ON 5-HYDROXYTETRAHYDROPROTOBERBERINE DERIVATIVES. SYNTHETIC STUDIES AND STEREOCHEMICAL ELUCIDATION

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Abstract - Stereochemical characterization of 5-hydroxy-8-methyl-2,3,9,10-tetramethoxyberbines (3) and (4) is established unambiguously on the basis of nmr data, supported by difference NOE measurements. Their synthesis starting from the adequate 3-aryltetrahydroisoquinoline (1) is reported.

The quaternary salts berberastine[1] and thalidastine[2] occupy a unique position in the ambit of protoberberine alkaloids. They are the only members of this group to be hydroxylated at C-5. The problem of establishing their absolute configuration was magnified by the fact that both compounds were obtained in small quantities and more importantly that they dehydrate on long standing to their corresponding ring B aromatic dehydroprotoberberinium salts. A posteriori, the absolute configuration at C-5, for the already mentioned protoberberine alkaloids was determined.[3]

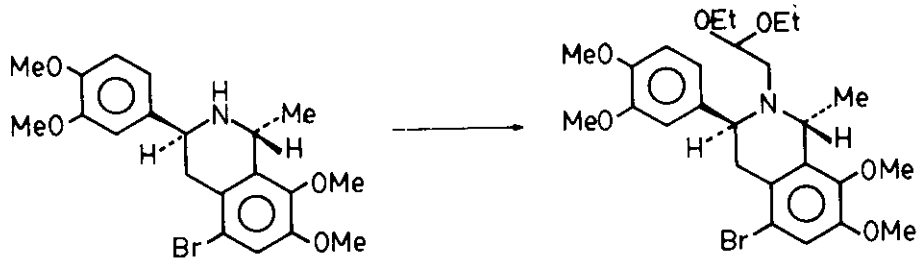
Few synthetic routes to these compounds and their analogues are known. In fact, the most frequent preparation of 5-hydroxytetrahydroprotoberberine skeleton involves Bobbit modification of the Pomeranz-Fritsch cyclization[4] of 3-aryltetrahydroisoquinoline intermediates. The different approaches differ in the synthetic procedure to obtain the N-alkylated 3-aryltetrahydroisoquinoline precursors, which were actually obtained by:

i) Pictet-Spengler cyclization, followed by N-alkylation with glycidol.[5]
ii) Treatment of the adequate isocoumarin with aminoacetaldehyde dimethyl acetal and subsequent reduction of the so-obtained pyridones.[6]
iii) Condensation of a deoxybenzoin with aminoacetaldehyde dimethyl acetal, followed by Mannich reaction.[7]

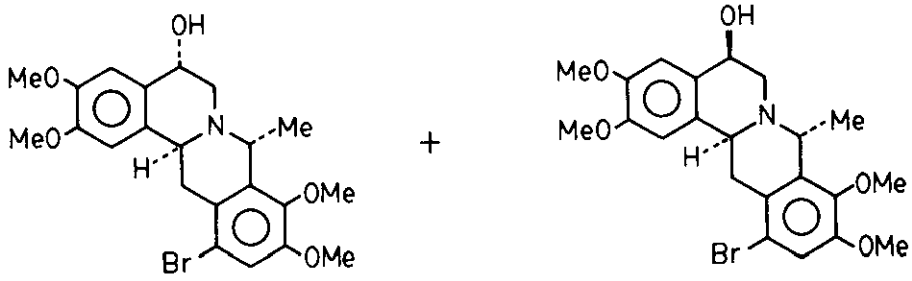
Initially, we extended the first of these approaches to the synthesis of a series of 8-substituted 5-hydroxytetrahydroprotoberberines.[8] In a continuation of our research in this area, we have recently developed[9] a new strategy for the preparation of 2,3,9,10,11-pentamethoxylated tetrahydroprotoberberines, via N-alkylation of 3-aryltetrahydroisoquinolines by using bromoacetaldehyde diethyl acetal. Although there are several reports on the synthesis of 8-methylberbines with oxygenated substituents at C-9 or C-10 positions, always obtained from the corresponding berbine methiodides,[10] only one synthesis of tetrahydroprotoberberines with simultaneous substitutions at the C-8, C-9 and C-10 positions has so far been reported,[11] probably due to the difficulties involved in their synthesis.[12]

The aim of this paper is to describe a convenient method for the preparation of 8-methyltetrahydroprotoberberines dialkoxylated at C-9 and C-10 positions, and to elucidate their stereochemistry by nmr spectroscopy (difference NOE measurements).

These model substances were synthesized in a simple two-stage reaction involving as the first step N-alkylation reaction of the *trans*-5-bromo-3-(3,4-dimethoxyphenyl)-7,8-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (1)[13] and bromoacetaldehyde diethyl acetal, and as the second step intramolecular cyclization by acidic treatment (6M HCl) of the resulting N-alkylated product (2). After basification (10% NH_4OH), from the obtained mixture two new epimeric 5-hydroxyprotoberberine derivatives were easily isolated (overall yield 67 %) by chromatography on a silica gel column: 5,14-*cis*- and 5,14-*trans*-12-bromo-5-hydroxy-2,3,9,10-tetramethoxy-8-methyl-5,6,13,14-tetrahydroprotoberberines (3) and (4).



(1) (2)



(3) (4)

Table. 250 MHz ^{1}H nmr Data and Proton Configuration Assignments of Protoberberines (3) and (4)

Protons	δ (ppm)		Multiplicity[1]		J (Hz)		Observed NOE		Configuration[2]	
	(3)	(4)	(3)	(4)	(3)	(4)	(3)	(4)	(3)	(4)
CH_3	1.48	1.32	d	d	6.7	6.5	H-1 H-14	H-1 H-6a H-14	a-α	a-α
H-13a	2.53	2.54	dd	dd	J_{AX}=11.4 J_{AB}=17.9	J_{AX}=10.7 J_{AB}=16.8	H-6a H-13e	—	a-β	a-β
H-6e	2.82	3.07	dd	m	J_{AX}= 2.7 J_{AB}=11.8	—	—	—	e-α	e-β
H-13e	2.85	3.28	dd	dd	J_{BX}= 5.8 J_{AB}=17.9	J_{BX}= 4.7 J_{AB}=16.8	—	—	e-α	e-α
H-6a	3.14	3.07	dd	m	J_{BX}= 2.7 J_{AB}=11.8	—	H-5 H-6e H-13a	—	a-β	a-α
OCH_3	3.85	3.86	s	s	—	—	—	—	—	—
OCH_3	3.87	3.88	s	s	—	—	—	—	—	—
OCH_3	3.90	3.90	s	s	—	—	—	—	—	—
OCH_3	3.92	3.92	s	s	—	—	—	—	—	—
H-8	4.16	4.31	q	q	6.7	6.5	CH_3 H-6e	CH_3 H-6e H-6a	e-β	e-β
H-14	4.35	4.17	dd	dd	J_{AX}=11.4 J_{BX}= 5.8	J_{AX}=10.7 J_{BX}= 4.7	CH_3 H-1	CH_3 H-1 H-13e	--α[3]	a-α
H-5	4.53	4.58	bt	bt	2.7[4]	2.5[4]	H-4 H-6a H-6e	H-4 H-6a H-6e	e-β	e-α
H-1	6.69	6.78	s	s	—	—	—	—	—	—
H-4	6.95	6.87	s	s	—	—	—	—	—	—
H-11	7.05	7.07	s	s	—	—	—	—	—	—

1. d:doublet, dd: doublet of doublets, bt: broad triplet, q: quartet, m: multiplet
2. a:axial, e: equatorial, β: above the plane containing the ring, α: below the same plane
3. The position of H-14 is axial towards ring C and equatorial towards ring B.
4. J values are calculated from $CDCl_3$ + D_2O solutions.

The stereochemical characterization of the isolated compounds (3) and (4) was carried out by spectroscopy (ir, nmr). The same configuration for ring C in both compounds was deduced. In fact, H-13 and H-14 appear as an ABX system in both derivatives, with coupling constants revealing the axial coupling between H-14 and the corresponding pseudoaxial H-13 proton. In addition to the above observation, the following behaviour was observed: an NOE between H-14 and the pseudoaxial methyl protons at C-8 and no NOE between H-14 and H-8 (see Figure and Table). In contrast with the method used by other authors based on δ values,[11] NOE measurements allow to establish unambiguously the ring C stereochemistry.

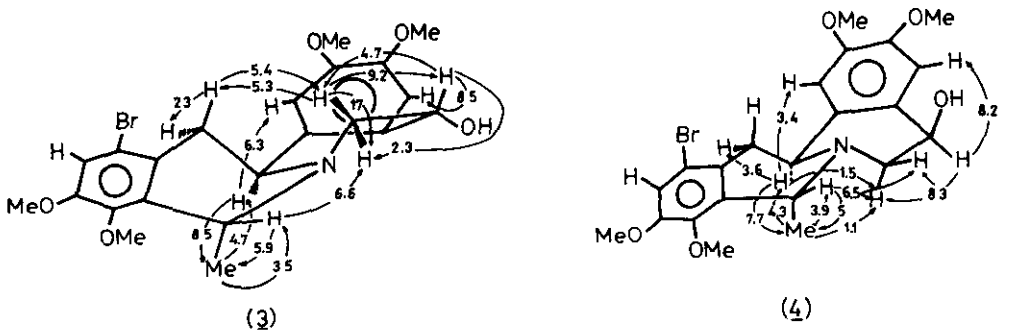


Figure. Results obtained from nuclear Overhauser experiments on protoberberines (3) and (4).

Besides, in *cis*-fused quinolizidine systems with different oxygenation patterns, no Bohlmann bands (2700-2800 cm^{-1}) are observed when the ir spectra are scanned in chloroform solution.[14] Since compound (3) does not show these bands under the reported conditions, a *cis* B/C juncture was assigned for the latter derivative. The above conclusion is supported by these data: observation of an NOE between the axial H-6 and the axial H-13 protons, and no NOE between the methyl group at C-8 and the H-6 protons or between the latter protons and H-14 (see Table).

Diastereomer (4) presents a *trans*-fused quinolizidine conformation: it shows an NOE between the axial H-6 proton and the protons of the C-8 methyl group and H-14, and vice versa; consequently no NOE is observed between H-6 and H-13 protons. Nevertheless, the ir spectrum of this compound does not exhibit Bohlmann bands, though we have stated from its nmr spectroscopic behaviour that it presents a *trans* B/C juncture. In a precedent paper,[9] we have already reported a similar exception to Bohlmann's rule, as in the case of 4-methylquinolizidines.[15] As the theoretical explanation for these low frequency C-H stretching vibrations remains unclear, although it is widely assumed that both hyperconjugation and vibrational coupling between two (or three) axial α C-H bonds accounts for the origin of the Bohlmann bands,[16] it seems therefore that the Bohlmann criterion must be used with caution when dealing with 4-substituted quinolizidines and 8-methyl berbines.

On the other hand, concerning the relative configurations for the C-5 substituents in both diastereomers: a similar NOE can be appreciated between H-5 and H-4 thus suggesting a pseudoequatorial conformation for H-5 in (3) and (4). In agreement

with the above proposed conformation, their infrared spectra exhibited a broad hydroxylic absorption at 3600-3300 cm^{-1} which proved to be concentration independent in chloroform solution over the range 10^{-3}-10^{-4} M and was thus in keeping with an intramolecular OH-N hydrogen bond. Therefore, the OH group must occupy a pseudo-axial position in both protoberberines.

In conclusion, from the above reported results we are able to propose that difference NOE measurements are an accurate technique in order to characterize unambiguously the correct stereochemistry for the quinolizidine system.

EXPERIMENTAL

Melting points were determined on either Electrothermal IA 6304 or Büchi apparatus and are uncorrected. All reactions were monitored by thin-layer chromatography (tlc) carried out on 0.2 mm silica gel 60 GF-254 (Merck) plates using uv light and Dragendorff's reagent[17] as the developing agent. Column chromatography was conducted with silica gel 60, 0.040-0.063 nm, 230-400 mesh (Merck). Infrared spectra were recorded on a Perkin-Elmer 1430 spectrophotometer and only noteworthy absorptions (cm^{-1}) are reported. The 250 MHz nmr spectra were performed on a Bruker WM-250 spectrometer at ambient temperature. ^1H-{^1H} NOE experiments were carried out in the difference mode.[18] Chemical shifts are reported in parts per million (ppm) downfield (δ) from internal tetramethylsilane; the solvent for nmr spectra was deuteriochloroform. Routine mass spectra were obtained using a Hewlett-Packard HP-5970 instrument. Combustion analyses were performed with a Perkin-Elmer model 240 B.

trans-5-Bromo-*N*-(2,2-diethoxyethyl)-3-(3,4-dimethoxyphenyl)-7,8-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (2)

A solution of the tetrahydroisoquinoline (1) (4 g, 10 mmol) in dry dioxane[19] (25 ml) was added under nitrogen to 0.3 g of sodium hydride (80 % suspension in oil) in dry dioxane (10 ml). The resulting suspension was stirred and heated at 110°C under nitrogen for 5 h. Then, the mixture was cooled to room temperature and bromoacetaldehyde diethyl acetal (3 ml, 20 mmol) was added dropwise. The reaction mixture was heated at 110°C under nitrogen for 24 h. The reaction was monitored by tlc ($CHCl_3$/MeOH, 9:1). Excess NaH was decomposed by dropwise addition of methanol and the resulting solution poured into toluene/water. The aqueous phase was extracted with toluene (3x30 ml). Evaporation of the solvent from the combined extracts afforded an oil which was crystallized from methanol to give the *N*-alkylated tetrahydroisoquinoline (2) (3.7 g, 70%), mp 108-109°C. Ir (KBr): ν_{max} 1285 (OCH_2). Nmr: δ 1.06 (t, J=7 Hz, 3H, $OCH_2\underline{CH_3}$), 1.19 (t, J=7 Hz, 3H, $OCH_2\underline{CH_3}$), 1.49 (d, J=6.7 Hz, 3H, $CH\underline{CH_3}$), 2.21 (dd, J_{AX}=5.8, J_{AB}=14.4 Hz, 1H, $\underline{CH_2}CH(OEt)_2$), 2.44 (dd, J_{BX}=4.7, J_{AB}=14.4 Hz, 1H, $\underline{CH_2}CH(OEt)_2$), 2.77 (dd, J_{AX}=11.6, J_{AB}=17.1 Hz, 1H, H-4), 2.93 (dd, J_{BX}=5, J_{AB}=17.1 Hz, 1H, H-4), 3.26-3.66 (m, 4H, OCH_2CH_3), 3.85 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.90 (s, 3H, OMe), 3.93 (s, 3H, OMe), 4.26 (dd, J_{AX}=11.6, J_{BX}=5 Hz, 1H, H-3), 4.39 (t, J=4.8 Hz, 1H, $\underline{CH}(OEt)_2$), 4.55 (q, J=6.7 Hz, 1H, H-1), 6.86 (d,

J_{ortho}=8.3 Hz, 1H, H-5'), 7.04 (dd, J_{ortho}=8.3, J_{meta}=1.8 Hz, 1H, H-6'), 7.06 (s, 1H, H-6), 7.16 (d, J_{meta}=1.8 Hz, 1H, H-2'). Anal. calcd. for $C_{26}H_{36}BrNO_6$: C, 57.98, H, 6.76; Br, 14.83; N, 2.60. Found: C, 58.02; H, 6.75; Br, 14.86; N, 2.60.

5,14-*cis*-12-Bromo-5-hydroxy-2,3,9,10-tetramethoxy-8-methyl-5,6,13,14-tetrahydroprotoberberine (3) and 5,14-*trans*-12-bromo-5-hydroxy-2,3,9,10-tetramethoxy-8-methyl-5,6,13,14-tetrahydroprotoberberine (4).

Hydrochloric acid (6M, 30ml) was added dropwise to tetrahydroisoquinoline (2) (3.5 g, 6.5 mmol), and the resulting solution was magnetically stirred overnight at room temperature. The reaction mixture was extracted with chloroform and the combined dried extracts were evaporated under reduced pressure to afford a solid residue which on tlc ($CHCl_3$/MeOH, 9:1) showed two spots attributed to the hydrochloride salts of protoberberines (3) and (4). A suspension of this mixture in water was basified (pH 10) by adding 10 % aqueous NH_4OH and stirred at room temperature for 6 h. The resulting aqueous solution was extracted with chloroform (3x20 ml) and dried (Na_2SO_4). Removal of the solvent afforded a residue (2.9 g), which was column chromatographed ($CHCl_3$/MeOH, 100-99.5 %) to afford diastereomers (3) and (4) in a 1:1 ratio.

Compound (3): R_f: 0.7 (silica gel, $CHCl_3$/MeOH, 9.5:0.5), yield: 1.4 g (48 %), colorless crystals of mp 186-187°C (from ethanol). Ir (KBr): ν_{max} 3600-3400 (OH). Nmr: see Table. Ms: m/z (%) 465(3) (M^++2), 463(3.6) (M^+), 450(94), 448(100), 258 (51.7), 256(51), 190(38.8), 162(65.2). Anal. calcd. for $C_{22}H_{26}BrNO_5$: C, 56.88; H, 5.65; Br, 17.22; N, 3.02. Found: C, 56.86; H, 5.66; Br, 17.24; N, 3.03.

Compound (4): R_f: 0.8 (silica gel, $CHCl_3$/MeOH, 9.5:0.5), yield: 1.4 g (48 %), colorless crystals of mp 160-161 °C (from ethanol). Ir (KBr): ν_{max} 3600-3300 (OH). Nmr: see Table. Ms: m/z(%) 465(3.4) (M^++2), 463(3.7) (M^+), 450(84), 448(100), 258 (56), 256(57), 190(18), 162(73). Anal. calcd. for $C_{22}H_{26}BrNO_5$: C, 56.88; H, 5.65; Br, 17.22; N, 3.02. Found: C, 56.91; H, 5.63; Br, 17.24; N, 3.01.

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