Bulgarian Chemical Communications, Volume 49, Special Edition B (pp. 103 – 110) 2017

Solution and solid state characterization of "sparteine surrogate" (+)-(1*R*,5*S*,11a*S*)-tetrahydrodeoxocytisine

S. P. Simeonov[1], S. D. Simova[1], B. L. Shivachev[2], R. P. Nikolova[2], V. B. Kurteva[1]*

[1] *Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Acad. G. Bonchev street, bl. 9, 1113 Sofia, Bulgaria*

[2] *Institute of Mineralogy and Crystallography "Acad. Ivan Kostov", Bulgarian Academy of Sciences, Acad. G. Bonchev street, bl. 107, 1113 Sofia, Bulgaria*

Received March 06, 2017; Revised March 16, 2017

Dedicated to Acad. Bogdan Kurtev on the occasion of his 100th birth anniversary

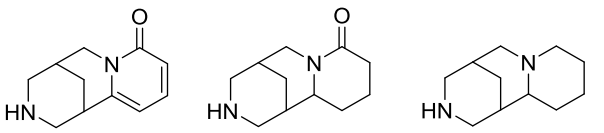
The „sparteine surogate" (+)-(1*R*,5*S*,11a*S*)-tetrahydrodeoxocytisine is obtained by two known protocols, direct and two-step procedure, and is characterized in solution and solid state as free base, mono-, and bis-hydrochloride. Unambiguous assignment of the proton and carbon NMR spectra of tetrahydrodeoxocytisine is reported for the first time. X-ray and NMR data are compared and structural preferences in solid state and solution are discussed.

Key words: tetrahydrodeoxocytisine; tetrahydrocytisine; NMR; single crystal XRD

INTRODUCTION

(-)-(*1R*,5*S*)-Cytisine is a nicotinic acetylcholine receptor agonist from Lupin alkaloids' family [1−5], firstly isolated from the seeds of *Cytisus Laburnum Med.* in 19th century [6, 7], which was widely applied to help with smoking cessation. The limitation in the natural sources availability has reasonably provoked extraordinary efforts directed towards developing new protocols for the synthesis of cytisine isomers and derivatives [8−10]. Among its reduced analogues (Fig. 1), tetrahydrocytisine has attracted the most significant attention. It is one of the major alkaloids in *Templetonia biloba* from Western Australia [11], which was firstly isolated from *Thermopsis chinensis* [12]. Several synthetic protocols have been further developed based mainly on applying different catalytic versions for hydrogenation of cytisine and finally, efficient conversion was achieved by using platinum oxide as a catalyst either in acetic acid at atmospheric pressure [13, 14] or in water under increased pressure of hydrogen [15−17].

By contrast, the "sparteine surrogate" tetrahydrodeoxocytisine, which has never been isolated from natural sources, is very poorly studied and is not fully characterized till nowadays. The (+)-isomer has been firstly obtained in 1906 via electrochemical reduction of cytisine in sulfuric acid at a lead cathode and was characterized as bis-hydrochloride and free base by elemental analysis and optical rotation of the salt [18]. The same isomer has been later obtained by hydrogenation in hydrochloric acid in the presence of platinum oxide as a catalyst [19, 20] and characterized as D-tartrate and dipicrate by elemental analysis and optical rotation of tartrate [21]. Recently, tetrahydrodeoxocytisine has been obtained and used immediately in further step without preliminary purification and characterization [22]. To the best of our knowledge, there are no records in the literature on the NMR and XRD characterization of unsubstituted tetrahydrodeoxocytisine.



cytisine tetrahydrocytisine tetrahydrodeoxocytisine

Fig. 1. Cytisine and its reduced derivatives.

Herein, we present a study on solution NMR and single crystal XRD characterization of the "spartein surrogate" (+)-(1*R*,5*S*,11a*S*)-tetrahydrodeoxocytisine as free base, mono- and bis-hydrochloride salts. The solid state structure of tetrahydrocytisine hydrochloride is also reported.

EXPERIMENTAL

Synthesis

All reagents were purchased from Aldrich, Merck and Fluka and were used without any further

* To whom all correspondence should be sent:
E-mail: *vkurteva@orgchm.bas.bg*

purification. Fluka silica gel/TLC-cards 60778 with fluorescent indicator 254 nm were used for TLC chromatography. The melting points were determined in capillary tubes on SRS MPA100 OptiMelt (Sunnyvale, CA, USA) automated melting point system with heating rate 1 °C/min. The NMR spectra were recorded on a Bruker Avance II+ 600 spectrometer (Rheinstetten, Germany) at 278K, 293K and 323K. The chemical shifts are quoted as δ-values in ppm using as an internal standard tetramethylsilane (TMS) or the solvent signal and the coupling constants are reported in Hz. The assignment of the signals is confirmed by applying 2D COSYDF, NOESY, HSQC and HMBC techniques. The spectra were recorded as 3×10^{-2} M solutions and were processed with Topspin 3.5 pl6 program. The NMR data are listed on Tables 1 and 2 using the numbering presented on Scheme 1. Molecular mechanics calculations were performed by MMFF94 in Spartan08. Specific optical rotation values were measured on Jasco P-2000 polarimeter (Tokyo, Japan) at D line of sodium lamp at 20 ºC by using 1 dm quartz cell. The $[\alpha]_D$ are given in deg.cm^3.g^{-1}.dm^{-1}, concentration in g.cm^{-3}. The IR spectra were recorded on a Bruker Tensor37 FTIR Spectrometer in KBr disks. The frequencies are given in cm^{-1}. The differential thermal analysis (DTA), thermogravimetric analysis (TGA) and gas-mass evolving (MS) were taken on a SETSYS Evolution TGA-DTA/MS (Setaram), up to 300 ºC.

*Synthesis of (+)-(1R,5S,11aS)-tetrahydrodeoxocytisine bis-hydrochloride (**2**.2HCl)*

To a solution of cytisine (**1**, 855 mg, 4.5 mmol) in MeOH (25 ml) and 36% aq. HCl (1 ml) platinum(IV) oxide (90 mg, 0.4 mmol) was added and the air was subsequently replaced by argon and hydrogen. The suspension was stirred vigorously under a hydrogen atmosphere overnight. The solid phase was removed by filtration through Celite. The solvent was removed *in vacuo* to afford the crude product (990 mg, 87%) as a colourless bis-hydrochloride salt. The analytically pure **2**.2HCl was obtained by recrystallization from *i*-PrOH: m. p. 274.0−274.2 °C (lit. [18] 282 °C; [20] 260 °C); $[\alpha]_D^{20}$ +20 (c=0.5, EtOH) (lit. [18] +10°15'; solvent, concentration, and temperature not indicated). IR (the most intensive bands): 3492, 3363, 2980, 2947, 2796, 1615, 1448, 995 and 470.

*Synthesis of (+)-(1R,5S,11aS)-tetrahydrodeoxocytisine hydrochloride (**2**.HCl)*

Tetrahydrocytisine (**3**) was synthesised *via* literature protocol [22] and was converted into hydrochloride salt by saturation of methanol solution with HCl vapours. The analytically pure compound was obtained by recrystallization from *i*-PrOH. To a solution of crude **3** hydrochloride (300 mg, 1.3 mmol) in MTBE (20 ml) $LiAlH_4$ (230 mg, 6 mmol) was added portion-wise at 0 °C. The suspension was stirred at room temperature under argon atmosphere overnight and was then diluted with MTBE (20 ml). The excess of $LiAlH_4$ was quenched with water at 0 °C. The solid phase was removed by filtration through Celite. The organic solution was dried over Na_2SO_4 and evaporated to dryness to give crude diamine **2** (159 mg, 68% yield). The latter was dissolved in MTBE (20 ml) and precipitated by slow addition of HCl vapours. The solid phase was filtered off, washed with MTBE and dried in desiccator. The analytically pure **2.**HCl was obtained by recrystallization from *i*-PrOH: m. p. 184.4−184.9 °C; $[\alpha]_D^{20}$ +24 (c=0.5, EtOH). IR (the most intensive bands): 3494, 3429, 3066, 2935, 2760, 1640, 1517, 1446, 1124, 1020 and 451.

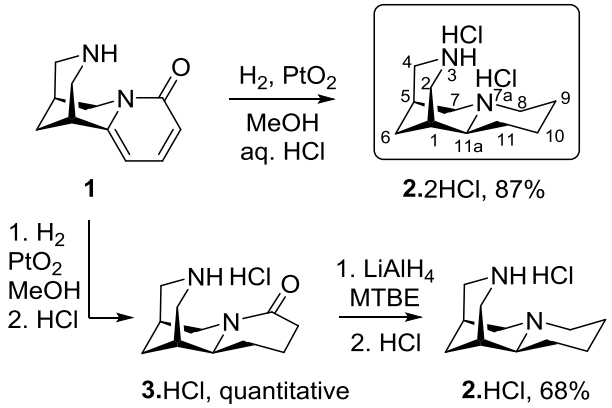
Crystallography

The crystals of **2.2**HCl, **2.**HCl and **3.**HCl were mounted of on a glass capillary and all geometric and intensity data were taken from these crystals. Crystallographic measurements were taken on an Agilent SupernovaDual diffractometer equipped with an Atlas CCD detector (**2**) and on an Enraf Nonius CAD4 diffractometer (**3**) using micro-focus Mo Kα radiation (λ = 0.71073 Å) at room temperature. The determination of the unit cell parameters, data collection and reduction were performed with Crysalispro software for **2** [23] and CAD-4 EXPRESS [24] for **3**. The structures were solved by direct methods and refined by the full-matrix least-squares method on F^2 with ShelxS and ShelxL 2016/6 programs [25]. All non-hydrogen atoms, including solvent molecules, were located successfully from Fourier maps and were refined anisotropically. Hydrogens adjoining N, O and H atoms of chiral centers were positioned from difference Fourier map. The H atoms on $C_{methylene}$ were placed in idealized positions (C—H = 0.97 Å). The hydrogens adjoining N7a, N3, C1, C5 and C11a were freely refined while the remaining H atoms were constrained to ride on their parent

atoms, with Uiso(H) = 1.2U_{eq}(C or O). The most important crystallographic and refinement indicators are listed on Table S1. Crystallographic data (with structure factors) for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, No. CCDC-1534860 (**2**.HCl), 1534861 (**2**.2HCl) and CCDC-1534862 (**3**.HCl). Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK. Fax: +44(1223)336-033, e-mail:deposit@ccdc.cam.ac.uk, or www: www.ccdc.cam.ac.uk.

RESULTS AND DISCUSSION

The "spartein surrogate" (+)-tetrahydro-deoxocytisine (**2**) was obtained from natural (-)-(*1R*,5*S*)-cytisine (**1**) *via* two independent protocols, shown on Scheme 1. Platinum oxide catalysed hydrogenation in methanol in the presence of hydrochloric acid at atmospheric pressure led directly to the target product as bis-hydrochloride salt. The two-step procedure ensured the intermediate tetrahydrocytisine (**3**) and the final tetrahydrodeoxocytisine (**2**) as free bases. Both compounds were converted into mono hydrochlorides while trying to grow single crystal phases. The latter provides the opportunity to study the influence of the type of both nitrogen atoms on the structural preferences of cytisine derivatives.



Scheme 1. Synthesis of (+)-(1*R*,5*S*,11a*S*)-tetrahydrodeoxocytisine salts **2.**2HCl and **2.**HCl.

The NMR spectra of cytisine (**1**), tetrahydrodeoxocytisine as free base (**2**) and as hydrochloride (**2.**HCl) and tetrahydrocytisine hydrochloride (**3.**HCl) were recorded in chloroform-d, while those of tetrahydro-deoxocytisine bis-hydrochloride (**2.**2HCl) in methanol-d_4 due to its very limited solubility in chloroform. The proton spectra of **2.**HCl showed broad signals for most of the groups in the temperature interval 278–323K without big changes in the chemical shifts. That is why the chemical shift determination was made at the highest temperature 323K where narrow signals for most protons were observed (see Fig. S1). Unambiguous assignment of the proton and carbon signals in the spectra (Tables 1 and 2) was achieved by analysing the specific interactions in homo- and heteronuclear 2D COSY, NOESY, HSQC and HMBC experiments (Figs. S2–S10). For comparison HSQC spectra of **2.**2HCl were also recorded at very low concentration (less than $1x10^{-3}$ M) in chloroform exacting the chemical shifts from the HSQC spectra.

Based on the known configuration of cytisine (1*R*,5*S*) the absolute configuration of the newly generated chiral centre in the products can be assigned as 11a*S* on the basis of the observed coupling and NOE information. The proton signal for H-11a is a doublet with a J-coupling bigger than 11 Hz, suggesting its axial position, confirmed by the observed close proximity of H-11a to H-1, H-11_{eq}, H-7_{ax}, H-8_{ax}, H-10_{ax} and H-6_1 in the NOESY spectra (Figs. S3, S6, and S8). The fact that the new chiral centre CH-11a possesses *S*-configuration is verified also by single crystal XRD.

Crystals suitable for X-ray diffraction analyses were grown from *iso*-propanol solutions by slow evaporation at room temperature for all compounds (**2** and **3**). All three compounds crystallized in non-centrosymmetric groups (Table S1) with one molecule in the asymmetric unit (Fig. 2). The location and positioning of hydrogens adjoining N7a, N3, C1, C5 and C11a was performed using difference Fourier maps. While for C1, C5 and C11a the assignment is unequivocal for all compounds, in the case of mono hydrochloride **2**.HCl the H atom position is more delicate. The following approach has been applied for the correct assignment of hydrogens adjoining nitrogen's. After the location of heavier atoms hydrogens were positioned on calculated positions and four cycles (*e.g.* "l.s. 4" instruction) of anisotropic refinement were performed. In the next step the N7a and N3 hydrogen atoms occupancy was set to "zero" and difference Fourier maps were generated based on existing structural parameters (l.s. 0 and "acta" instruction removed). The obtained maps (Fig. 3) show the presence (excess) of electron density (in red) along with the positioning of the H atoms (from chemically sensible positions). One can clearly recognize that in the case of **2**.2HCl there is an excess of electron density near N3 and N7a,

Table 1. Chemical shifts, multiplicities[a] and coupling constants (in Italic) in the ^{1}H NMR spectra of compounds **1**-**3**.

proton	**1**[b]	**2**[b]	**2**.HCl[c]	**2.**2HCl[d]	**2.**2HCl[e]	**3**[b]
H-1	2.907 qt *2.6*	1.378 bs	1.795 bs	2.25	2.296 bs	1.945 q *3.2*
H-2$_{ax}$	3.059 dd *12.1,2.3*	2.803 ddd *13.8,2.6,1.6*	3.178 dd *13.3,3.6*	3.52	3.343 dd *14.2,4.8*	3.20 bt
H-2$_{eq}$	3.002 ddd ov *12.5,2.5,1.5*	3.298 d *13.7*	3.663 ddd *13.3,3.2,2.3*	3.52	3.635 bd *14.2*	3.790 d *13.4*
H-4$_{ax}$		2.999 dt *13.4, 2.6*	3.328 dt *12.9,2.9*	3.51 and *3.56*	3.401 ddd *13.5,4.3,1.6*	3.28 bt
H-4$_{eq}$	3.105 dd *12.5,2.5*	3.120 dt *13.4,2.5*	3.527 ddd *13.0,3.6,2.3*		3.518 bd *13.3*	3.580 d *13.1*
H-5	2.328 m	1.713 bs	2.120 bs	2.49	2.448 bs	2.24 m
H-6$_1$	1.962 t *3.3*	1.73 ov	1.846 m	2.13	2.083 t *3.5*	1.86 bd
H-6$_2$		1.890 dm *12.0*	1.971 dq *13.0,2.8*			2.063 dq *13.2, 2.9*
H-7$_{ax}$	3.903 ddd *15.6,6.7,1.3*	2.425 dt *11.2,2.6*	2.533 bs	3.26	3.279 bdd *13.2,4.0*	2.889 d *13.6*
H-7$_{eq}$	4.129 d *15.6*	2.887 dt *11.2,2.4*	3.025 bd *12.4*	3.58	3.547 d *13.2*	4.682 dt *13.9,2.1*
H-8$_{ax}$	-	1.75 ov	1.926 vb	3.52 ov.	3.46 d ov	-
H-8$_{eq}$	-	2.754 dqt *11.2,2.1*	2.881 d *10.9*	3.03	3.100 td *13.3,2.4*	-
H-9$_{ax}$	6.463 dd *9.1,1.5*	1.519 qm ov	1.648	2.26	2.324 qt *14.2,4.3*	2.923 ddd *17.0,13.9,6.4*
H-9$_{eq}$		1.60 dm *13.1*		1.83	1.88 d ov	2.390 ddd *17.0,4.9,2.3*
H-10$_{ax}$	7.302 dd *9.1, 6.9*	1.297 qt *12.9,4.0*	1.329 qt *13.0,4.0*	1.69	1.704 qt *13.2,4.0*	1.675 qdd *13.4,4.8,2.9*
H-10$_{eq}$		1.791 d *12.0*	1.853 m	2.08	1.981 dm *13.6,4.0,2.7*	1.983 m
H-11$_{ax}$	6.002 dd *6.9,1.5*	1.536 qm ov	1.630 m	2.54	2.113 qd *12.7,3.7*	2.255 qd *12.8,3.2*
H-11$_{eq}$		1.430 dm *12.7*	1.520 dq *13.5,3.5*	1.89	1.84 d ov	1.762 dqt *13.3,3.1*
H-11a		2.157 dm *11.2*	2.334 br	3.37	3.47 d ov	3.464 dt *12.0,6.5*
NH			10.86 bs	11.46, bs 11.28, bs 10.14, bs		9.79, bs 8.12, bs

[a] s – singlet, d – doublet, t – triplet, q – quartet, qt – quintet, b – broad, v – very broad; m – multiplet, and ov – overlapped signals; [b] In $CDCl_3$ at 293K; [c] In $CDCl_3$ at 323K; [d] Chemical shifts from HSQC; [e] In CD_3OD at 293K.

Table 2. Chemical shifts in the ^{13}C NMR spectra of compounds **1-3.**

Carbon	**1**[a]	**2**[a]	**2.**HCl[b]	**2.**HCl[c]	**2.**2HCl[a]	**2.**2HCl[d]	**3**[a]
C-1	35.60	34.08	31.58	32.00	30.74	31.76	30.94
C-2	53.98[e]	47.92	45.83	45.67	39.85	41.42	42.78
C-4	52.99	52.01	49.64	49.57	44.59	46.04	47.34
C-5	27.76	29.68	27.09	27.47	25.89	27.31	25.92
C-6	26.30	34.60	32.28	32.38	28.31	28.49	30.54
C-7	49.75[e]	61.73	60.68	60.77	56.32	56.99	46.12
C-8	163.69	57.27	56.45	56.67	58.25	58.82	173.01
C-9	116.74	26.03	25.29	25.38	22.75	23.77	33.15
C-10	138.82	24.72	23.91	24.12	22.32	23.74	20.48
C-11	105.02	30.58	29.86	30.06	27.55	28.71	27.41
C-11a	151.07	66.23	65.34	65.65	65.71	66.65	60.10

[a] In $CDCl_3$ at 293K; [b] In $CDCl_3$ at 278K; [c] In $CDCl_3$ at 323K; [d] In CD_3OD at 293K; [e]Assignment in [5] is interchanged due to printing error.

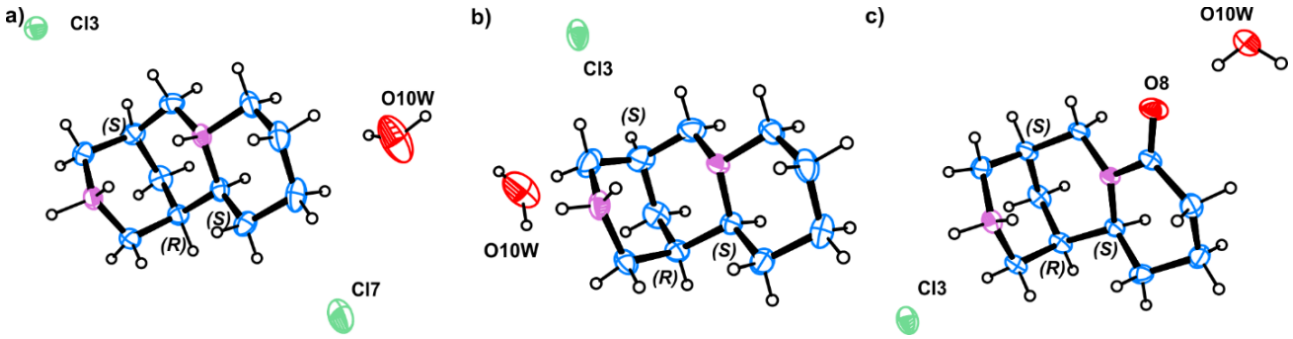


Fig. 2. ORTEP drawings of **2**.2HCl (a), **2**.HCl (b), and **3**.HCl (c) with the atomic numbering scheme (ellipsoids are at 50% probability), the hydrogen atoms are shown as small spheres of arbitrary radii; the atomic numbering is shown on Scheme 1, compound **2**.2HCl.

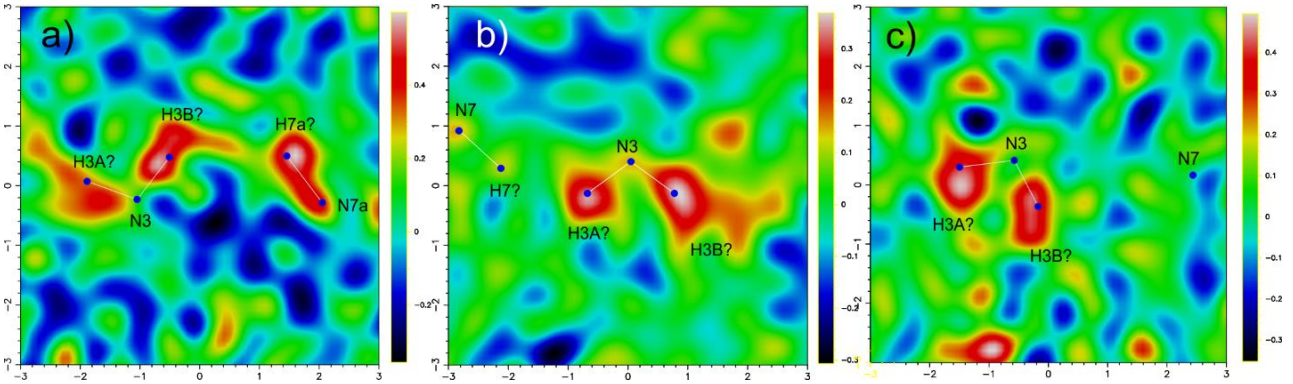


Fig. 3. X-ray difference Fourier maps in the region of N3 and N7a in **2**.2HCl (a), **2**.HCl (b), and **3**.HCl (c) showing the peak (excess of electron density in red) due to the hydrogen.

while in the cases of mono chloride (**2**.HCl and **3**.HCl) the excess is only near N3 and thus only one of the N centres is protonated, which is expected for amide **3**.HCl. In addition to the location of the H atoms near the N centres the **2**.2HCl structure disclosed one more peculiarity. The initial structure refinement of **2**.2HCl did not include a solvent water molecule as the maximum residual electron density in the map was 0.86 e. However the CIF check generated a PLAT094 alert: Ratio of Maximum / Minimum Residual Density 2.16 *e.g.* "The ratio of the maximum and minimum residual density excursions is unusual. This might indicate unaccounted for twinning or missing atoms (*e.g.* associated with disordered solvent)".

Therefore, in order to assess if water was present in **2**.2HCl we performed FT-IR (Fig. S11). As the results were inconclusive, due to the overlap of NH^+, NH_2^+ and water OH vibrations, a DTA-TGA-MS of **2**.2HCl was conducted (Fig. S12). The thermal analyses showed an *endo* effect around ~70 ºC, accompanied by ~2.5% of mass losses while the MS detected the release of water. This indicates the presence of week bonded water (physisorption or solvent) in the sample. To minimize the residual density, solvent water was introduced in the crystal structure and its occupancy was refined. The comparison of the values obtained from the structure refinement (O10W occupancy of 29%) and TGA loss are in agreement *e.g.* 2.4% *vs* 2.5%.

There are no significant differences in distances or angles within the molecules of the three cytisine derivatives (**2**.2HCl, **2**.HCl and **3**.HCl) as can be seen from the overlay of the three molecules (Fig. 4 and Table S2).

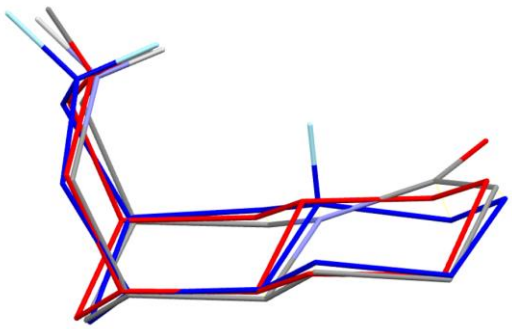


Fig. 4. Relative orientation in **2**.2HCl (blue), **2**.HCl (red), and **3**.HCl (grey); *rmsd* of 0.1498 Å and 0.189 Å for **2**.2HCl *vs* **2**.HCl and **2**.HCl *vs* **3**.HCl, respectively.

It is interesting to note the geometry of the protonated and deprotonated N7a centre with respect to the plane formed by C7-C8-C11a. The N7a distance to the plane is 0.444, 0.433 and 0.190 Å in **2**.2HCl, **2**.HCl and **3**.HCl respectively. The

observed "flattening" C7-C8-C11a-N7A in **3**.HCl is due to the presence of a carbonyl group (C8=O8) and the resulting conjugation effects. In all structures Cl3 is closer to N3 with distance between Cl3…N3 slightly bigger than 3.0 Å. In **2**.2HCl the second Cl7 is located near N7a (N7a…Cl7 distance of 3.099(5) Å). The solvent water molecules present on all structures interact mainly with chlorine. In **3**.HCl due to the presence of a carbonyl group (strong acceptor) the interaction is Cl…H-O-H…O=C, while in **2**.2HCl and **2**.HCl the interaction is Cl…H-O-H…Cl (Fig. 5). In both **2**.2HCl and **2**.HCl the water position occupancy is not full suggesting that its presence may not be essential for the crystal structure. Indeed, in addition to the typical hydrogen bonding interactions the three-dimensional packing of the molecules is stabilized by several other weak interactions (Table S3).

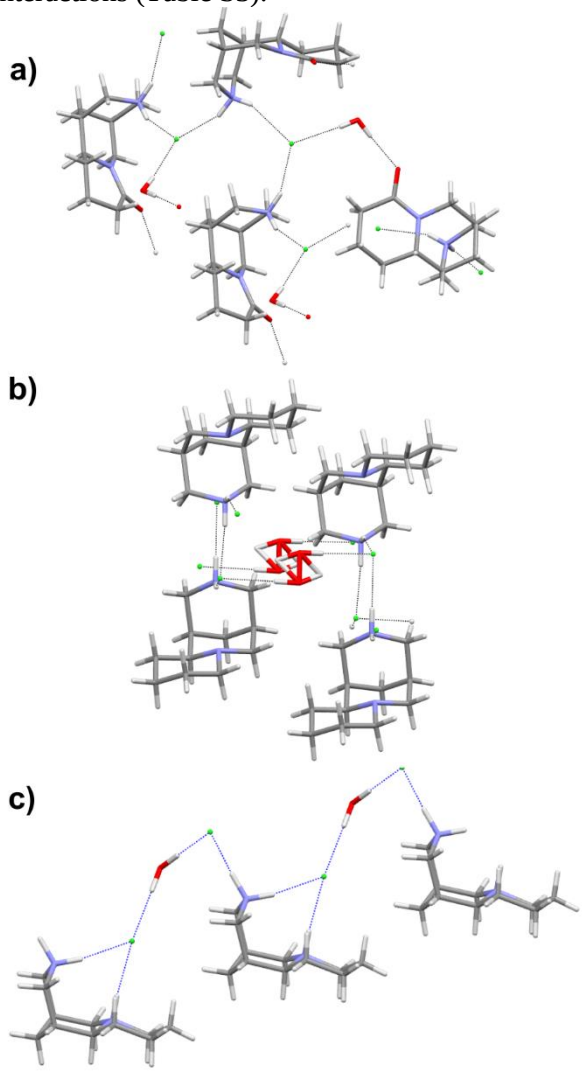


Fig. 5. Observed solvent (water) interactions in a) **3**.HCl, b) **2**.HCl, and c) **2**.2HCl; the water position occupancy in **2**.HCl is 0.41%, while in **2**.2HCl it is 0.29%.

The solution proton and carbon NMR data (Tables 1 and 2) are fully consistent with the X ray observations. It should be, however, noted that while the NMR data for **3**.HCl are compatible with a single conformer, both proton and carbon spectra indicate the presence of more conformers for **2**.HCl and **2**.2HCl. Literature examples [26, 27] predict that the end rings in **2** could principally exist as chair and boat conformation as shown on Fig. 6. Molecular mechanics calculations [28] for **2**.HCl provide evidence that the major conformer constitutes of three chair rings, that corresponds to the X ray structure. Some small amounts of the two possible minor conformers lead to signal broadening that is detected both in the carbon and more pronounced in the proton spectra.

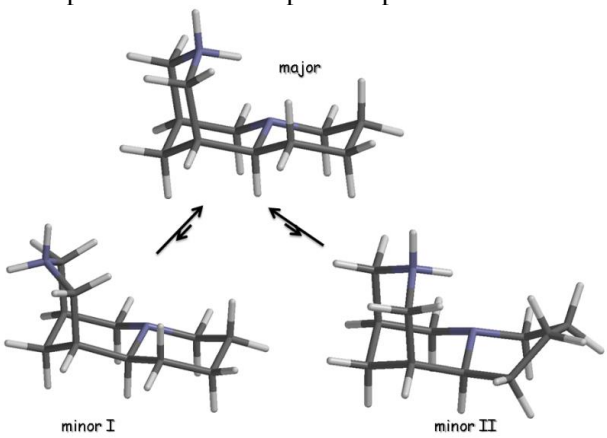


Fig. 6. Possible conformers for **2**.HCl.

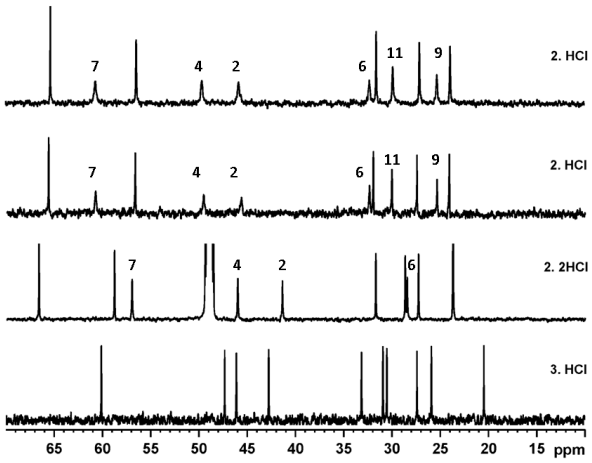


Fig. 7. Aliphatic part of the carbon spectra of the products, ordered from top to bottom: **2**.HCl at 293K, **2**.HCl at 323K, **2**.2HCl at 293K, and **3**.HCl at 293K. The broadened signals in the spectra are indicated.

Inspection of the carbon spectra of the three compounds (Fig. **7**) indicates that most broadened signals are observed for **2**.HCl. These signals imply possible presence of two "boat-chair-chair" conformers (denoted as minor I and minor II),

corroborated by the broadened carbon signals for C-7, C-2, C-4, C-6, C-9 and C-11. On the contrary, compound **2**.2HCl does not show any broadening of the C-9 and C-11 signals, indicating exchange only in the N-3 containing ring (minor I conformer). Both salts **2** differ from **3**.HCl, where no signal broadening is observed.

Detailed inspection and comparison of the proton spectra of the compounds studied confirm that the all chair conformer is the major one. Main facts in this respect are some chemical shift differences and coupling patterns. H-11a is a clear doublet with a coupling larger than 10 Hz in all studied compounds, indicating its axial position. A reversal of the usual order of the equatorial-axial protons for H-9 and H-11 is observed, confirming 1,3-*syn* diaxial interaction between hydrogen atoms and N unshared electron pairs [29]. The somewhat broadened signal multiplicities of both H-1 and H-5 does not indicate considerable presence of a boat form, since no big coupling constant as expected for J_{H1H2} and J_{H4H5} in such case is observed.

CONCLUSION

The „sparteine surogate" (+)-(1*R*,5*S*,11a*S*)-tetrahydrodeoxocytisine is characterized for the first time by NMR spectroscopy in solution and single crystal XRD in solid state. The detailed analyses of the data indicate only the all chair conformation in solid state and as predominant in solution.

Acknowledgements: *The financial support by the Bulgarian Science Fund, infrastructure projects UNA-17/2005, DRNF-02-13/2009, DRNF-02/01, and BG161PO003-1.2.04-0007-C0001, is gratefully acknowledged.*

Electronic Supplementary Data available here

REFERENCES

1. J. P. Michael, *Nat. Prod. Rep.*, **25**, 139 (2008).
2. N. J. Leonard, in: The Alkaloids, Chemistry and Physiology, R. H. F. Manske, H. L Holmes, (eds.), vol. III, Academic Press, New York, NY, 1953, p. 119.
3. S. Ohmiya, K. Saito, I. Murakoshi, in: The Alkaloids, G. A. Cordell (ed.), vol. 47, Academic Press, New York, 1995, p 2.
4. K. Saito, I. Murakoshi, in: Studies in Natural Products Chemistry. Structure and Chemistry (Part C), Atta-ur-Rahman (ed.), Vol. 15, Elsevier, Oxford, 1995, p 519.
5. S. Berger, D. Sicker, Classics in Spectroscopy, Isolation and Structure Elucidation of Natural Products, Wiley-VCH Verlag GmbH & Co., KGaA, Weinheim, 2009, Chapter 1.5, p. 65.
6. A. Husemann, W. Marmé, *Z. Chem.*, **1**, 161 (1865).
7. A. Husemann, T. Husemann, Die Pflanzenstoffe in Chemischer, Physiologischer, Pharmakologischer und Toxikologischer Hinsicht, Verlag von Julius Springer, Berlin, 1871, p 64.
8. E. G. Pérez, C. Méndez-Gálvez, B. K. Cassels, *Nat. Prod. Rep.*, **29**, 555 (2012).
9. J. Rouden, M.-C. Lasne, J. Blanchet, J. Baudoux, *Chem. Rev.*, **114**, 712 (2014).
10. D. Bartusik, D. Aebisher, P. Tutka, *Modern Org. Chem. Res.*, **1**, 10 (2016).
11. R. Greinwald, C. Henrichs, G. Veen, J. H. Ross, L. Witte, F.-C. Czygan, *Biochem. Syst. Ecol.*, **23**, 649 (1995).
12. K. Saito, S. Takamatsu, M. Yamazaki, S. Ohmiya, I. Murakoshi, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu*, **32**, 268 (1990); CA **114**, 203603 (1991).
13. F. Bohlmann, E. Winterfeldt, H. Overwien, H. Pagel, *Chem. Ber.*, **95**, 944 (1962).
14. M. J. Johansson, L. Schwartz, M. Amedjkouh, N. Kann, *Tetrahedron: Asymmetry*, **15**, 3531 (2004).
15. F. Galinovsky, O. Vogl, W. Moroz, *Monatsh. Chem.*, **85**, 1137 (1954).
16. A. V. Ivachtchenko, S. E. Tkachenko, Y. B. Sandulenko, V. Y. Vvedensky, A. V. Khvat, *J. Comb. Chem.*, **6**, 828 (2004).
17. Y. B. Sandulenko, A. V. Ivashchenko, D. V. Kravchenko, S. E. Tkachenko, V. Y. Vvedensky, *Russ. Chem. Bull.*, **57**, 1999 (2008).
18. M. Freund, P. Horkheimer, *Ber. Dtsch. Chem. Ges.*, **39**, 814 (1906).
19. F. Galinovsky, E. Stern, *Chem. Ber.*, **77**, 132 (1944).
20. S. Okuda, H. Kataoka, K. Tsuda, *Chem. Pharm. Bull.*, **13**, 491 (1965).
21. F. Galinovsky, O. Vogl, W. Moroz, *Monatsh. Chem.*, **83**, 242 (1952).
22. I. Philipova, G. Stavrakov, N. Vassilev, R. Nikolova, B. Shivachev, V. Dimitrov, *J. Organomet. Chem.*, **778**, 10 (2015).
23. CrysAlis PRO, Agilent Technologies, UK Ltd, Yarnton, England, 2011.
24. XCAD4, Harms & Wocadlo, University of Marburg, Germany, 1995.
25. G. M. Sheldrick, *Acta Cryst.*, **C71**, 3 (2015).
26. A. Gogoll, H. Grennberg, A. Axen, *Magn. Res. Chem.*, **35**, 13 (1997).
27. H.-J. Schneider, L. Sturm, *Angew. Chem. Int. Ed. Engl.*, **15**, 545 (1976).
28. https://www.wavefun.com/products/spartan.html.
29. W. M. Golebiewski, *Magn. Res. Chem.*, **24**, 105 (1986).

ОХАРАКТЕРИЗИРАНЕ В РАЗТВОР И ТВЪРДО СЪСТОЯНИЕ НА "СПАРТЕИНОВИЯ СУРОГАТ" (+)-(1*R*,5*S*,11a*S*)-ТЕТРАХИДРОДЕОКСОЦИТИЗИН

С. П. Симеонов[1], С. Д. Симова[1], Б. Л. Шивачев[2], Р. Н. Петрова[2], В. Б. Куртева[1]*

[1] *Институт по Органична Химия с Център по Фитохимия, Българска Академия на Науките, ул. Акад. Г. Бончев, бл. 9, 1113 София, България*
[2] *Институт по Минералогия и Кристалография „Акад. Иван Костов", Българска Академия на Науките, ул. Акад. Г. Бончев, бл. 107, 1113 София, България*

Постъпила на 06 март 2017 г.; Коригирана на 16 март 2017 г.

(Резюме)

„Спартеиновият сурогат" (+)-(1*R*,5*S*,11a*S*)-тетрахидродеоксоцитизин е синтезиран по две известни процедури, директна и дву-стъпкова, и е охарактеризиран в разтвор и твърдо състояние под формата на свободна база, моно- и ди-хидрохлорид. За първи път е представено еднозначно отнасяне на сигналите в протонните и въглеродни ЯМР спектри на тетрахидродеоксоцитизин. Направен е сравнителен анализ на данните от монокристална рентгенова дифракция и ЯМР спектроскопия и са дискутирани предпочетените структури в твърдо състояние и в разтвор.