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3-HYDROXYDIABOLINE, A TERTIARY ALKALOID FROM *STRYCHNOS CASTELNAEANA**

C. GALEFFI, M. PATAMIA†, M. NICOLETTI†, I. MESSANA and G. B. MARINI-BETTOLO†

Laboratorio di Chimica del Farmaco, Istituto Superiore di Sanità, v. le Regina Elena 299, Roma, Italy; †Cattedra di Chimica Generale ed Inorganica, Istituto dell'Orto Botanico, Università degli Studi di Roma, L. Cristina di Svezia 24, Roma, Italy and Centro CNR di Chimica dei Recettori e delle Molecole Biologicamente Attive, Istituto di Chimica, Università Cattolica del Sacro Cuore, via della Pineta Sacchetti 644, Roma, Italy

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Key Word Index—*Strychnos castelnaeana*; Loganiaceae; alkaloids; 3-hydroxydiaboline; ^{13}C NMR.

Abstract—A new alkaloid, 3-hydroxydiaboline, together with diaboline, was isolated from the upper stem bark of *Strychnos castelnaeana*. The structure of 3-hydroxydiaboline was confirmed by partial synthesis involving rearrangement of diaboline *N*-oxide; in this reaction, 5-oxodiaboline was obtained, as a secondary product. 3-Hydroxydiaboline in a tautomeric keto-aminic form, reacts with methyliodide giving rise to an *N*-methyl-*sec*-pseudo derivative.

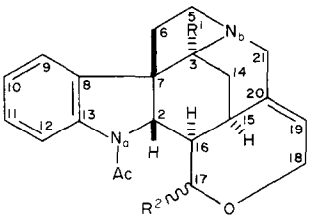
INTRODUCTION

Strychnos castelnaeana is a South American *Strychnos* which was described as the main ingredient of Ticuna curare [1]. In 1787 in Florence this curare was the first to be studied by Felice Fontana, who could in effect detect its particular activity, later indicated as curarizing. In the root bark of *S. castelnaeana* (no. 43, R. Cardosa de Oliveira, B. da Silva & A. Silva [2], collected in the Rio Solimões basin, Brazil, diaboline (**2**) and alkaloid D were identified, whereas from the lower and the middle stem bark, **2** and jobertine (α-*O*-acetyldiaboline) (**8**) were obtained. The isolation and identification of a new alkaloid, 3-hydroxydiaboline (**1**) (0.004%), together with **2** (0.011%) from the upper trunk bark is now reported.

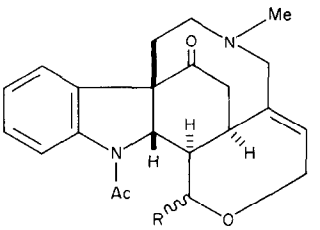
RESULTS AND DISCUSSION

1, $C_{21}H_{24}N_2O_4$, mp 218–221°, M^+ *m/z* 368 (3%), is a N_a-acyl-indolinic alkaloid on the basis of its UV spectra. The IR spectrum shows carbonyl group absorption at 1660 cm^{-1} and that of a hydroxy group at 3480 cm^{-1}, whereas the peaks at *m/z* 130 and 144 [3] in the mass spectrum suggest the indoline-β-CH_2CH_2-N_b sequence. Owing to the restricted rotational mobility of the N_a-acetyl group (δ 2.32, *s*) and the resulting *cisoid* and *transoid* conformations (l.c.), the ^1H NMR spectrum of **1** is remarkably complicated, whereas in the ^{13}C NMR PND spectrum many more signals than the expected 21 carbon atoms are present.

As with diaboline, **2**, the ^1H NMR spectrum of **1** shows typical signals of an oxepinic ring, such as the olefinic H-19, between δ 5.6 and 5.9, and the anomeric H-17 (δ 5.21, *d*, J = 2 Hz), which moves to δ 6.07 in the acetyl derivative (**6**), $C_{23}H_{26}N_2O_5$, mp



		R^1	R^2	
1	3-Hydroxydiaboline	OH	OH	
2	Diaboline	H	OH	
3	Diaboline *N*-oxide	H	OH	$N_b \rightarrow O$
4	5-Oxo-diaboline	H	OH	5-oxo
6	α-*O*-Acetyl-3-hydroxydiaboline	OH	OAc	
8	α-*O*-Acetyl diaboline	H	OAc	



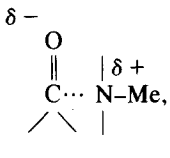
5	*N*-Methyl-*sec*-pseudo-diaboline	R=OH
6	α-*O*-Acetyl-*N*-methyl-*sec*-pseudo-diaboline	R=OAc

*Part 37 in the series "On the Alkaloids of *Strychnos*". For Part 36 see Galeffi C. and Marini-Bettolo G. B. (1981) *Tetrahedron* **37**, 3167.

210–211°, obtained by the action of pyridine and acetic anhydride. In **6** a pseudo-axial α-configuration can be assigned to the *O*-acetyl group on the basis of the chemical shift value of the anomeric proton, similar to that observed in α-*O*-acetyldiaboline (**8**), δ 6.13, $J = 2$ Hz (in β-*O*-acetyldiaboline δ 5.78, $J = 1$ Hz) [4].

Comparison of molecular rotation values of **1** and **6** ($[M]_D = +316$ and $+308$, respectively) with those of diaboline (+147), α-*O*-acetyldiaboline (+192) and β-*O*-acetyldiaboline (−131) (l.c.), is in accordance with the previous assignment of an α-position for the *O*-acetyl group in **6**. Differently from diaboline, not only one (that in the 12 position) but two aromatic hydrogens are at low field in the ^{1}H NMR spectrum of **1** and **6**. This long distance deshielding has already been observed in pseudostrychnine (3-hydroxystrychnine) [5] and other alkaloids [3], and accordingly suggested the presence of a 3-hydroxy group also in **1**. The dipolar electric moment and anisotropy of the magnetic susceptibility of the 3-hydroxyl affect the sterically close aromatic proton H-9.

In agreement with this structure, alkaloid **1** reacted with methyl iodide in the keto-aminic form, tautomeric with the carbinolamine form, giving rise to a compound belonging to the so-called *N*-methyl-*sec*-pseudo series [3] (**5**), $C_{22}H_{26}N_2O_4$, mp 138–139°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650 and 1670. The transannular interaction in **5** between N_b-methyl and carbonyl groups,



makes a further methylation with methyl iodide to form a 'classical' quaternary salt impossible.

In spite of the scarcity of information supplied by ^{1}H NMR spectra of **1** and **6**, the data hitherto collected suggested for the alkaloid **1** the structure of 3-hydroxydiaboline, which was confirmed by partial synthesis from diaboline. In fact by analogy with the preparation of 3-hydroxystrychnine from strychnine [6], diaboline *N*-oxide, mp 195–197°, supplied a product identical with alkaloid **1** by reaction with potassium chromate. In the same reaction, as a by-product, neutral compound **4**, identified as 5-oxodiaboline, $C_{21}H_{22}N_2O_4$, IR $\nu_{max}^{CHCl_3}$ 1700 cm^{-1} (γ-pyrrolidonic ring), was isolated. The same rearrangement of diaboline *N*-oxide to 3-hydroxydiaboline, related to the Polonowsky reaction, was induced from ferric tartrate as reported for other *t*-amine oxides [7].

^{13}C NMR chemical shifts of α-*O*-acetylderivatives of **1** and **5**, and **6** and **7**, respectively, are reported in Table 1. In their spectra the effects of N_a-acetyl group conformers are evident. For **6**, carbon atoms affected by the N_a-acetyl group (C-2, C-8, C-10, C-11, C-12, C-13, C-17) are split into two resonance signals. It is remarkable to note the identity of a C-17 value with that of isocondensamine (α-*O*-acetyl-11-methoxydiaboline) (δ 93.6) [8] which has a preferred conformation for the N_a-acetyl on account of the presence of an aromatic methoxy group [3]. In comparison with henningsamine (β-*O*-acetyldiaboline) [9] the additional 3-hydroxy group of **6** deshields C-3 (32.7 ppm) by an α-effect, C-7 and C-14 (4.8 and 8.3 ppm respectively) by a β-effect as well as C-9 (4.5 ppm) by the mechanism already described in the ^{1}H NMR spectrum.

Table 1. ^{13}C NMR chemical shift assignments for alkaloid acetates **6** and **7***

	6	**7**
C-2	63.1, 63.7	61.9
C-3	91.3	186.0
C-5	49.4	48.6
C-6	44.6	40.6
C-7	58.6	56.6
C-8	133.2, 135.4	126.3
C-9	125.6	126.3
C-10	124.1, 124.2	124.3
C-11	126.9, 127.0	127.5
C-12	116.5, 119.2	117.5
C-13	141.7, 142.1	134.5
C-14	33.7	40.8
C-15	30.2	31.8
C-16	47.9	40.8
C-17	93.6, 97.0	94.8
C-18	58.9	62.5
C-19	126.8	127.5
C-20	137.9	140.5
C-21	53.0	62.5
NCOMe	168.6	169.9
OCOMe	168.2	168.2
NCOMe	21.7	23.1
OCOMe	20.8	20.8
NMe		41.2

*In δ values downfield from TMS; δ (TMS) = δ ($CDCl_3$) + δ 77.0.

For **7** the restricted mobility of the N_a-acetyl group results in intense broadening of C-12, C-13 and C-17, whereas the transannular interaction between the N_b-methyl and the carbonyl group, which delocalizes the positive charge far from the carbon atom, results in its upfield resonance (δ 186.0).

EXPERIMENTAL

Plant material. The upper trunk bark (5 kg) of *S. castelnaeana* Wedd. (no. 43, R. Cardosa de Oliveira, B. da Silva & A. Silva) [2] was collected in the Rio Solimões area of Igarapè (Brazil).

Extraction. Acidic extraction of the bark and separation of tertiary alkaloids by CCD, between $CHCl_3$ and buffer (mobile phase) at discontinuously decreasing pH's, were carried out according to a routine procedure [10]. Quaternary alkaloids were absent. The following alkaloids were eluted: at pH 6.4, **2**, $K_rK_b = 9 \times 10^{-8}$, 560 mg and at pH 5.8, **1**, $K_rK_b = 4 \times 10^{-9}$, 196 mg.

Alkaloid **1**: *3-hydroxydiaboline.* Crystals from EtOAc and *n*-hexane, mp 218–221°. (Found: C, 68.02; H, 6.38; N, 7.47. $C_{21}H_{24}N_2O_4$ requires: C, 68.46; H, 6.57; N, 7.60%.) UV λ_{max}^{MeOH} nm: 250, 277 sh, 284 (log ε 4.03, 3.31, 3.26). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480 and 1660. $[\alpha]_D^{20} = +86°$ ($CHCl_3$; *c* 0.6). ^{1}H NMR ($CDCl_3$): δ 7.8–8.0 (2H, *m*, H-9 and H-12), 6.9–7.2 (2H, *m*, H-10 and H-11), 5.6–5.9 (1H, *m*, H-19), 5.21 (1H, *br d*, $J = 2$ Hz, H-17), 2.32 (3H, *s*, MeCON). MS *m/z* (%): 368

$[M]^+$ (3), 350 (42), 332 (35), 323 (15), 321 (26), 195 (37), 180 (26), 168 (40), 144 (40), 130 (25), 85 (76), 43 (100).

Alkaloid **2**: *diaboline*. Crystals from EtOAc, mp 187–188°. The IR, ^{1}H NMR and MS as well as the optical rotation were identical to those of diaboline [11].

α-O-Acetyl-3-hydroxydiaboline (**6**). Alkaloid **1** was acetylated with C_5H_5N–Ac_2O overnight. The reagents were evaporated under vacuum and the residue purified by CCD between $CHCl_3$ and buffer at pH 3.8, $K_rK_b = 2.3 \times 10^{-11}$. Crystals from EtOAc, mp 210–211°. (Found: C, 67.14; H, 6.08; N, 6.61. $C_{23}H_{26}N_2O_5$ requires: C, 67.30; H, 6.39; N, 6.83%.) $[\alpha]_D^{20} = +75°$ ($CHCl_3$; *c* 1). ^{1}H NMR ($CDCl_3$): δ 7.8–8.1 (2H, *m*, H-9 and H-12), 7.0–7.3 (2H, *m*, H-10 and H-11), 6.07 (1H, *br d*, *J* = 2 Hz, H-17), 5.5–5.8 (1H, *m*, H-19), 2.34 (3H, *s*, MeCON), 2.03 (3H, *s*, MeCOO). MS *m/z* (%): 410 $[M]^+$ (12), 350 (13), 185 (100), 144 (71), 130 (32), 43 (76).

N-*Methyl*-sec-*pseudo-diaboline* (**5**). A soln of alkaloid **1** (95 mg) in MeI (3 ml) was refluxed for 30 min. The residue after evaporation of MeI was purified by CCD between $CHCl_3$ and buffer at pH 5.8, $K_rK_b = 1.3 \times 10^{-8}$. Crystals from EtOAc and *n*-hexane, mp 138–139°. (Found: C, 69.24; H, 6.47; N, 7.24. $C_{22}H_{26}N_2O_4$ requires: C, 69.09; H, 6.85; N, 7.33%.) IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650 and 1670. $[\alpha]_D^{20} = +157°$ ($CHCl_3$; *c* 0.5). ^{1}H NMR ($CDCl_3$): δ 7.79 (1H, *dd*, *J* = 2 and 8 Hz, H-12), 7.0–7.4 (3H, *m*, H-9, H-10 and H-11), 5.7–6.0 (1H, *m*, H-19), 5.39 (1H, *br d*, *J* = 2 Hz, H-17), 2.40 (3H, *s*, MeCON), 2.02 (3H, *s*, MeN). MS *m/z* (%): 382 $[M]^+$ (26), 353 (21), 277 (13), 185 (23), 144 (64), 44 (100).

α-O-Acetyl-N-methyl-sec-*pseudo-diaboline* (**7**). Compound **5** was acetylated with C_5H_5N–Ac_2O overnight. After evaporation of reagents under vacuum, the residue crystallized from EtOAc and *n*-hexane as needles, mp 172–173°. (Found: C, 67.72; H, 6.70; N, 6.11. $C_{24}H_{28}N_2O_5$ requires: C, 67.90; H, 6.65; N, 6.60%.) $[\alpha]_D^{20} = +114°$ ($CHCl_3$; *c*0.7). ^{1}H NMR ($CDCl_3$): δ 7.78 (1H, *dd*, *J* = 2 and 8 Hz, H-12), 7.0–7.4 (3H, *m*, H-9, H-10 and H-11), 6.22 (1H, *br d*, *J* = 2 Hz, H-17), 5.8–6.0 (1H, *m*, H-19), 2.39 (3H, *s*, MeCON), 2.04 (6H, *s*, MeCOO and MeN). MS *m/z* (%): 424 $[M]^+$ (38), 364 (21), 186 (49), 185 (52), 144 (89), 130 (42), 43 (100).

Diaboline N-*oxide* (**3**). A mixture of **2** (200 mg), H_2O (6 ml) and 30% H_2O_2 (0.2 ml) was refluxed for 1 hr. The soln was then boiled for 5 min with Pt wire, the H_2O evaporated and the residue crystallized from MeOH and EtOAc (147 mg), mp 195–197°. (Found: C, 67.75; H, 6.60; N, 7.38. $C_{21}H_{24}N_2O_4$ requires: C, 68.46; H, 6.57; N, 7.60%.) $[\alpha]_D^{20} = +149°$ (H_2O; *c* 1.3).

Conversion of **3** *into* **1** *by potassium chromate*. A soln of potassium chromate (5 mg) in H_2O (5 ml) was added to a soln of diaboline *N*-oxide (100 mg) in H_2O (10 ml) and the temp. progressively increased up to 100° within 30 min. The cloudy soln obtained was extracted with $CHCl_3$ and from the residue of the organic phase by CCD between $CHCl_3$ and buffer at pH 6.4 3-hydroxydiaboline (33 mg) was obtained. After crystallization from EtOAc, the compound was identified as **1** by direct comparison. As a by-product the neutral compound **4** (12 mg), mp 94–96° (from EtOAc and *n*-hexane) was obtained, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3490, 1700 (γ-pyrrolidonic ring) and 1660. MS *m/z* (%): 366 $[M]^+$ (4) ($C_{21}H_{22}N_2O$) 351 (12), 350 (58), 332 (50), 319 (29), 304 (25), 195 (25), 168 (32), 85 (90), 43 (100).

Conversion of **3** *into* **1** *by* Fe^{+3} *induced rearrangement*. An aq. soln (100 ml) of diaboline *N*-oxide (0.6 g), anhydrous $Fe(NO_3)_3$ (2 g) and tartaric acid (0.9 g), the pH of which was adjusted to 5 by adding $NaHCO_3$ was heated at 100° for 30 min. The pH was then adjusted to 8 and the soln was extracted with $CHCl_3$. From the residue of the organic phase diaboline **2** (0.36 g) and 3-hydroxydiaboline **1** (0.16 g) were obtained by CCD according to the aforementioned procedure.

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