

Molecular and Crystal Structures of Three Berberine Derivatives

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Abstract: Berberine azide, berberine thiocyanate, and 8-cyano-8*H*-berberine were prepared from berberine chloride, a quaternary protoberberine alkaloid. The molecular and crystal structures of all compounds are reported and discussed.

Keywords: Protoberberine alkaloids, berberine azide, berberine thiocyanate, 8-cyano-8*H*-berberine, X-ray crystallography.

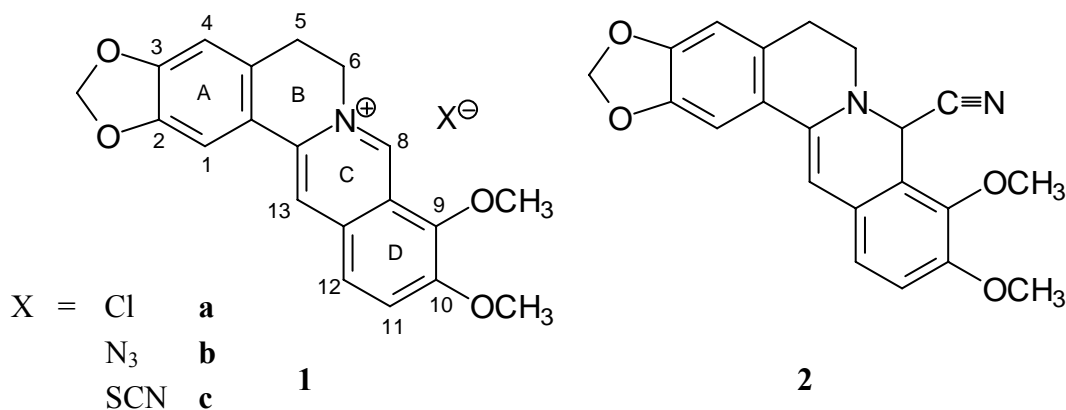
Introduction

Berberine (**1**) is a yellow quaternary protoberberine alkaloid occurring in many plant species of the *Berberidaceae* and other families. Berberine is known as an antimicrobial agent for the treatment of eye infections, gastrointestinal disorders, and other diseases [1,2]. The chemistry of berberine and related alkaloids may deal either with side chains alterations to form structural analogs [3] or with nucleophile attack on the iminium C=N⁺ bond [4,5]. Continuing our research on the conversions of isoquinoline alkaloids with nucleophiles we investigated the reactions of berberine chloride with azide, thiocyanate, and cyanide ions.

Results and Discussion

The protoberberine skeleton is derived from 5,6-dihydrodibenzo[*a,g*]quinolizinium. Berberine (**1**) is a tetrasubstituted alkaloid with a methylenedioxy group at C2 and C3, and two methoxy groups at C9 and C10. The susceptibility of berberine to nucleophilic attack at carbon C8 is known and several adducts are described in literature, especially those with oxygen- and carbon-nucleophiles [4,5]. An early example is the reaction with cyanide which provides 8-cyano-8*H*-berberine (**2**) (8-cyanodihydroberberine, berberine pseudocyanide) [6]. Little is known about reactions of berberine with nitrogen- and sulfur-nucleophiles.

We tried to prepare berberine adducts by reaction with azide and thiocyanate ions. Under the described experimental conditions, berberine chloride (**1a**) did not give expected adducts. An excess of sodium azide led to a mere exchange of counter-anions so that we isolated berberine azide (**1b**) as a principal product. The IR spectrum of **1b** indicated an intensive band of the antisymmetric valence vibration of azide ion $[N=N=N]^-$ at 2035 cm^{-1} . The reaction of **1a** with sodium thiocyanate proceeded similarly to yield berberine thiocyanate (**1c**). On the other hand, the reaction of berberine chloride with NaCN, performed according to literature [7], gave 8-cyano-8*H*-berberine (**2**). After slow recrystallizations, all the three products afforded crystals suitable for X-ray data collection.



Crystal data and selected geometric parameters of the compounds **1b**, **1c**, **2** are summarized in Tables 1, 2. All bond lengths and angles are within normal range. The quaternary cations in **1b** and **1c** are relatively planar species (Fig. 1, Fig. 2). Planarity is disturbed only in a partially saturated ring B. The ring B adopts a twisted half-chair conformation with the atoms C5 and C6 significantly deviated from the best plane of the aromatic rings A and C. The shortest bond length, $1.334(3)\text{ \AA}$ (**1b**), $1.332(4)\text{ \AA}$ (**1c**), is for the iminium N7-C8 bond in the ring C. The longest bonds are C4a-C5 ($\text{sp}^2\text{-sp}^3$) and C5-C6 ($\text{sp}^3\text{-sp}^3$) (Table 2). Similar findings were made in other berberine salts (chloride, bromide, iodide, sulfate, hydrogen sulfate) [8,9] and jatrorrhizine chloride, a protoberberine alkaloid with a different substitution pattern [10]. In the molecule of berberine, two aromatic parts can be distinguished, the ring A and the fused rings C,D. The least-squared planes calculated for these two parts are twisted by 10°

(**1b**) and 15° (**1c**), respectively. The azide ion is linear with the angle $N21-N22-N23$ $178.9(3)^\circ$ and quite symmetrical with both the bond lengths of $1.179(3)$ Å. Berberine azide crystallized with one molecule of acetonitrile. The thiocyanate ion in **1c** is also nearly linear, the $N21-C22-S23$ angle is $176.9(4)^\circ$. The bond lengths are $1.186(6)$ Å ($C22-N21$) and $1.625(6)$ Å ($S23-C22$).

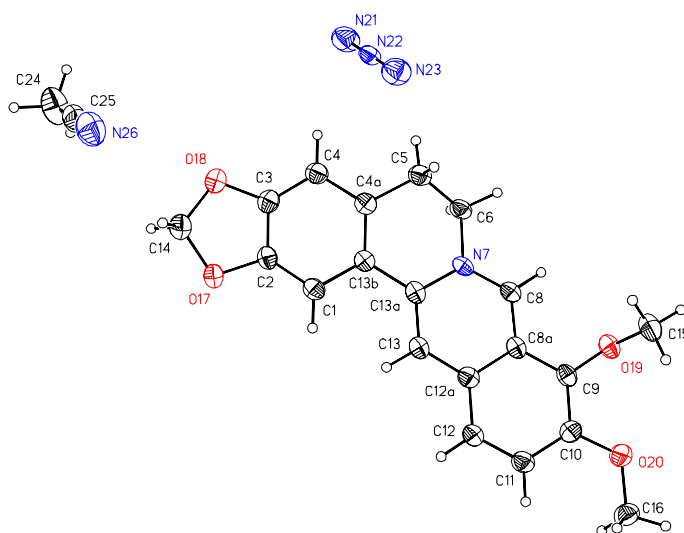


Figure 1. A perspective view of berberine azide (**1b**)

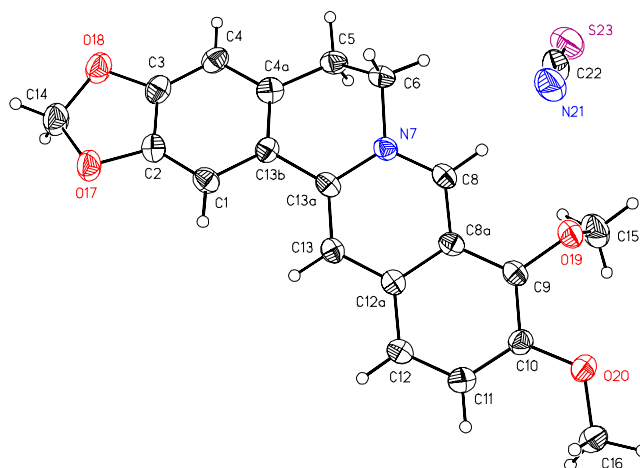


Figure 2. A perspective view of berberine thiocyanate (**1c**)

Table 1. Crystal data of the compounds **1b**, **1c**, and **2**

Parameter	1b	1c	2
Empirical formula	C ₂₀ H ₁₈ N ₄ O ₄ · CH ₃ CN	C ₂₁ H ₁₈ N ₂ O ₄ S	C ₂₁ H ₁₈ N ₂ O ₄
Formula weight	419.44	394.43	362.37
Temperature (K)	150(2)	293(2)	150(2)
Crystal system	Triclinic	Triclinic	Monoclinic
Space group	<i>P</i> -1	<i>P</i> -1	<i>P</i> 2(1)/ <i>c</i>
<i>a</i> (Å)	8.571(2)	7.037(1)	10.634(1)
<i>b</i> (Å)	9.367(2)	10.613(2)	18.328(1)
<i>c</i> (Å)	13.003(3)	12.344(2)	9.789(1)
α (°)	88.21(3)	101.18(3)	90
β (°)	75.94(3)	94.37(3)	116.30(1)
γ (°)	81.25(3)	97.69(3)	90
Volume (Å ³)	1000.9(4)	895.1(3)	1710.4 (3)
<i>Z</i>	2	2	4
Calc. density (Mg/m ³)	1.392	1.463	1.407
Crystal size (mm)	0.4 × 0.1 × 0.1	0.2 × 0.1 × 0.1	0.5 × 0.5 × 0.3
Crystal colour	Yellow	Yellow	Orange-red
θ range (°)	3.57 - 25.00	3.22 - 28.46	2.57 - 25.00
Index ranges	<i>h</i> -5 → 10 <i>k</i> -11 → 11 <i>l</i> -15 → 15	<i>h</i> -6 → 9 <i>k</i> -13 → 13 <i>l</i> -16 → 15	<i>h</i> -12 → 8 <i>k</i> -21 → 21 <i>l</i> -11 → 11
Reflections collected / Unique	6219 / 3353	6394 / 3808	16293 / 3008
Data / Restraints / Parameters	3353 / 0 / 281	3808 / 0 / 254	3008 / 0 / 245
Final <i>R</i> indices [<i>I</i> > 2σ (<i>I</i>)]	0.0629 / 0.1618	0.0829 / 0.2195	0.0436 / 0.0984
<i>R</i> indices (all data)	0.0835 / 0.1961	0.1149 / 0.2790	0.0494 / 0.1050
Hydrogen atoms treatment	Constrained	Constrained	Constrained
Largest diff. peak and hole (e.Å ⁻³)	0.432 and -0.348	0.620 and -0.675	0.222 and -0.230

Table 2. Selected geometric parameters of compounds **1b**, **1c**, and **2** (Å, °)

Bond / Angle	1b	1c	2
C4a-C13b	1.400(3)	1.402(5)	1.400(2)
C4a-C5	1.504(4)	1.506(5)	1.505(2)
C5-C6	1.509(4)	1.500(5)	1.515(2)
C6-N7	1.492(3)	1.484(4)	1.462(2)
N7-C13a	1.391(3)	1.390(4)	1.416(2)
C13a-C13b	1.464(3)	1.469(5)	1.474(2)
N7-C8	1.334(3)	1.332(4)	1.451(2)
C8-C8a	1.398(3)	1.400(4)	1.515(2)
C8a-C12a	1.423(3)	1.410(4)	1.401(2)
C12a-C13	1.404(3)	1.406(4)	1.445(2)
C2-O17	1.380(3)	1.366(4)	1.379(2)
O17-C14	1.433(3)	1.433(5)	1.441(2)
C14-O18	1.442(3)	1.430(5)	1.433(2)
O18-C3	1.379(3)	1.366(4)	1.372(2)
C9-O19	1.376(3)	1.364(4)	1.3854(19)
O19-C15	1.443(3)	1.427(5)	1.441(2)
C10-O20	1.358(3)	1.350(4)	1.3699(19)
O20-C16	1.431(3)	1.436(4)	1.428(2)
C8-N7-C6	117.5(2)	118.6(3)	114.12(13)
C8-N7-C13a	122.3(2)	122.4(3)	115.94(13)
C13a-N7-C6	120.1(2)	118.9(3)	118.55(13)
C8a-C9-O19	118.8(2)	119.7(3)	119.63(14)
C9-O19-C15	113.3(2)	115.0(3)	112.75(13)
C10-C9-O19	121.2(2)	121.1(3)	120.64(14)
C9-C10-O20	116.7(2)	116.7(3)	115.61(14)
C10-O20-C16	118.0(2)	117.5(3)	117.09(13)
C11-C10-O20	123.6(2)	124.3(3)	124.86(14)

8-Cyano-8*H*-berberine (**2**) is an adduct of berberine with CN⁻ ion. The nucleophilic attack altered the nature of the ring C so that it is partially saturated. The nitrogen atom N7 is trivalent and the C8 atom has the sp³ hybridization. The shortest bond length is in the cyano group C21-N22 1.145(2) Å, the longest bonds are C5-C6 in ring B and C8-C8a in ring C, both 1.515(2) Å. The ring C is in a half-chair conformation with atom C8 deviated from the mean plane of the ring. The ring B conformation resembles those in berberine azide and thiocyanate (Fig. 3). The puckering parameters of the six-membered heterocyclic rings in all three derivatives were calculated [12] and the values are listed in Table 3.

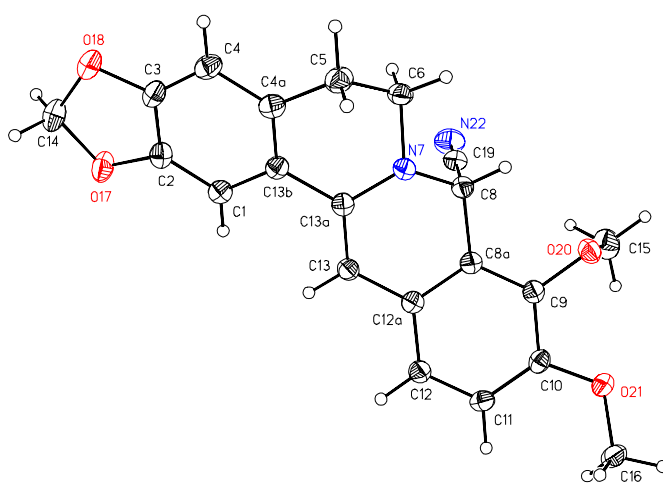


Figure 3. A perspective view of 8-cyano-8*H*-berberine (**2**)

Table 3. Puckering parameters of the compounds **1b**, **1c**, and **2**

Compound / Ring	Q [Å]	θ [°]	φ [°]
1b / B (N7 to C13a)	0.428(3)	117.3(4)	269.8(4)
1b / C (N7 to C13a)		τ = 0.8 °	
1c / B (N7 to C13a)	0.504(4)	65.8(5)	83.9(4)
1c / C (N7 to C13a)		τ = 2.0 °	
2 / B (N7 to C13a)	0.523(2)	115.9(2)	265.7(2)
2 / C (N7 to C13a)	0.411(2)	67.1(3)	30.2(3)

In all three compounds, the dioxolane ring C2-O17-C14-O18-C3 is reasonably planar, the methoxy group at C10 (O20-C16) more or less in-plane, and the methoxy group at C9 almost perpendicular to the D-ring plane (Table 4).

Table 4. Selected torsion angles in compounds **1b**, **1c**, and **2** (°)

Torsion angle	1b	1c	2
C8a-C9-O19-C15	96.8(3)	-97.1(4)	-103.08 (17)
C10-C9-O19-C15	-86.3(3)	84.1(4)	78.90(18)
C9-C10-O20-C16	-179.0(2)	167.1(3)	168.27(14)
C11-C10-O20-C16	0.9(4)	-12.1(5)	-13.00(14)

In both ionic structures of **1b** and **1c**, the organic cations pack in centrosymmetric pairs which in turn form columns, mutually parallel. Similar arrangement has been reported for other berberine salts [9]. The spaces between columns are occupied by anions (**1b**, **1c**) and solvent molecules (**1b**). On the other hand, no similar pairing can be observed in the spatial arrangement of neutral 8-cyano-8*H*-berberine (**2**).

Acknowledgements

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Experimental

General

Melting points were determined on a Kofler hot-plate Rapido 792106 and are uncorrected. Infrared spectra were measured on a ATI Mattson Genesis FT IR spectrometer in KBr pellets (wavenumbers in cm^{-1}). ^1H - and ^{13}C -NMR spectra (δ , ppm; J , Hz) were recorded on a Bruker Avance DRX 500 spectrometer in DMSO- d_6 with TMS as an internal standard. ^1H and ^{13}C assignments were based on H,H-COSY, NOESY, and HBMC experiments. Mass spectra were determined on a Finnigan MAT TSQ 700 instrument in electron impact mode (70 eV). Berberine chloride (**1a**), m.p. 200-206 °C, isolated from *Berberis vulgaris* L., was obtained from the Department of Biochemistry, Faculty of Medicine, Masaryk University Brno.

X-ray diffraction analysis

Diffraction data were collected on a KUMA KM-4 κ -axis diffractometer using either ω -2 θ (**1b**, **1c**) or ω scan mode (area detector, **2**). Both structures were solved by direct methods and refined by full-matrix least-squares methods using SHELXTL program package [11].

Syntheses

Berberine azide (1b).- Berberine chloride (100 mg, 0.23 mmol) was suspended in water and sodium azide (500 mg, 7.7 mmol) was added. The mixture was refluxed for 1 h. After cooling to room temperature a yellow precipitate was collected, washed with water and dried. Yield: 76 mg (74 %). M.p. 196-201 °C. IR (KBr) 3007, 2945, 2945, 2920, 2847, 2035 (s, N₃⁻), 1600, 1506, 1388, 1362, 1331, 1272, 1235, 1102, 1037 cm⁻¹. ¹H-NMR spectrum (DMSO-d₆) was in agreement with that of berberine chloride [13]. Slow evaporation of saturated acetonitrile solution afforded a single crystal for X-ray diffraction analysis.

Berberine thiocyanate (1c).- Berberine chloride (100 mg, 0.23 mmol) was suspended in water and sodium thiocyanate (500 mg, 6 mmol) was added. The mixture was refluxed for 2 h. After cooling to room temperature a yellow precipitate was collected, washed with water and dried. Yield: 81 mg (76 %). M.p. 224-227 °C. IR (KBr) 3052, 2989, 2943, 2912, 2845, 2051 (s, SCN⁻), 1600, 1504, 1388, 1362, 1337, 1274, 1231, 1102, 1034 cm⁻¹. ¹H-NMR spectrum (DMSO-d₆) was in agreement with that of berberine chloride [13]. Slow evaporation of saturated aqueous solution afforded a single crystal for X-ray diffraction analysis.

8-Cyano-8H-berberine (2).- Sodium cyanide (160 mg, 2.5 mmol) dissolved in water was added to a solution of berberine chloride (100 mg, 0.23 mmol) in methanol. The mixture was refluxed for 15 min. After slow cooling to 5 °C a brown precipitate was separated and recrystallized from diethyl ether. Yield: 13 mg (13 %) of red-orange crystals. M.p. 163-172 °C. IR (KBr) 3056, 2938, 2911, 2845, 2224 (w, C≡N), 1603, 1502, 1389, 1363, 1338, 1276, 1233, 1168, 1092, 1038 cm⁻¹. ¹H-NMR (DMSO-d₆): 2.75-2.90 (m, 2H, H5); 3.10-3.18 + 3.47-3.52 (m, 2H, H6); 3.83 (s, 3H, 10-OMe); 3.87 (s, 3H, 9-OMe); 5.97 (s, 1H, H8); 6.02 + 6.03 (2× s, 2H, OCH₂O); 6.35 (s, 1H, H13); 6.79 (s, 1H, H4); 6.89 (d, 8.4 Hz, 1H, H12); 7.05 (d, 8.4 Hz, 1H, H11); 7.35 (s, 1H, H1). ¹³C-NMR (DMSO-d₆): 29.1 (C5), 47.3 (C6), 49.5 (C8), 56.4 (10-OMe), 61.0 (9-OMe), 98.1 (C13), 101.5 (OCH₂O), 104.2 (C1), 108.3 (C4), 114.7 (C11), 117.0 (C8a), 117.3 (CN), 119.9 (C12), 123.9 (C13b), 127.1 (C12a), 129.1 (C4a), 138.5 (C13a), 144.4 (C9), 147.1 (C2), 147.8 (C3), 150.7 (C10). EIMS m/z (%): 362 (M⁺, 63), 347 (18), 320 (52), 306 (27), 292 (28), 278 (47).

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Sample Availability: Samples may be synthesized by the authors on request.