Phytochemistry, Vol. 26, No. 10, pp. 2839–2846, 1987.
Printed in Great Britain.

0031–9422/87 $3.00 + 0.00

ALKALOIDS OF *STRYCHNOS JOHNSONII*

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(*Revised received* 12 *March* 1987)

Key Word Index—*Strychnos johnsonii*; Loganiaceae; indole alkaloids.

Abstract—Twenty-three alkaloids have been identified in the root bark and stem bark of *Strychnos johnsonii* from Zaire. They are demethoxycarbonyl-3,14-dihydro-gambirtannine, angustine, dihydro-cycloakagerine, *O*-ethylakagerine, *O*-ethylakagerine lactone, dihydro decussine, normalindine, oxojanussine, tetrahydroalstonial, ajmalicinial, norepimalindine, norharman, harman, akagerine, akagerine lactone, janussines A and B, tetrahydro akagerine, demethoxycarbonyl-3,14,15,16,17,18-hexahydro-gambirtannine, dihydrocorynantheol, anthirine lactone, anthirine and isoanthirine.

INTRODUCTION

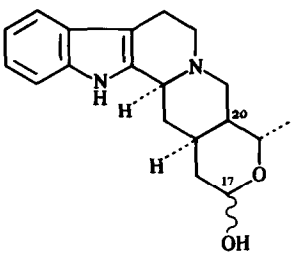
Strychnos johnsonii Hutch et M. B. Mass is a liane from Central and West Africa [1] which belongs to the little studied Brevitubae section of the genus *Strychnos* (Loganiaceae). As part of our studies on African *Strychnos* species [2], we herein report our results on the alkaloid content of the stem bark and root bark of *S. johnsonii*.

RESULTS AND DISCUSSION

All extractions were performed in the usual fashion [2]; alkaloid mixtures were obtained with the following yields: 2.5 g/kg (root bark) and 2 g/kg (stem bark). The alkaloids were separated by medium pressure liquid chromatography; analytical samples were obtained by preparative TLC of selected fractions. The complexity of some of the fractions has precluded an accurate determination of the percentages of alkaloids and the values given in brackets are approximate.

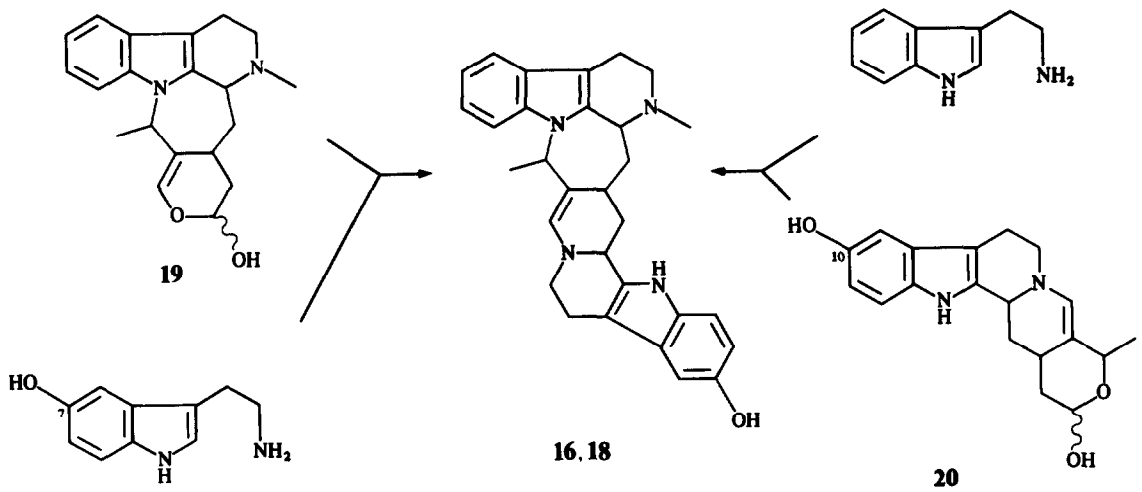
Eighteen alkaloids were isolated from the root bark. They were in order of elution from silica gel: demethoxycarbonyl-3,14-dihydro-gambirtannine (**1**, 1% of the alkaloids), angustine (**2**, 0.2%), dihydro-cycloakagerine (**3**, 4%), *O*-ethylakagerine (**4**, 3%), *O*-ethylakagerine lactone (**5**, 0.2%), dihydro-decussine (**6**, 0.1%), normalindine (**7**, 0.5%), oxojanussine (**8**, 0.2%), tetrahydroalstonial (**9**, 0.5%), ajmalicinial (**10**, 2%), norepimalindine (**11**, 0.2%), norharman (**12**, 0.2%), harman (**13**, 0.2%), akagerine (**14**, 15%), akagerine lactone (**15**, 2%), janussine A (**16**, 6%), tetrahydro-akagerine (**17**, 3%) and janussine B (**18**, 3%). Among these to the best of our knowledge, alkaloids **3**, **4**, **5**, **7**, **8**, **11**, **16**, **17** and **18** are novel; alkaloids **9**, **10**, **12** and **13** were compared to synthetic or semisynthetic material. Alkaloids **1**, **2**, **6**, **14** and **15** were identified by comparison of their spectral properties with literature data. Demethoxycarbonyl-3,14-dihydro-gambirtannine (**1**) and harman (**13**) are seldom isolated in *Strychnos* species but they have been found in *S. usambarensis* [3, 4] along with the *N*-methylated derivative of **12** [5].

The yellow base angustine (**2**) is an ubiquitous *Strychnos* alkaloid, detected so far in 30 species [6]. Akagerine (**14**), the major alkaloid of *S. johnsonii* was originally isolated in *S. usambarensis* [7] and later in several African *Strychnos* species [8, 9]. Akagerine lactone (**15**) is an alkaloid from *S. decussata* [10]; the ^{1}H NMR and mass spectra of **14** and **15** matched those reported in the literature. Ajmalicinial (**10**) and tetrahydroalstonial (**9**) have already been encountered as natural products in *S. dale* [11], but are better known as derivatives of ajmalicine or ajmalicinine [12] and of tetrahydroalstonine [13]; both occur as C-17 mixtures of isomers.



9 20*S*
10 20*R*

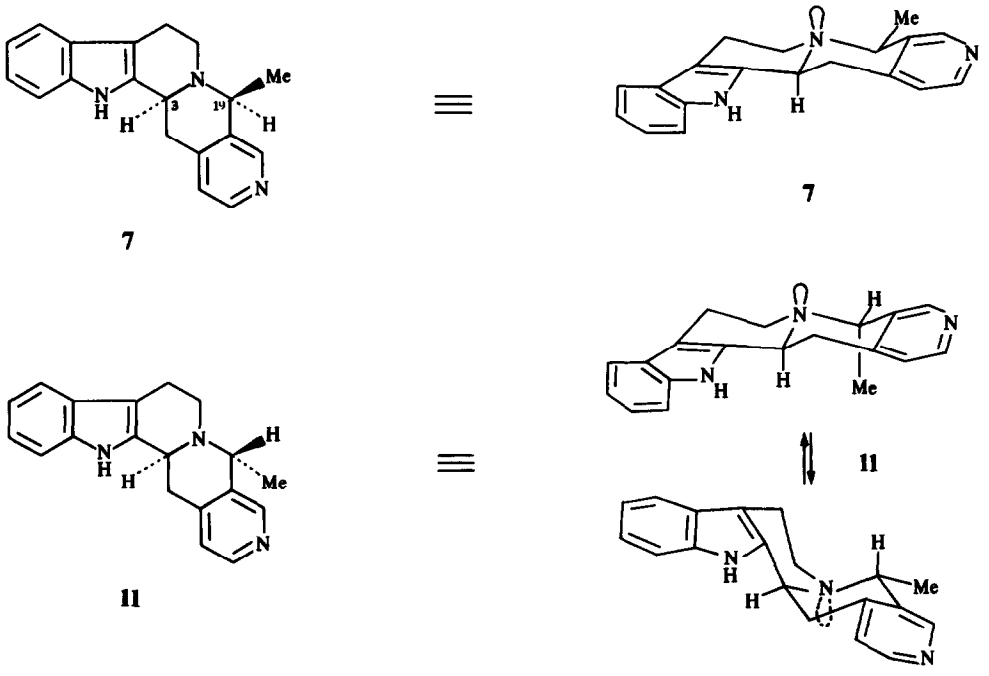
Quasi dimers janussines A and B (**16** and **18**) and their oxo-derivative oxojanussine (**8**) are three of the major alkaloids of *S. johnsonii*. These three derivatives display the unique feature of a double appearance: either decussine (**19**) [14] plus 7-hydroxytryptamine or 10-hydroxycathenamine (**20**) plus *N*(b)-methyltryptamine (Scheme I). The establishment of these structures has been the subject of a preliminary note [15]. A full description of the



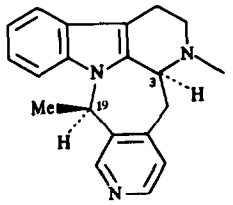
Scheme 1. Biosynthetic hypothesis for the formation of the janussines.

spectroscopic characteristics of **16** and of **18** is given in the experimental section. Despite intense investigations the stereochemistry of these quasidimers has not so far been unravelled.

Alkaloids **7** and **11** are isomers and possess similar UV and mass spectra. Their UV spectra display maxima at 228, 263, 270, 282 and 290 nm, i.e. the superimposition of indole and of alkyl substituted pyridine chromophores. The presence of an odd mass molecular ion at *m/z* 289 points to three nitrogen atoms in the structure and therefore eliminates the hypothesis of a pyridine in rings C or D of a type I alkaloid. The main fragments in the mass spectrum correspond to loss of a proton (*m/z* 288), of a methyl (*m/z* 274) and of a dihydro-*β*-carboline ring system (*m/z* 169). Examination of the ^{1}H NMR spectra of **7** and **11** led to the conclusion that these compounds were pyrido-indoles similar to malindine [16] and isomalindine [17]. Both spectra show signals for three protons of a 3,4-disubstituted pyridine, for an indole nucleus (four aromatic protons + one exchangeable NH) and for a CH-Me system. The presence of an indole-NH ruled out dihydrodecussine type structures [14] and it is therefore proposed that **7** and **11** have normalindine structures. The least polar substance is assigned a *cis*-3*RS*,19*SR* stereostructure (**7** = normalindine) while **11** is the *trans* 3*RS*,19*RS* isomer (norisomalindine); the main argument for this assignment is the observation of a series of Bohlmann bands in **7** indicating a *trans*-quinolizidine arrangement in which the methyl group is equatorial in a chair six-membered ring. In the same conformation, the methyl group of **11** would be forced into an unfavorable axial position, which can only be relieved by inversion of the nitrogen atom. This results in a *cis*-quinolizidine arrangement, as shown by the downfield shift of H-3 (*δ* 4.34).



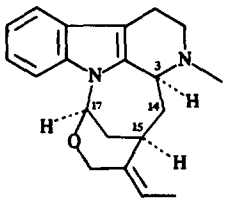
Alkaloid **6** is also a compound with an odd molecular ion and with a UV spectrum similar to that of **7** and **11**. Its molecular ion (*m/z* 303) corresponds to a $C_{20}H_{21}N_3$ formula and the main fragments at *m/z* 260 [M $-CH_2NMe]^+$ and 184 (100%) indicate a *N*(4)-methylated alkaloid. These data, as well as the NMR spectra, provide evidence for a dihydro-decussine mostuenine [19] formula. Comparison of our NMR data with those of the aforementioned compound [14, 18] and of its isomer [19] demonstrate the identity of compound **6** with dihydro-decussine from *S. decussata* and *S. dale* and with mostuenine from *Mostuea brunonis*. They have recently been proved to have the 3*SR*,19*RS* configuration [20].



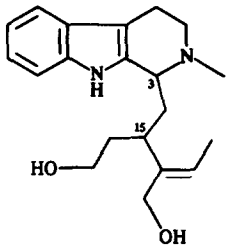
6

Alkaloid **4** is an indole derivative (UV maxima at 230, 275, 282 and 292 nm) whose NMR spectrum presents similarities with the spectrum of akagerine (**14**): N-Me (δ2.53), CH_3–CH=C–CHO unit (9.33, CHO) and a one-proton doublet at 5.78 (6.16 in **14**). The main differences between these spectra are the presence of signals for a supplementary ethyl chain (three-proton triplet at 1.07 and two one-proton double quadruplets at 3.33 and 3.10). Consequently the molecular ion of **4** is 28 higher than the corresponding ion of **14**. Comparison of the spectra of **4** with those of the recently described *O*-methyl-akagerine (**21**) [9] led to the conclusion that **4** was *O*-ethyl akagerine. Similarly, alkaloid **5** was found to be *O*-ethyl-akagerine lactone. Although this has not been checked in this study, it is possible that **4** and **5** might be isolation artefacts formed from **14**, **15**, EtOH or AcOEt. An intriguing feature of the mass spectra of **4**, **5** and **21** is their common base peak which appears at *m/z* 213. Scheme 2 gives a tentative explanation for the genesis of this ion.

Amongst the major alkaloids of the plant, a non polar compound **3**, displays the *m/z* 213 ion as the base peak of its mass spectrum. Other features of the mass spectrum are a molecular ion at *m/z* 308.1851 ($C_{20}H_{24}N_2O$) and fragments at *m/z* 265.1447 ($C_{18}H_{19}NO$, loss of CH_2NCH_3) and 185 (*N*-methyldihydro-β-carboline nucleus), which allow classification of **3** into the akagerine family of alkaloids. The ^{1}H NMR spectrum of **3** shows signals for an N-methyl group (δ2.55), an ethylidene chain (1.68, *d*, 3H; 5.33, *q*, 1H, J = 7 Hz) and for a carbinolamine type proton (6.03, *br d*, J = 4.5 Hz). A series of double resonance experiments performed at 400 MHz has allowed identification of a chain of protons similar to the one found in akagerine, except for an isolated CH_2 appearing instead of the C(21) aldehyde. These considerations led to the hypothesis of a dihydro-cycloakagerine structure for **3**. The measurement of coupling constants between H-3, H-14, H-15 and inspection of molecular models allow determination of the relative configurations of H-3 and H-15; the annulation of a seven membered ring on the pyran ring implies a *cis*-relationship between H-15 and H-17. The configuration of C-3 and C-15 of **3** is thus the same as found in akagerine; the configuration of C-17 is opposite but this fact is of no biosynthetic relevance since this centre is epimerizable. ^{13}C NMR data (Table 1) have also been obtained; they compare favorably to literature data and fit well to the proposed structure.



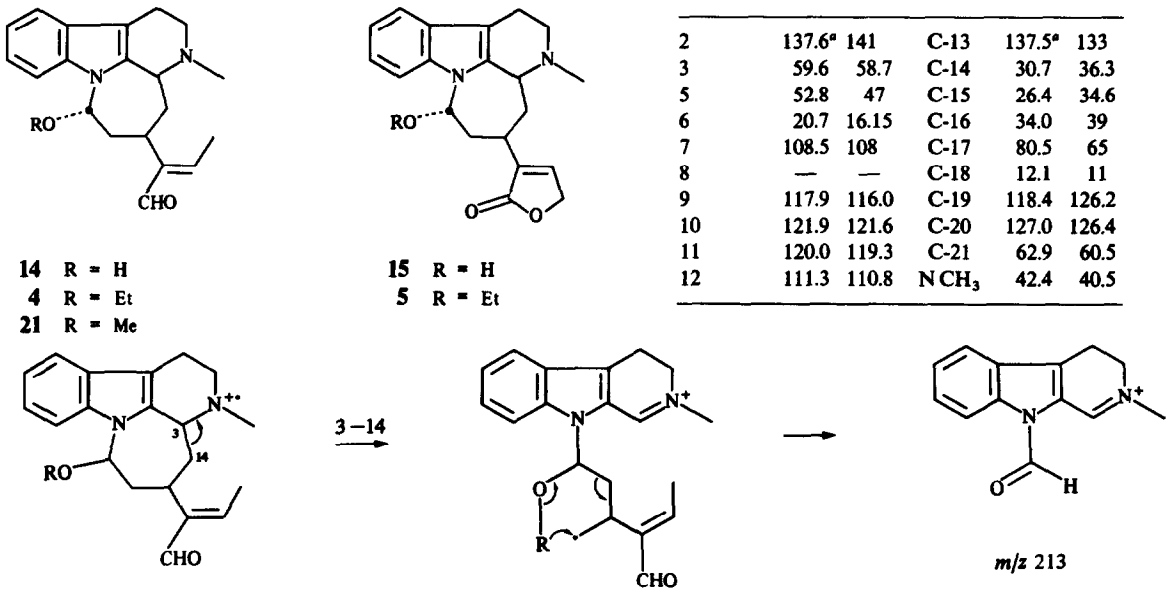
3



17

Table 1. ^{13}C NMR spectral data for compounds **3** and **17**

Carbon	3	17		3	17
2	137.6[a]	141	C-13	137.5[a]	133
3	59.6	58.7	C-14	30.7	36.3
5	52.8	47	C-15	26.4	34.6
6	20.7	16.15	C-16	34.0	39
7	108.5	108	C-17	80.5	65
8	—	—	C-18	12.1	11
9	117.9	116.0	C-19	118.4	126.2
10	121.9	121.6	C-20	127.0	126.4
11	120.0	119.3	C-21	62.9	60.5
12	111.3	110.8	NCH_3	42.4	40.5



14 R = H
4 R = Et
21 R = Me

15 R = H
5 R = Et

3–14

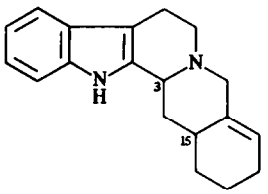
m/z 213

Scheme 2. Mass spectral fragmentation of akagerine ethers.

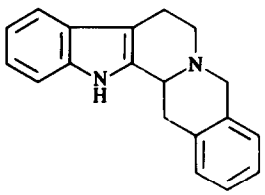
The last unknown compound **17** is also a substituted *N*(4)-methyl tetrahydro-β-carboline derivative as shown by the *m/z* 185 base peak in the mass spectrum. The molecular ion of **17** is of weak intensity and is detected at *m/z* 328.2134; it corresponds to a $C_{20}H_{28}N_2O_2$ formula. The ^{1}H NMR spectrum of **17** shows a system of protons resembling those found in akagerine and in **3**; the major difference between them is caused by an indole N–H resonance in the spectrum of **17**. The observation on the ^{13}C NMR spectrum of **17**, of two signals in the vicinity of 60 ppm suggests the presence of two oxymethylenes (Table 1). One of these is linked to an isolated ^{1}H AB system whereas the other corresponds to part of a complex ABXY system. These data as well as decoupling experiments suggested that **17** was the diol corresponding to a reduction of the 'carbonyl' functions of akagerine. In order to prove this and to provide information on the relative configurations of **17** and of **3**, we attempted to reduce akagerine **14**. However, under varied reaction conditions the carbinolamine function of **14** did not open and no product at the oxidation level of a diol could be obtained.

The stem bark alkaloid mixture from *S. johnsonii* is complex but only slightly different from the root bark alkaloids. Thirteen alkaloids were isolated which included the above mentioned **1**, **3**, **9**, **10**, **15**, **16**, **17** and **18**. Other alkaloids were demethoxycarbonyl-hexahydro-gambirtannine (**22**), dihydrocorynantheol (**23**), anthirine lactone (**24**), anthirine (**25**) and isoanthirine (**26**).

Alkaloid **22** is an indole as shown by its UV spectrum. Its mass spectrum is dominated by the molecular ion appearing at *m/z* 278 ($C_{19}H_{22}N_2$), by the $[M-1]^+$ ion of indoloquinolizidines and by the 183 and 169 ions of tetrahydro-β-carbolines. The ^{1}H NMR spectrum of **22** shows a single olefinic resonance at δ5.65 ($W_{1/2}$ = 8 Hz), four aromatic protons and a series of complex multiplets below 3.45. These data favour a dehydroyohimbane type structure: Δ^{15} or Δ^{19} yohimbanes ($\Delta^{3(14)}$ and Δ^{20} olefins would be prone to retro-Diels–Alder type fragmentation, *m/z* 250 $[M-CH_2{=}CH_2]$. It is therefore proposed that **22** has the structure of a yohimb-19-ene which is related to demethoxycarbonyl-3, 14-dihydro-gambirtannine (**1**) of the same plant but the configuration of C-3 and C-15 are not known.

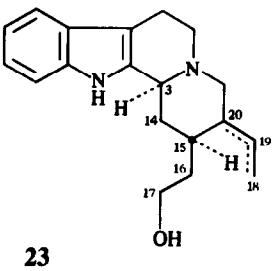


22



1

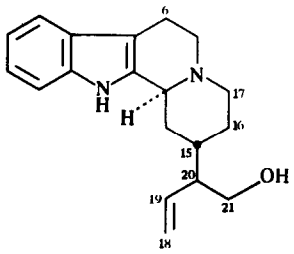
Anthirine (**25**) and dihydrocorynantheol (**23**) are both ubiquitous alkaloids, which have been identified by direct comparison with authentic samples. Despite the fact that anthirine (**25**) and corynantheol (**27**) are frequently encountered, they are not easily distinguished on the basis of their mass spectra and low field ^{1}H NMR spectra. In mass spectrometry (Scheme 3) both alkaloids lose a C_4H_8O fragment, corresponding to C-18/C-19/C-20/C-21 in the case of **25** and to C-14/C-15/C-16/C-17 in the case of **27**. The high field NMR spectra of **25** and of **27** show almost identical patterns for the aromatic and vinylic protons. The 1–4 ppm region of both spectra are highly complicated but it may be noted that the high field resonances of anthirine are broadened at room temperature. Full interpretations of the ^{1}H NMR and ^{13}C NMR spectra of anthirine are found in ref. [21]; as a comparison a completely assigned spectrum of corynantheol is given in the Experimental. Table 2 gives the ^{13}C NMR resonances of **25** and **27** which provide a good means of distinction especially when considering the high field resonances. The highly congested shape of anthirine caused by the *cis*-quinolizidine ring junction and by the intramolecular O–H . . . . N hydrogen bond induces strong shielding for several carbon resonances, the most noticeable being the shielding of C-6 (δ17.4). This is not the case for corynantheol where resonances occur at expected values for *trans*-quinolizidines [22].



23

27 Δ^{18}

28 Δ^{19}



25

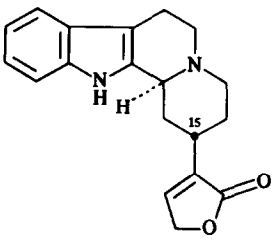
The mass spectrum of compound **26** displays a strong molecular ion at *m/z* 296 analysed for $C_{19}H_{24}N_2O$; it is accompanied by an intense $[M-1]^+$ fragment. This alkaloid is thus an isomer of anthirine (**25**), of corynantheol (**27**) or of geissoschizol (**28**) but direct comparison showed that it was none of these compounds. Inspection of the ^{1}H NMR spectrum of **26** shows signals for an ethylidene side chain and it was first considered that **26** could be the 3β-isomer of geissoschizol or one of the corresponding *Z*-olefins [23]. These hypotheses however were rejected because of the important discrepancies between the mass spectra of **26** and **28** (Fig. 1). Further examination of the ^{1}H NMR spectrum of **26** revealed the presence of a deshielded broad resonance at δ4.6, which could be attributed to a proton (H-3) located at the ring junction of a *cis*-quinolizidine; this spectrum also showed the AB quartet of an isolated allylic methylene centered at 4.12 (*J* = 12 Hz). This methylene is far more deshielded than other allylic aminomethylenes such as C-21 of geissoschizol. Given other already mentioned properties of **26**; it was thus concluded that this CH_2 was an oxymethylene and that **26** contained a Me–CH =C–CH_2–OH unit. The only tetracyclic alkaloids which can accommodate such a sub-unit belong to the so-called anthirine vallesiachotane group and therefore the structure of isoanthirine (**26**) is proposed for this novel alkaloid. The configuration of the C-15 of **26** is assumed to be 15*S* as found in anthirine for biogenetic reasons and the configuration of C-3 is 3*S* to account for the observed deshielding of H-3. Isoanthirine also possesses a *cis*-quinolizidine arrangement locked by an intramolecular hydrogen bond.

The last compound with an unknown structure is **24**, a $C_{19}H_{20}N_2O_2$ compound as shown by HRMS (308.1522).

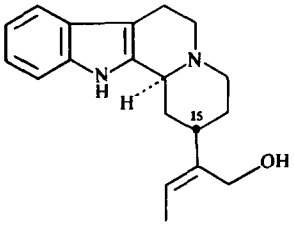
Table 2. ^{13}C NMR spectral data for compounds **24**, **25**, **27** and **28**

Carbon	Anthirine (25)	Corynantheol (27)	Geissoschizol (28)	Anthirine lactone (24)
2	132.4	134.5	133,2	136.0
3	53.9	60.0	52.2	54.4
5	49.2	52.9	49.3	—
6	17.4	21.4	16.8	—
7	105.6	107.0	104.0	107.7
8	126.6	127.0	125.3	127.2
9	116.9	117.8	115.8	118.0
10	120.2	121.0	118.8	121.7
11	118.1	118.9	116.7	119.5
12	110.4	110.8	109.3	111.2
13	135.7	136.1	135.6	136.6
14	30.7	34.1	31.2	31.6
15	30.4	37.0	29.7	28.7
16	27.3	35.9	34.6	28.7
17	46.0	61.0	57.7	51.5
18	116.5	116.9	11.2	70.4
19	137.8	139.2	117.9	144.2
20	51.0	46.8	134.4	—
21	62.6	59.9	53.1	—

Beside a strong $[M-15]^+$ peak, other mass spectral fragments appear at *m/z* 184 (90%), 210 (35) and 223; these three peaks were also found in isoanthirine **26**. More insight into the structure of **23** was obtained by ^{1}H NMR spectroscopy which revealed the absence of any ethyl, vinyl or ethylidene side chain and the presence of a deshielded proton (δ7.15) coupling with a two-proton broad singlet at δ4.8. These data, as well as characteristic IR bands (1740 and 1660 cm^{-1}), were reminiscent of the corresponding features found in akagerine lactone. As mentioned above, the only way to insert a γ-lactone such as the one found in akagerine lactone into the basic framework of an indole alkaloid is to select the skeleton of anthirine for **24**. This lead to the formulation of anthirine lactone for **24** with the same configuration at C-3 and at C-15 as in **25** and **26**. These conclusions were not contradicted by ^{13}C NMR spectroscopy (Table 2).



24



26

The activity of compounds **3**, **14**, **16** and **18** against *Staphyllococus aureus*, *Mycobacterium smegmatis*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans* and *Aspergillus niger* was assayed using the paper disk–agar technique. The only noticeable activity was found for compounds **3** and **4** against *M. smegmatis* (inhibition diameters of 35 and 15 mm at 100 μg/disk level).

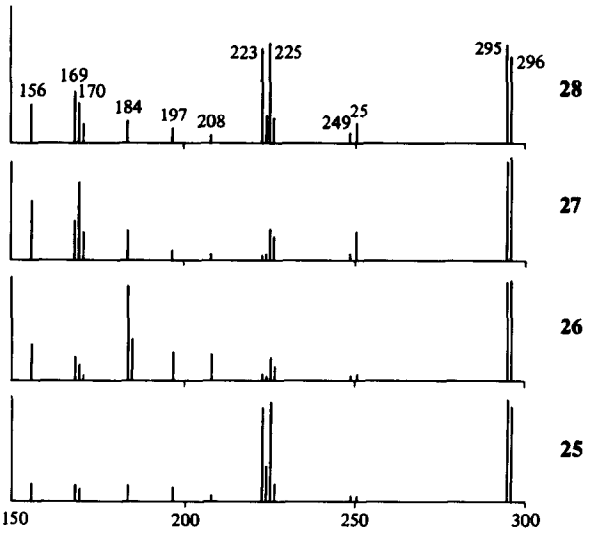
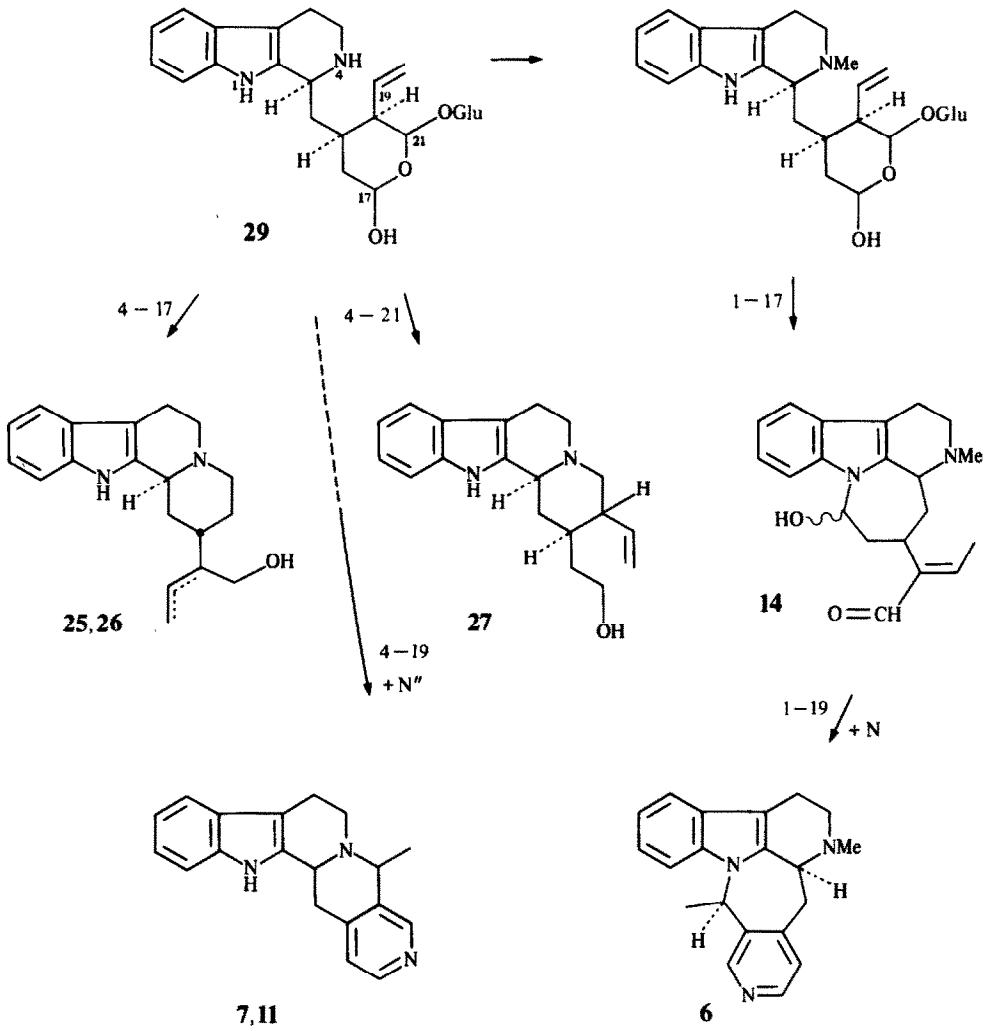


Fig. 1. Mass spectra of compounds **25–28**.

CONCLUSION

The wealth of alkaloids isolated from *S. johnsonii* is rather unique not in terms of number but rather in terms of variety of represented skeletons. The biosynthesis of these alkaloids does not follow unusual pathways and most probably involves strictosidine and demethoxycarbonylated analogs such as **29** (Scheme 3). At variance with other similar plant species, there does not seem to be any major ongoing pathway and one finds compounds in which N(4) has reacted with either of the latent aldehydes C-17 (**24**, **25**, **26**) or C-21 (**1**, **9**, **10**, **22**, **23**). Methylation of this nitrogen atom blocks these routes and an alternative then consists of reacting these aldehydes with N(1) leading



Scheme 3. Biosynthesis of the *Strychnos johnsonii* alkaloids.

to the akagerine-decussine type of alkaloids (**3**, **4**, **5**, **14**, **15**, **17**). In the cases where all these mechanisms proved to be inefficient, trapping of the intermediate may be effected by another molecule of tryptamine leading to the janussines (**8**, **16**, **18**). The coexistence of all these biosynthetic pathways either denotes a rich enzymatic material or its partial inefficiency.

EXPERIMENTAL

General. Plant material was collected by one of us (C. D) in Zaire and identified by H. Breyne. Plant material was collected under the 'Etude Phytochimique de flores Africaines' research project. A herbarium specimen is deposited in the Brussels National Gardens under No. HB 4071. ^{1}H NMR were measured at 400 MHz with a prototype built at the Institut d'Electronique Fondamentale, Université de Paris-Sud, Orsay or at 300 MHz with a Bruker AC 300 spectrometer.

Typical extraction procedure. Finely ground root bark (830 g) was wetted with 500 ml of conc NH_4OH half diluted in H_2O and extracted overnight in 25 l of EtOAc. The organic soln was extracted with 2% H_2SO_4 until Mayer's test was negative, the acid layer separated, made alkaline with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with H_2O, dried (Na_2SO_4) and evapd *in vacuo*. This gave 2.08 g of crude alkaloid mixture, yield 2.5 g/kg. In a similar fashion 480 g of milled stem bark yielded 1 g of alkaloid mixture (2 g/kg).

Typical separation procedure. The alkaloid mixture from the root bark (2 g) was fractionated on 500 g Merck silica gel H-60 (elution pressure 10 bar). After 700 ml 'dead volume', 30 ml fractions were collected. Solvents were $CHCl_3$ (fr. 1–199) and mixtures of $CHCl_3$–MeOH (99:1) (fr. 200–294), (49:1) (fr. 295–430), (19:1) (fr. 431–576), (9:1) (fr. 577–694). Alkaloid **1** was in fr. 115–127, angustine (**2**) in fr. 234–254; fr. 234–257 were pure **3**; fr. 258–272 contained **3** and **4**, fr. 273–294 were pure **4**; fr. 324–340 contained **5**, **6** and **7**, fr. 394–430 contained **8**, **9**, **10**, **11** and **12**, fr. 476–500 contained **10** and **14**; fr. 501–589 were 90% pure akagerine **14**; fr. 588–605 contained **15** and **16**: fr. 606–620: **17** and fr. 621–650: **18**; **13** was in fr. 449–467. The stem-bark alkaloid mixture was purified according to the same procedure: Alkaloid **22** was in fr. 172–180; fr. 221–235 were pure **3**; fr. 356–380 were pure **9**, fr. 459–480 were pure **10**; fr. 486–503 were pure **23**; fr. 573–581 were pure **14**; fr. 582–597 were **15**; fr. 645–659 were **17** and **24**; **25** was in fr. 768–798 and **26** was in fr. 842–864; **16** and **18** were in fr. 601–611 and 645–659, respectively.

Description of alkaloids. Demethoxycarbonyl-3,14-dihydro-

gambirtannine (**1**) (CR grey); $\{\alpha\}_D = -232°$ (EtOH; $c = 0.37$); MS *m/z* (rel. int.): 274 $[M]^+$ (100), 273 (85), 244 (20), 170 (15), 169 (42), 105 (22), 104 (20); ^{1}H NMR (400 MHz, $CDCl_3$): δ7.85 (*s*, NH), 4.08 (*d*, $J = 15$ Hz, H-21), 3.75 (*br d*, $J = 15$ Hz, H-21), 3.6 (*br d*, $J = 12$ Hz, H-3), 3.3 (*dd*, $J = 11, 5$ Hz, H-5), 3.2 (*dd*, $J = 15, 4$ Hz, H-14), 3.02 (*dd*, $J = 15, 12$ Hz, H-14), 3.01 (*m*, H-6), 2.78 (*br d*, 14 Hz, H-6), 2.72 (*dt*, $J = 5, 11$ Hz, H-5).

Dihydro-cycloakagerine (**3**) (CR yellow); $\{\alpha\}_D = -239°$ (MeOH; $c = 0.33$); UV λ_{max}^{MeOH} nm: 226 ($\log\varepsilon$ 4.38), 275 (3.8), 282 (3.81), 291 (3.74); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2850, 2790, 2690, 1460, 1375, 1320, 1305, 1105, 1040, 750; MS *m/z* (rel. int.): 308.1851 $[M]^+$ (50) (calc. for $C_{20}H_{24}N_2O$: 308.1886), 265.1447 (20), (calc. for $C_{18}H_{19}NO$: 265.1465), 224 (30), 213 (100), 185 (60), 184 (40), 183 (40), 169 (10), 156 (50), 144 (20); ^{1}H NMR (400 MHz, $CDCl_3$): δ7.5 (*d*, $J = 8$ Hz, 2H), 7.23 (*t*, $J = 8$ Hz, 1H), 7.16 (*t*, $J = 8$ Hz, 1H), 6.03 (*dd*, $J = 4.5, 1$ Hz, H-17), 5.33 (*br q*, $J = 7$ Hz, H-19), 4.15 (*br d*, $J = 13$ Hz, H-21), 3.72 (*d*, $J = 13$ Hz, H-21), 3.61 (*br d*, $J = 12.5$ Hz, H-3), 3.34 (*m*, H-15), 3.17 (*m*, H-5), 2.95 (*m*, H-6), 2.76 (*m*, 2H, H-5 + H-6), 2.62 (*ddd*, $J = 14, 11, 3$ Hz, H-14), 2.52 (*dd*, $J = 14.5, 4.5$ Hz, H-16), 2.55 (*s*, N–CH_3), 2.25 (*dt*, $J = 14.5, 4.5$ Hz, H-16), 1.68 (*br d*, $J = 7$ Hz, CH_3-18), 1.62 (*ddd*, $J = 14, 12.5, 6.5$ Hz, H-14). ^{13}C NMR see above.

O-Ethyl-akagerine **4** (CR yellow); $\{\alpha\}_D = -13°$ (MeOH; $c = 0.6$); UV λ_{max}^{MeOH} nm: 230, 275, 282, 292; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2850, 2800, 2720, 1685, 1635, 1455, 1380, 1350, 1310, 1215, 1095, 850; MS *m/z* (rel. int.): 352 $[M]^+$ (50) 323 (10), 307 (20), 306 (40), 277 (15), 226 (10), 213 (100), 198 (10), 185 (15), 184 (20), 183 (15), 180 (15); ^{1}H NMR (400 MHz, $CDCl_3$): δ9.33 (*s*, H-21), 6.55 (*d*, $J = 7$ Hz, H-19), 5.78 (*br d*, $J = 4$ Hz, H-17), 3.76 (*br d*, $J = 11$ Hz, H-3), 3.68 (*br t*, $J = 12$ Hz, H-15), 3.33 (*dq*, $J = 10, 7$ Hz, 1H, OCH_2Me), 3.10 (*dq*, $J = 10, 7$ Hz, 1H, –O–CH_2–Me), 3.08 (*m*, 1H, H-5), 2.53 (*s*, N–Me), 2.3 (*t*, $J = 13$ Hz, H-16), 2.15 (*q*, $J = 11$ Hz, H-14), 2.07 (*m*, H-16), 2.05 (*d*, $J = 7$ Hz, Me-18), 1.98 (*br d*, $J = 11$ Hz, H-14), 1.07 (*t*, $J = 7$ Hz, –O–CH_2Me).

O-Ethyl-akagerine lactone **5** (CR yellow); $\{\alpha\}_D = -12°$ ($CHCl_3$; $c = 0.4$); UV λ_{max}^{MeOH} nm: 227, 275, 282, 292; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2790, 2770, 1750, 1380, 1345, 1310, 1090, 1065, 840; MS *m/z* (rel. int.): 366 $[M]^+$ (50), 351 (15), 320 (50), 223 (35), 213 (100), 185 (10), 184 (15), 183 (10), 180 (15), 167 (10); ^{1}H NMR (400 MHz, $CDCl_3$): δ7.05 (*br s*, H-20), 5.82 (*d*, $J = 5$ Hz, H-17), 4.75 (*br s*, 2H CH_2-21), 3.75 (*br d*, $J = 11$ Hz, H-3), 3.4 (*br t*, $J = 11$ Hz, H-15), 3.3 (*dq*, $J = 10, 7$ Hz, 1H, OCH_2 – Me), 3.03 (*m*, 2H, OCH_2Me + H-5), 2.55 (*s*, N-Me), 2.46 (*d*, $J = 11$ Hz, H-14), 1.7 (*t*, $J = 11$ Hz, H-16), 1.55 (*d*, $J = 11$ Hz, H-14), 1.05 (*t*, $J = 7$ Hz, OCH_2Me).

Normalindine **7** (CR grey-yellow); $\{\alpha\}_D = -103°$ ($CHCl_3$; $c = 0.1$) UV λ_{max}^{MeOH} nm: 228, 263, 270, 282, 290; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 3300, 1720, 1650, 1215; MS *m/z* (rel. int.): 496 $[M]^+$ (15) ($C_{30}H_{32}N_4O_3$), 282 (10), 281 (100), 197 (15); ^{1}H NMR (400 MHz, $CDCl_3$): δ8.55 (*s*, N–H), 7.92 (*s*, NCHO), 7.56 (*d*, $J = 7$ Hz), 7.44 (*d*, $J = 7$ Hz), 7.27 (*t*, $J = 7$ Hz), 7.18 (*t*, $J = 7$ Hz), 7.15 (*d*, $J = 7$ Hz), 6.78 (*d*, $J = 2$ Hz), 6.73 (*dd*, $J = 7, 2$ Hz), 5.51 (*q*, $J = 7$ Hz, H-19), 5.27 (*d*, $J = 11$ Hz, H-17), 3.82 (*br dd*, $J = 7, 10$ Hz), 3.5 (*br d*, $J = 12$ Hz), 2.53 (*s*, N–Me), 1.6 (*t*, $J = 12$ Hz), 1.5 (*d*, $J = 7$ Hz, Me-18).

Tetrahydroalstonial **9** (CR yellow) MS *m/z* (rel. int.): 312 $[M]^+$ (90), 311 (100), 294 (20), 293 (20), 225 (20), 223 (30); ^{1}H NMR (300 MHz, $CDCl_3$): 5.35 (*br s*, H-17), 4.52 (*dq*, $J = 10, 7$ Hz, H-19): minor isomer; 4.9 (*br d*, $J = 7$ Hz, H-17), 4.1 (*dq*, $J = 10, 7$ Hz, H-19): major isomer.

Ajmalicinial **10** (CR yellow) MS same as above; ^{1}H NMR (400 MHz, $CDCl_3$): δ5.35 (*d*, $J = 5$ Hz, H-17), 3.92 (*dq*, $J = 10, 7$ Hz, H-19), 1.12 (*d*, $J = 7$ Hz, Me-18): minor isomer; 4.82 (*dd*, $J = 4, 9$ Hz, H-17), 3.35 (*dq*, $J = 10, 7$ Hz, H-19), 1.16 (*d*, $J = 7$ Hz, Me-18): major isomer.

Norepimalindine **11** (CR yellow) $\{\alpha\}_D = -276°$ ($CHCl_3$; $c = 0.1$) UV λ_{max}^{MeOH} nm: 228, 263, 270, 282, 290; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 3170, 1720 (w), 1650 (w), 1600, 1455, 1275, 760; MS *m/z* (rel. int.): 289 $[M]^+$ (100) ($C_{19}H_{19}N_3$), 288 (55), 274 (90), 245 (20), 185 (10), 170 (30), 169 (70); ^{1}H NMR (400 MHz, $CDCl_3$): δ8.42 (*s*, H-21), 8.35 (*d*, $J = 5$ Hz, H-17), 7.92 (*s*, NH), 7.08 (*d*, $J = 5$ Hz, H-16), 4.4 (*q*, $J = 7$ Hz, H-19), 4.34 (*dd*, $J = 10, 4$ Hz, H-3), 1.42 (*d*, $J = 7$ Hz, Me-18).

Norharman **12** (CR colourless); UV λ_{max}^{MeOH} nm: 235, 250 (sh), 283, 289, 340, 352; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3140, 1720 (w), 1650 (w), 1630, 1565 (w), 1500, 1450, 1330, 1245, 850, 840; MS *m/z* (rel. int.): 168 $[M]^+$ (100), ($C_{11}H_8N_2$).

Janussine A **16**: (CR: brown); $\{\alpha\}_D = +492$ (MeOH; $c = 0.5$); UV λ_{max}^{MeOH} nm: 228 ($\log\varepsilon = 4.31$), 278 (3.84), 285 (sh); IR ν_{max}^{KBr} cm^{-1}: 3420, 1650, 1600, 1550, 1455, 1375, 1330, 1220, 1185, 1160; MS *m/z* (rel. int.): 464.2596 $[M]^+$ (35), ($C_{30}H_{32}N_4O$: 464.2575), 449 (10), 295 (15), 277 (55), 265 (70), 264 (60), 263 (50), 185 (90), 182 (50), 156 (30), 143 (100); ^{1}H NMR ($CDCl_3$, 400 MHz): δ6.74 (*m*, 2H), 6.18 (*br s*, H-21), 4.93 (*q*, $J = 7$ Hz, H-19), 4.1 (*br d*, $J = 10$ Hz, H-3), 3.78 (*m*), 2.42 (*s*, N-Me), 1.65 (*d*, $J = 7$ Hz, Me-18); ^{13}C NMR see ref [15].

Tetrahydro-akagerine (**17**) (CR yellow) $\{\alpha\}_D = +49°$ (MeOH; $c = 0.2$); UV λ_{max}^{MeOH} nm: 228, 275, 282, 290; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3220, 1470, 1455, 1300, 1215, 1160, 1060, 1030, 1005, 760, 740; MS *m/z* (rel. int.): 328.2134 $[M]^+$ (4), ($C_{20}H_{28}N_2O_2$: 328.215), 310.2036 $[M]^+$ (12), $C_{20}H_{26}N_2O$: 310.2043, 285 (5), 198 (10), 186 (100), 185 (100), 169 (15), 156 (35), 144 (50); ^{1}H NMR (300 MHz, $CDCl_3$): 8.54 (*br s*, N-H), 5.8 (*q*, $J = 7$ Hz, H-19), 4.16 (*d*, $J = 11.3$ Hz, H-21), 3.95 (*d*, $J = 11.3$ Hz, H-21), 3.67 (*dt*, $J = 10.7, 5.8$ Hz, H-17), 3.58 (*dt*, $J = 10.9, 6.6$ Hz, H-17), 3.5 (*br d*, $J = 6.5$ Hz, H-3), 2.38 (*s*, N-Me), 2.12 (*ddd*, $J = 7.8, 10.9, 14$ Hz), 2.09 (*ddd*, $J = 2.4, 5.0, 14$ Hz), 1.74 (*d*, $J = 7$ Hz, Me-18); ^{13}C NMR see Table 1.

Janussine B (**18**) (CR brown) $\{\alpha\}_D = +153°$ (MeOH; $c = 0.2$); UV λ_{max}^{MeOH} nm: 228 ($\log\varepsilon = 4.44$), 284 (4.0), 292 (3.93); IR ν_{max}^{KBr} cm^{-1}: 3410, 3300, 2800, 1650, 1455, 1370, 1330, 1185, 740; MS same as **16**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ6.61 (*br s*), 6.2 (*br s*), 4.91 (*q*, $J = 7$ Hz, H-19), 4.32 (*m*, $W_{1/2} = 24$ Hz), 3.75 (*m*, $W_{1/2} = 20$ Hz), 2.47 (*s*, N-Me), 1.51 (*d*, Me-18).

Demethoxycarbonyl-3,14,15,16,17,18-hexahydrogambirtannine (Δ^{19} yohimbene) **22** (CR grey-yellow) $\{\alpha\}_D = -138°$: λ_{max}^{MeOH} nm: 227, 274, 283, 290; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 3200, 1450, 1380, 1320, 1260; MS *m/z* (rel. int.): 278 $[M]^+$ (100) ($C_{19}H_{22}N_2$), 277 (90), 183 (30), 170 (40), 169 (70), 156 (35).

Anthirine lactone (**24**) (CR yellow): UV λ_{max}^{MeOH} nm: 228, 282, 290; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 1740, 1660, 1460, 1345, 1295, 1110, 1065, 750; MS *m/z* (rel. int.): 308.1522 $[M]^+$ (100), ($C_{19}H_{20}N_2O_2$, calc.: 308.1523), 307 (60), 293 (35), 223 (30), 221 (8), 210 (35), 199 (90), 197 (20), 184 (90), 169 (40), 156 (55); ^{1}H NMR (400 MHz, $CDCl_3$): 8.2 (*s*, NH), 7.15 (*br s*, H-19), 4.8 (*br s*, H-18), 4.15 (*m*, H-3).

Isoanthirine (**26**) (CR yellow): $\{\alpha\}_D = -15°$ (MeOH; $c = 0.1$); UV λ_{max}^{MeOH} nm: 228, 275, 282, 290; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 3250, 1450, 1320, 1290, 1110, 1010, 760; MS *m/z* (rel. int.): 296.1856 $[M]^+$ (60), ($C_{19}H_{24}N_2O$: calc. 296.1887), 295 (60), 223 (30), 210 (20), 197 (25), 184 (100), 170 (25), 169 (30), 156 (50); ^{1}H NMR (400 MHz, $CDCl_3$): δ8.02 (*s*, NH), 5.58 (*q*, $J = 7$ Hz, H-19), 4.6 (*m*, H-3), 4.16 and 4.1 (AB *q*, $J = 12$ Hz, 2H-21), 1.55 (*d*, $J = 7$ Hz, Me-18).

NMR data for corynantheol (**27**): ^{1}H NMR ($CDCl_3$–CD_3OD: 19 1; 300 MHz): δ9.4 (*s*, NH), 7.25 (*m*, H-9), 7.2 (*m*, H-12), 7.05 (*m*, H-10 + H-11), 5.57 (*ddd*, $J = 17.1, 10.2, 8.3$ Hz, H-19), 5.15 (*dd*, $J = 17.1, 2$ Hz, H-18), 5.09 (*dd*, $J = 10.2, 2$ Hz, H-18), 3.7 (*m*, H-17), 3.27 (*dd*, $J = 11.4, 2$ Hz, H-3), 3.09, 2.99, 2.77 and 2.62 (4*m*, H-5 + H-6), 2.93 (*dd*, $J = 10.6, 3.4$ Hz, H-21), 2.4 (*ddd*, $J = 12, 9, 3, 2.2$ Hz, H-14), 2.27 (*t*, $J = 11$ Hz, H-21), 2.2 (*m*, H-20), 1.93 (*dq*, $J = 3, 7$ Hz, H-16), 1.55 (*m*, H-15), 1.3 (*m*, H-14 + H-16);

^{13}C NMR ($CDCl_3$–CD_3OD, 75 MHz): 139.9 (C-19), 136.9 (C-13), 135.2 (C-2), 127.6 (C-8), 121.6 (C-10), 119.6 (C-11), 118.4 (C-9), 117.5 (C-12), 107.6 (C-7), 61.6 (C-17), 60.6 (C-3), 60.5 (C-21), 53.5 (C-5), 47.4 (C-20), 37.7 (C-15), 36.5 (C-16), 34.7 (C-14), 22.0 (C-6).

Acknowledgements—Support of this work by 'Ministère de la coopération au développement de Belgique' (C.D.), the Université de Reims Champagne-Ardenne and D. C. R. I. (R.V. and C.D.) is gratefully acknowledged. We thank Dr S. K. Kan for giving us access to his NMR spectrometer and Dr C. Caron for performing antimicrobial assays.

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