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STRYCHNOZAIRINE, AN INDOLE ALKALOID FROM *STRYCHNOS VARIABILIS*

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Key Word Index—*Strychnos variabilis*; Loganiaceae; root bark; indoline alkaloids; strychnozairine; structural elucidation.

Abstract—Through a combination of spectroscopic techniques (UV, IR, mass spectrometry and NMR) it has been possible to show that strychnozairine, an alkaloid isolated from the root bark of *Strychnos variabilis*, is N_1-acetyl-16-*R*-formyl-19-oxo-20,21-didehydrostrychnane.

INTRODUCTION

Extensive studies in our laboratory on the constituents of the African plant *Strychnos variabilis* de Wildeman have resulted in the isolation of a number of alkaloids, of which 22 have been fully characterized [1–12]. We now wish to report on the structural elucidation of a remaining minor alkaloid, which we have named strychnozairine. The name strychnozairine was chosen because *S. variabilis* was collected in the province of Kinshasa in Zaire, where the species is abundant but endemic. As will be shown, its structure **1** is of interest because of its unusual oxidation pattern.

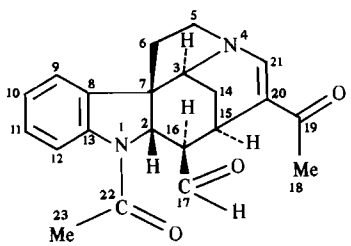
RESULTS AND DISCUSSION

The elemental composition $C_{21}H_{22}N_2O_3$ was established by high-resolution mass measurement of the $[M]^+$ (observed value: 350.1630; calculated value: 350.1630). The peaks at *m/z* 322 and 307 are due to the loss of >C=O and –C(=O)–Me. Besides the ubiquitous *m/z* 130, 143, 144 ions characteristic of the tryptamine moiety, the most diagnostic peaks were found at *m/z* 186 (indole nitrogen acetylated) and 135 (acetylpiperideine instead of ethylpiperidine with *m/z* 121, 122 ions).

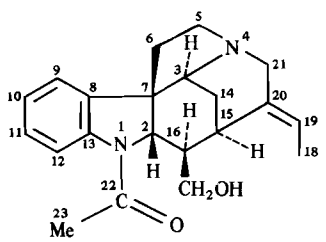
The UV absorption spectrum, suggestive of an indoline, in addition exhibited a strong extinction in the 305 nm region, which revealed the existence of a second chromophore. The UV spectrum was similar to that of vallesiachotamine (high extinction in the 290 nm region attributed to β-diethylaminocrotonyl chromophore [13]).

The IR spectrum exhibited a band at 1725 cm^{-1} assignable to a saturated carbonyl, e.g. aldehyde grouping, and a broad band at 1640 cm^{-1} attributable to an *N*-acetyl indoline and to an $\alpha > \beta$ unsaturated carbonyl grouping.

A more detailed understanding of the structure of the molecule was gained from its 360 MHz ^1H NMR spectrum. As in other *N*-acetyl indolinic alkaloids, the restricted rotation around the >N–C(=O)–Me bond can give rise to two rotamers: rotamer **a** (12%) with acyl oxygen oriented towards the aromatic ring and rotamer **b** (88%) shown in **1**. Conspicuous signals are an aldehydic proton at δ9.30 (H-17); four aromatic signals from an *N*-acetyl indoline moiety at δ7.13, 7.16, 7.22 and 7.30; a singlet at 7.42 due to H-21; and two methyl singlets at δ2.38 and 2.26. Other signals are attributable to systems of mutually coupled hydrogens, $-CH_2-CH_2$ (C5–C6), >CH–CH_2–CH< (C3–C14–C15), >CH–CH–CH< (C2–C16–C17), previously recognized in the spectra of



1 Strychnozairine



2 Isoretuline

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Table 1. ^{13}C NMR spectral data of strychnozairine rotamer **b** (**1**) and isoretuline (**2**)

Carbon	1	2 [19]
2	62.84*	70.2
3	59.40*	61.6
5	49.64	53.8
6	39.6	42.4
7	53.1	52.3
8	134.8	137.2
9	122.4†	122.3
10	124.6†	125
11	128.4†	127.3
12	116.4†	117.2
13	140.4	140.4
14	24.15‡	28.4
15	24.71‡	31.5
16	56.55*	47.3
17	201.9	64.7
18	23.47‡	12.8
19	194.2	120.2
20	n.s.	135.2
21	151.6	58.8
22	172.8	170.0
23	23.47‡	22.8

*,†,‡These values may be interchanged.
Chemical shift, ($CDCl_3$) + 76.9 ppm. n.s.: not seen.

isoretuline (**2**) and related alkaloids. However, there was no signal for an ethylidenic chain, suggesting that this region of the molecule had become part of an enone system.

The 50.29 MHz ^{13}C NMR spectrum of the alkaloid showed three carbonyl resonances at δ201.95 (aldehyde), 194.0 (enone) and 172.0 (amide). In addition, it confirmed the constitution of the enone moiety. There was a monoprotonated sp^2 carbon atom at δ151.6, a value characteristic of the β-atom in a β-dialkylaminoenone (the protonated α-carbon lies at $\sim \delta$130 [14, 15]). This settled the constitution of strychnozairine as shown in **1**. The remainder of the ^{13}C spectrum showed the aromatic resonances of the indoline and the aliphatic carbons with their proper multiplicities. The limited amount of the alkaloid precluded their firm assignment by the usual double-resonance techniques.

There are marked similarities in the CD spectra of strychnozairine and other *N*-acylindoline alkaloids, such as strychnine [16], retuline and derivatives [10], which show a 2β-H, 7β configuration in the vicinity of the main chromophoric group. Thus, the configurations of C-2 (2*S*) and C-7 (7*R*) are deduced from negative CD in the spectral region of 210–220 nm, and positive CD in the region of 240–250 nm. The 15α-H (15*R*) and 3α-H (3*S*) configurations are strictly dependent on the configuration of C-7 [17] and are in close agreement with the biogenetic hypothesis. (In this communication, the numbering system is that of Le Men and Taylor [18] is used.)

The stereochemistry of C-16 was examined by ^1H NMR spectroscopy. The observation of a 10 Hz vicinal coupling constant between H-16 and H-2 suggested the 16α-H (16*R*) configuration, as in isoretuline [4]. Using the analysis of the ^1H NMR parameters published [4], one may build a molecular stereo-model of strychnozairine in which the E-ring is in a chair form and the D-ring in a half-chair conformation.

EXPERIMENTAL

Plant material. Root bark of *S. variabilis* was collected by M. Franz (voucher specimen Evrard 6592, Herbarium of the Botanical Garden of Belgium) in the province of Kinshasa, Zaire.

Isolation. Extraction followed the usual protocol, which has been described elsewhere [2]. Strychnozairine is present in the fraction containing aldehydic alkaloids (isoretulinal and derivatives) and strychnopivotine [6, 7]. Complex mixtures were purified by a combination of medium pressure LC (Lobar®) and prep. TLC on silica gel (2 mm) in the system Me_2CO–MeOH–40–60° petrol (25:25:1).

Spectral analysis of **1**. UV λ_{max}^{MeOH} nm (log ε): 305 (4.1), 251 (3.98), 212 (4.3). IR ν_{max}^{KBr} cm^{-1}: 2935 (C–H), 1725 (>C=O), 1638 (N–C(=O)–Me, >C=C–C(=O)–), 1600 (C=C), 1487, 1400, 1120, 925, 775 (*O*-disubstituted C_6H_6). MS **a** EI *m/z* (rel. int.): 350 (14) $[M]^+$ ($C_{21}H_{22}N_2O_3$—measured: 350.1630; calc.: 350.1630), 322 (58), 307 (39), 280 (8), 279 (15), 265 (2), 263 (2), 251 (2), 236 (3), 221 (2), 207 (2), 194 (2), 186 (15), 180 (5), 168 (8), 167 (9), 158 (7), 156 (6), 150 (5), 149 (6), 145 (22), 144 (100), 143 (16), 136 (5), 135 (28), 130 (19), 117 (8), 115 (6), 43 (36). MS **b** FAB *m/z* (rel. int.): 352 (10), 351 (39) $[M+1]^+$, 322 (3), 180 (3), 170 (3), 158 (3), 156 (4), 144 (44), 143 (6), 136 (1), 130 (10), 115 (6), 44 (76), 42 (100). ^1H NMR (360 MHz, $CDCl_3$, 273 K) (superscripts a and b indicate assignments for rotamers **a** and **b**, respectively): δ9.57 (*s*, H-17^a), 9.30 (*d*, H-17^b, $J_{17,16}$ = 6 Hz), 7.87 (H-12^a), 7.42 (H-21^b), 7.32 (H-21^a), 7.30 (*t*, H-10^b), 7.22 (*d*, H-9^b), 7.16 (*t*, H-11^b), 7.13 (*d*, H-12^b), 4.78 (*d*, H-2^b, $J_{2,16}$ = 10 Hz), 4.28 (*d*, H-2^a), 3.78 (*br s*, H-3^b, $W_{1/2}$ = 7.5 Hz), 3.71 (H-5A^b, $J_{5A,5B}$ = 11.2 Hz), 3.53 (H-5B^b), 2.79 (*d*, H-16^a), 2.40 (H-6A^b and Me-23^a), 2.38 (Me-23^b), 2.26 (H-16^b and Me-18^b), 2.20 (Me-18^a), 2.17 (H-14A^b, $J_{14A,14B}$ = 12.5 Hz), 1.92 (H-14B^b), 1.83 (H-6B^b). ^{13}C NMR (50.29 MHz, $CDCl_3$, 273 K): see Table 1. CD: $\Delta\varepsilon_{212} - 9.27$; $\Delta\varepsilon_{243} + 1.75$; $\Delta\varepsilon_{259} - 1.75$; $\Delta\varepsilon_{305} + 16.45$ (MeOH; *c* 0.004).

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