Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 16, pp. 2693–2695, 1997

Printed in Great Britain
PII: S0957-4166(97)00317-0 0957-4166/97 $17.00 + 0.00

The absolute configuration of (1*S*)-(+)- and (1*R*)-(−)-1-phenyl-1,2,3,4-tetrahydroisoquinoline. A revision of the literature assignment

Matthias Ludwig,[a] Herbert Beer, Hermann Lotter[b] and Klaus Th. Wanner[a,*]

[a] Institut für Pharmazie und Lebensmittelchemie der Ludwig-Maximilians-Universität München, Sophienstrasse 10, 80333 München, Germany

[b] Institut für Pharmazeutische Biologie der Ludwig-Maximilians-Universität München, Karlstrasse 29, 80333 München, Germany

Abstract: The title compounds (*S*)-(+)-**8** and (*R*)-(−)-**8** have been prepared by an asymmetric synthesis that is based on stereoselective additions to the chiral *N*-acylisoquinoliniumion **3**. The absolute configuration of these compounds has been determined by an X-ray analysis performed on the intermediate **5**. According to the results of this study the stereochemical assignment for (*S*)-(+)-**8** and (*R*)-(−)-**8** described in the literature has to be revised. © 1997 Elsevier Science Ltd

According to a study of N. Gray *et al.*[1] tetrahydroisoquinolines, especially those with a 1-aryl substituent are potent ligands of the ion channel binding site (PCP binding site) of the NMDA-receptor complex, which is a subtype of the excitatory amino acid receptors having potential for the treatment of various neurological disorders. For numerous chiral ligands of the PCP binding site it is known that their enantiomers exhibit different binding affinities (e.g. MK801[2]). As the study of Gray *et al.* had been performed only with racemic mixtures, we were curious whether these compounds exhibit the phenomenon of enantioselectivity of binding as well and, in addition, what the absolute configuration of the more potent enantiomer may be.

Thus, to address these questions it was necessary to gain access to the requisite 1-aryl substituted 1,2,3,4-tetrahydroisoquinolines in enantiomerically pure form and to establish unequivocally their absolute configuration.

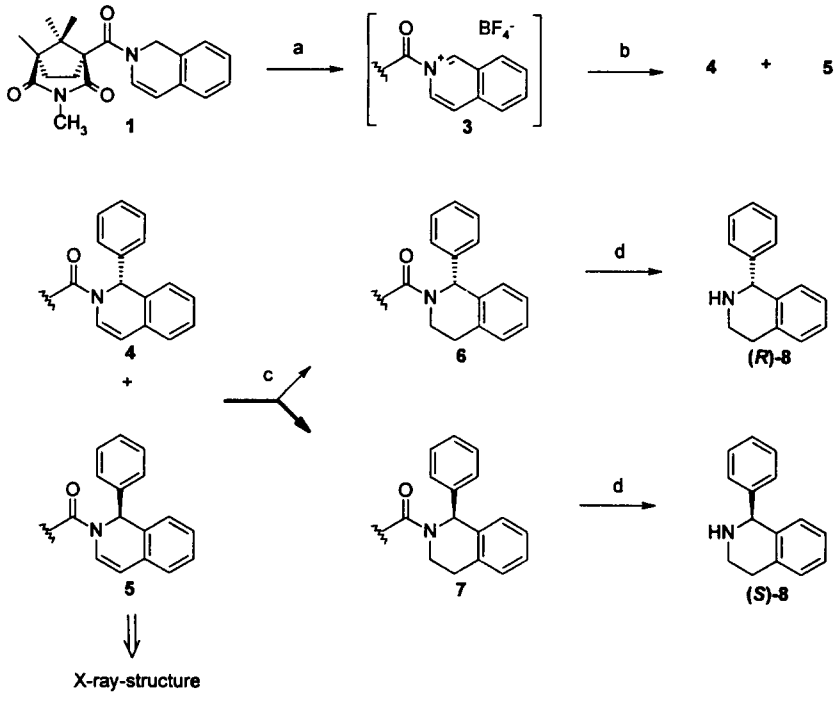
In this paper we wish to report our results concerning the asymmetric synthesis and the determination of the absolute configuration of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **8** as a representative of this class of compounds, according to which results the literature assignment of the absolute configuration of **8** has to be revised.

The synthesis of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **8** was accomplished by asymmetric electrophilic α-amidoalkylation[3] (Scheme 1) employing the chiral *N*-acylisoquinoline **1**. Reaction of **8** with 1.1 equivalents of triphenylcarbeniumtetrafluoroborate **2** (in CH_2Cl_2 for 16 h at room temperature)[4] led to the *N*-acylisoquinolinium ion **3** which upon treatment with various organometallic reagents gave the addition products **4** and **5** with a reasonable to good diastereoselectivity. In the case of PhMgBr (2.0 eq.) the diastereoselectivity (determined by HPLC, SiO_2, hexane/Et_2O 80/20) amounted to 19.6/80.4 (yield 82%), and could be raised to 4.8/95.2 (yield 77%) when $ZnCl_2$/PhMgBr (0.6/1.0, 1.0 eq.) was used.

The mixture of diastereomers obtained after purification of the crude product by flash chromatography was subjected to a catalytic hydrogenation (H_2, Pd/C, EtOH) to afford the *N*-acyltetrahydroisoquinolines **6** and **7** (yield 93%). These diastereomers were separated by preparative HPLC (SiO_2, hexane/EtOAc 80/20) and the diastereomeric purity of each of the two diastereomers, **6** and **7**, was verified to be >99.5% (de) by HPLC (SiO_2, hexane/Et_2O 80/20).

† Dedicated with best wishes to Prof. G. Wurm on the occasion of his 60th birthday.

* Corresponding author. Email: wanner@pharmchem.uni-muenchen.de



Scheme 1. (a) $Ph_3C^+BF_4^-$ (**2**), CH_2Cl_2, rt, 16 h; (b) RM, CH_2Cl_2, −78°C, 2 h; (c) H_2, Pd/C, EtOH, r.t., 48 h; (d) $LiAlH_4$, Et_2O, 0°C, 48 h.

The next step was the removal of the chiral auxiliary which could be effected by reductive cleavage of the amide bond of **6** and **7** with $LiAlH_4$. (4.0 eq. 1.0 M Et_2O) providing (*R*)-**8** and (*S*)-**8** in 55% and 42% yield, respectively.

As we had doubts regarding the reliability of the assignment of the absolute configuration of **8** described in the literature[5] we decided to perform an X-ray structure analysis of the major diastereomer **5** to identify the absolute configuration of the free amine (*S*)-**8**.

To this end diastereomer **5** was isolated by preparative HPLC (de >99.5%; SiO_2, hexane/Et_2O 80/20) and recrystallised from EtOAc providing suitable crystals for the X-ray analysis.

According to the results of this analysis[6] (Figure 1) compound **5**, with the stereoconfiguration of the chiral auxiliary being known from the synthesis, exhibits (*S*)-configuration at the stereocenter at C-1 of the isoquinoline skeleton. For the amine (*S*)-(+)-**8**, derived from **5** we observed a specific rotation of $[\alpha]_D$=+12.3 (c=0.57, CH_2Cl_2) {$[\alpha]_D$=+12.7 (c=0.47, $CHCl_3$)} and for (*R*)-(−)-**8** of $[\alpha]_D$=−12.3 (c=1.55, CH_2Cl_2).

The data in the literature are in contrast with our results with regard to the sign of the specific rotation. Therefore the stereochemical assignment for (*S*)-(+)-**8** and (*R*)-(−)-**8** given in the literature is incorrect and has to be revised.

Acknowledgements

We thank S. Lukassen for excellent technical assistance. Financial support of this work by Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie is gratefully acknowledged.

References

1. Gray, N. M.; Cheng, B. K.; Mick, S. J.; Lair, C. M.; Contreras, P. C. *J. Med. Chem.* **1989**, *32*, 1242.

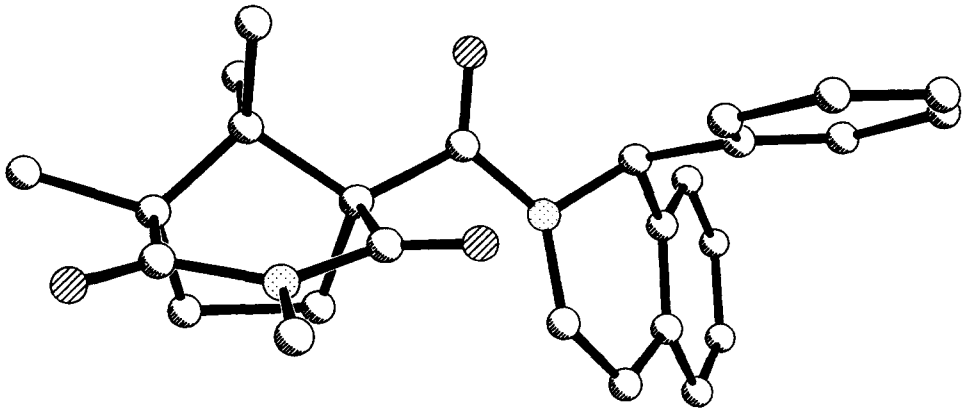


Figure 1. X-ray structure of **5**.

2. Wong, E. H. F.; Kemp, J. A.; Priestly, T.; Knight, A. R.; Woodruff, G. N.; Iversen, L. L. *Proc. Nat. Acad. Sci. (USA)* **1986**, *83*, 7104.
3. (a) Wanner, K. Th.; Praschak, I.; Höfner, G.; Beer, H. *Arch. Pharm.* **1996**, *329*, 11; (b) Wanner, K. Th.; Beer, H.; Ludwig, M. publication in preparation.
4. All new compounds gave satisfactory spectroscopic and analytical results.
5. (a) Yamato, M.; Hashigaki, K.; Qais, N.; Ishikawa, S. *Tetrahedron* **1990**, *46*, 5909; (b) McNab, H.; Monahan, L. C. *J. Chem. Soc. Perkin Trans. I* **1988**, 869.
6. Crystal structure of **5**: $C_{27}H_{28}N_2O_3$, M=428.5, orthorhombic space group $P2_12_12_1$, a=14.318(4), b=17.813(4), c=8.884(2) Å, F(000)=912, Z=4, D=1.256 g/cm^3. Intensities were measured at room temperature on a Siemens R3m diffractometer, Cu K_α radiation, I=1.5418 Å, 1768 independent reflections collected, observed 1326. The structure was solved by direct methods using SHELXTL [G. M. Sheldrick, A Program for Crystal Structure Determination: SHELXTL, Release 4.2 (1981), Göttingen]. The refinement with calculated H-atoms converged at wR=5.68% for the observed data. Full crystallographic data are deposited at the Cambridge Crystallographic Data Centre.

(Received in UK 10 June 1997; accepted 16 July 1997)