HETEROCYCLES, Vol. 30, No. 1, 1990

R-(+)- AND S-(-)-TETRAHYDROHARMINE*: PREPARATION OF OPTICALLY PURE ALKALOIDS AND ACID-CATALYZED RACEMIZATION

Linda A. Chrisey and Arnold Brossi*
Medicinal Chemistry, Laboratory of Analytical Chemistry, NIDDK,
National Institutes of Health, Bethesda, MD 20892, USA

Abstract - Chemical resolution of (±)-tetrahydroharmine (2) with optically active 10-camphorsulfonic acids afforded 1R-(+)-tetrahydroharmine (3A) as well as the 1S-(-)-isomer, 3B. Hplc analysis of ureas obtained by reaction with 1R-(+)-(1-phenylethyl)isocyanate demonstrated that the bases were greater than 98% optically pure. Racemization of 3A occurred in acidic solutions.

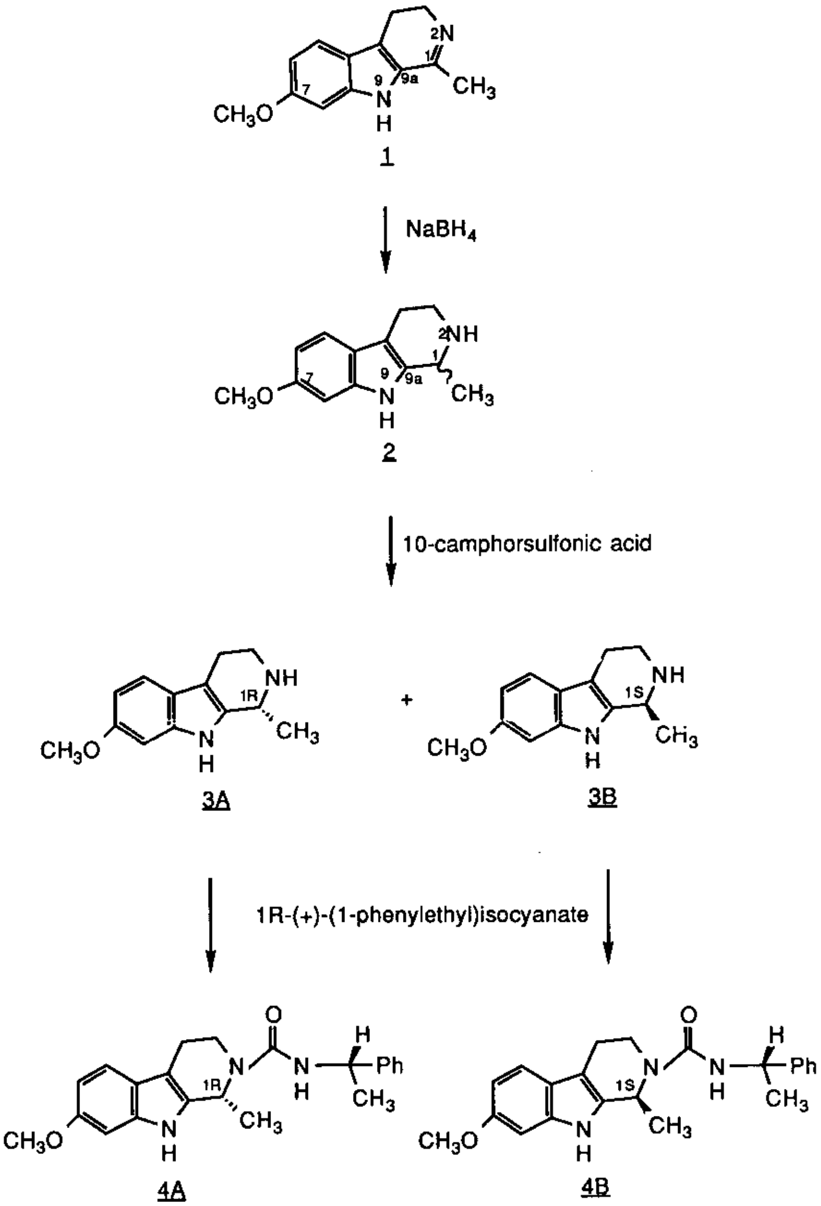
Opically active R-(+)-tetrahydroharmine (3A) was isolated from Banisteria caapi Spruce[1] and South American snuff powder.[2] The R-configuration of 3A was established by oxidative degradation of (+)-tetrahydroharmine obtained by chemical resolution.[3] The specific rotation reported for the naturally occurring base ($[\alpha]_D$ +32°, $CHCl^3$, lit.[1]) differs considerably from that reported for material obtained by chemical resolution ($[\alpha]_D$ -42°, $CHCl_3$, lit.[3]; $[\alpha]_D$ +61°, $CHCl_3$, lit.[4]). As the optical purity of the tetrahydroharmine enantiomers previously described[1-4] had never been demonstrated analytically, we decided to prepare optically pure R-(+)- and S-(-)-tetrahydroharmines by chemical resolution, and to verify the optical purity using hplc. Establishment of an analytical method to distinguish between the two enantiomers seemed especially warranted as it was noted that samples of 3A racemized upon standing in chloroform solutions.[5]

The racemic starting material 2 was obtained from harmaline (1) following the published procedure[4] (Scheme 1). Admixture of 95% ethanolic solutions of 2 and 1R-(-)-10-camphorsulfonic acid afforded a 35% yield of a crystalline salt, mp 228-230°C, $[\alpha]_D$ +5.3° (MeOH). After one recrystallization of salt from 95% ethanol, the free base 3A was precipitated by addition of potassium hydroxide of an aqueous solution of the salt. After recrystallization of the base from water, R-(+)-tetrahydroharmine (3A) of specific rotation +70.9° ($CHCl_3$, dried by filtration through Al_2O_3) was obtained, mp 210-211°C (racemate, mp 198-200°, lit.[4]). The mother liquid from the initial resolution, which was highly enriched in 3B, was concentrated and then taken up in H_2O and made alkaline with

---

*IUPAC name: (1R)- or (1S)-1,2,3,4-tetrahydro-7-methoxy-1-methyl-1H-pyrido[3,4b]indole.

Scheme 1



potassium hydroxide. Colorless crystals of free base were collected and taken up in 95% ethanol. 1S-(+)-10-Camphorsulfonic acid (1.05 equivalents) in 95% ethanol was added and, after 12 h, colorless crystals (26%) of mp 234-235°C were obtained, $[\alpha]_D$ +0.8° (MeOH). The free base crystallized from an aqueous solution of the salt after addition of potassium hydroxide. Recrystallization from 95% ethanol afforded S-(-)-tetrahydroharmine (3B) of mp 211-212°C, $[\alpha]_D$ -69.6°, ($CHCl_3$, dried by filtration through Al_2O_3).

To establish optical purity 3A and 3B were converted into the diasteromeric ureas 4A and 4B by stirring with optically pure 1R-(+)-(1-phenylethyl)isocyanate[6] in methylene chloride for 1 h. Each reaction was washed with 2% aqueous hydrochloric acid, dried ($MgSO_4$) and concentrated. Analysis on an analytical 5μM silica gel column[7] in 75% hexane/24.7% ethyl acetate/0.3% methanol (3.5 ml/min, uv detection at 267 nm) indicated an optical purity of greater than 99% for 3A and greater than 98% for 3B. The retention time observed for 4A was 29 min, and 4B eluted after 35 min under the above conditions.

The following experiments illustrate the racemization of optically active tetrahydroharmine by acid. Racemization of 3A occurred after treatment with 0.2N aqueous hydrochloric acid at 80°C for 2 days. The initial specific rotation of +33° (0.2N HCl) decreased 92% to +2.7°. Treatment of the reaction mixture with base was followed by extraction of the base into ethyl acetate. After drying ($MgSO_4$) and concentration, the solid obtained was identified by tlc and chemical ionization ms as tetrahydroharmine (2). A portion of this material was stirred in methylene chloride with optically pure 1S-(-)-(1-phenylethyl)isocyanate for 1 h, and analyzed as described above by hplc. Hplc analysis revealed that 3A had racemized to yield a nearly 1:1 mixture of 3A and 3B. Racemization also occurred in aqueous 1N hydrochloric acid at room temperature (66% after 3 days), and at reflux (100% after 2 h); in refluxing 1N methanolic hydrochloric acid (100% after 5 h); in refluxing 1N n-butanolic hydrochloric acid (100% after 1 h), and in chloroform (100% after 5 days). Under more forceful conditions, formation of tetrahydroharmol was often observed. The racemization of 3A by acid is reminiscent of the conversion of reserpine into isoreserpine[8] and 1,3-cis-substituted tetrahydro-β-carbolines into their respective 1,3-trans-isomers.[9]

There are several mechanisms by which one could explain a racemization of 3A and 3B.[10] Breaking the C(1)-C(9a)-bond, rather than the C(1)-N(2) or C(9a)-N(9)-bond, would relate to reactions occurring in the Pictet-Spengler synthesis of tetrahydro-β-carbolines from tryptamine and aldehydes,[11] and has, for this reason, some attraction. At present, without further data, we have not excluded either of the reaction pathways.

ACKNOWLEDGEMENT

We would like to thank Professor Nelson J. Leonard, Fogarty Scholar-in Residence, National Institutes of Health, Bethesda, MD (1989), for many helpful discussions.

REFERENCES

1. F. A. Hochstein and A. M. Paradies, J. Amer. Chem. Soc., 1957, 79, 5735.

2. K. Bernauer, Helv. Chim. Acta, 1964, 47, 1075.

3. Z. Koblicova and J. Trojanek, Chem. and Ind., 1966, 1342.

4. B. Schönenberger and A. Brossi, Helv. Chim. Acta, 1986, 69, 1486.

5. B. Schönenberger: unpublished data.

6. R-(+)- and S-(-)-(1-phenylethyl)isocyanates needed for measuring optical purity of the optically active amines are best prepared from optically pure 1-phenylethylamines (obtained after several recrystallizations as tartrate salts from dimethylformamide) by reaction with phosgene (see B. deCosta, C. George, R. B. Rothman, A. E. Jacobson, and K. C. Rice, FEBS Lett., 1987, 223, 335).

7. DuPont Zorbax silica gel, 5μM particle size, 250 x 4.6 mm column dimensions.

8. R. B. Woodward, F. E. Bader, H. Bickel, and A. J. Frey, J. Amer. Chem. Soc., 1956, 78, 2023, 2657.

9. L. H. Zhang and J. M. Cook, Heterocycles, 1988, 27, 1357.

10. T. Kametani and M. Ihara, Heterocycles, 1976, 5, 649.

11. P. D. Bailey, Tetrahedron Lett., 1987, 28, 5181.

Received, 31st July, 1989