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THE STEREOCHEMISTRY OF REDUCED PROAPORPHINES

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Abstract: Controlled catalytic hydrogenation of the proaporphine (+)-stepharine (1) proceeded by preferential approach of the catalyst from the side opposite H-6a to provide (+)-8,9-dihydrostepharine (3), accompanied by smaller amounts of (-)-11,12-dihydrostepharine (4) and (+)-tetrahydrostepharine (5). $NaBH_4$ reduction of 5 led to (+)-α- and (+)-β-hexahydrostepharine (6 and 7). Complete spectral and optical data were obtained for all reduction products, thus supplying reliable standards for the characterization of reduced proaporphine alkaloids.

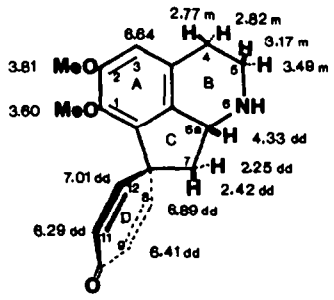
In the course of a recent investigation of the alkaloids of Turkish Roemeria species (Papaveraceae), we obtained a series of proaporphine and reduced proaporphine alkaloids. While several reduced proaporphines have been reported in the literature, no complete NMR spectral data were available. Additionally, no finite correlations had been drawn between specific rotations and CD curves on the one hand, and relative and absolute configurations on the other.[2]

Fortunately, we had on hand a supply of the known proaporphine (+)-stepharine (1) which had been obtained from the roots of Thai Stephania venosa Spreng. (Menispermaceae). Our objective was thus to carry out a study of stepharine itself, as well as its various reduction products, with the aim of setting up reliable spectral and optical standards by which to assign the structures of novel proaporphinoids. This approach was deemed particularly relevant since it did not entail the destruction of any new natural product for the purpose of chemical correlation.

The absolute configuration of a proaporphine may be determined simply by the sign of its specific rotation, since it is known that compounds of the C-6a S configuration possess a negative rotation, while those of the C-6a R series are dextrorotatory.[3,4] In practice, however, all proaporphines with a dienone system such as (+)-stepharine (1), are unstable and lead to oxidation products upon standing for even a half hour. The resulting colored solutions make optical measurements difficult if not impossible.

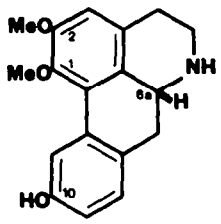
Alternatively, CD measurements may also lead to the assignment of absolute configuration, since proaporphine dienones of the S configuration exhibit a maximum near 235 nm, with a negative tail beyond 220 nm; while for the R configuration, as in the case of (+)-stepharine (1), the opposite pattern is observed.[3,4]

Since CD spectrometers are not commonly available in some laboratories, a reliable method for the determination of absolute configuration consists of the acid catalyzed dienone-phenol rearrangement of the proaporphine to supply the corresponding aporphine. The latter is usually stable, and its specific rotation may be readily measured. For the aporphines, it is well known that the C-6a S configuration displays positive specific rotation, and the opposite R configuration has a negative rotation.[4] In the present instance, acid rearrangement of (+)-stepharine (1) led to (-)-tuduranine (2).

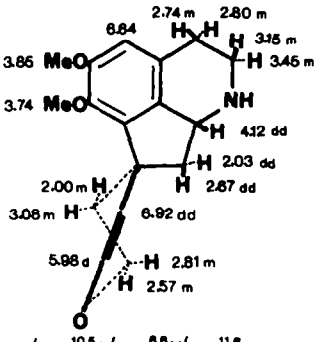


$J_{6a,7\alpha}$ 10.5 ; $J_{6a,7\beta}$ 6.3 ; $J_{7\alpha,7\beta}$ 12.0
$J_{8,9}$ 9.9 ; $J_{11,12}$ 9.9 ; $J_{8,12}$ 2.8 ; $J_{9,11}$ 1.9

1

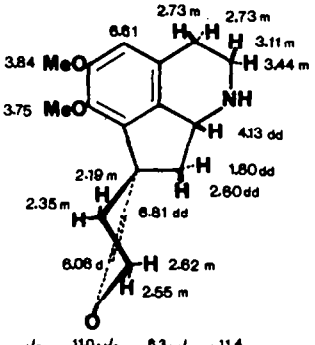


2



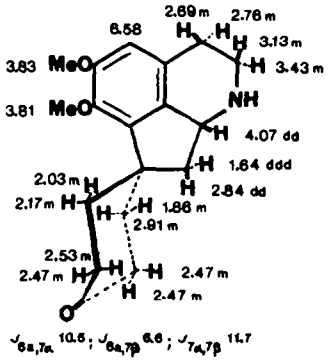
$J_{6a,7\alpha}$ 10.5 ; $J_{6a,7\beta}$ 6.6 ; $J_{7\alpha,7\beta}$ 11.6
$J_{11,12}$ 10.1 ; $J_{8\text{-}eq,12}$ 1.3

3*



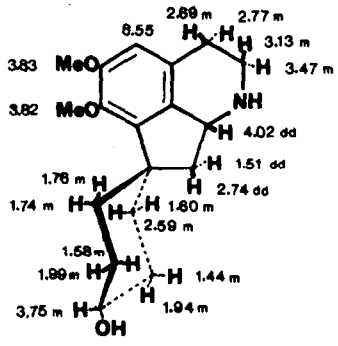
$J_{6a,7\alpha}$ 11.0 ; $J_{6a,7\beta}$ 6.3 ; $J_{7\alpha,7\beta}$ 11.4
$J_{8,9}$ 10.1 ; $J_{8,11\text{-}eq}$ 1.3

4*



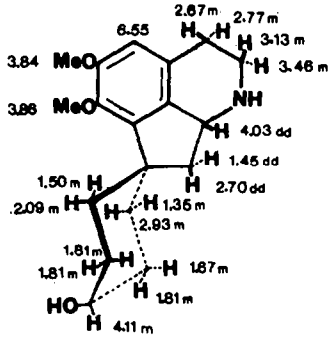
$J_{6a,7\alpha}$ 10.5 ; $J_{6a,7\beta}$ 6.6 ; $J_{7\alpha,7\beta}$ 11.7
$J_{7\alpha,12ax}$ 1.3

5



$J_{6a,7\alpha}$ 9.9 ; $J_{6a,7\beta}$ 7.1 ; $J_{7\alpha,7\beta}$ 11.9

6



$J_{6a,7\alpha}$ 10.6 ; $J_{6a,7\beta}$ 6.5 ; $J_{7\alpha,7\beta}$ 11.6
$J_{9ax,10}$ 2.7

7

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* It is important to note that for each of the dihydro proaporphines 3 and 4, two different half-chair conformations of ring D are possible. The one drawn here is that shown to exist in the x-ray analysis of 11,12-dihydroglaziovine hydrobromide.[2] Additionally, molecular models indicate that the conformation adopted here for species 3 and 4 is the less sterically hindered.

The assignment of the ^1H chemical shifts for (+)-stepharine is indicated around expression 1, and is based upon spin decoupling as well as NOEDS studies. It is in accord with related spectral data available for the proaporphines (+)-pronuciferine and (-)-glaziovine.[6] An important difference, however, is that in (+)-stepharine (1) the amine function is secondary rather than tertiary. This leads to a downfield shift of some of the aliphatic protons, particularly those at C-5 and C-6a.

It will be noted that the difference in chemical shifts ($\Delta\delta$) between adjacent vinylic protons on ring D depends upon their stereochemical relationship to H-6a. For example, in the (+)-stepharine (1) case with the C-6a R configuration, $\Delta\delta_{8,9}$ is 0.48 ppm, while $\Delta\delta_{11,12}$ is 0.72 ppm. For the S configuration, these values will be reversed, given that the numbering system for the proaporphines is independent of absolute configuration.

In order to obtain the two dihydroproaporphine diastereomers incorporating an enone system in ring D, (+)-stepharine (1) was subjected to a controlled catalytic hydrogenation using 5% palladium on charcoal. After thirteen minutes, a mixture of starting material 1, the two dihydrostepharine diastereomers 3 and 4, and tetrahydrostepharine (5) was obtained.

Initially, some difficulty was encountered in separating this mixture. Eventually, however, after some forty different TLC solvent systems were tried, it was found that the best separation could be achieved by successive column chromatography on TLC quality silica gel, using first acetonitrile-benzene-ethyl acetate-methanol-ammonium hydroxide (40:30:20:5:5), and then hexane-chloroform-methanol-ammonium hydroxide (4:5:1:trace).

It is interesting to note that although proaporphines have been known for almost twenty-five years, the present effort is the first attempt to obtain dihydro derivatives starting from a proaporphine dienone. The first concern was in finding out which side of the molecule would reduce preferentially. Several hydrogenations of (+)-stepharine (1) were, therefore, carried out, and from all of these the two dihydro isomers 3 and 4 were obtained in a ratio of 70:30. The hydrogenation catalyst thus prefers to approach the dienone moiety from the side opposite H-6a.

As an initial step in the structure elucidation of species 3 and 4, detailed NMR spin decoupling and NOE studies were undertaken. It was demonstrated (Experimental) that H-6a, which is known to be in the beta configuration (R series), is syn the H-7β ($\sim\delta$ 2.60) and anti to H-7α ($\sim\delta$ 1.90).

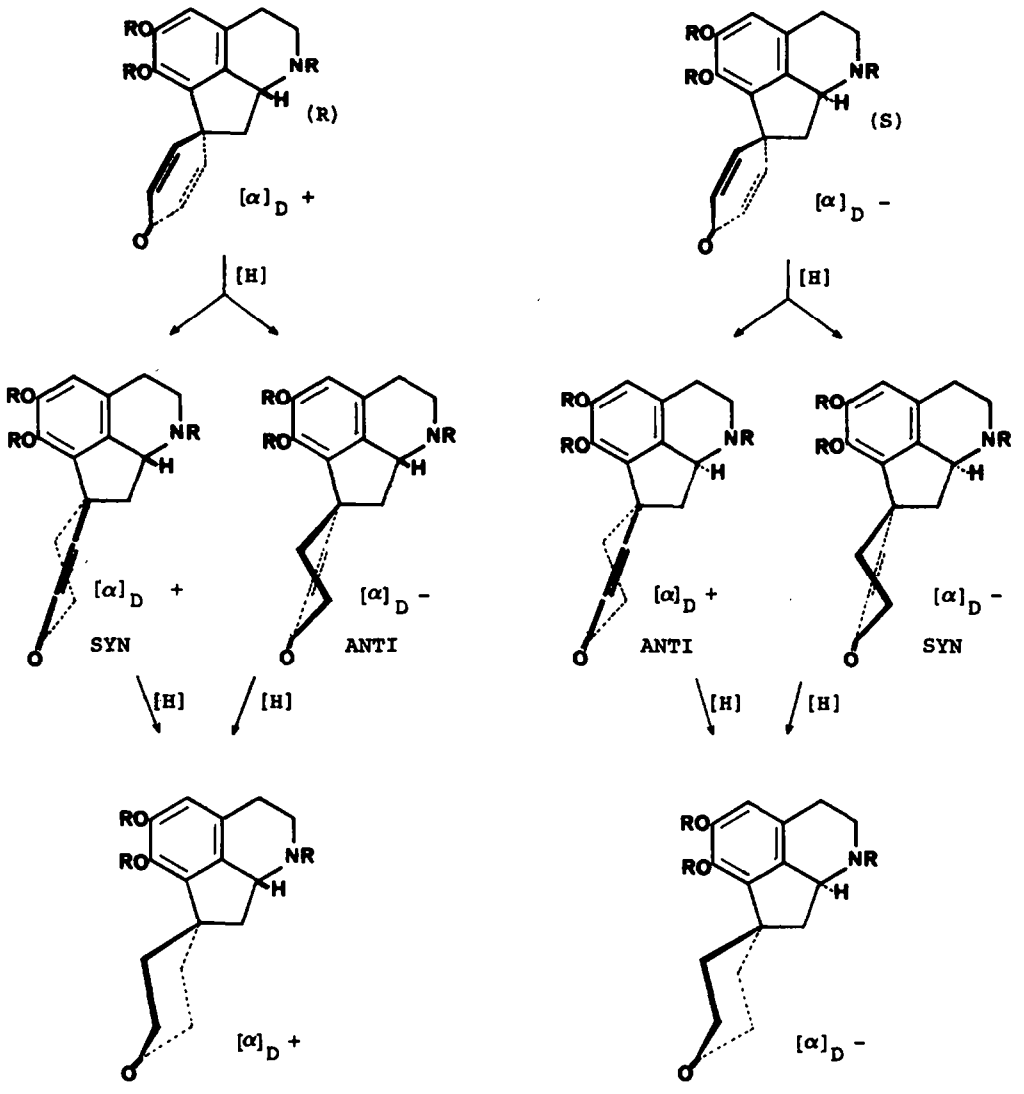
The major dihydro product proved to be (+)-8,9-dihydrostepharine (3). The relative configuration of this species was determined through NMR spin decoupling and NOE experiments. Irradiation of H-6a (δ 4.12) enhanced H-12 (δ 6.92) which indicated that the double bond in ring D lies syn to H-6a. An insight into the conformation of ring D could be derived from the observed W long range coupling between H-12 (δ 6.92) and H-$8_{\psi eq}$ (δ 2.00) pointing to these hydrogens being essentially in the same plane.

The minor dihydro stereomer corresponds to (-)-11,12-dihydrostepharine (4). Irradiation of H-7α (δ 1.80) led to enhancement of H-8 (δ 6.81) indicating that the double bond of ring D is situated anti to H-6a. Again, in this instance, a W long range coupling could be observed between H-8 (δ 6.81) and H-$12_{\psi eq}$ (δ 2.19) so that these hydrogens must also lie nearly in one plane.

The difference in NMR chemical shifts ($\Delta\delta$) between the two vinylic protons of a dihydroproaporphine is significant and diagnostic of the relative configuration. In the case of syn species 3, in which H-6a and the ring D unsaturation are on the same side of the molecule, the $\Delta\delta$ = 6.92 - 5.98 = 0.94 ppm. In the anti example 4, $\Delta\delta$ = 6.81 - 6.06 = 0.75 ppm. Thus, even a cursory analysis of the NMR spectrum of a dihydroproaporphine allows for differentiation between the syn and anti series.

A significant observation is that dihydro derivatives 3 and 4 show opposite specific rotations, with the main product 3 exhibiting $[\alpha]_D$ +190° (c 0.1, $CHCl_3$), while the minor component 4 presents $[\alpha]_D$ -95° (c 0.1, $CHCl_3$). These differences are also reflected in the CD spectra.

Scheme I



If the catalytic hydrogenation were allowed to proceed for an hour, the main product was (+)-tetrahydrostepharine (5). The ring D conformation was derived from NMR spin decoupling and NOE studies (Experimental). Particularly telling were two W long range couplings. The first was between H-8_{eq} (δ 1.86) and H-12_{eq} (δ 2.03), and the second between H-12_{ax} (δ 2.17) and H-7 (δ 1.64), so that each of these pairs of hydrogens lie on a plane. Such an arrangement is possible only when ring D exists in a chair conformation as indicated in expression 5.

The specific rotation for species 5 was positive, as expected of a tetrahydroproaporphine of the R configuration. The CD curve exhibited a trough at 240 nm.

Since naturally occurring hexahydroproaporphines are known, the tetrahydroproaporphine 5 was reduced with sodium borohydride. Two hexahydro derivatives were obtained. The main product was (+)-α-hexahydrostepharine (6) which incorporates an equatorial hydroxyl on ring D. The minor component was (+)-β-hexahydrostepharine (7) which bears a C-10 axial hydroxyl.

Through spin decoupling and NOE experiments, all of the chemical shifts for the protons of rings C and D of alcohols 6 and 7 could be assigned unequivocally. In both instances, ring D assumes a chair conformation. The H-10 signal at δ 3.75 for alcohol 6 appeared as a broad

multiplet which is diagnostic of an axial configuration. Furthermore, significant NOE interactions could be detected (Experimental) between H-10 (δ 3.75) and $H\text{-}9_{eq}$ (δ 1.94) and $H\text{-}11_{eq}$ (δ 1.99), as well as between H-10 and $H\text{-}8_{ax}$ (δ 2.59) and $H\text{-}12_{ax}$ (δ 1.74). Finally, NOE interactions were also present between H-6a (δ 4.02) and $H\text{-}12_{eq}$ (δ 1.76).

Turning now to the minor alcohol 7, the shape of the H-10 absorption was narrow, indicating small coupling constants with the vicinal protons characteristic of an equatorial configuration. Detailed spin douplings allowed for a complete assignment of all the protons of rings C and D. Important NOE's were recorded between H-10 (δ 4.11) and $H\text{-}9_{ax}$ (δ 1.67), and $H\text{-}9_{eq}$ (δ 1.81), $H\text{-}11_{eq}$ (δ 1.81) and $H\text{-}11_{ax}$ (δ 1.81) (Experimental). Additional NOE interactions obtained between H-6a (δ 4.03) and $H\text{-}12_{eq}$ (δ 1.50). As expected, H-10 appeared further downfield when equatorial (δ 4.11) than when axial (δ 3.75).

Both alcohols 6 and 7 were dextrorotatory, with $[\alpha]_D$ values of +49° and +40° in chloroform, respectively.

Some interesting generalizations concerning the sign and magnitude of the specific rotations for the proaporphines and reduced proaporphines can now be drawn, and have been summarized in Scheme I. A dextrorotatory proaporphine dienone of the R configuration will lead to two dihydro proaporphines. The syn dihydro species will show a relatively large positive specific rotation, while the anti analog will display a negative rotation of smaller magnitude. Through further reduction, both dihydroproaporphines can lead to tetrahydro and hexahydro derivatives, all of which will show dextro rotation. Proaporphines of the opposite C-6a S configuration will, of course, exhibit the opposite optical activity.

A final relevant observation derives from perusal of the NMR spectra for the six proaporphines described here. This indicates that the chemical shifts for the protons at C-4 and C-5 remain essentially constant, regardless of the degree of reduction in ring D - a consequence of the conformation of rings A, B and C for proaporphines being rigid and unchanging. An important, reciprocating, NOE may, in fact, always be observed between H-6a and $H\text{-}5_{\psi}ax$ (Experimental).

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Experimental

All compounds are amorphous. NMR spectra were obtained in $CDCl_3$ at 360 MHz. Merck F-254 silica gel was used for the chromatography.

Dienone-Phenol Rearrangement of (+)-Stepharine (1): Dienone 1 (5 mg) was dissolved in HOAc (2 mL) and concd. HCl (2 drops) added. After 48 h standing, the soln was basified with $NaHCO_3$ and extracted with $CHCl_3$. Further work-up provided (-)-tuduranine (4 mg).

Catalytic Hydrogenation of (+)-Stepharine (1): Pure 1 (20 mg) was dissolved in MeOH (2 mL) and 5% Pd/C (10 mg) added. The mixture was stirred in a hydrogen atmosphere for 13 min. Following work-up, the crude reaction mixture was subjected to double development TLC using the solvent system acetonitrile-benzene-methyl acetate-methanol-ammonium hydroxide (40:30:20:5:5). Elution supplied (+)-stepharine (1) (6 mg, 30%), (+)-tetrahydrostepharine (5) (4 mg, 20%), and a mixture of dihydro stereomers 3 and 4 (10 mg, 50%). The dihydro mixture was then partially separated by double development TLC using the system hexane-chloroform-methanol-ammonium hydroxide (40:50:10:trace). The top part of the band gave pure (+)-8,9-dihydrostepharine (3) (3 mg), while the bottom part provided (-)-11,12-dihydrostepharine (4) (1 mg). Alternatively and preferably, the same solvent systems could be used in succession on chromatographic columns using Merck Silica Gel H for TLC, to provide the same quality of separation. If the catalytic reduction were allowed to proceed for an hour, (+)-tetrahydrostepharine (5) was obtained in 92% yield.

Reduction of (+)-Tetrahydrostepharine (5): Ketone 5 (20 mg) was dissolved in methanol (1 mL) and $NaBH_4$ (10 mg) was added. Work-up, including TLC using the system hexane-chloroform-methanol-

ammonium hydroxide (25:60:15:trace) led to (+)-α-hexahydrostepharine (6) (10 mg, 50%) and (+)-β-hexahydrostepharine (7) (3 mg, 15%). Compounds 5-7 are not readily visible under 254 nm light on a fluorescent plate, but can be detected using the Dragendorff reagent.

(+)-Stepharine (1), $C_{18}H_{19}NO_3$; $[\alpha]_D$ +100°(c 0.1, $CHCl_3$); CD (MeOH) Δε (nm) 0 (310), +2 (263), 0 (245), -0.3 (240), positive tail near 235 nm.

Principal NMR NOE's are MeO-2 to H-3 (24%), H-3 to MeO-2 (13%), H-4α to H-3 (8%), H-3 to H-4α (4%), H-5β to H-6a (9%), H-6a to H-5β (7%), H-6a to H-7β (7%), H-7β to H-6a (6%), H-6a to H-12 (14%), H-12 to H-6a (6%), H-7α to H-8 (15%), H-8 to H-7β (5%).

(+)-8,9-Dihydrostepharine (3), $C_{18}H_{21}NO_3$; $[\alpha]_D$ +190° (c 0.1, $CHCl_3$); CD (MeOH) Δε (nm) 0 (310), +3 (228), negative tail near 210 nm;

m/z 299 (M^+, 64), 298 (100), 297 (25), 282 (10), 270 (81), 256 (23), 257 (22).

Principal NMR NOE's are MeO-2 to H-3 (20%), H-3 to MeO-2 (11%), H-5β to H-6a (4%), H-6a to H-5β (4%), H-6a to H-7β (2%), H-7β to H-6a (5%), H-6a to H-12 (6%), H-12 to H-6a (2%).

(-)-11,12-Dihydrostepharine (4), $C_{18}H_{21}NO_3$; $[\alpha]_D$ -95° (c 0.1, $CHCl_3$); CD (MeOH) Δε (nm) 0 (290), + 0.2 (270), 0 (254), -1.4 (225), positive tail near 218 nm;

m/z 299 (M^+, 70), 298 (100), 282 (12), 270 (78), 256 (23), 227 (21).

Principal NMR NOE's are MeO-2 to H-3 (8%), H-3 to MeO-2 (20%), H-3 to H-4 (2%), H-4 to H-3 (6%), H-5β to H-6a (5%), H-6a to H-5β (5%), H-6a to H-7β (2%), H-6a to $H\text{-}12_{\psi eq}$ (2%), $H\text{-}12_{\psi eq}$ to H-6a (4%), H-7α to H-8 (8%), H-8 to H-7α (4%).

(+)-Tetrahydrostepharine (5), $C_{18}H_{23}NO_3$; $[\alpha]_D$ +89° (c 0.25, $CHCl_3$); CD (MeOH) Δε (nm) 0 (250), +0.6 (225), negative tail near 215 nm.

m/z 301 (M^+, 36), 300 (100), 299 (12), 273 (15), 272 (75).

Principal NMR NOE's are MeO-2 to H-3 (25%), H-3 to MeO-2 (17%), H-3 to H-4β (3%), H-4β to H-3 (10%), H-5β to H-6a (9%), H-6a to H-5β (7%), H-6a to H-7β (4%), H-7β to H-6a (8%), H-6a to $H\text{-}12_{\psi eq}$ (3%), $H\text{-}12_{eq}$ to H-6a (6%), H-7β to $H\text{-}11_{ax}$ (6%), $H\text{-}11_{ax}$ to H-7β (3%), $H\text{-}8_{ax}$ to $H\text{-}12_{ax}$ (3%), $H\text{-}8_{eq}$ to H-7α (4%).

(+)-α-Hexahydrostepharine (6), $C_{18}H_{25}NO_3$; $[\alpha]_D$ +49° (c 0.6, $CHCl_3$);

m/z 303 (M^+, 32), 302 (100), 275 (12), 274 (60).

Principal NMR NOE's are H-6a to H-5β (4%), H-6a to H-7β (5%), H-7β to H-6a (5%), H-6a to $H\text{-}12_{eq}$ (4%), $H\text{-}12_{eq}$ to H-6a (2%), $H\text{-}8_{ax}$ to H-10 (8%), H-10 to $H\text{-}8_{ax}$ (3%), $H\text{-}12_{ax}$ to H-10 (7%), H-10 to $H\text{-}12_{ax}$ (2%), H-10 to $H\text{-}9_{eq}$ (3%), H-10 to $H\text{-}11_{eq}$ (4%).

(+)-β-Hexahydrostepharine (7), $C_{18}H_{25}NO_3$; $[\alpha]_D$ +40° (c 0.25, $CHCl_3$);

m/z 303 (M^+, 30), 302 (100), 275 (10), 274 (53).

Principal NMR NOE's are MeO-2 to H-3 (14%), H-3 to MeO-2 (9%), H-3 to H-4β (2%), H-4β to H-3 (5%), H-5β to H-6a (4%), H-6a to H-5β (2%), H-6a to H-7β (3%), H-7β to H-6a (5%), H-6a to $H\text{-}12_{eq}$ (2%), $H\text{-}12_{eq}$ to H-6a (5%), H-10 to H-11 and $H\text{-}9_{eq}$ (4%).

References and Footnotes

1. Permanent address: Faculté de Médecine et de Pharmacie, Université de Limoges, 87025 Limoges Cedex, France; or CNRS, UA 496, Centre d'Etudes Pharmaceutiques, 92290 Chatenay-Malabry, France.
2. The sole previously reliable work on the stereochemistry of the dihydroproaporphines was based on an x-ray analysis of racemic 11,12-dihydroglaziovine hydrobromide. No CD data was presented. See C. Casagrande, L. Canonica and G. Severini-Ricca, J. Chem. Soc., Perkin I, 1652 (1975); and C. Casagrande, L. Canonica and G. Severini-Ricca, J. Chem. Soc., Perkin I, 1659 (1975); and A. Colombo, J. Chem. Soc., Perkin I, 1218 (1976).
3. M. Shamma "The Isoquinoline Alkaloids", Academic Press, N.Y. (1972), pp. 177-193. See also G. Snatzke and G. Wollenberg, J. Chem. Soc (C), 1681 (1966).
4. H. Guinaudeau, M. Leboeuf and A. Cavé, J. Nat. Prod., 46, 761 (1983), and references listed therein.