nujol mull was the result of an intermolecular hydrogen bonding as evident from the shift of the band to the normal frequency (ϑ_{max} 1725 cm^{-1}) on running the spectrum in chloroform solution.

A 19R configuration for the δ-lactone **D** and hence for 19-epi-(+)-echitoveniline and its other transformation products also followed from a logical analysis of the result of LAH reduction of **11**. Reduction of **11** with LAH in THF gave exclusively a compound **E**, $C_{20}H_{26}N_2O_2$ ($M^{\cdot+}$ 326), m.p. 134–136°, $[\alpha]_D$ +73.6° (EtOH), showing a typical indoline UV spectrum, λ_{max} 245 and 300 nm (log ∈ 3.72 and 3.43). The IR spectrum of **E** lacks the carbonyl band of **11** and, instead, shows bands at 3480 (OH), 3380 (NH), 2800 and 2730 (Bohlmann bands) cm^{-1}. The PMR spectrum of **E** in d_6-DMSO exhibits, in addition to the signals at δ 0.94 (3H, d, J 6.5 Hz; $-\overset{|}{C}H-CH_3$) and 6.3–6.94 (4H, m, Ar-H), a two-proton broad signal at δ 5.60 with fine splitting, assignable to lactol-methine and lactol-OH protons. These data coupled with its MS showing diagnostic peaks at *m/e* 253 (M-73), 196 (base peak), 140, and 124, established the lactol structure **12** for compound **E**. It may be noted in this connection that Döpke *et al.*[23] have earlier shown that the δ-lactone derived from (−)-minovincinine yielded upon LAH reduction a diol or a lactol depending upon whether the configuration at C-19 is, respectively, *R* or *S*. The results of our previous investigation[8,10,11,15] on the LAH reduction of the δ-lactone derived from **2a**, **2c** and **2d** and that obtained from **2f**,[15] **2g**,[11] **2h**[15] and **2i**[8] (with figure "**a**" illustrating C-19 configuration in each), all belonging to the (−)-vincadifformine series, are also in consonance with this observation. There is, however, no report of similar transformation in the (+)-vincadifformine series to which 19-epi-(+)-echitoveniline belongs. One plausible rationale for the exclusive formation of the lactol **12** by LAH reduction of **11** may be a straight forward extension of our explanation[15] in the (−)-vincadifformine series. Construction of Dreiding models showed that the perferred conformation of the δ-lactone derived from the (+)-vincadifformine series should be represented by **13**. The alternative conformation in which the δ-lactone ring has a boat form is decisively more crowded than its chair counterpart as in **13**. As in the case of the 19S-δ-lactone **14b** of the (−)-vincadifformine series, a 19R-δ-lactone **13a** derived from 19-epi-(+)-echitoveniline, upon LAH reduction, would be expected to give an intermediate **15a** which is practically free from any nonbonded interaction between the $OAlH_2$ and the 19-methyl groups (Scheme 1). The reaction, therefore, stops at this stage and gives the lactol **15b** as the exclusive product. A 19S-configuration (**13b**) of the 19-epi-(+)-echitoveniline-derived δ-lactone, on the other hand, upon similar LAH reduction would initially form the intermediate **16a**, which, unlike the species **15a**, would be under severe 1:3 diaxial interaction between the $OAlH_2$ and the 19-methyl groups. Such interaction is expected to force open the ring *F* of **16a** leading to the intermediate aldehyde **16b** which would be finally reduced to the heretofore unknown diol **17** (Scheme 1). Mechanistically, the formation of the latter would be analogous to the derivation of the diastereoisomeric diol from the 19R-δ-lactone **14a** of the (−)-vincadifformine series.



Scheme 1.

The above stereochemical representation of 19-epi-(+)-echitoveniline and its transformation products, incidentally, also accounts for certain apparently inexplicable spectral data. For example, the significant upfield shift of the lactone-methine proton (C-19H) signal (δ 4.11) in the PMR spectrum of **11** may now be explained as being partly due to its axial nature and partly due to the diamagnetic anisotropic effect of the lactone >C=O. However, the most interesting and stereochemically most significant is the chemical shift value of the C-16 carbomethoxy protons of 19-epi-(+)-echitoveniline, when compared with those of the 19-aroyloxy alkaloids of the (−)-vincadifformine series. Thus, whereas the PMR spectra of **2a**, **2c**, **2f** and **2g** all display queerly a uniform upfield shift of the C-16 carbomethoxy signals appearing at δ 3.45, 3.45, 3.49 and 3.50, respectively, that for 19-epi-(+)-echitoveniline appears surprisingly at a slightly downfield position (δ 3.81). For both the stereochemical series construction of Dreiding models shows that the preferred conformation in either case would be the one in which the methyl group (C-18) of the aroyloxyethyl side chain is lying away from ring *A* to ensure least steric crowding. This is evident from the normal chemical shift of the secondary methyl protons (C-18) (δ 1.05) in each of these alkaloids, which would have been appreciably shielded by the diamagnetic anisotropic effect of ring *A* if it were indeed facing the latter. From the Dreiding models of the preferred conformations it may be seen that whereas the C-16 carbomethoxy protons in the 19R-19-aroyloxy-(−)-vincadifformines are indeed expected to suffer significant upfield shift as they fall within the shielding zone of the aromatic residue in the C-20-ethyl side chain, in the (+)-vincadifformine series only a 19S configuration assures such an effect. On the other hand, for a 19S configuration in the (−)-vincadifformine series and a 19R configuration in the (+)-vincadifformine series, the C-16 carbomethoxy protons are not only found to be away from such shielding zone but are expected to suffer, if anything, a slight downfield shift because they lie close to the deshielding zone of the 19-aroyloxy moiety. Thus the downfield shift of C-16 carbomethoxy protons of 19-epi-(+)-echitoveniline [belonging to the (+)-vincadifformine series], in sharp contrast with the upfield position of the same for the 19R-19-aroyloxy alkaloids of the (−)-vincadifformine series studied so far, is accounted for only by a 19R configuration assigned to it. This also constitutes an additional evidence in support of the above stereochemical formulation. In fact, the foregoing generalisation holds out the promise of a diagnostic PMR spectral method for determining the C-19 configuration of this type of alkaloids.

The co-occurrence of 19-epi-(+)-echitoveniline, **5c** and **5d** with **2a**, **2c**, **2d**, **2f**, **2g**, **2h** and **2i** belonging to antipodal series of vincadifformine skeleton in the same plant presents an interesting biogenetic feature.

EXPERIMENTAL

Unless otherwise stated, column chromatography was carried out over silica gel (60–100 mesh) and tlc over silica gel G. The petrol used boiled in the range 60–80°. All non-hydroxylic organic solvents were dried over anhyd Na_2SO_4. Analytical samples were dried over P_2O_5 at 55–110° (depending upon the m.p. of the compound) for 24 hr *in vacuo* and were tested for purity by tlc and mass spectrometry. UV spectra were recorded in 95% EtOH (aldehyde free). IR spectra were run in nujol mulls except for 19-epi-(+)-echitoveniline itself and the lactol **E** for which KBr discs were used. Identity of known compounds were established by mixed m.p., co-tlc and superimposable IR spectra. m* denotes metastable peak.

Isolation of 19-*epi*-(+)-*echitoveniline* (**5b**). Air-dried, finely ground leaves (1 kg) of *A. venenata* were extracted with petrol in a soxhlet apparatus for 48 hr. The extract (~4l) was concentrated to ~200 ml, churned with 5% aq citric acid (1 l) for 6 hr and filtered. The filtrate was extracted successively with C_6H_6 and $CHCl_3$. The $CHCl_3$ extract was washed with dil NH_4OH soln followed by water. It was then dried, concentrated and chromatographed using as eluents petrol and mixtures of petrol/EtOAc in order of increasing polarity. The middle fractions of petrol/EtOAc (10:1) eluates, containing mainly **5b** (tlc), on repeated chromatography furnished shiny crystals of **5b** which recrystallised from petrol/EtOAc mixture in white prisms (yield 0.003%), m.p. 168–69°, $[\alpha]_D$ +462° (EtOH), (Found: C, 67.70; H, 6.65; N, 5.12. $C_{31}H_{36}N_2O_7$ requires: C, 67.88; H, 6.57; N, 5.11%), differential UV spectrum against methyl trimethylgallate, λ_{max} 230, 299 and 330 nm (log $\in$ 3.93, 3.94 and 4.18); *m/e* (relative intensity): 548 ($M^{\cdot+}$, 26.2), 338 (23), 337 (77), 336 (23), 335 (26.2), 334 (88.5), 3.09 (13.1), 228 (21.3), 214 (11.5), 212 (19.7), 195 (100), 181 (31.2), 169 (23), 168 (55.7), 167 (29.5), 154 (23), 153 (11.5), 152 (21.3), 139 (11.5), 124 (16.4), 123 (70.5), 122 (44.3), 119 (49.2), 110 (32.8) and 100 (21.3).

Indolenine **6b** *and TMGA from* **5b**. A soln of **5b** (0.2 g) in 3N HCl (20 ml) was taken in a hard glass tube which was then evacuated and sealed. The tube was then heated in a glycerine bath at 110° ± 2° for 7 hr and then cooled. The seal was broken open and the mixture was diluted with water and extracted with ether. The ethereal extract was washed with water, dried and evaporated to give a residue which crystallised from petrol in glistening needles of TMGA (0.05 g), m.p. 168° (Found: C, 56.4; H, 5.75. $C_{10}H_{12}O_5$ requires: C, 56.60; H, 5.66%). The aq acidic layer was basified with dil NH_4OH soln and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried, concentrated and chromatographed. The petrol/EtOAc (12:1) eluate on evaporation deposited crystals of **6b** (0.065 g) which after repeated crystallisations from petrol/EtOAc mixture melted at 184°, $[\alpha]_D$ +216.7° (c 0.36; EtOH) (Found: C, 77.2; H, 8.02; N, 9.40. $C_{19}H_{24}N_2O$ requires: C, 77.02; H, 8.11; N, 9.46%); *m/e* (relative intensity): 296 ($M^{\cdot+}$, 38), 253 (10), 252 (45), 251 (100), 249 (8), 223 (20), 209 (12), 208 (20), 206 (14), 195 (30), 194 (47), 193 (20), 182 (25), 181 (25), 180 (40), 168 (30), 167 (35), 158 (22), 157 (28), 156 (40), 154 (30), 144 (20), 143 (37), 142 (15), 141 (15), 140 (20), 130 (40), 128 (35), 116 (24), 115 (60), 110 (17), 109 (87), 108 (16), 103 (12), 102 (15) and 101 (12); m* 213 and 150.

(−)-19-*Hydroxyquebrachamine* (**9b**) *from* **6b**. The indolenine **6b** (0.06 g) was refluxed with an excess of $NaBH_4$ (0.15 g) in 1N methanolic KOH (15 ml) for 3 hr. MeOH was removed under reduced pressure and the residue was diluted with water and extracted with ether, the extract washed with water, dried, concentrated and chromatographed over Brockmann alumina column (activity 1). $C_6H_6/CHCl_3$ (4:1) eluate on evaporation gave a solid (0.045 g) which was dissolved in MeOH (2 ml) and treated with a soln of picric acid in MeOH. The orange-red picrate that separated on standing was filtered off and recrystallised from MeOH to give the pure picrate, m.p. 210°. The free base was regenerated from it by treating its aq suspension with a conc NaOH aq and then extracted with ether. The ether extract was washed, dried and evaporated to give a solid which crystallised from MeOH to give pure **9b** in fine needles, m.p. 75°, $[\alpha]_D$ −110° (*c* 0.31, $CHCl_3$) (Found: C, 76.4; H, 8.75; N, 9.45. $C_{19}H_{26}N_2O$ requires: C, 76.51; H, 8.72; N, 9.4%); *m/e* (relative intensity): 298 ($M^{\cdot+}$, 90), 297 (7), 254 (16), 253 (68), 169 (12), 168 (12), 157 (18), 156 (15), 154 (14), 149 (14), 144 (17), 143 (20), 142 (35), 141 (25), 140 (25), 130 (9), 125 (10), 124 (22), 123 (10), 122 (5), 111 (24), 110 (100), 109 (20), 108 (24), 97 (28), 96 (29) and 95 (18); m* 214, 48, 44.5, 36.5.

δ-*Lactone* **11** *and TMGA from* **5b**. A soln of **5b** (0.1 g) in 10% methanolic H_2SO_4 (15 ml) was refluxed with an excess of Zn dust (0.25 g) for 8 hr. Unreacted Zn was filtered off while the soln was hot and the MeOH was removed from the filtrate under reduced

pressure. The residue was diluted with water to make 2N with respect to H_2SO_4 and then refluxed for 10 hr. The cooled resultant mixture was extracted with ether, the extract washed with water, dried and evaporated to give TMGA (0.035 g). The aq acid soln left after ether extraction was cooled in ice, neutralised with aq NH_4OH soln and extracted with ether. The extract was washed with water, dried and evaporated to give granular crystals of **11** (0.04 g). The crude material after repeated crystallisation from ether melted at 209°, $[\alpha]_D + 35°$ (*c* 0.4, EtOH) (Found: C, 74.2; H, 7.3; N, 8.75. $C_{20}H_{24}N_2O_2$ requires: C, 74.07; H, 7.41; N, 8.64%); λ_{max} 245 and 302 nm (log ∈ 3.78 and 3.48); ν_{max} 3300 (NH), 1710 (δ-lactone) cm^{-1}; δ (ppm): 1.28 (3H, d, J 6.5 Hz; -C<u>H</u>-C<u>H</u>$_3$), 4.11 (1H, q, J 6.5 Hz; -C<u>H</u>-CH$_3$), 6.58–7.26

(4H, m; Ar<u>H</u>); *m/e* (relative intensity): 324 (M^+, 34.5), 254 (5), 253 (23), 252 (3.4), 195 (15), 194 (100), 144 (7.6), 143 (3.4), 130 (3.9), 123 (5.2) and 122 (3.9); m* 197.5, 116 and 77.

(+)-Minovincinine (**5c**) *and TMGA from* **5b**. Metallic Na (0.06 g) was added in parts to anhyd MeOH (20 ml). After the metal had completely dissolved, **5b** (0.1 g) was added and the mixture refluxed for 8 hr under anhyd condition in an atmosphere of N_2. The solvent was then removed under reduced pressure, residue diluted with 30 ml of water, cooled in ice, acidified with 1:1 HCl aq and extracted with ether. The extract was evaporated and the residue was refluxed with 10 ml of 5% methanolic KOH for 2 hr. MeOH was removed under reduced pressure, residue diluted with water, acidified with HCl aq and extracted with ether. The ether extract was washed free of mineral acid, dried and evaporated to give a white residue crystallising from petrol in fine needles of TMGA (0.02 g).

The acidified aq part containing the basic component of the methanolysate was cooled in ice, basified with dil aq NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was dried, concentrated and chromatographed. The petrol/EtOAc (2:1) eluate on evaporation gave fine needles of the compound **C** (0.02 g), m.p. 148°, $[\alpha]_D + 503°$ (*c* 0.2, EtOH), identical in all respects with an authentic sample of the natural base (+)-minovincinine; O-acetyl derivative (**5d**), m.p. 170°, $[\alpha]_D + 640°$ (*c* 0.3, $CHCl_3$), identified with echitovenine.

Lactol **12** *from δ-lactone* **11**. A soln of **11** (0.03 g) in anhyd THF (2 ml) was added dropwise to a slurry of LAH (0.15 g) in THF (10 ml) at 0° under anhyd condition with continuous stirring. The mixture was allowed to slowly attain room temp and then refluxed for 5 hr. The soln was cooled, excess of LAH was destroyed with EtOAc and the mixture was then decomposed with ice-cold water and filtered. The residue on the filter paper was repeatedly washed with boiling $CHCl_3$. The filtrate and washings were combined, evaporated to dryness, dissolved in 2 ml $CHCl_3$ and chromatographed. The petrol/EtOAc (3:1) eluate on concentration furnished the lactol **12** (0.025 g) as needles which after repeated crystallisations from petrol/EtOAc mixture melted at 134–36°; $[\alpha]_D + 73.6°$ (*c* 0.57, EtOH) (Found: C, 73.5; H, 8.03; N, 8.65. $C_{20}H_{26}N_2O_2$ requires: C, 73.62; H, 7.98; N, 8.59%); *m/e* (relative intensity): 326 ($M^{+\cdot}$, 81), 253 (23), 197 (14), 196 (100), 144 (19), 140 (41), 130 (12) and 124 (56); m* 161.8, 117.9 and 47.2.

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