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A series of 5-hydroxytetrahydroprotoberberines has been prepared from 3-aryltetrahydroisoquinoline derivatives *via* successive *N*-alkylation, oxidation and cyclization in acidic media. The relative configurations of the resulting diastereomeric 5-hydroxytetrahydroprotoberberines are reported.

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The protoberberine nucleus has received continued synthetic attention because of its varied physiological activity [1,2] and as a model molecular framework on which to exercise advances in synthetic methodology directed at the construction of heteropolycycles [1,3].

Although the tetracycle has been approached in a variety of ways, none of them have generated simultaneous substitution in the C-8 and C-9 positions. Moreover, only little work has been done on the synthesis of C-8 methylated protoberberines [4] and none on the C-8-phenyl substituted ones. Herein, we wish to report the synthesis of 8-methyl- and 8-phenyl-substituted 5-hydroxytetrahydroprotoberberines, starting from adequate 3-aryltetrahydroisoquinoline derivatives **1**. This pathway provides access to a varied substitution pattern in the D-ring of the protoberberine structure. Besides, some of the compounds obtained represent a model to study the effect of the simultaneous C-8 and C-9 substitution on the resulting stereochemistry of the protoberberine skeleton.

atives **2**, without isolation, were oxidized with sodium periodate to provide the expected aldehydes **3**.

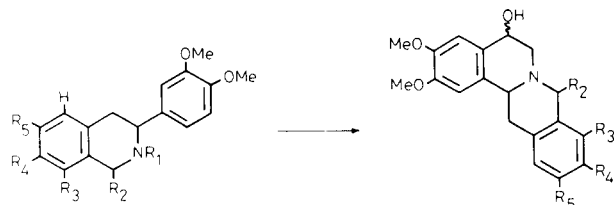
The latter compounds, without further purification (ir band at 1730 cm^{-1}), were dissolved in 6*M* hydrochloric acid and the solutions were left at room temperature overnight, affording the diastereomeric mixture of the expected 5-hydroxytetrahydroprotoberberine derivatives **4** and **5** as the corresponding hydrochlorides [7]. Prior to separation by column chromatography, the so-obtained salts were converted into the free bases and this *modus operandi* finally afforded separately stereoisomers **4** and **5**.

The stereochemical assignment of these derivatives was effected by their spectroscopic data (ir, pmr), taking into account that the formation of 5-substituted tetrahydroprotoberberines implies a new chiral centre.

In the ir spectra of tetrahydroprotoberberines **4a**, **5a**, **4b** and **5b**, Bohlmann bands [8] in the region 2700-2800 cm^{-1} , characteristic of a *trans*-junction of ring B/C were observed. Moreover, in their pmr spectra the angular C-14 proton resonates at a field higher than 3.8 ppm [9]. These data allow to establish the *trans* conformation **A**, for the quinolizidine ring system in the former compounds.

In contrast, isomers **4c** and **5c** show no Bohlmann bands and exhibit a pmr signal at δ 4.0, downfield than δ 3.8 due to the C-14 methine proton [9]. These observations indicate that this proton is *cis* to the nitrogen lone pair, thus implying a *cis*-fused quinolizidine conformation such as **B**.

In the pmr spectra of all tetrahydroprotoberberines synthesized, a large coupling constant between the angular proton and the protons at the C-13 position was always observed, in agreement with a pseudoaxial conformation for the angular C-14 proton [10]. Table 1.



- | | |
|---|-----------|
| 1 a, b, c: $R_1 = \text{H}$ | 4 a, b, c |
| 2 a, b, c: $R_1 = \text{CH}_2 - \text{CHOH} - \text{CH}_2\text{OH}$ | 5 a, b, c |
| 3 a, b, c: $R_1 = \text{CH}_2\text{CHO}$ | |
| a: $R_2 = \text{Me}$, $R_3 = \text{H}$; $R_4 = R_5 = \text{OMe}$ | |
| b: $R_2 = \text{Ph}$, $R_3 = \text{H}$; $R_4 = R_5 = \text{OMe}$ | |
| c: $R_2 = \text{Me}$; $R_3 = R_4 = R_5 = \text{OMe}$ | |

As starting materials the following 3-aryltetrahydroisoquinolines **1** were used: 1-methyl- and 1-phenyl-3-(3,4-dimethoxyphenyl)-6,7-dimethoxytetrahydroisoquinolines (**1a**) and (**1b**) [5] and 1-methyl-3-(3,4-dimethoxyphenyl)-6,7,8-trimethoxytetrahydroisoquinoline (**1c**) [6].

To attain addition of a two-carbon unit, the 3-aryltetrahydroisoquinolines **1** were reacted with glycidol (2,3-epoxy-1-propanol) and the intermediate aminoglycol deriv-

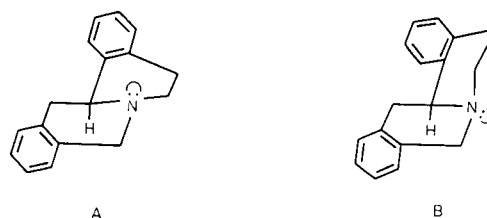


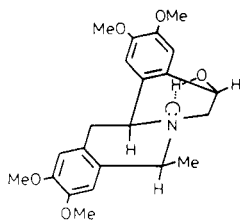
Table 1

Spectral Data for the Tetrahydroprotoberberines (4) and (5)

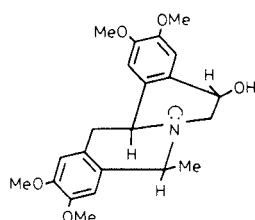
Product No.	PMR (Deuteriochloroform/TMS) [a] δ (ppm), J (Hz)	MS m/z (%)
4a	1.53 (d, J = 6.20, 3H, CH ₃), 2.66 (dd, J = 1.73 and 11.70, 1H, H-6), 2.83 (dd, J = 11.10 and 15.40, 1H, H-13), 3.15 (dd, J = 2.90 and 15.40, 1H, H-13), 3.46 (s, 1H, OH), 3.50 (dd, J = 2.80 and 11.70, 1H, H-6), 3.68 (dd, J = 2.90 and 11.10, 1H, H-14), 3.77 (q, J = 6.20, 1H, H-8), 3.88 (s, 3H, OCH ₃), 3.89 (s, 3H, OCH ₃), 3.91 (s, 6H, 2 x OCH ₃), 4.53 (broad s, 1H, H-5), 6.67 (s, 2H, H-1 and H-12), 6.77 (s, 1H, H-9), 6.89 (s, 1H, H-4)	385 (M ⁺ , 8), 370 (M-15, 73), 190 (13), 179 (17), 178 (100), 163 (14)
5a	1.57 (d, J = 6.60, 3H, CH ₃), 2.38 (broad d, 1H, OH), 2.62 (dd, J = 6.10 and 10.10, 1H, H-6), 2.88 (dd, J = 10.70 and 16.20, 1H, H-13), 2.98 (dd, J = 4.80 and 16.20, 1H, H-13), 3.22 (dd, J = 4.00 and 10.10, 1H, H-6), 3.85 (s, 3H, OCH ₃), 3.88 (s, 3H, OCH ₃), 3.89 (s, 3H, OCH ₃), 3.90 (s, 3H, OCH ₃), 3.92 (dd, J = 4.80 and 10.70, 1H, H-14), 4.02 (q, J = 6.60, 1H, H-8), 4.73 (dd, J = 6.10 and 4.00, 1H, H-5), 6.60 (s, 1H, H-12), 6.66 (s, 1H, H-1), 6.69 (s, 1H, H-9), 7.02 (s, 1H, H-4)	385 (M ⁺ , 6), 370 (M-15, 50), 190 (12), 179 (17), 178 (100), 163 (15)
4b	2.55 (dd, J = 1.70 and 11.70, 1H, H-6), 2.75 (broad d, J = 9.60, 1H, OH), 3.05 (dd, J = 11.00 and 15.30, 1H, H-13), 3.10 (dd, J = 2.60 and 11.70, 1H, H-6), 3.32 (dd, J = 3.30 and 15.30, 1H, H-13), 3.57 (s, 3H, OCH ₃), 3.88 (s, 3H, OCH ₃), 3.89 (dd, J = 3.30 and 11.00, 1H, H-14), 3.90 (s, 3H, OCH ₃), 3.93 (s, 3H, OCH ₃), 4.53 (broad s, 1H, H-5), 4.61 (s, 1H, H-8), 6.12 (s, 1H, H-12), 6.69 (s, 1H, H-1), 6.85 (s, 1H, H-9), 6.89 (s, 1H, H-4), 7.35 (m, 5H, Ph-H)	447 (M ⁺ , 19), 430 (M-17, 9), 240 (91), 239 (43), 210 (21), 209 (100), 208 (19)
5b	2.24 (dd, J = 9.50 and 10.00, 1H, H-6), 3.02 (dd, J = 11.00 and 15.00, 1H, H-13), 3.21 (dd, J = 5.10 and 10.00, 1H, H-6), 3.25 (broad d, 1H, OH), 3.46 (dd, J = 3.20 and 15.00, 1H, H-13), 3.58 (s, 3H, OCH ₃), 3.86, 3.89 and 3.92 (s x 3, 10H, 3 x OCH ₃ and H-14), 4.46 (dd, J = 5.10 and 9.50, 1H, H-5), 4.57 (s, 1H, H-8), 6.13 (s, 1H, H-12), 6.66 (s, 1H, H-1), 6.79 (s, 1H, H-9), 7.03 (s, 1H, H-4), 7.32 (m, 5H, Ph-H)	447 (M ⁺ , 19), 430 (M-17, 6), 240 (95), 239 (44), 210 (18), 209 (100), 208 (21)
4c	1.43 (d, J = 7.00, 3H, CH ₃), 2.69 (dd, J = 12.20 and 18.40, 1H, H-13), 2.72 (dd, J = 3.60 and 12.50, 1H, H-6), 2.74 (dd, J = 5.70 and 18.40, 1H, H-13), 2.84 (broad d, J = 11.00, 1H, OH), 3.21 (dd, J = 3.60 and 12.50, 1H, H-6), 3.79 (s, 3H, OCH ₃), 3.84 (s, 3H, OCH ₃), 3.88 (s, 6H, 2 x OCH ₃), 3.93 (s, 3H, OCH ₃), 4.03 (q, J = 7.00, 1H, H-8), 4.31 (dd, J = 12.20 and 5.70, 1H, H-14), 4.55 (broad d, J = 11.00, 1H, H-5), 6.36 (s, 1H, H-12), 6.63 (s, 1H, H-1), 6.94 (s, 1H, H-4)	415 (M ⁺ , 1.5), 400 (M-15, 100), 194 (11), 193 (72), 190 (30), 178 (23), 165 (14), 162 (16)
5c	1.30 (d, J = 6.60, 3H, CH ₃), 2.72 (dd, J = 10.00 and 15.80, 1H, H-13), 3.05 (m, J = 2.30, 2H, H-6), 3.12 (d, J = 11.00, 1H, OH), 3.20 (dd, J = 4.20 and 15.80, 1H, H-13), 3.82 (s, 3H, OCH ₃), 3.85 (s, 3H, OCH ₃), 3.89 (s, 6H, 2 x OCH ₃), 3.95 (s, 3H, OCH ₃), 4.10 (dd, J = 10.00 and 4.20, 1H, H-14), 4.20 (q, J = 6.60, 1H, H-8), 4.52 (broad d, J = 11.00, 1H, H-5), 6.44 (s, 1H, H-12), 6.71 (s, 1H, H-1), 6.84 (s, 1H, H-4)	415 (M ⁺ , 1.7), 400 (M-15, 100), 194 (12), 193 (72), 190 (30), 178 (22), 165 (14), 162 (16)

[a] s, singlet; d, doublet; dd, doublet of doublets; m, multiplet; q, quartet.

Besides, tetrahydroprotoberberine derivatives **4a** and **5a** showed the C-8 methyl group at δ 1.53 and 1.57 respectively as doublets ($J = 6.5$ Hz) and the previously mentioned Bohlmann bands, while compounds **4c** and **5c** showed the C-methyl group at δ 1.40 and 1.31 respectively also as doublets ($J = 6.5$ Hz) and no Bohlmann bands. This fact indicates that the former two compounds have *cis* related hydrogens at C-8 and C-14 positions, while the corresponding hydrogens in the latter two compounds **4c** and **5c** are *trans* [11]. Therefore, taking into account the above established pseudoaxial conformation for the hydrogen at C-14, the C-8 methyl group must occupy predominantly pseudoequatorial and pseudoaxial positions respectively.



4 a

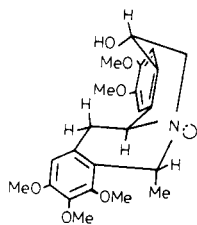


5 a

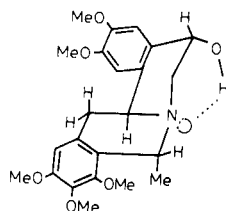
Finally, analysis of its coupling constants ($J > 8$ Hz) reveals diaxial coupling between the sole proton at C-5 and the corresponding pseudoaxial proton at C-6 for compounds **5a** and **5b**, thus proving a *trans* configuration for protons at C-5 and C-14. To support the configuration proposed above, it is relevant to point out that the pmr spectra of both compounds also exhibit singlets at δ 7.02 and 7.03 respectively for H-4, revealing that this proton is close to the pair of electrons on the pseudoequatorial alcoholic oxygen at C-5 in both cases [12].

On the other hand, in the C-5 epimeric compounds **4a** and **4b** the presence of a smaller J in the resonance of the C-5 and C-6 protons indicates the expected *cis* configuration for the protons at C-5 and C-14 positions. In agreement with the configuration proposed for the former compounds, is the fact that their infrared spectra exhibited a broad hydroxyl absorption at 3500 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-H hydrogen bond [13].

The relative configurations of the diastereomeric compounds **4c** and **5c** was established by their spectroscopic data (ir, pmr) and are shown below.



4 c



5 c

The mass spectral fragmentation pattern of the 5-hydroxytetrahydroprotoberberine derivatives synthesized fitted well with the proposed structures for all of them. In fact, while protoberberine derivatives with no substitution at C-9 showed the base peak due to a fragmentation involving a retro-Diels-Alder type process, compounds **4c** and **5c** with simultaneous C-8 methyl and C-9 methoxy substitution, gave the $(M-CH_3)^+$ fragment as the base peak [14]. Table 2.

Table 2

Synthetical Data for the Tetrahydroprotoberberines **4** and **5** Obtained

Product No.	Yield [a] %	Mp ($^{\circ}C$) (methanol)	Formula	Calcd. (Found) (%)		
				C	H	N
4a	26	102-104	$C_{22}H_{27}O_5N$	68.57 (68.57)	7.01 (7.00)	3.64 (3.63)
5a	25	121-123	$C_{22}H_{27}O_5N$	68.57 (68.56)	7.01 (7.00)	3.64 (3.64)
4b	24	154-156	$C_{27}H_{29}O_5N$	72.48 (72.29)	6.48 (6.46)	3.13 (3.11)
5b	22	165-167	$C_{27}H_{29}O_5N$	72.48 (72.52)	6.48 (6.51)	3.13 (3.12)
4c	23	148-150	$C_{23}H_{29}O_6N$	66.51 (66.50)	6.99 (6.98)	3.37 (3.38)
5c	23	174-176	$C_{23}H_{29}O_6N$	66.51 (66.48)	6.99 (6.98)	3.37 (3.37)

[a] Overall yield from **1**.

EXPERIMENTAL

Melting points were determined on either Electrothermal 1A 6304 or Büchi apparatus and are uncorrected. For thin-layer chromatography Merck Kieselgel GF 254 plates (0.2 mm thick) were used. Visualization was accomplished by uv light or by spraying with Dragendorff's reagent. Column chromatography was carried out on silica gel 60 Merck (230-400 mesh). Microanalyses were performed by the "Colegio Universitario de Alava". The ir spectra were recorded on a Perkin-Elmer 1430 spectrophotometer and only noteworthy absorptions (cm^{-1}) are listed. The pmr spectra were run on a Varian XL-200 (200 MHz) instrument using deuteriochloroform as solvent and tetramethylsilane as internal standard. Chemical shifts are reported in ppm downfield (δ) from tetramethylsilane. Mass spectra were measured with a Hewlett-Packard HP-5970 apparatus.

Preparation of *N*-Formylmethyltetrahydroisoquinolines **3**. (General Procedure).

A mixture of 1 mmole of the tetrahydroisoquinoline (**1**) and 0.1 g (1.2 mmoles) of 2,3-epoxy-1-propanol was heated until fusion on a steam bath. The reaction was complete within 2 hours, affording the corresponding glycolic derivative **2**; ir (potassium bromide): 3700 - 3100 cm^{-1} (O-H).

Compound **2**, without further purification, was treated with chloroform (5 ml) and water (5 ml) under vigorous stirring. After cooling to $0^{\circ}C$, a solution of sodium periodate (2.6 mmoles) in water (6 ml) was added dropwise. The resulting mixture was then made alkaline (pH 8) by adding 1M sodium hydroxide and stirred for 3-4 hours (tlc monitoring). The so-obtained organic layer was separated, washed with water and dried over anhydrous sodium sulfate. Removal of the solvent afforded a pale yellow residue, which was identified as the *N*-formylmethyltetrahydroisoquinoline (**3**); ir (film): 1730 cm^{-1} (C=O).

Synthesis of the 5-Hydroxytetrahydroprotoberberines **4** and **5** (General Procedure).

Thirty ml of 6*M* hydrochloric acid was added dropwise to the obtained *N*-formylmethyltetrahydroisoquinoline derivative **3**, and the resulting solution was stirred at room temperature overnight. The reaction mixture was extracted with chloroform and the combined dried extracts evaporated under reduced pressure. The solid residue showed on tlc (silica gel, chloroform/methanol, 9.5:0.5) two spots attributed to the protoberberine hydrochlorides **4** and **5**. A suspension of this mixture in water was basified by adding 10% aqueous ammonium hydroxide and stirred at 0° for 3 hours. After the usual work-up, the residue was column chromatographed on silica gel eluting with chloroform/methanol 9.5:0.5 to afford diastereomers **4** and **5** in a 1:1 ratio. Spectral and synthetic data of all new compounds obtained are given in Tables 1 and 2.

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