Phytochemistry, Vol. 27, No. 2, pp. 595–597, 1988.
Printed in Great Britain.

0031-9422/88 $3.00 + 0.00

STRYCHNOCHROMINE, AN UNUSUAL C_{18} INDOLINE ALKALOID FROM *STRYCHNOS GOSSWEILERI*

LUC ANGENOT, CLAUDE COUNE,* JOËLLE QUETIN-LECLERCQ and DIRK TAVERNIER†

Laboratoire de Pharmacognosie, Université de Liège, Rue Fusch, 5, B-4000 Liège, Belgium; † Laboratorium voor Organische Chemie, Rijksuniversiteit Gent, Krijgslaan, 281 (S4), B 9000 Gent, Belgium

(*Received* 7 *May* 1987)

Key Word Index—*Strychnos gossweileri*; Loganiaceae; indole alkaloid; strychnochromine; plane structure; relative configuration.

Abstract—Through a combination of spectroscopic techniques (UV, IR, MS, ^{1}H and ^{13}C NMR) it has been possible to deduce the plane structure and the relative configuration of strychnochromine, a dextrorotatory alkaloid, isolated from the root bark of *Strychnos gossweileri*. The alkaloid is 4a-(2-hydroxyethyl)-4-oxo-1,2,2a,3,4,4a,5,10,11,12a-decahydropyrrolizino-[1,7-*cd*]-carbazol.

INTRODUCTION

Extensive study of the constituents of the African plant *Strychnos gossweileri* has resulted in the isolation of a number of alkaloids among which is the new and peculiar compound, strychnochromine [1–5]. The name strychnochromine, derived from χρωμα (Greek = colour), was chosen by one of us (C.C.) because this substance was the only alkaloid from *ca* 100 isolated at Liège from numerous Strychnos species, to present notable and stable colours with various TLC spray reagents (see Experimental) [3, 6]. As will be shown, its structure (**1**) is of interest because of its unusual skeleton.

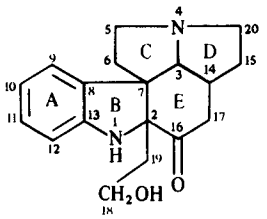
RESULTS AND DISCUSSION

The elemental composition $C_{18}H_{22}N_2O_2$ was established by high-resolution mass measurement of the $[M]^+$ at *m/z* 298. Beside the ubiquitous *m/z* 130, 143 and 144 characteristic of the tryptamine moiety, the most important peaks were found at *m/z* 229, 200 (base peak), 187, 182 and 112.

The presence of a hydroxyl group, suspected by the peak at *m/z* 281 (loss of OH), was confirmed by acetylation of **1** (pyridine–Ac_2O) at room temperature. Comparison of the mass spectrum of **1** with that of the acetylated derivative revealed that the peaks at *m/z* 298, 229, 200 and 187 were shifted to 340 $[M]^+$, 271 $[M-C_4H_5O]^+$, 242 $[M-C_5H_8NO]^+$ and 229 $[M-C_6H_9NO]^+$, respectively, in the monoacetylated derivative.

The UV absorption spectrum, suggestive of an indoline, exhibited in addition a significant absorbance in the 330 nm region, which revealed the existence of a further chromophore. The UV spectrum is somewhat reminiscent of that of a 2-acylindole [7, 8]. [The lone-pair electrons of the amino function (N-1) attached to the benzene ring may interact with the π-system of the carbonyle chromophore]. The IR spectrum exhibited a band at 1700 cm^{-1} assignable to a carbonyl, possibly a ketone, and a band at 745 cm^{-1}, attributable to an *ortho*-disubstituted benzene ring.

A more detailed understanding of the structure of the molecule was gained from its 360 MHz ^{1}H NMR spectrum (Table 1). In addition to the expected foursome of resonances from the aromatic nucleus, there are two mobile protons (NH/OH) and three mutually non-interacting spin systems, two $-CH_2CH_2-$ units and one $-C(=O)-CH_2-CH(-CH)-CH_2CH_2-$ system. One of the ethylene units is due to an hydroxyethyl ($HOCH_2CH_2-$) appendage, as is shown by the characteristic high-frequency shift of the $-OCH_2$ resonances in *O*-acetyl strychnochromine. The second ethylene unit probably arises from a tryptamine moiety; it features a noteworthy chemical shift difference of δ1.31 for the two diastereotopic hydrogen atoms of one of the methylenes. In the eight spin system $-C(=O)-CH_2-CH(-CH)-CH_2CH_2-$ the presence of a carbonyl next to the lone methylene group rests on two properties of the hydrogen atoms. Firstly the magnitude of the *gem* coupling constant (−17 Hz) and secondly their very easy exchange for deuterium on treatment of strychnochromine with de-



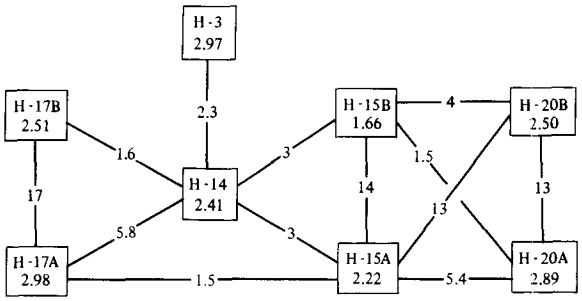
1

*Present address: Technical Secretariat of the European Pharmacopœia Commission, Council of Europe, F 67006 Strasbourg Cédex, France.

Table 1. Chemical shifts of hydrogens in **1** (360 MHz, $CDCl_3$*, TMS as internal standard)

H	Chemical shift	H	Chemical shift
3	2.97	15A	2.22
5A	3.18	15B	1.66
5B	2.95	17A	2.98
6A	3.27	17B	2.51
6B	1.96	18A	3.94
9	6.94	18B	3.95
10	6.62	19A	2.50
11	7.02	19B	2.18
12	6.53	20A	2.89
14	2.41	20B	2.50

*Certain shift equivalences in $CDCl_3$ are raised in mixtures of $CDCl_3$–C_6H_6, sometimes at the expense of creating new ones. All couplings were verified by double irradiation experiments. Resolution enhancement was used in the extraction of the coupling constants. Coupling constants (Hz) $J_{6A,6B}=12.8$; $J_{5A,5B}=12.4$; $J_{6A,5A}=6$; $J_{6A,5B}=8.5$; $J_{6B,5A}=10.5$; $J_{6B,5B}=4$; $J_{18A,18B}=11.2$; $J_{19A,19B}=14.8$.



Scheme 1. Chemical shifts and coupling constants of selected ^1H spin systems of **1**.

uterium oxide. The chemical shift of the distal methylene and of the methine shows that they must be bonded to nitrogen.

On the basis of the above data, we propose that strychnochromine has structure **1**. The formula explains why after reacting strychnochromine with an excess of methyl iodide/sodium hydride the FAB mass spectrum indicates $[M]^+$ at *m/z* 355, i.e. an increment of 57 mass units. There are indeed four methylation sites, OH, NH (indoline), N (quaternization) and the enol form of the ketone.

The ^{13}C NMR chemical shifts of strychnochromine are presented in Table 2; they are fully supportive of structure **1**. There is a ketonic carbonyl, four protonated and two non-protonated aromatic carbon atoms, one of which has a relatively small δ value, while the aliphatic region contains two non-protonated carbons, two methines and seven methylenes. Three of the methylenes, C-17 and those of the hydroxyethyl side-chain, were unambiguously assigned by reference to C-17 deuterated and to *O*-acetyl strychnochromine, respectively. The pair of methylenes at δ55 and 44 has a larger sum of ^1J H, ^{13}C coupling than the pair of methylenes at *ca* δ28, which shows that the former carbons are bonded to nitrogen and must be assigned to the pair (C-5, C-20). It follows that the pair (C-15, C-6) lies at *ca* δ28 and such a δ value for C-6 is rather small in comparison with numerous other indoline alkaloids [9].

There remains to consider the stereochemistry of strychnochromine, i.e. the relative configuration of the four asymmetric carbon atoms. The small ^3J H-3, H-14 (2.3 Hz) shows that the rings E and D are *cis*-fused. In ring D, the CH_2CH_2 fragment features for one pair of vicinal protons a very large coupling constant (13 Hz), and for the other pair a very small one (1.5 Hz) which constitutes evidence that this ring assumes a unique conformation with a large torsion angle C-14–C-15–C-20–N-4. But because the opposite part of the D ring must be relatively unpuckered, rings C and D are *cis*-fused. Based on the following facts and reasoning, E and C are also *cis*-fused. H-14 is equatorial with respect to ring D, because ^3J to both C-15 hydrogens is small, but also with respect to ring E, and for the same reason. This peculiar orientation is confirmed by a long-range coupling of 1.5 Hz between the axial H-15 atom and one of the H-17 atoms, which implies that the torsion angles defined by the atoms H–C-17–C14–C-15–H under consideration are both *anti* (*W* pattern of long-range coupling). Thus, not only is C-14–C-17 axial with respect to D, but C-17–C-16 continues that path away from D, and then for geometric reasons E and C and *cis*-fused. As a corollary, a twist conformation may be ascribed to ring E—nothing exceptional for a cyclohexanone. The tricyclic moiety C, D, E is thus all-*cis* configured. As far as the B, E fusion is concerned, a number of chemical shift phenomena that we have drawn attention to earlier are rationalized by accepting a *syn*-periplanar (eclipse) orientation of the C-7–C-6 and the C-2–C-19 bonds: the truly enormous chemical shift difference of H-6 A and H-6 B, the low frequency position of C-6 and perhaps even the chemical shift of C-8. By implication, the rings E and B are *cis*-fused.

Concerning the absolute stereochemistry of strychnochromine, we feel that it would be hazardous to deduce it from the presently reported chiroptical properties because adequate model or reference compounds are lacking. The absolute configuration can in principle also be obtained by Bijvoet X-ray diffraction on single crystals but so far we have failed to obtain strychnochromine in the crystalline state.

Structure **1** is notable for two reasons, the pyrrolizidine moiety (rings C and D) instead of the concomitant presence of pyrrolidine (ring C) and piperidine (ring D) and the hydroxyethyl side chain located at C-2 rather than at C-20. Strychnochromine presents some analogies but also striking differences from desethylibophyllidine and other alkaloids of the 21-nor-(+) pandolane type, previously isolated from the leaves of *Tabenanthe iboga*, *T. subsessilis* and *Tabernaemontana albiflora* [10, 11]. Therefore, **1** might arise biogenetically by oxidative fission of the 20–21 bond of a hypothetical precursor and loss of C-21 followed by contraction of the usual piperidine ring and migration of the sidechain (C-18–C-19) to C-2.

Table 2. ^{13}C NMR spectral data of **1** (22.4 MHz, $CDCl_3$, TMS as internal standard)

C	Chemical shift	Multiplicity	C	Chemical shift	Multiplicity
2	58.4	*s*	12	112.0	*d*
3	67.3	*d*	13	143.6	*s*
5	44.7[a]	*t*	14	40.5	*d*
6	27.5[b]	*t*	15	28.0[b]	*t*
7	53.8	*s*	16	206.7	*s*
8	119.2	*s*	17	42.0	*t*
9	126.4	*d*	18	58.5	*t*
10	116.9	*d*	19	38.5	*t*
11	128.0	*d*	20	55.2[a]	*t*

[a,b] These values may be interchanged.

EXPERIMENTAL

Plant material. Root bark of *S. gossweileri* Exell. was collected at Matadi in the Bas-Zaïre region (province of Kinshasa) of Zaïre (Voucher specimen DUVIGNEAUD 193, Herbarium of the National Botanical Garden of Belgium at Meise).

Isolation. Extraction followed the usual procedure, which has been described elsewhere [1, 3]. Strychnochromine is a minor alkaloid present in the fraction of tertiary alkaloids containing mainly dolichantoside. The mixt. was purified by prep. TLC on silica gel (2 mm) in the system EtOAC–*iso*PrOH–NH_4OH (16:3:1) and elution with MeOH from which **1** is pptd by Et_2O. The free base is a white and amorphous powder, sol. in $CHCl_3$ and MeOH. NMR spectra were run in $CDCl_3$ (^{13}C) or in $CDCl_3$–C_6D_6 (^1H). Strychnochromine must be stored in a cool, dry place, protected from light.

Detection of **1** *by TLC.* Colour reactions [12]: (i) H_2SO_4 gives a violet colour, stable for several years [6], (ii) $Ce(SO_4)_2$ in H_2SO_4 gives a red colour turning violet after some hr, (iii) $FeCl_3$ in $HClO_4$ also gives a red colour turning violet, (iv) Van Urk's reagent (*p*-dimethylaminobenzaldehyde–HCl) gives a colour varying from turquoise to violet after some hr, (v) Gibbs's reagent (dibromoquinonechlorimide) also gives a turquoise colour slowly turning violet.

Spectral analysis of **1**. UV λ_{max}^{MeOH}: nm (log ε) 208 (4.46), 248 (4.23), 330 (3.43). IR ν_{max}^{KBr} cm^{-1} 3400, 2930, 1700 (>C=O), 1600, 1480, 1440, 1405, 1320, 1260, 1105, 1040, 745 (unsubstituted indoline ring) cm^{-1}. EIMS 70 eV, *m/z* (rel. int.) 298 $[M]^+$ ($C_{18}H_{22}N_2O_2$ obs. 298.1681; calc. 298.1672), 281 (12), 253 (5), 229 (27), 200 (100), 187 (52), 182 (27), 172 (22), 169 (15), 156 (8), 154 (8), 144 (9), 130 (10), 112 (18). Peak matching measurements on acetylated **1**: 340.1783 ($C_{20}H_{24}N_2O_3$ requires 340.1786), 281.1648 ($C_{18}H_{21}N_2O$ requires 281.1653), 271.1443 ($C_{16}H_{19}N_2O_2$ requires 271.1446), 242.1175 ($C_{15}H_{16}NO_2$ requires 242.1181), 229.1104 ($C_{14}H_{15}NO_2$ requires 229.1103), 182.0969 ($C_{13}H_{12}N$ requires 182.0970). CD: $\Delta\varepsilon(\lambda_{max})$: +28.3 (330 nm), −4.3 (288 nm), −13 (265 nm), +8.6 (235 nm) in MeOH (c = 0.005). $[\alpha]_D^{20}$: +600° (MeOH; c 0.05). ^1H and ^{13}C NMR data: see Tables 1 and 2.

Acknowledgements—We sincerely thank Prof. N. G. Bisset (King's College, University of London) for his kind interest and discussion of this work. Thanks are also due to Dr E. De Pauw (Institut de Chimie, Université de Liège) for MS measurements.

REFERENCES

1. Coune, C. and Angenot, L. (1978) *Planta Med.* **34**, 53.
2. Coune, C. and Angenot, L. (1978) *Phytochemistry* **17**, 1447.
3. Coune, C. (1978) *Pl. Med. Phyt.* **12**, 106.
4. Coune, C. and Angenot, L. (1980) *Herba Hungarica* **19**, 189.
5. Coune, C., Tavernier, D., Caprasse, M. and Angenot, L. (1984) *Planta Med.* **50**, 93.
6. Denoël, A., Jaminet, F., Detilleux, G., Van Sumsen, M. and Merveille, L. (1953) *Contribution à l'étude chimique des Strychnos du Congo Belge* p. 155. Ministère des colonies, Bruxelles.
7. Tits, M. Tavernier, D. and Angenot, L. (1980) *Phytochemistry* **19**, 1531.
8. Verpoorte, R. (1986) *J. Nat. Prod.* **49**, 1.
9. Verpoorte, R., Van Beek, T. A., Riegman, R. L. M., Hylands, P. J. and Bisset, N. G. (1984) *Org. Magn. Res.* **22**, 328 and 345.
10. Khuong-Huu, F., Cesario, M., Guilhem, J. and Goutarel, R. (1976) *Tetrahedron* **32**, 2539.
11. Kan, C. Husson, H. P., Jacquemin, H., Kan, S. K. and Lounasmaa, M. (1980) *Tetrahedron Letters* 55.
12. Baerheim-Svendsen, A. and Verpoorte, R. (1983) *J. Chromatogr. Library* Vol **23A**, *Chromatography of Alkaloids* part A *TLC*. Elsevier, Amsterdam.