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Hünlich Base: (Re)Discovery, Synthesis, and Structure Elucidation after a Century

Stephan Rigol,[†] Lothar Beyer,[‡] Lothar Hennig,[†] Joachim Sieler,[‡] and Athanassios Giannis*[,†]

Institut für Organische Chemie and Institut für Anorganische Chemie, Fakultät für Chemie und Mineralogie, Universität Leipzig, Johannisallee 29, 04103 Leipzig, Germany

giannis@uni-leipzig.de

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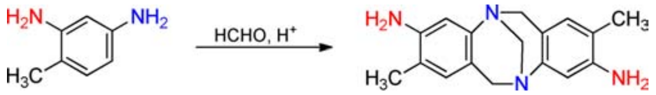
ABSTRACT



After almost 100 years, the structure of the product of the reaction between 2,4-diaminotoluene and formaldehyde was elucidated: derivative 3, which we call the Hünlich base, was synthesized on a multigram scale and its enantiomers were easily separated in preparative amounts. Furthermore, transformation of the NH_2 groups to the corresponding bis-iodides and bis-azides is presented. The latter was also used for desymmetrization by click chemistry.

Serendipity, the "faculty of making happy and unexpected discoveries" plays an important role in science and technology, and in the past, countless of accidental discoveries have been reported.[1a−c] In this paper, we present such an example which occurred during the planning and organization of the Symposium on the occasion of Julius Tröger's 150th birthday last year in Leipzig, Germany.[2]

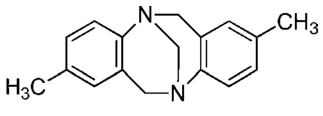


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Figure 1. Tröger's base.

In 1887, Julius Tröger reported on the synthesis of base **1** (Figure 1) identified with his name.[3] Following its structure elucidation by Spielman in 1935,[4] Prelog recognized the chiral nature of Tröger's base (2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine) and was able to separate chromatographically its enantiomers using lactose as chiral stationary phase.[5] The structure of Tröger's base was confirmed by X-ray in 1986.[6] In the past 125 years, a plethora of Tröger's base analogues have been synthesized[7a−c] and used in the development of synthetic

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[†] Institut für Organische Chemie.

[‡] Institut für Anorganische Chemie.

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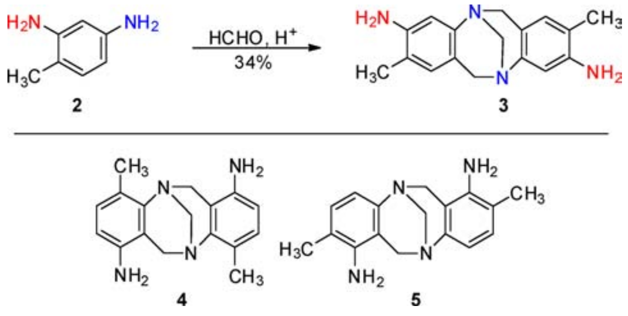
receptors,[7d,e] investigation of intramolecular interactions, design of molecular torsion balances,[7f−h,i,j] template synthesis of fullerene derivatives,[7k,l] conformationally restricted scaffolds for peptidomimetics,[7m] asymmetric transformations,[7n,o] etc.

Of particular interest for the above-mentioned investigations are Tröger's base analogues carrying several substituents in the aromatic moiety of **1**. Such functionalized derivatives can be obtained usually by multistep procedures[8] or following the original procedure or modifications of it.[7] In the latter, anilines were condensed with formaldehyde or its synthetic equivalent under acidic conditions. The amino derivatives of Tröger's base were not accessible by this route since the reaction of diaminobenzenes with formaldehyde obviously afforded polymeric products.[9]

Taking this into consideration, we were surprised to find an old reaction described in 1914 by Walter Hünlich in his Ph.D. thesis at the University of Leipzig (cover page of thesis and the structures proposed by Hünlich in the thesis are included in the Supporting Information).[10] He condensed 2,4-diaminotoluene **2** with formaldehyde in the presence of sulfuric acid and obtained gram amounts (11−13% yield) of a crystalline solid with the molecular formula $C_{17}H_{20}N_4$.

Scheme 1. Synthesis of Hünlich's Base



However, he was not able to determine the structure, which remained obscure ever since (see the Supporting Information). Hünlich died in World War I,and his work was never published and subsequently forgotten. Driven by curiosity and necessity, we decided to reinvestigate Hünlich's procedure and to elucidate the structure of the formed product. We were pleased to isolate a crystalline solid in 31−34% yield. The structure of this solid, which we call "Hünlich's base" (**3**, Scheme 1), was elucidated by NMR spectroscopy and unambiguously confirmed by X-ray diffraction analysis (Figure 2). Apparently and contrary to the commonly accepted opinion, it is possible to use at least 2,4-diaminotoluene in the frame of synthesis of Tröger's base analogues. It appears that the amino group in the *para*-position to the methyl group in 2,4-diaminotoluene is more reactive under the conditions of Hünlich's base synthesis, whereas the methyl group prevents (probably by steric hindrance) further reaction of the formed product **3** with formaldehyde. Interestingly formation of the two other possible isomers **4** and **5** was not observed.

Next we envisaged the isolation of both enantiomers of Hünlich's base. Toward this goal we first synthesized amides **7** and **8** using *N*-Boc-L-phenylalanine and *N*-Boc-L-valine, respectively (Scheme 2).

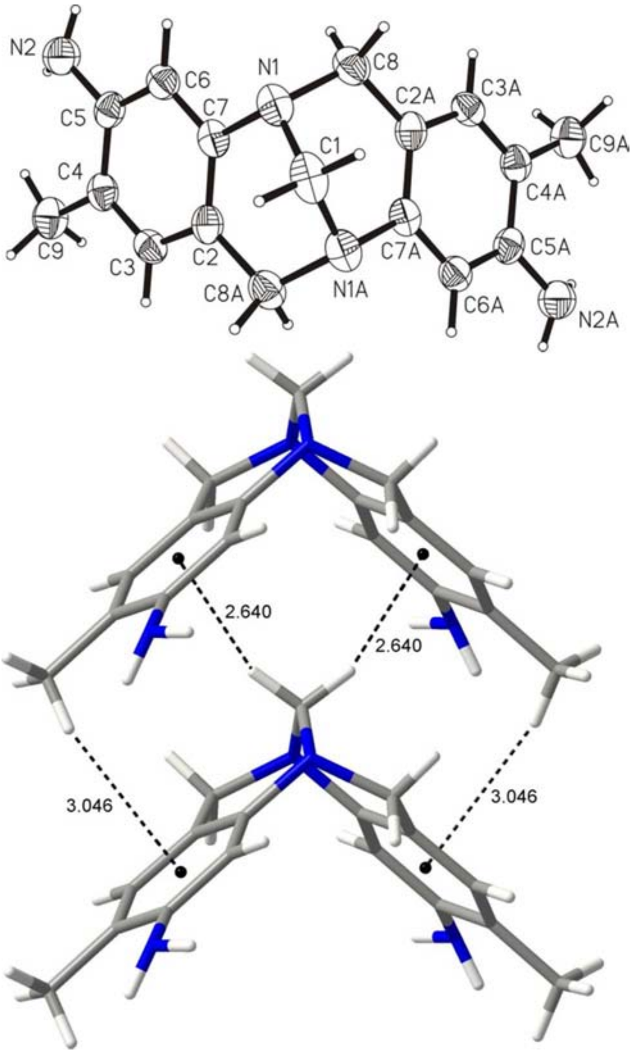


Figure 2. Drawings of Hünlich's base **3** with thermal ellipsoids scaled to 50% probability (top); detail of the elementary unit showing CH−alkane−aromatic interactions (bottom).

The resultant diastereomers **7a** and **7a′** as well as **8a** and **8a′** were easily separated by chromatography and subjected to alkaline hydrolysis to afford the pure enantiomers **3a** and **3a′** in almost quantitative yield (Scheme 3).

Taking Wilen's work[11] into consideration, we assigned structure **3a** to the dextrorotatory enantiomer ($[\alpha]_D^{22}$ = +58

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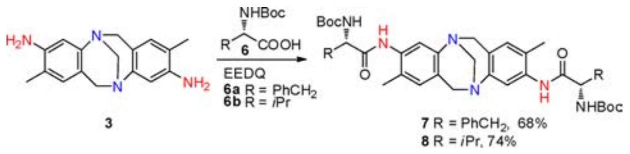
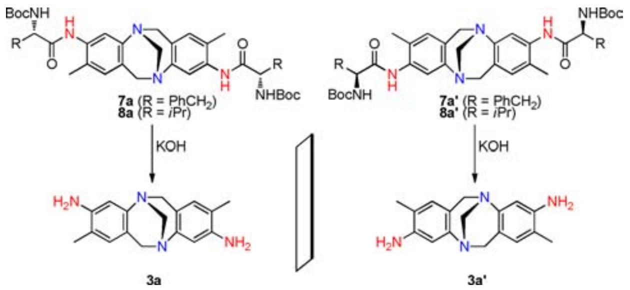
Scheme 2. Synthesis of Amino Acid Derivatives **7** and **8**



(c = 1, MeOH)) and formula **3a′** to the levorotatory one ($[\alpha]_D^{22}$ = −63 (c = 0.33, MeOH)). However, it should be pointed out that this assignment is tentative as the absolute configuration is still unclear.

In agreement with other studies using Tröger's base derivatives, we observed racemization of **3a** and **3a′** under acidic conditions ($t_{1/2} \approx$ 12 h, 1.5 M HCl/EtOH).

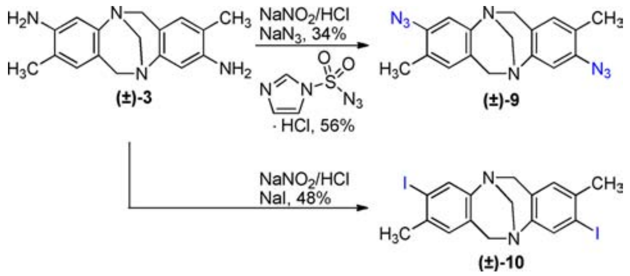
Scheme 3. Resolution of Hünlich's Base Enantiomers



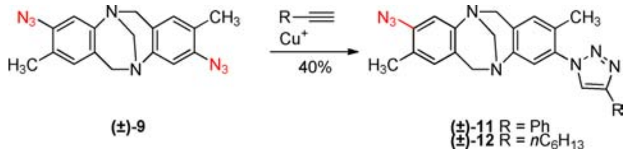
The presence of two free amino groups in compound **3** offers many possibilities for the facile entry to several Hünlich's base derivatives carrying additional functional side chains. For example, transformation of Hünlich's base into the corresponding bis-azide **9** as well as into the bis-iodide **10** was possible in multigram-scale (Scheme 4).

It is important to note that bishalogeno derivatives of Tröger's base are accessible under the conditions published by Wärnmark,[12] whereas bis-azides like **9** are usually synthesized starting from the corresponding bromo- or iodo-derivatives.[13] Bis-azide **9** was also obtained via a copper(I)-catalyzed diazo transfer under mild conditions.[14] In addition we were able to desymmetrize bis-azide **9** and to obtain triazoles **11** and **12** in the presence of copper(I) salts starting from phenylacetylene and 1-octyne, respectively, as depicted in Scheme 5.

Scheme 4. Synthesis of Bis-azido and Bis-iodo Derivatives



Scheme 5. Desymmetrization by Click Chemistry



In summary, after almost 100 years, the structure of the product of the reaction between 2,4-diaminotoluene and formaldehyde was elucidated. In fact, derivative **3**, which we call Hünlich's base, was synthesized on a multigram scale, and its enantiomers were easily separated in preparative amounts.

In addition, Hünlich's base was transformed in one step into the corresponding bis-iodo as well as into bis-azido derivatives, which in turn are valuable starting materials in the frame of transition-metal-catalyzed cross-coupling reactions and click chemistry, respectively.[9,15a−15d]

The accessibility of Hünlich's base and its derivatives in preparative amounts opens new possibilities in the fields of chiral catalysis and chromatography, supramolecular chemistry, and molecular recognition to name a few.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 919389 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: (int)+44-1223/336-033. E-mail: deposit@ccdc.cam.ac.uk.

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The authors declare no competing financial interest.