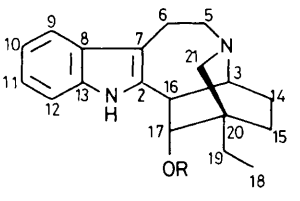
Isolation and Structure Determination of (±)-16-Hydroxy-*allo*-ibogamine from *Strychnos ngouniensis*

Georges Massiot,[a]* Marie-José Jacquier,[a] Philippe Thepenier,[a] Jean Lévy,[a] Louisette Le Men-Olivier,[a] Clément Delaude,[b] Jean Guilhem,[c] and Claudine Pascard[c]

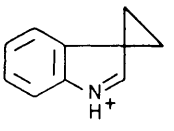
[a] *Faculté de Pharmacie, ERA au CNRS n° 319, 51 rue Cognacq-Jay, 51096 Reims Cédex, France*
[b] *Université de Liège, Sart-Tilman, 4000, Liege, Belgium*
[c] *Institut de Chimie des Substances Naturelles, CNRS, 91190 Gif-sur-Yvette, France*

The isolation and structure of (±)-16-hydroxy-*allo*-ibogamine (**1**) the first natural *allo* iboga alkaloid, are described.

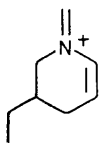
Although the conversion of tabersonine into *allo* catharanthine was reported more than a decade ago,[1] such rearranged alkaloids have not yet been found in nature. While investigating the minor alkaloids of *Strychnos ngouniensis*[2] from Zaire,† we have isolated (±)-16-hydroxy-*allo*-ibogamine (**1**),‡ the first natural member of the *allo* iboga class of alkaloids. Compound (**1**) is an indole as shown by its u.v. absorptions: λ_{max} (MeOH) (log ϵ): 228 (4.43), 285 (3.85), and 292 nm (3.81). Its empirical



(1) R = H
(2) R = COMe
(3) R = C(:O)C_6H_4Br-*p*



(a)
m/z 144



(b)
m/z 124

† Plant samples were collected under the 'Etude phytochimique de la flore du Zaire' research project.

‡ Amorphous: $[\alpha]_D$ 0° ($CDCl_3$); R_f 0.38 (CH_2Cl_2–MeOH–NH_4OH, 94.5:5:0.5, Whatman plate K6F); transient blue colour with Ce^{IV} spray; approximate yields 8% (root) and 4% (stem) of the crude alkaloid mixture; ^1H n.m.r. (402 MHz; $CDCl_3$; $SiMe_4$) δ 8.42 (1H, s, NH), 3.74 (1H, br. s, $w_{\frac{1}{2}}$ 4 Hz, 17-H), 3.25 (2H, m, 5-H), 3.16 (1H, br. d, *J* 4 Hz, 3-H), 2.87 (1H, d, *J* 11 Hz, 21-H), 2.83 (2H, t, *J* 2 Hz, 16-H), 2.74 (1H, br. d, *J* 11 Hz, 21-H′), 2.70 (1H, m, 6-H), 1.98 (1H, ddd, *J* 4, 10, and 11 Hz, 14-H), 1.72 (3H, m, 6-H, 6-H′, and 15-H), 1.46 (1H, br. t, *J* 10 Hz, 14-H′), 1.33 (2H, m, 19-H), and 0.78 (3H, t, *J* 7 Hz, 18-H); ^{13}C n.m.r. (CD_3OD) δ 138.8 (C-2), 134.9 (C-13), 128.8 (C-8), 120.7 (C-11), 118.5 (C-10), 117.3 (C-9), 110.2 (C-12), 108.5 (C-7), 77.1 (C-17), 55.5 (C-3), 53.4 (C-21), 50.7 (C-5), 50.6 (C-16), 35.9 (C-20), 27.6 (C-19), 27.3 (C-14), 21.9 (C-15), 19.6 (C-6), and 7.2 p.p.m. (C-18).

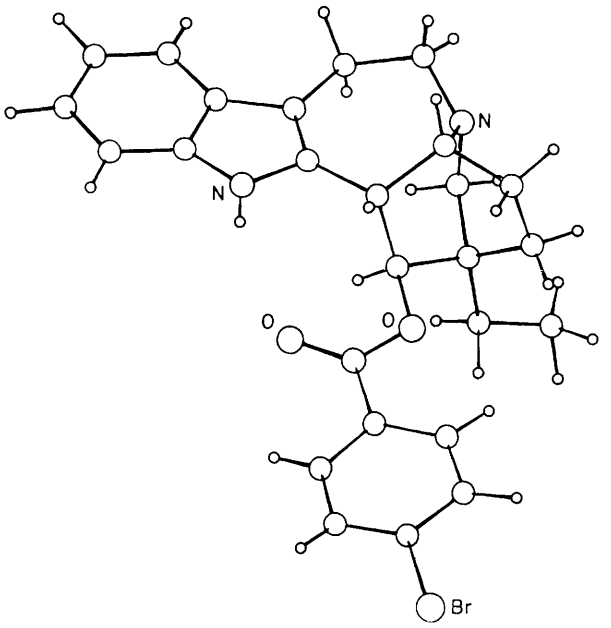
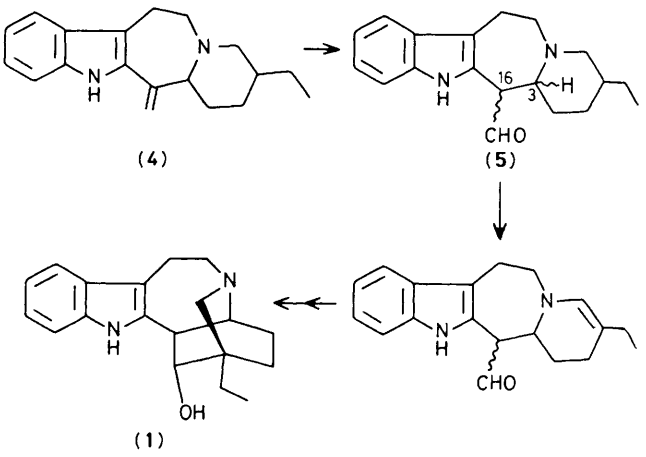


Figure 1. A perspective view of (**3**). H, C, N, O, and Br atoms are shown as circles of increasing diameter.

formula, determined by high resolution mass spectroscopy, is $C_{19}H_{24}N_2O$ (M^+ *m/z* 296.1862, 100%); main fragments are found at *m/z* 278 ($M^+ - H_2O$), 267 ($M^+ - C_2H_5$), 249 ($M^+ - H_2O - C_2H_5$), 172 ($M^+ - 124$), 144 (a), and 124 (b). Its i.r. spectrum shows NH and/or OH bands at 3390 and 3260 cm^{-1} (KBr), but no CO vibrations. Its ^1H n.m.r. spectrum can be only partly analysed at 402 MHz;‡ the most salient feature is the presence of signals corresponding to an ethyl chain bound to a quaternary carbon atom, a rare characteristic among *Strychnos* alkaloids. More structural insight is gained from its ^{13}C n.m.r. spectrum,‡ which shows signals for 8 low field (4 CH + 4 C) and 11 high field carbons (1 C, 3 CH, 6 CH_2, 1 CH_3). This accounts for 22 of the 24 protons of (**1**); the remaining two protons are an indole N–H and an O–H. The presence of an alcohol function is supported by the conversion of (**1**) into the acetate (**2**).§

Despite the fact that these data only fitted a limited number of structures, among which (**1**) was favoured, as a further check the structure of the *p*-bromobenzoate (**3**)¶ was determined by *X*-ray crystallography (Figure 1). A yellowish crystal, *ca.* 0.5 × 0.2 × 0.05 mm^3, was mounted on a diffractometer and 2704 reflections were collected [$I > 3\,\sigma(I)$]. No symmetry was detected and the cell parameters are a = 12.676(6), b = 11.584(6), c = 7.756(4) Å, α = 92.90(4), β = 101.38(6), γ = 88.03 (4)°. The structure was solved by the heavy atom method in the space group $P1$. Comparison between both molecules in the asymmetric unit proved the compound to be racemic and so the space group $P\bar{1}$ was adopted. All hydrogen atoms were located in Fourier difference syntheses and their positions refined. Large-block least-squares anisotropic refinement led to an *R* factor of 6.6%, and the structure is shown in Figure 1.**



Scheme 1

Compound (**1**) possesses the *allo* iboga skeleton with the ethyl side chain in a bridgehead position; the secondary hydroxy group is *endo* on the tryptamine side of the isoquinuclidine system. The most unexpected aspect of (**1**) is the fact that it is racemic. Although the occurrence of racemic compounds among indole alkaloids is known and may be related to thermal processes through achiral intermediates,[3,4] the substitution pattern of (**1**) makes this kind of reaction electronically disfavoured. The presence of ngouniensine (**4**),[5] and of epingouniensine,[2] along with (**1**) suggests another biogenetic pathway to (**1**), involving oxidation of ngouniensine (**4**) to aldehyde (**5**), a compound in which C-3 and C-16 may be epimerized; final ring closure may be brought about through enamine chemistry followed by reduction (Scheme 1). Aldehyde (**5**) may also be derived from preakuammicine according a scheme analogous to the one proposed for the formation of (**4**).[5]

Alternative pathways, in which (**1**) would originate from *aspidosperma* precursors, are probably unfavourable since no related compounds have been isolated.

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References

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2 For other alkaloids of *S. ngouniensis* and details of the extraction procedure, see: G. Massiot, P. Thepenier, M. J. Jacquier, J. Lounkokobi, C. Mirand, M. Zeches, L. Le Men-Olivier, and C. Delaude, *Tetrahedron*, 1983, in the press.
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§ Mass spectrum: 338 (M^+, 100%), 295, 279 (60%), 208 (60%), 172, 144, 124, 122, 111, and 85 (70%); i.r.: 3420, 1730, and 1250 cm^{-1}; ^1H n.m.r. (402 MHz) δ 9.02 (s, 1H), 4.51 (br. s, 1H), 3.35 (br. s, 1H), 3.06 (br. s, 1H), 2.17 (s, 3H), 1.3 (m, 2H), and 0.74 (t, *J* 7 Hz, 3H).

¶ Crystals from MeOH–H_2O; m.p. 165 °C (softening) then 183—188 °C; u.v. λ_{max} (MeOH): 230, 247, 275, 285, and 290 nm; mass spectrum: 480, 478 (M^+, 60%), 350, 348 (20%), 295, 279 (100%), 278 (65%), 249, 208, 185, 183 (40%), 130, 124, 122, and 85 (15%); i.r.: 3420, 1710, 1590, and 1270 cm^{-1}.

** The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.