Stereochemistry of Caracurine V

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The 3D structure of the *Strychnos* alkaloid caracurine V was determined by means of NMR spectroscopy and semiempirical calculations. The previously unknown absolute configuration in the central eight-membered ring was assigned as (16*R*, 16′*R*, 17*R*, and 17′*R*).

Caracurine V (**1**) is an alkaloid that occurs in the stem bark of several African *Strychnos* species.[1] It is a toxic compound exhibiting strong muscle-relaxant activity.[2] The *N*,*N*′-bisquaternary derivative, caracurine V dimethochloride, is closely related to the calabash curare alkaloid C-toxiferine I. Intramolecular addition of both allyl alcohol moieties of C-toxiferine I to the central double bonds leads to the caracurine V skeleton.[3]

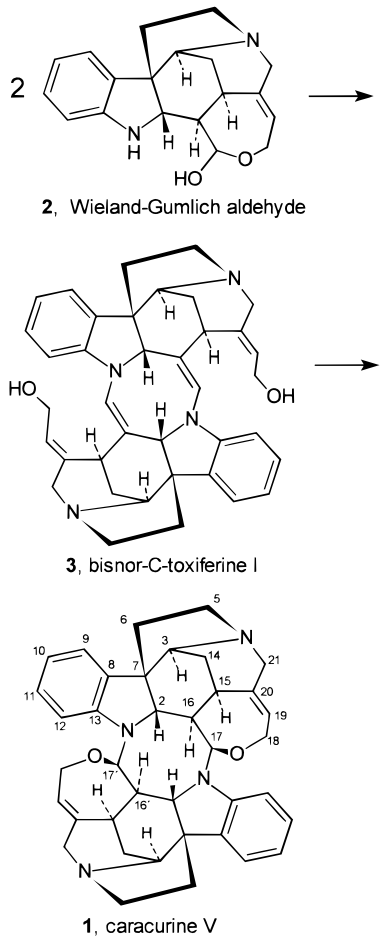
The neuromuscular blocking activity of caracurine V dimethochloride was reported to be about 50-fold lower than that of toxiferine.[4] The corresponding allyl derivatives, *N*,*N*′-diallylcaracurine V dichloride and alcuronium, are very potent enhancers of antagonist binding to the muscarinic M_2 receptors with nearly the same EC_{50} values.[5] To investigate the binding mode of caracurine derivatives with both nicotinic and muscarinic acetylcholine receptors, knowledge of the exact stereochemistry of the central eight-membered ring, which has a great influence on the 3D structure of the whole molecule, is necessary. Thus, the goal of this study was to determine the 3D structure of caracurine V by means of NMR spectroscopy and semiempirical calculations.

Caracurine V (**1**) was obtained from the dimerization of the Wieland−Gumlich aldehyde (**2**) using pivalic acid according to the procedure of Battersby and Hodson.[6] The structure was established using NMR (H−H COSY, C−H COSY) and HRMS data. Because both ^{1}H and ^{13}C NMR spectra show only single signal sets, the molecule must have a 2-fold symmetry axis. This limits the unknown absolute configuration for C-16, C-17, C-16′, and C-17′ to four possibilities. Dimerization of **2** to **1** probably proceeds via intramolecular alcohol addition to the enamine double bonds of bisnor-C-toxiferine I (**3**) (Scheme 1). Depending on the stereochemical course of this intramolecular alcohol addition, four different caracurine V stereoisomers (**1a**−**1d**) can be formed. A *syn*-addition gives the stereoisomers **1a** and **1b**, whereas *anti*-addition leads to stereoisomers **1c** and **1d** (Figure 1). Another possible mechanism for dimerization of **2** involves a nucleophilic substitution of the semiacetal oxonium group by the indole nitrogen giving directly **1b** or **1c**. The four possible 3D structures (**1a**−**1d**) were generated using PC SPARTAN.[7] The starting geometries were based on the X-ray data of strychnine, which was a starting compound for the synthesis of **2**. Semiempirical calculations (AM1) revealed considerable differences in the heats of formation, which ranged from 95.1 to 127.2 kcal/mol (Figure 1). The configuration with the lowest heat of formation corresponds to the *anti*-addition product **1c**.

The central eight-membered ring of **1** is incorporated in a highly fused ring system and, therefore, the molecular flexibility is rather limited. This makes conformational analysis using NMR spectroscopy reliable. The configuration of the central ring of **1** was determined by the vicinal coupling constants and by NOE experiments. The coupling constants J_{16-2} = 10.7 Hz, J_{16-15} = 2.4 Hz, and J_{16-17} = 2.1 Hz reflect an antiperiplanar orientation of H-16 and H-2. This is the only *trans*-diaxial relation within the central ring and is in agreement with the configuration exclusively existing in stereoisomer **1c**.

Relevant coupling constants were calculated for each configuration using PC MODEL 4.1 (Serena Software) (Table 1) to confirm the geometry hypothesized above. The experimental data correspond very well to the data calculated for stereoisomer **1c**. Further indication for the **1c**

Scheme 1. Formation of Caracurine V (**1**) by Dimerization of Wieland−Gumlich Aldehyde (**2**)



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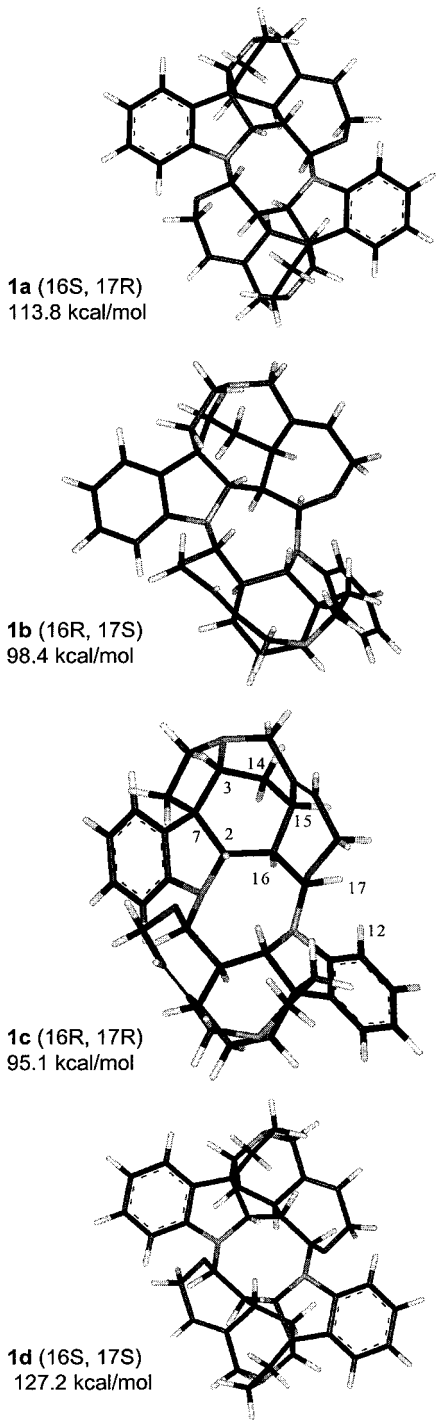

Figure 1. Possible configurations of caracurine V (**1**) obtained by semiempirical calculations (AM1).[7]

Table 1. Dihedral Angles (∠, deg) and Calculated Vicinal Coupling Constants (*J*, Hz) (PC MODEL) Between Selected Protons of Possible Caracurine V Stereoisomers (**1a**−**1d**)

	16H−17H		16H−2H		16H−15H	
	∠	*J*	∠	*J*	∠	*J*
1a	154	8.1	47	4.4	131	6.2
1b	152	9.7	152	9.6	54	3.6
1c	62	**1.8**	157	**10.3**	62	**2.5**
1d	2	8.4	59	2.5	145	8.9
found		**2.1**		**10.7**		**2.4**

configuration is given by strong NOEs between protons 16−17, 16−15, 15−17, and 17−12 (Table 2). The findings indicate that caracurine V (**1**) and its bisquaternary derivatives have the stereochemistry shown for **1c** and that the configuration is (2*S*,2′*S*,3*S*,3′*S*,15*R*,15′*R*,16*R*,16′*R*,17*R*,17′*R*).

Table 2. NOE Effects (%) of Caracurine V ($CDCl_3$, 300 MHz) and the Distances (Å) Between the Corresponding Protons in the **1c** Stereoisomer

	16−17	16−15	16−12	16−14	17−15	16−2	17−12	17−18
%	8	6	2	5	8	2	15	9
Å	2.4	2.5	3.3	2.2	2.3	3.1	2.3	2.1

Experimental Section

General Experimental Procedures. IR spectra were recorded on a Perkin-Elmer PE−298 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on a Varian XL-300 spectrometer. Proton chemical shifts (ppm) are referred to residual chloroform (7.24 ppm) and carbon chemical shifts to the solvent ($^{13}CDCl_3$ = 77 ppm). The mass spectrum was run on a Krotos MS-50.

Synthesis of Caracurine V (1). Compound **2**[8] (2.5 g, 8 mmol) was heated with 20 g of pivalic acid at 120 °C for 14 h in an evacuated sealed tube. After removal of pivalic acid under reduced pressure, water (100 mL) was added, and the mixture was made basic with 25% ammonia. Extraction with $CHCl_3$, drying over $MgSO_4$, and evaporation of the extract gave a brown foam that was purified on a Si gel column (Fluka 0.063−0.2 nm), eluting with $CHCl_3/CH_3OH$/25% NH_3 (132:10:1). Alternatively, a neutral alumina containing 10% H_2O, eluting with toluene/$CHCl_3$ (2:1), can be used for purification.

Compound 1: (1.14 g, 49%) slightly yellow crystalline solid; $[\alpha]^{25}_D$ −5.5° (*c* 1, $CHCl_3$); IR (KBr) ν_{max} 2940, 2860, 1600, 1480 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.09 (1H, t, J = 7.6 Hz, H-11), 6.98 (1H, d, J = 7.5 Hz, H-9), 6.77 (1H, t, J = 7.6 Hz, H-10), 6.40 (1H, d, J = 7.6 Hz, H-12), 5.87 (1H, m, H-19), 4.67 (1H, d, J = 2.1 Hz, H-17), 4.24 (1H, dd, J = 14.0, 7.1 Hz, H-18^b), 4.10 (1H, d, J = 10.7 Hz, H-2), 4.07 (1H, m, H-3), 3.90 (1H, dd, J = 14.0, 4.8 Hz, H-18^a), 3.79 (1H, d, J = 15.0 Hz, H-21^b), 3.23 (1H, m, H-5^b), 2.92 (1H, m, H-5^a), 2.83 (1H, m, H-15), 2.80 (1H, d, J = 15.0 Hz, H-21^a), 2.29 (1H, dt, J = 14.0, ca. 4.0 Hz, H-14^b), 2.20 (1H, dd, J = 12.1, 5.8 Hz, H-6^b), 1.92 (1H, dt, J = 10.7, ca. 2.4 Hz, H-16), 1.65 (1H, dm, J = 14.0 Hz, H-14^a), 1.57 (1H, m, H-6^a); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.29 (C-13), 141.66 (C-8), 133.80 (C-20), 128.02 (C-11), 126.71 (C-19), 121.56 (C-9), 119.25 (C-10), 109.98 (C-12), 98.88 (C-17), 66.59 (C-18), 59.59 (C-3), 56.89 (C-2), 55.52 (C-7), 53.53 (C-21), 52.66 (C-16), 51.31 (C-5), 40.97 (C-6), 34.20 (C-15), 26.34 (C-14); EIMS *m*/*z* 586 $[M + 2]^+$ (11), 585 $[M + 1]^+$ (43), 584 $[M]^+$ (100), 293 (17), 144 (37); HREIMS *m*/*z* 584.3143 (calcd for $C_{38}H_{40}N_4O_2$, 584.3151).

Supporting Information Available: ^1H and ^{13}C NMR and NOE-difference spectra of caracurine V (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

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