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# ALKALOIDS OF *ALSTONIA LANCEOLATA**

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**Key Word Index**—*Alstonia lanceolata*; Apocynaceae; indole alkaloids.

**Abstract**—Thirteen alkaloids were isolated from the stem bark of *Alstonia lanceolata*. They were lochnericine, gentianine, 10,11-dimethoxy-1-methyl-deacetylpicraline 3′,4′,5′-trimethoxybenzoate, 10,11-dimethoxy-1-methyl-picraline, 10,11-dimethoxy-1-methyl-deacetylpicraline, picraline, Ψ-akuammigine, akuammicine, 10-methoxy-compactinervine, compactinervine, cathafoline, lanceomigine and lanceomigine *N*(4)-oxide.

## INTRODUCTION

As part of the chemotaxonomic study of the New Caledonian *Alstonia*, we describe in the present publication the alkaloids isolated from the stem bark of *A. lanceolata* V. Heurck and Mull. Arg. [1] collected in the Paala Forest of Tiebo Pass and identified by one of us (T. S., voucher no. Sévenet—Pusset 1615). The alkaloid content of the bark of the root was essentially identical to that of the stem and was not separately investigated. A Mayer test on the leaves was very weak (less than 50 mg per kg) and a study on the leaves was not pursued.

## RESULTS AND DISCUSSION

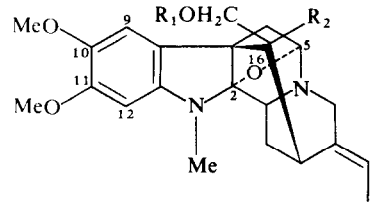
The stem bark alkaloid mixture (AM; 8.3 g/kg) was obtained in the usual fashion. Thirteen alkaloids were separated by column chromatography and preparative TLC, among which four had not previously been described. They are in order of increasing polarity:

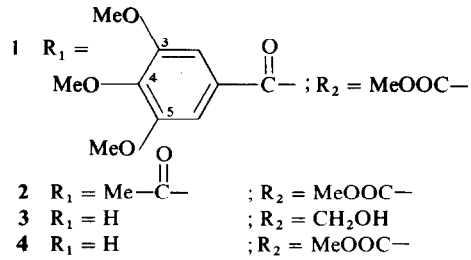
(1) (−)-lochnericine (0.1% of AM), identified by spectral comparison with the literature [2];

(2) gentianine (0.1% of AM) identified by direct comparison with an authentic sample [3];

(3) 10,11-dimethoxy-1-methyl-deacetylpicraline 3′,4′,5′-trimethoxybenzoate (**1**) (30% of AM), identified by direct comparison with an authentic sample [4];

(4) 10,11-dimethoxy-1-methyl-picraline (**2**) (25% of AM), a new alkaloid, the structure of which was established by spectral examination and chemical correlation. The mass spectrum of **2** showed a $M^+$ at *m/z* 484 ($C_{26}H_{32}O_7N_2$) and major fragments at *m/z* 231, 313 and 411, 74 amu greater than the corresponding peaks of picraline [6], accounting for one extra Me and two extra OMe groups. The $^1H$ NMR spectrum, mostly superimposable on that of picraline, differed in the aromatic part (two singlets at $\delta$ 7.05 and 6.25) and in the high-field area (3 Me singlets at 3.85, 3.80 and 2.90). As in picraline and akuammiline [7], the acetate Me was shielded at 1.60 ppm as a result of the stereochemistry at C-16. These data favored structure **2** in which the location of the methoxy groups was dictated by the absence of a detectable coupling constant between the aromatic protons. Furthermore, **2** was reduced ($LiAlH_4$, THF, reflux) to a diol **3**, in all respects identical with the diol derived from **1**.




(5) 10,11-dimethoxy-1-methyl-deacetylpicraline (**4**) (4% of AM) [4, 5];

(6) picraline (0.4% of AM) [6];

(7) pseudoakuammigine (0.5% of AM) [6];

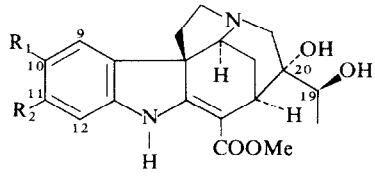
(8) akuammicine (0.7% of AM) [8], identified with reference samples;

(9) 10-methoxycompactinervine (**5**) (7% of AM), a new alkaloid whose structure was established from its spectral properties. The mass spectra of **5** ($M^+$ *m/z* 386, $C_{21}H_{26}N_2O_5$) and of alstovine (**6**, 11-methoxy-compactinervine) [9] were almost identical but the IR and NMR spectra showed significant differences. The

* Part LXIX in the series "Plants from New Caledonia". For Part LXVIII see Baasou, S., Mehri, H., Rabaron, A., Sévenet, T. and Plat, M. (1980) *Phytochemistry* (submitted).

high-field parts (0 → 5 ppm) of the NMR spectra of **5** and of compactinervine (**7**) [10] matched, except for a supplementary three proton-singlet at 3.85 ppm (OMe) found in **5**, thus establishing configurations at C-19 and C-20. The position of the extra OMe group on the aromatic nucleus was secured by the UV spectrum (maxima found at 235, 290 and 337 nm in **5** and at 261, 307 and 331 in **6**) and by the $^1$H NMR spectrum recorded in $C_6D_6$ (ABX pattern with $J_{AB} = 6$ Hz, $J_{AX} = 0$, $J_{BX} = 1.5$ Hz) ruling out substitution at C9 and C12.

(10) Compactinervine (**7**) (1% of AM) [10], identified by comparison of its spectra with literature data;



**5** $R_1$ = OMe; $R_2$ = H
**6** $R_1$ = H; $R_2$ = OMe
**7** $R_1$ = $R_2$ = H

(11) Cathafoline (0.2% of AM) identified by direct comparison with a reference sample [11].

Two new alkaloids, with almost identical IR and UV spectra (see Experimental) were further isolated from the more polar fractions. The less polar one, **8**, which was given the name lanceomigine, was isomeric with 17-hydroxypseudoakuammigine* and corymine [12], as shown by its $M^+$ at *m/z* 382 ($C_{22}H_{26}N_2O_4$). The more polar compound, **9**, displayed a weak $M^+$ at *m/z* 398 and fragments similar to those of lanceomigine. Both **8** and **9** showed signals for a Me ester, a N-Me, an ethylidine sidechain and a carbinolamine-type proton in their $^1$H NMR spectra. They differed essentially in the 4–5 ppm region, which integrated for 2 protons for **8**, and for 3 protons for **9** (after $D_2O$ exchange).

Partial synthesis of **8** from 17-hydroxy-Ψ-akuammigine* suggested structure **8a** for lanceomigine, a hypothesis which was strongly supported by its reduction (triethylsilane, TFA, room temperature) to the desoxy derivative **10**, $C_{22}H_{26}N_2O_3$. Compound **10** was also obtained upon reduction of **9** under similar conditions [13].

Finally, the gross structure of the discussed alkaloids was established by an X-ray analysis of **10**. The extra oxygen present in **8** was located at C-17 in order to account for the carbinolamine singlet at $\delta$ 4.80. Location on C-21 was excluded on the basis of the existing long-range coupling between Me-18, H-19 and the protons on C-21, on the one hand, and of the interaction between the OH17 and the keto group on C-2 on the other (see below). It is worthwhile noting the chemoselectivity of the triethylsilane reduction, which affected a carbinolamine in the presence of a ketone, an ester and an isolated double bond.

Structure **8a** agreed with the $^{13}$C NMR spectra (Table 1), except for the absence of a ketone carbonyl for **8**. Instead, a singlet was found at 110 ppm, which more likely agrees with a quaternary carbon bearing two oxygens. This can be explained by the formation of a hemiketal between the C-17 hydroxy and the C-2 ketone, due to the extreme proximity of the two carbons (less than 0.3 nm measured in compound **10**).

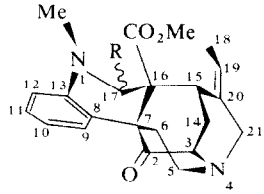
Table 1. $^{13}$C NMR of **8** and **9**

| | **8** | **9** | | **8** | **9** |
|---|---|---|---|---|---|
| C(2) | 110.9 | 110.3 | C(14) | 22.9 | 21.2 |
| C(3) | 57.7 | 80.1 | C(15) | 36.5 | 34.4 |
| C(5) | 48.3 | 64.0 | C(16) | 57.0 | 56.2 |
| C(6) | 27.4 | 25.6 | C(17) | 92.3 | 92.8 |
| C(7) | 50.1 | 47.9 | C(18) | 12.6 | 13.0 |
| C(8) | 126.4 | 126.2 | C(19) | 118.8 | 123.3 |
| C(9) | 128.7* | 128.7* | C(20) | 140.0 | 130.6 |
| C(10) | 118.2 | 118.4 | C(21) | 53.8 | 72.3 |
| C(11) | 127.3* | 127.3* | $-\underset{\underset{OMe}{\diagdown}}{\overset{O}{\overset{\|}{C}}}$ | 170.6 | 170.1 |
| C(12) | 112.3 | 112.4 | $CO_2\underline{Me}$ | 51.5 | 51.7 |
| C(13) | 144.7 | 144.0 | N(4)<u>Me</u> | 37.9 | 38.0 |

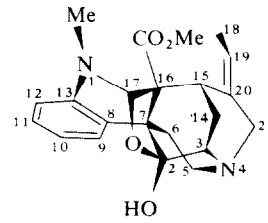
* Values within the same column may be interchanged.

The most salient features of the $^{13}$C NMR spectrum of **9** were the deshielding (*ca* 20 ppm) of all carbons bound to N-4 and the shielding of C-20.† These data and the mass spectrum indicated that **9** was the *N*-oxide of lanceomigine, a hypothesis which was confirmed by the partial synthesis of **9** from **8** (paranitroperbenzoic acid, quantitative yield).

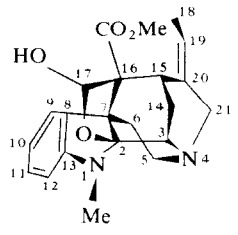
Full details on the X-ray structure will be given elsewhere along with details of the chemistry of **8** and **9**, and biogenetical implications pertaining to the rare bond between N-1 and C-17.



**8a** R = OH
**10** R = H



**8** Lanceomigine
**9** N(4)-oxide lanceomigine $N^+(4)-O^-$



17-Hydroxypseudoakuammigine

* Isolated from the seeds of *Hunteria congolana* (J. Vercauteren (1979), Thèse de 3ème cycle, Reims), manuscript in preparation.

† For $^{13}$C NMR of *N*-oxides see: Rolland, Y., Kunesch, N., Poisson, J., Hagaman, E. W., Schell, F. M. and Wenkert, E. (1975) *J. Org. Chem.* **41**, 3270; Wenkert, E., Bindra, J. S., Chang, C.-J., Cochran, D. W. and Schell, F. M. (1974) *Acc. Chem. Res.* **7**, 46.

## EXPERIMENTAL

Mps are uncorr. Rotations were determined in $CHCl_3$. Unless otherwise stated, NMR spectra were taken in $CDCl_3$ solns and chemical shifts are given in $\delta$ with TMS as the int. standard; coupling constants are given in Hz: *s* = singlet, *d* = doublet, *t* = triplet, *q* = quadruplet, *m* = multiplet. Chromatography columns were packed with Merck Kieselgel 60 (70–230 mesh). HPLC was carried out using Merck H60 Si gel. Prep. TLC plates were Merck 60F-254. Colour reactions (CR) were obtained by spraying plates with a soln of cerium (IV) ammonium sulfate.

*Extraction and isolation of alkaloids.* The dried, ground stem bark (3 kg) was wetted with 50% $NH_4OH$ and lixiviated by means of 80 l. of EtOAc. (Same yields and composition were obtained from $Et_2O$ lixiviation.) The lixiviate was extracted with 2% $H_2SO_4$, and the aq. phase made alkaline with $NH_4OH$ and extracted with $CHCl_3$. The $CHCl_3$ layers were dried ($Na_2SO_4$) and evapd *in vacuo* to give 27 g of crude alkaloid mixture (yield: 9 g/kg). The mixture (20 g) was placed on a Si gel column (200 g) packed in $CHCl_3$ which was eluted in 300 ml fractions with $CHCl_3$ (7 l.), $CHCl_3$–MeOH (99:1) (8.5 l.), $CHCl_3$–MeOH (49:1) (5.2 l.) and $CHCl_3$–MeOH (9:1) (7 l.). Fractions 1 → 10 yielded lochnericine (20 mg); fractions 11 → 20 yielded gentianine (20 mg) and small amounts of 10,11-dimethoxy-1-methyl-deacetylpicraline 3′,4′,5′-trimethoxybenzoate (**3**) and 10,11-dimethoxy-1-methyl-picraline (**4**). Larger amounts of **3** and **4** together with 10,11-dimethoxy-1-methyl-deacetylpicraline (**6**) were isolated by fractional crystallization from fractions 32–46. Fractions 50 → 60 gave picraline (80 mg), pseudo-akuammigine (100 mg) and akuammicine (140 mg) purified by TLC. Fractions 61 → 71 were combined and the mixture (4.9 g) was purified by HPLC on 500 g of Merck H60 Si gel ($CHCl_3$–MeOH: 19:1; 25 ml fractions). Tubes 8 → 33 (2.1 g) gave 10-methoxycompactinervine and compactinervine which were separated by prep. TLC. From tubes 34 → 55 (0.7 g) cathafoline and lanceomigine were obtained; lanceomigine *N*-oxide was present in tubes 56 → 90 and was purified by TLC.

*New alkaloids.* 10,11-Dimethoxy-1-methyl-picraline (**2**) (CR orange brown): mp: 228° ($Et_2O$–MeOH); $[\alpha]_D$ −124° (*c* = 0.67); UV $\lambda_{max}^{EtOH}$ nm (log $\varepsilon$): 215, 246 (3.84), 305 (3.68); IR ($CHCl_3$) $cm^{-1}$: 3010, 2960, 1620, 1500, 1250, 1200; MS *m/z* (rel. int.): 484 (60), 469, 425, 411 (100), 313 (90), 231 (85); $^1H$ NMR: $\delta$ 7.05 (*s*, 1 H), 6.25 (*s*, 1 H), 5.40 (*q*, *J* = 7 Hz, 1 H), 4.70 (*d*, *J* = 3 Hz, 1 H), 4.50 (*d*, *J* = 12 Hz, 1 H), 3.85 (*s*, 3 H), 3.80 (*s*, 3 H), 3.65 (*s*, 3 H), 2.90 (*s*, 3 H), 1.60 (*s*, 3 H), 1.55 (*b d*, *J* = 7 Hz, 3 H).

10-Methoxycompactinervine (**5**) (CR blue then yellow): amorphous, $[\alpha]_D$ −204° (*c* = 1.9); UV $\lambda_{max}^{EtOH}$ (log $\varepsilon$): 235, (3.85), 290 (3.50), 337 (3.82); IR ($CHCl_3$) $cm^{-1}$: 3440, 3380, 1670, 1590; MS *m/z* (rel. int.): 386, 354, 313, 298, 287, 256 (100); $^1H$ NMR: 8.50 (*bs*, 1 H), 6.85 (*m*, 3 H), 3.85 (*s*, 6 H), 1.10 (*d*, *J* = 7 Hz, 3 H); ($C_6D_6$): 8.80 (*s*, 1 H), 7.0 (*d*, *J* = 6 Hz, 1 H), 6.85 (*d*, *J* = 1.5 Hz, 1 H), 6.55 (*dd*, *J* = 6, 1.5 Hz, 1 H), 4.0 (*bt*, *J* = 2 Hz, 1 H), 3.55 (*s*, 3 H), 3.50 (*s*, 3 H), 1.40 (*bd*, *J* = 7 Hz, 3 H).

Lanceomigine (**8**) (CR pink then blue): amorphous, $[\alpha]_D$ +32° (*c* = 1.0); UV $\lambda_{max}^{EtOH}$ nm: 225, 257, 295, $\lambda_{max}^{EtOH,HClO_4}$ nm: 235, 290; IR ($CHCl_3$) $cm^{-1}$: 3640, 3400, 1750, 1740, 1600, 1500; MS *m/z* (rel. int.): 382, 367, 354, 353, 338, 337, 323, 295, 278, 264, 216, 194, 181, 170, 167, 157; $^1H$ NMR: 5.45 (*m*, 1 H), 4.80 (*s*, 1 H), 3.55 (*s*, 3 H), 2.95 (*s*, 3 H), 1.50 (*bd*, *J* = 7 Hz, 3 H).

Lanceomigine *N*-oxide (**9**) (CR pink then blue): amorphous, $[\alpha]_D$ +79° (*c* = 0.63); UV $\lambda_{max}^{EtOH}$ nm: 225, 257, 295, $\lambda_{max}^{EtOH,HClO_4}$ nm: 235, 290; IR ($CHCl_3$) $cm^{-1}$: 3640, 3400, 1750, 1740, 1600, 1500; MS *m/z* (rel. int.): 398, 382, 367, 354, 338, 337, 336, 323, 279, 228, 194, 167, 157; $^1H$ NMR: 5.50 (*m*, 1 H), 4.75 (*s*, 1 H), 3.55 (*s*, 3 H), 2.95 (*s*, 3 H), 1.50 (*bd*, *J* = 7 Hz, 3 H).

*Reduction of* 10,11-*dimethoxy*-1-*methyl-picraline* (**2** → **3**). Alkaloid **2** (47 mg) was dissolved in 20 ml dry THF to which 50 mg $LiAlH_4$ was added. After refluxing the soln for 48 hr, excess hydride was carefully destroyed with wet $Et_2O$ and a few drops of $H_2O$. The white ppt. was filtered off and the filtrate distilled *in vacuo*. The residue showed a major spot on TLC and was purified by prep. TLC ($CHCl_3$–MeOH; 9:1: orange then yellow spot). The purified product was identical with the product derived from the trimethoxybenzoate of 10,11-dimethoxy-1-methyl-picraline (mmp, IR, UV, MS).

*Oxidation of lanceomigine* (**8** → **9**). Lanceomigine (**8**) (5 mg) was dissolved in 0.5 ml $CH_2Cl_2$ to which 5 mg *p*-nitroperbenzoic acid was added. After 20 min the soln was stirred with 1 ml 2 M NaOH and usual treatment of the organic layer yielded 4 mg lanceomigine *N*-oxide identical in all respects to the natural product.

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