Phytochemistry, 1970, Vol. 9, pp. 1293 to 1298. Pergamon Press. Printed in England.

THE ALKALOIDS OF *VOACANGA THOUARSII* VAR. *OBTUSA**

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(*Received* 18 *September* 1969)

Abstract—Voacangine (3), ibogaine (2), voacamine (7), vobtusine (10), voacristine (1), iboluteine (4), vobasine (6), 18′-decarbomethoxyvoacamine (9) and voaluteine (5) are shown to be present in the crude extract from the bark of *Voacanga thouarsii*, Roem. et Schult. var. *obtusa* Pichon. All are known compounds. The absolute configuration C-17 R is proposed for the spirannic carbon atom of the pseudoindoxyle (5). Applied to voacristine (1), Brewster's method shows C-20 to have the *S*-configuration.

The present work concerns a re-examination of the alkaloid contents of *Voacanga thouarsii*, Roem. et Schult. var. *obtusa* Pichon (Apocynaceae).

This species was studied in 1955 by Janot and Goutarel[1] who obtained for the first time voacangine (3), voacamine (7) and vobtusine (10). These bases were later found in several other genera of this family.[2]

Since that period, a large number of papers have been devoted to the structural determination of indole alkaloids but there is no report of a more extensive study of the minor alkaloids of the above species.

A large sample of *V. thouarsii*, var. *obtusa*, was collected near Lubumbashi (Republic of Congo) in January 1966 by Mr. J. Grégoire and the botanical identification was performed by Professor J. J. Symoens, both of Lubumbashi University, whose help is gratefully acknowledged. As the botanical identification is fairly complicated, the trees were identified during

Table 1

Alkaloid	% of the crude extract
Voacangine (3)	14·5
Ibogaine (2)	2·0
Voacamine (7)	1·4
Vobtusine (10)	1·0
Voacristine (1)	0·2
Iboluteine (4)	0·04
Vobasine (6)	0·04
18′-Decarbomethoxyvoacamine (9)	0·03
Voaluteine (5)	0·02

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* Part XXIII in the series "Indole Alkaloids"; for Part XXII, see A. Goldblatt, C. Hootele and J. Pecher, *Chimia* 23, 400 (1969).

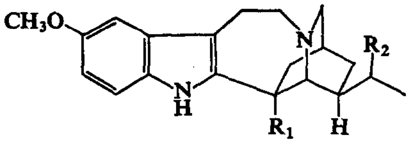
† Chargé de Recherches du Fonds National de la Recherche Scientifique.

[1] M. M. Janot and R. Goutarel, *Compt. rend. hebd. Séances Acad. Sci.* 240, 1719, 1800 (1955).

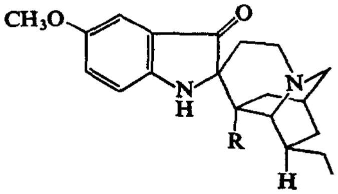
[2] M. Hesse, *Indolalkaloide in Tabellen*, Springer-Verlag, Berlin (1964, 1968).

the flowering and fructification period. Fruit and flower of the species are characteristic and consistent with Pichon's description.[3] The bark, however, was collected at a more convenient moment, during the dry season.

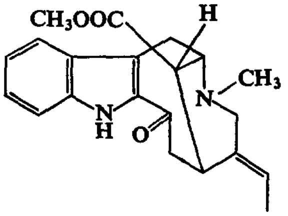
From this material, six more alkaloids (see Table 1) were obtained after a separation performed mostly by counter-current distribution, as indicated in the Experimental section. All these alkaloids are known compounds. The pertinent chemical literature is cited extensively in Hesse's *Indolalkaloide in Tabellen*.[2] All the alkaloids were identified by their physical properties and, with the exception of (5) and (9), by reference to authentic samples.



(1) R_1: $COOCH_3$; R_2: OH
(2) R_1: H ; R_2: H
(3) R_1: $COOCH_3$; R_2: H



(4) R: H
(5) R: $COOCH_3$



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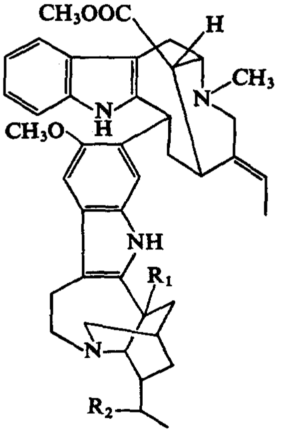
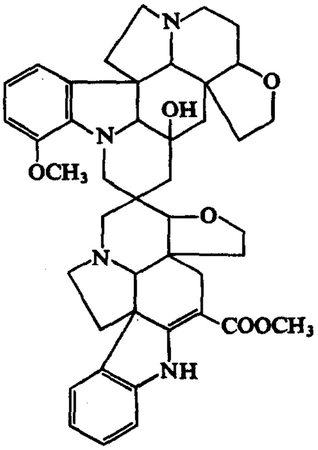


(7) R_1: $COOCH_3$; R_2: H
(8) R_1: $COOCH_3$; R_2: OH
(9) R_1: H; R_2: H



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[3] M. PICHON, *Bull. Mus. Hist. Nat., Paris*, **19**, 409 (1947).

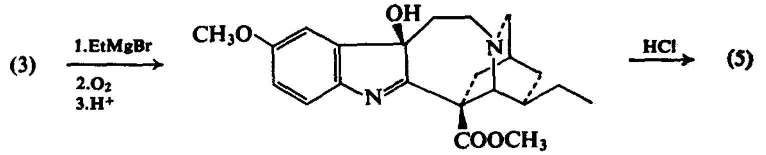
DISCUSSION

The alkaloid contents of *Voacanga thouarsii* is similar to that of the other *Voacanga* species, in that none of the bases departs from the general structures previously isolated from these species (the only known exception is *V. chalotiana*, which contains no *Iboga*-type bases, but only akuammidine-type alkaloids and vobtusine (10)).[4] The aromatic substitution pattern of the *Iboga* bases of this species seems to be exclusively 1,2,4- as opposed to *V. africana* which also contains ring A unsubstituted compounds.[5]

The results of many attempts (counter-current distribution and thin-layer chromatography) performed on several fractions suspected to contain voacorine (8), showed unambiguously that this alkaloid does not occur in *V. thouarsii*, var. *obtusa*. This base is present in most other *Voacanga* species, although it is less common than voacamine (7) and vobtusine (10). The absence of voacorine in *V. thouarsii* is remarkable, considering that voacristine (1) and vobasine (6), its two constitutive parts, are both present in the plant.

The alkaloids iboluteine (4) and voaluteine (5) are respectively oxidation products of ibogaine (2) and voacangine (3).

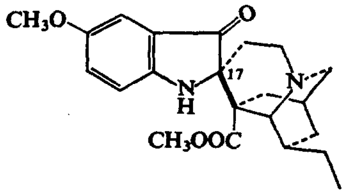
In order to obtain a reference compound for alkaloid (5), a synthetic sample was prepared according to the scheme proposed by Guise *et al.*:[6] Synthetic voaluteine was identical with the natural compound (see Experimental).



(11)

On the basis of the absolute stereochemistry of (11) (proposed by us[7] and independently by Biemann,[8]) and of the well-known stereochemical course of Wagner–Meerwein type rearrangements, we tentatively propose the indicated absolute stereochemistry for (5) at C-17 as R giving the projection formula (11).

The alkaloid (9) appeared to be a dimeric indole base by mass spectrometry and proved to be more basic [pK_a (MCS/H_2O 80/20): 7·15] than voacamine (pK_a (MCS/H_2O 80/20): 6·15]. Its i.r. and u.v. spectra are closely similar to those of voacamine. The NMR



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[4] G. Tirions, M. Kaisin, J. C. Braekman, J. Pecher and R. H. Martin, *Chimia* **22**, 87 (1968).

[5] D. W. Thomas and K. Biemann, *Lloydia* **31**, 1 (1968).

[6] G. B. Guise, E. Ritchie and W. C. Taylor, *Australian J. Chem.* **18**, 1279 (1965).

[7] C. Hootele, R. Lévy, M. Kaisin, J. Pecher and R. H. Martin, *Bull. Soc. Chim. Belges*, **76**, 300 (1967).

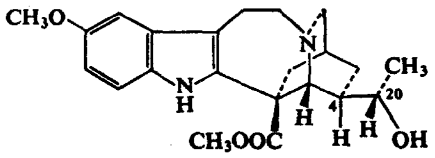
[8] D. W. Thomas and K. Biemann, *Tetrahedron* **24**, 4223 (1968).

spectrum ($CDCl_3$) shows the presence of two NH signals (7·8–7·6 [1H] and 7·5–7·3 ppm [1H]), one multiplet of aromatic protons (7·1–6·6 ppm [6H]), one ethylidene proton multiplet (5·4–4·8 ppm [1H]), one singlet of shielded vobasine-type methyl ester[9] (2·58 ppm [3H]), one singlet of N-methyl group (2·45 ppm [3H]) and one triplet (methyl of the ethyl side-chain (0·88 ppm, $J = 7$ c/s [3H]).

Except for the presence of a second methyl ester singlet at 3·62 ppm in the spectrum of voacamine (7), the two spectra are very similar. The aromatic patterns of both spectra are superposable: this proves that the aromatic substitution is the same for voacamine and the new base. The mass spectrum shows a molecular ion at 646 m.u., in agreement with the formula $C_{41}H_{50}O_3N_4$. The observed fragmentation pattern shows, in addition, the characteristic intermolecular methyl group transfer ion at 660 as previously observed with other dimeric alkaloids.[3,8] If the spectrum is recorded immediately after introduction in the direct inlet system, the peak at 646 is more intense than that at 660. After 10 min, the intensities of the peaks are inversed and 20 min after the introduction, both peaks have vanished. This parallels the behaviour of voacamine (7) described by G. Büchi.[10]

The compound was also submitted to an acid-catalysed cleavage following the method proposed by Winkler.[11] The resulting mixture was studied by thin-layer chromatography. Ibogaïne is the main constituent; small spots indicated the presence of the vobasinol degradation products.[11] On the basis of the preceding chemical and physical properties, it appears that this compound is 18′-decarbomethoxyvoacamine (9). This compound was previously isolated in minute amounts (which prevented a complete description of its properties) from *V. africana*[5,12] and from *Conopharyngia longiflora.*[13]

The absolute configuration of voacristine (1), as established by Poisson,[14] was further confirmed. Voacristine (1) has been chemically related to voacangine (5),[15] the absolute configuration of which is known.[16] This provides the absolute configuration of all asymmetric centres in (1) but C-20. Poisson[14] proposed the absolute configuration *S* for the carbon atom C-20 of voacristine on the basis of molecular rotation differences by reference with the 20-hydroxy epimers of the 17-α-pregnane series. Brewster's method[17] led us to the same conclusion in that *O*-benzoylation of (1) caused a strong positive shift in rotation: viz., $[M]_D$ voacristine: −111°; $[M]_D$ *O*-benzoylvoacristine: +17°; $\Delta[M]_D$: +128°. The previous suggested C-20 *S* configuration is therefore established on much firmer ground and voacristine is correctly represented by (12):



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[9] U. RENNER and H. FRITZ, *Tetrahedron Lett.* **6**, 283 (1964).
[10] G. BÜCHI, R. E. MANNING and S. A. MONTI, *J. Am. Chem. Soc.* **86**, 4631 (1964).
[11] W. WINKLER, *Arch. der Pharmazie* **12**, 895 (1962).
[12] D. W. THOMAS and K. BIEMANN, *J. Am. Chem. Soc.*, **87**, 5447 (1965).
[13] A. GOLDBLATT, *Mémoire de Licence*, ULB (Belgium) (1966).
[14] J. POISSON, F. PUISIEUX, C. MIET and M. B. PATEL, *Bull. Soc. Chim. France* 1965, 3549.
[15] U. RENNER and D. A. PRINS, *Experientia* **17**, 106 (1961).
[16] J. P. KUTNEY, R. T. BROWN and E. PIERS, *Can. J. Chem.* **44**, 637 (1966).
[17] J. H. BREWSTER, *Tetrahedron* **13**, 106 (1961).

EXPERIMENTAL

The NMR spectra were recorded on a Varian A60 spectrometer using dilute $CDCl_3$ solutions (TMS = 0 c/s). Mass spectra were recorded on a single focusing RMU-6D Hitachi Perkin–Elmer mass spectrometer with direct insertion into the source. M.ps. were determined on a Koefler microscope and are uncorrected. U.v. spectra were recorded in MeOH on a Perkin–Elmer 137 u.v. spectrophotometer and on a Zeiss PMQ II spectrophotometer and the i.r. spectra on a Perkin–Elmer i.r. 237 spectrophotometer. TLC was on silica gel G (Merck-Stahl), using MeOH as solvent and iodine vapour to reveal the alkaloids.

Extraction

The 10% aqueous NH_4OH moistened bark (6·6 kg) was exhaustively extracted by MeOH in a soxhlet. The concentrated extracts were thoroughly mixed with 10% aqueous AcOH, filtered and extracted with $CHCl_3$. The mixture obtained after neutralization and evaporation of the $CHCl_3$ solution (129 g, 1·9% by weight of the bark) was separated by counter-current distribution.

Separation of the Alkaloids

The counter-current distributions were performed in the system $CHCl_3$–citrate–Na_2HPO_4 buffer, Table 2, Fig. 1.

TABLE 2. COUNTER-CURRENT DISTRIBUTION OF ALKALOIDS

CCD No.	pH (and concentration) of the buffer*	Fraction	Partition Coefficient	Alkaloids
1	2·0 (*c.* = 0·4)*	B1	0·6	Voacangine (3) Vobtusine (10)
2 (Fraction C from 1)	2·9 (*c.* = 0·2)	C2 D2	0·84 3·4	Voacristine (1) Voacamine (7) Vobasine (6) 18′-Decarbomethoxy-voacamine (9)
3 (Fraction E from 2)	4·0 (*c.* = 0·2)	B3 C3 E3	0·5 2·0 11·5	Voaluteine (5) Ibogaine (2) Iboluteine (4)

* The concentration of the buffer is given in terms of molarity of the citric acid constituent: *c.* = 0·4 refers to a buffer prepared from 0·4 M citric acid and 0·8 M sodium dihydrogenophosphate, respectively.[18]

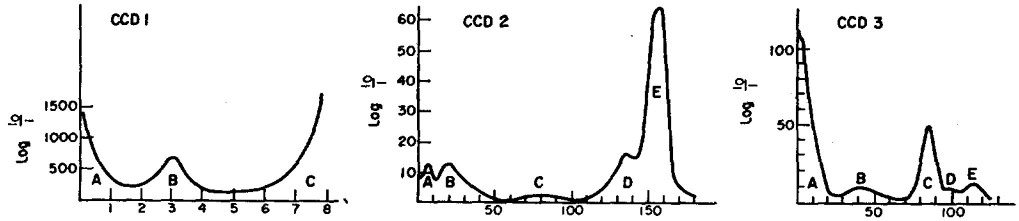

FIG. 1. COUNTER-CURRENT DISTRIBUTION CURVES (SEE TABLE 2).

Voacangine (3) is the major alkaloid of the plant: fractional crystallization of B1 (MeOH) yielded 18·9 g of the product. The u.v. and i.r. spectra and the m.p. (136–137°, unchanged mixture m.p.) were identical to those of an authentic sample (R_f = 0·65; ref.: authentic voacangine: 0·65).

Ibogaine (2). Fraction C3 yielded, after crystallization from MeOH, 2·4 g of ibogaine (m.p. = 152·5–153·5°, unchanged mixture m.p.), characterized by u.v., i.r., MS and NMR and compared to an authentic sample (R_f = 0·35; ref.: authentic ibogaine = 0·35).

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[18] C. D. HODGMAN, *Handbook of Chemistry and Physics*, 35th ed., p. 1617, The Chemical Rubber Co. (1953–1954).

Voacamine (7). Was isolated from fraction D2. Crystallization from MeOH yielded 1·806 g of pure voacamine, identical in all respects to an authentic sample (MS, NMR, u.v., i.r., m.p. and $[\alpha]$) ($R_f = 0{\cdot}57$; ref.: authentic (7) = 0·57). pK_a (MCS/H_2O 80/20): 6·15.

Vobtusine (10). Fractional crystallization of fraction B1 yielded 1·238 g of vobtusine (MeOH) whose u.v. and i.r. spectra and m.p. were identical to those of an authentic sample ($R_f = 0{\cdot}44$; ref.: authentic (10) = 0·44).

Voacristine (1). Fraction C2 yielded, after crystallization from benzene–light petroleum (60–80°), 216 mg of pure voacristine, identified by u.v., i.r., MS, NMR and compared with an authentic sample. M.p. = 167–169° (change of crystalline form at 91–96°), unchanged mixture m.p. ($R_f = 0{\cdot}75$; ref.; authentic (1) = 0·75).

Iboluteine (4). 58·5 mg of bright yellow crystalline iboluteine were obtained from fraction E3 (MeOH). The compound was characterized by SM, u.v. and i.r. ($R_f = 0{\cdot}23$; ref.: authentic (4) = 0·23). The m.p. of iboluteine (141–142°)[19] is preceded by a change of crystalline form at 88–94°.

Vobasine (6) was isolated from fraction D2. The 53 mg obtained were homogenous (TLC). The mass, i.r. and u.v. spectra were identical to those of an authentic sample ($R_f = 0{\cdot}44$; ref.: authentic (6) = 0·44).

Voaluteine (5). 20·4 mg of bright yellow crystalline voaluteine (m.p. 190–196°, MeOH) were isolated from fraction B3. The mass, i.r. and u.v. spectra confirmed the structure ($R_f = 0{\cdot}57$; ref.: voacangine–hydroxyindolenine (11) = 0·77). $[\alpha]^{25}_{D} = -117°$ ($c. = 0{\cdot}12$, $CHCl_3$).

The reference compound was prepared according to Guise *et al.*[7] (see Scheme 1); yield (3–11): 30% and (11–5): 97%. M.p. (methanol) = 195–196° (mixture m.p. = 190–192°). ($R_f = 0{\cdot}57$; ref.: voacangine-hydroxyindolenine (11) = 0·77). $[\alpha]^{25}_{D} = -120°$ ($c. = 0{\cdot}3$, $CHCl_3$).

18′Decarbométhoxyvoacamine (9). TLC (MeOH) of fraction D2, followed by crystallization from MeOH–Et_2O, yielded 34·8 mg of (9). M.p. = 208–210° dec. (sealed capillary). The i.r. spectrum shows bands at 1470 and 1730 cm^{-1} (KBr) and 1470, 1724 and 3470 cm^{-1} ($CHCl_3$). U.v. spectrum: $\lambda_{max} = 225$ ($\epsilon = 57{,}000$), 287 (20,500) and 295 nm (20,600). $\lambda_{min} = 258$ nm (12,300).

The mass spectrum shows peaks at m/e 660 (M + CH_2), 646 (M), 615, 588, 529, 477, 464, 453, 451, 438 and 420. The NMR spectrum ($CDCl_3$) is described above. (Anal.: found N 8·28: calc. 8·68%.) pK_a (MCS/H_2O 80/20) = 7·15.

Acid cleavage of 18′-*decarbomethoxyvoacamine* (9). 5 mg of (9) were refluxed with 2 ml HCl 2 N for 90 min. After cooling, the solution was basified with 10% NH_4OH and extracted with $CHCl_3$. The resulting mixture was studied by TLC: (1) R_f(MeOH): 0·08, 0·23, 0·34 and 0·44 (ref.: authentic ibogaine (2) = 0·34). (2) R_f (EtOAc): 0·04, 0·20, 0·30 and 0·54 (ref.: authentic ibogaine = 0·54).

O-*benzoylvoacristine*. 165·5 mg of voacristine (1), 1 ml of benzoyl chloride and 3 ml of dry pyridine were heated for 1 hr in a sealed flask at 100°. The mixture was allowed to cool and extracted with $CHCl_3$ after neutralization by NH_4OH. The reaction products were separated by preparative TLC yielding 34 mg of pure *O*-benzoylvoacristine.

The i.r. spectrum shows 2 C=O bands (1730 and 1755 cm^{-1} in CCl_4 and 1730 and 1740 cm^{-1} in KBr), together with a strong band at 730 cm^{-1} attributed to the benzene ring of the benzoate. The mass spectrum shows a molecular ion at 488 m.u. and fragmentation peaks at 473, 429, 399, 383, 366, 340, 283, 244, 225, 194, 184, 160, 149, 136, 122 and 105 m.u. $[\alpha]^{25}_{D} = +3{\cdot}4°$ ($c. = 1{\cdot}5$, $CHCl_3$); $[M]^{25}_{D} = +17°$.

Acknowledgements—The authors wish to thank Professor R. H. Martin for his stimulating interest. They also thank the "Institut pour l'encouragement de la Recherche Scientifique dans l'Industrie et l'Agriculture" (A. G.) and the "Fonds National de la Recherche Scientifique" (C. H.) for the award of fellowships to two of them and the "Fonds de la Recherche Scientifique Fondamentale Collective" for financial support.

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[19] D. F. Dickel, C. L. Holden, R. C. Maxfield, L. E. Peszek and W. I. Taylor, *J. Am. Chem. Soc.* **80**, 123 (1958).