iso-Caracurine V, a Novel Unexpected Decomposition Product of Caracurine V

Darius Paul Zlotos*

Institut für Pharmazie und Lebensmittelchemie der Universität Würzburg, Am Hubland, 97074 Würzburg, Germany

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The structure of *iso*-caracurine V (**3**), an unexpected decomposition product of the *Strychnos* alkaloid caracurine V (**1**), was determined by NMR spectroscopy. Compound **3**, which was probably previously regarded as bisnortoxiferine I (**2**), is a one-sided ring closed product of **2**.

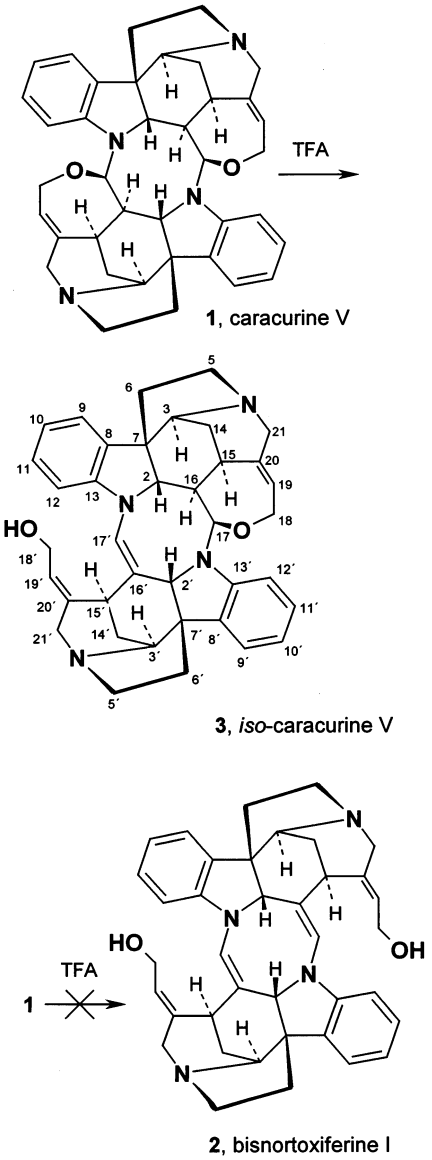
Caracurine V (**1**), the main alkaloid from the stem bark of *Strychnos toxifera*, has been reported to be very sensitive to exposure to acids.[1] In 1954 it was reported that treatment of **1** with dilute aqueous acids led to a mixture of caracurine II and Wieland-Gumlich aldehyde via a not clearly defined intermediate compound, caracurine Va.[2] Later work suggested that the structure of caracurine Va was identical with that of bisnortoxiferine I (**2**) due to the fact that methylation of caracurine Va gave the bisquaternary *calabash* curare alkaloid toxiferine I.[3] However, no spectroscopic evidence except a UV spectrum was given to support this assumption.[2]

Our group recently reported the allosteric effect on antagonist binding of a series of bisquaternary caracurine V analogues at muscarinic M_2 receptors.[4] To extend our studies to the bisnortoxiferine ring system, we were interested in synthesizing large quantities of the nortoxiferine I base (**2**). Surprisingly, treatment of **1**[5] with organic acids provided not **2**, but a novel alkaloid **3**, which is a one-sided ring opened product of **1**, or alternatively, a one-sided ring closed product of **2**. This paper describes the optimized synthesis and structure determination of *iso*-caracurine V (**3**) by NMR spectroscopy. Comparison of UV spectroscopic data suggested that the compound previously regarded as **2** was probably **3**. Since aqueous acids lead to a rapid degradation of the caracurine V ring system to a Wieland-Gumlich aldehyde,[2] nonaqueous conditions were used for the preparation of the bisnortoxiferine I ring skeleton. Berlage et al. obtained toxiferine I (75%) by treatment of caracurine V dimethochloride for 15 min with *p*-toluenesulfonic acid in glacial acetic acid.[6] The same procedure was empoyed in an attempt to convert **1** into **2**. However, even after prolonging the reaction time to 12 h, only **3** (20%) and unchanged **1** could be isolated. A better yield of **3** (78%) was achieved using trifluoroacetic acid.

Compound **3** had the same molecular formula ($C_{38}H_{40}N_4O_2$) as strating material **1**. The UV spectrum of **3** displayed absorption maxima at 291 nm (log ϵ 1.21), 263 nm (log ϵ 0.70), and 209 (log ϵ 2.57), which is in agreement with the UV data previously reported for caracurine Va hydrochloride.[2]

The structure determination of **3** required extensive NMR studies that included analysis of HH-COSY, HMQC, and HMBC spectra. While both ^{1}H and ^{13}C NMR spectra of the symmetrical compound **1** (2-fold symmetry axis) displayed only a single set of signals,[5] the NMR signals of **3** doubled, which implied a nonsymmetrical compound. Half of the ^{1}H and ^{13}C NMR shifts of **3** coincided with those of **1**,[5] which indicated that one-half of the caracurine V ring system remained intact. Examination of the aliphatic region of both ^{1}H and ^{13}C spectra of **3** revealed that all signals that belonged to the caracurine-like half of the molecule had their counterparts on the other side of the ring system, except the resonances for H-16 (δ 2.02), H-17 (δ 4.81), C-16 (δ 52.3), and C-17 (δ 96.6). The corresponding signals for C-16′, H-17′, and C-17′ could be assigned starting from the HMBC correlation from H-17 to C-2′ (δ

Scheme 1



* Tel: 0931/8885489. Fax: 0931/8885494. E-mail: zlotos@pharmazie.uni-wuerzburg.de.

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60.5). HMQC correlation from C-2′ revealed H-2′ (δ 4.69) as a narrow doublet (J = 1.7 Hz) due to the allylic spin−spin coupling with H-17′. The resonances for H-17′ (δ 6.01) and C-17′ (δ 129.9) were assigned by way of the COSY correlation from H-2′ to H-17′ and the H-17′−C-17′ HMQC correlation. Finally, the HMBC correlations from H-2′ and from H-17′ revealed the signal for C-16′ to be also in the aromatic/olefinic region (δ 125.1). From the fact that the chemical shifts for H-17′, C-16′, and C-17′ are in the aromatic/olefinic region and from the absence of the H-16′ signal, the presence of a double bond between C-16′ and C-17′ could be concluded. The double bond also explained the downfield shift of H-2′ (δ 4.69) compared to H-2 (δ 3.49). Therefore, **3** most likely would have formed as a result of an intramolecular alcohol elimination from one seven-membered ring of **1**. A proton belonging to the resulting alcohol group appears in the ^{1}H NMR spectrum recorded in DMSO-d_6 as a triplet exchangeable with D_2O (δ 4.8). The position of the alcohol function adjacent to the C-18′ methylene group was confirmed by COSY correlations between 18′-OH and H-18a′ and H-18b′, respectively.

Due to a presence of one hydroxy group, **3** is a more polar compound than **1**. TLC on silica gel ($CHCl_3$−MeOH−25% aqueous NH_3, 130:10:1) revealed R_f values of 0.45 and 0.20 respectively for **1** and **3**. The R_f value of **2** would also be expected to be lower than that of **3** due to the presence of two hydroxy groups. Since the reaction mixture showed no other slower moving TLC spots, the seven-membered ring of **3** was stable under the reaction conditions.

Experimental Section

General Experimental Procedures. Optical rotations were measured with a Perkin-Elmer model 241 polarimeter. UV spectra were obtained with a Varian Cary 50 Bio spectrometer. IR spectra were recorded on a Biorad FT-IR Pharmalyzir spectrometer. ^{1}H and ^{13}C NMR spectra were taken on a Bruker Avance AV-400 spectrometer. ^{1}H chemical shifts (ppm) were referenced to residual C*H*Cl_3 (δ 7.24 ppm) and ^{13}C chemical shifts to the solvent ($^{13}CDCl_3$ = 77.0 ppm). The mass spectrum was obtained using a Finnigan MAT 8200 spectrometer (70 eV).

Synthesis of *iso*-Caracurine V (3). Caracurine V (**1**)[5] (0.5 g, 0.85 mmol) was stirred for 15 h under Ar with 10 mL of absolute TFA at room temperature. After removal of TFA under reduced pressure, 25% aqueous NH_3 (10 mL) was added to the ice-cooled residue and the mixture was stirred under Ar for 20 min. After extraction with $CHCl_3$ (3 × 20 mL), the combined organic layers were washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo to give a white foam, which was purified by column chromatography on neutral alumina containing 10% H_2O, eluting with $CHCl_3$.

***iso*-Caracurine V (3):** (0.39 g, 78%) colorless crystalline solid; $[\alpha]^{20}_D$ +70° (*c* 2, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 291 (1.21), 263 (0.70), 209.1 (2.57) nm, IR (ATR) ν_{max} 2851, 1655, 1597, 1483, 1458 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.09 (1H, ddd, J = 7.6, 7.6, 1.0 Hz, H-11), 7.06 (1H, ddd, J = 7.6, 7.6, 1.0 Hz, H-11′), 6.99 (1H, dd, J = 7.6, 1.0 Hz, H-9), 6.96 (1H, dd, J = 7.6, 1.0 Hz, H-9′), 6.82 (1H, ddd, J = 7.6, 7.6, 1.0 Hz, H-10), 6.76 (1H, ddd, J = 7.6, 7.6, 1.0 Hz, H-10′), 6.47 (1H, d, J = 7.6 Hz, H-12), 6.39 (1H, d, J = 7.6 Hz, H-12′), 6.01 (1H, d, J = 1.7 Hz, H-17′), 5.91 (1H, m, H-19), 5.52 (1H, t, J = 6.3 Hz, H-19′), 4.81 (1H, d, J = 3.0 Hz, H-17), 4.69 (1H, d, J = 1.7 Hz, H-2′), 4.24 (1H, dd, J = 12.9, 6.3 Hz, H-18b′), 4.17 (1H, dd, J = 14.0, 7.1 Hz, H-18b), 4.14 (1H, dd, J = 12.9, 6.3 Hz, H-18a′), 3.99 (1H, s, br, H-3), 3.96 (1H, dd, J = 14.0, 5.5 Hz, H-18a), 3.89 (1H, s, br, H-3′), 3.74 (1H, d, J = 15.1 Hz, H-21b), 3.69 (1H, d, J = 15.4 Hz, H-21b′), 3.49 (1H, d, J = 10.4 Hz, H-2), 3.20−3.12 (3H, m, H-15′, H-5b, H-5b′), 2.95 (1H, s, br, H-15′), 2.92 (1H, d, J = 15.4 Hz, H-21a′), 2.79−2.89 (2H, m, H-5a, H-5a′), 2.75 (1H, d, J = 15.1 Hz, H-21a), 2.31 (1H, br, OH), 2.27 (1H, ddd, J = 14.1, 4.1, 4.1 Hz, H-14b), 2.11−2.22 (2H, m, H-6b′, H-14b′), 2.02 (1H, ddd, J = 10.4, 3.0, 3.0 Hz, H-16), 1.88 (1H, dd, J = 12.5, 5.8 Hz, H-6b), 1.62−1.72 (3H, m, H-14a′, H-6a, H-6a′), 1.57 (1H, d, J = 14.1 Hz, H-14a); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.5 (C-13), 149.2 (C-13′), 142.5 (C-20′), 140.4 (C-20), 135.1 (C-8′), 133.6 (C-8), 129.9 (C-17′), 128.9 (C-11), 128.4 (C-11′), 127.6 (C-19), 127.2 (C-19′), 125.1 (C-16′), 122.0 (C-9), 121.9 (C-9′), 120.7 (C-10′), 119.9 (C-10), 111.2 (C-12′), 110.3 (C-12), 96.6 (C-17), 67.1 (C-2), 65.7 (C-18), 60.8 (C-3), 60.7 (C-3′), 60.5 (C-2′), 58.8 (C-18′), 56.4 (C-7), 55.7 (C-7′), 55.4 (C-21), 53.2 (C-21′), 52.6 (C-5), 52.3 (C-16), 52.0 (C-5′), 42.5 (C-6), 42.2 (C-6′), 38.9 (C-15′), 32.9 (C-15), 26.8 (C-14′), 26.3 (C-14); EIMS m/z 586 [M + 2]$^+$ (12), 585 [M + 1]$^+$ (30), 584 [M]$^+$ (100), 293 (17), 568 (15), 567 (15), 554 (12), 553 (20); HREIMS m/z 584.3143 (calcd for $C_{38}H_{40}N_4O_2$, 584.3148).

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Supporting Information Available: ^{1}H, ^{13}C, HH-COSY, HMQC, and HMBC NMR spectra of *iso*-caracurine V (**3**) in $CDCl_3$. This material is available free of charge via the Internet at http://pubs.acs.org.

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