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TRÖGER'S BASE ANALOGS. NEW STRUCTURAL UNITS FOR THE PREPARATION OF CHIRAL HOSTS AND METAL LIGANDS.

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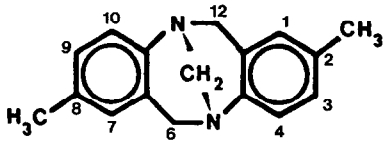
Several Tröger's base analogs are prepared and presented as practical, structurally well defined and unique "folded" armatures for the preparation of chelating or macrocyclic host molecules.

To efficiently overcome important contemporary challenges in the synthesis of biomimetic molecular systems, synthetic enzymes, and anion receptors, new synthetic strategies are required. Tröger's base (2,8-dimethyl-6H,12H-(5,11)-methanodibenzo[b,f][1,5]diazocine, 1) was



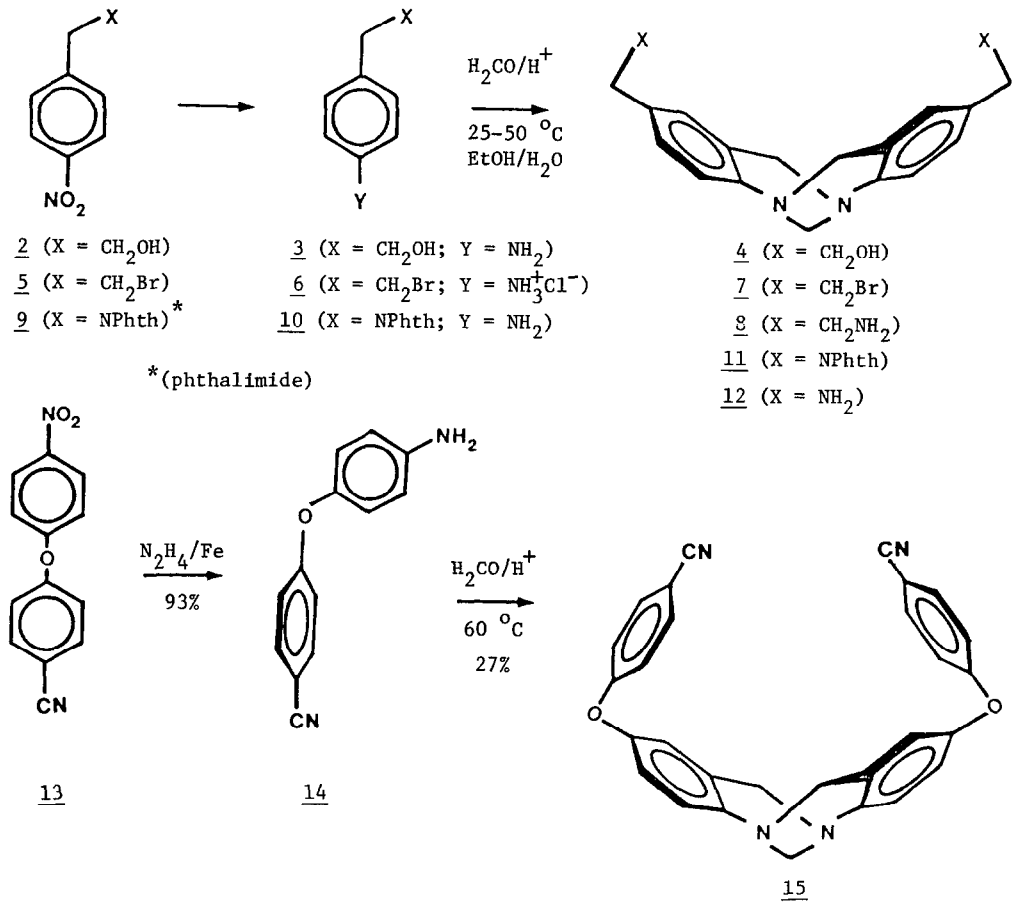
1

first described in 1887 and has been the subject of several interesting investigations.[1] Molecular modeling studies suggest that analogs of Tröger's base may provide relatively rigid, chiral armatures for the construction of chelating or biomimetic systems. To examine this possibility, an exploration of the chemistry of Tröger's base analogs has been undertaken. In this paper the preparation of several new Tröger's base analogs and an x-ray crystallographic structure determination of the parent system will be described.

Initial work centered on the preparation of analogs of Tröger's base wherein relatively short side chains at C-2 and C-8 carried amino-, hydroxyl-, or halo- functional groups. Such side chains would allow the attachment of catalytic side chains or incorporation of the dibenzodiazocene unit within a macrocyclic ring. Results are presented in Chart 1.

Reduction of 4-nitrophenethyl alcohol 2 ($NaBH_4$, 5% Pd/C) afforded the amine 3 (mp 106-107 °C) in 97% yield.[8] Treatment of this amine with formaldehyde and aqueous acid provided the racemic diol, Tröger's base analog 4 (mp 135-137 °C), in 46% yield after chromatography on alumina.[9] The corresponding phenethyl bromide analog was prepared by the action of formaldehyde and aqueous acid on the amine hydrochloride 6.[10] In this way Tröger's base analog 7 (mp 128.5-130 °C) was obtained in 37% yield. Phenethylamine analog 8 is prepared from the dibromide via the Gabriel procedure in 75% overall yield.[11]

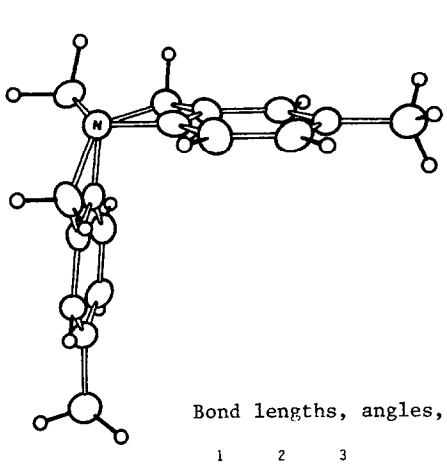
Chart 1. Preparation of new Tröger's base analogs.

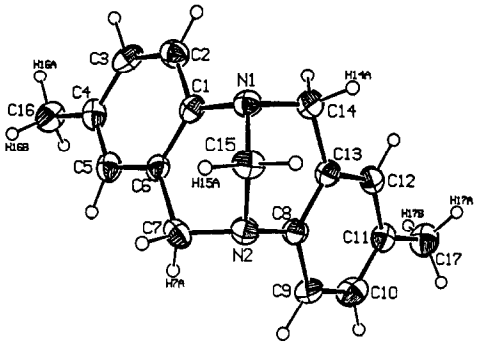


A lower homolog of diamine 8 was prepared from p-nitrobenzyl chloride via N-(p-nitrobenzyl)-phthalimide 9. Reduction of nitro compound 9 (PtO_2/H_2, 60 psi, EtOH-EtOAc) afforded the amine 10 (mp 198.5-199.5 °C; lit[12] mp 197-198 °C) in 86% yield and this amine, on treatment with formaldehyde and acid provided the bis-phthalimide 11 (mp 262-265 °C, darkening at 260 °C), which on subsequent deprotection (N_2H_4, EtOH, 78 °C) afforded 2,8-bis(aminomethyl)-6H,12H,(5,11)-methanodibenzo[b,f][1,5]diazocine 12 (33% overall yield from 10).

These experiments show that functionalized analogs of Troger's base are readily prepared. The possibility of preparing analogs which carry rather large groups at C-2 and C-8 was also determined. The reaction of 4-cyanophenol with 4-fluoro-1-nitrobenzene (KOH, DMSO, 55 °C) afforded the p-nitrophenylether 13 (mp 160-162 °C; lit[13] mp 162-163 °C) in 98% yield. Reduction (N_2H_4, $FeCl_3/C$)[14] of this ether and treatment of the resulting amine 14 with formaldehyde and acid afforded the bis(phenoxy) Troger's base derivative 15 in 25% yield. Although the unoptimized yield in this reaction is low the experiment suggests that a strategy for macromolecule synthesis based on the dimerization of p-substituted aniline derivatives is feasible.

Figure 1. Two ORTEP drawings of 1 with thermal ellipsoids scaled to 50% probability.





Bond lengths, angles, and torsional angles for bonds of the central rings.

1	2	3	1 - 2	1-2-3
C(1)	N(1)	C(14)	1.439(6)	112.5(4)
C(14)	N(1)	C(15)	1.451(7)	107.5(4)
C(15)	N(1)	C(1)	1.467(7)	110.3(4)
C(7)	N(2)	C(8)	1.458(7)	112.7(4)
C(8)	N(2)	C(15)	1.443(6)	110.9(4)
C(15)	N(2)	C(7)	1.467(7)	107.0(4)
C(2)	C(1)	C(6)	1.405(7)	118.9(4)
C(2)	C(1)	N(1)		118.7(4)
C(6)	C(1)	N(1)	1.393(7)	122.3(4)
C(7)	C(6)	C(1)	1.513(8)	119.6(4)
C(7)	C(6)	C(5)		121.4(5)
C(1)	C(6)	C(5)		119.0(5)
N(2)	C(7)	C(6)		112.6(4)
C(9)	C(8)	C(13)	1.389(7)	119.7(5)
C(9)	C(8)	N(2)		118.8(4)
C(13)	C(8)	N(2)	1.397(7)	121.5(4)
C(14)	C(13)	C(8)	1.521(7)	119.9(4)
C(14)	C(13)	C(12)		121.6(5)
C(8)	C(13)	C(12)		118.4(5)
N(1)	C(14)	C(13)		112.7(4)
N(1)	C(15)	N(2)		111.8(4)

1	2	3	4	1-2-3-4
C(1)	N(1)	C(14)	C(13)	-74.3(5)
C(14)	N(1)	C(1)	C(2)	-75.9(6)
C(14)	N(1)	C(1)	C(6)	103.6(5)
C(14)	N(1)	C(15)	N(2)	-70.1(5)
C(15)	N(1)	C(1)	C(2)	164.1(4)
C(15)	N(1)	C(1)	C(6)	-16.5(6)
C(15)	N(1)	C(14)	C(13)	47.3(5)
C(7)	N(2)	C(8)	C(9)	-75.6(6)
C(7)	N(2)	C(8)	C(13)	104.5(5)
C(8)	N(2)	C(7)	C(6)	-73.3(5)
C(8)	N(2)	C(15)	N(1)	52.6(5)
C(15)	N(2)	C(7)	C(6)	48.8(6)
C(15)	N(2)	C(8)	C(9)	164.6(5)
C(15)	N(2)	C(8)	C(13)	-15.3(6)
N(1)	C(1)	C(6)	C(7)	-1.4(7)
C(1)	C(6)	C(7)	N(2)	-15.7(7)
C(5)	C(6)	C(7)	N(2)	162.3(5)
N(2)	C(8)	C(13)	C(14)	-3.8(7)
C(8)	C(13)	C(14)	N(1)	-13.1(7)
C(12)	C(13)	C(14)	N(1)	163.7(4)
N(1)	C(15)	N(2)	C(7)	-70.6(5)
N(2)	C(15)	N(1)	C(1)	52.8(5)

The rational use of Tröger's base analogs for the synthesis of biomimetic molecular systems requires a detailed knowledge of the structure of this polycyclic system. For this reason, an x-ray analysis of 1 was carried out.[15] The structure (Figure 1) reveals that, as expected on the basis of molecular models, the molecule is substantially "folded". There are two types of molecules in the cell, eight have dihedral angles between the planes of the aromatic rings of 92.8° and for four others that angle is 97.4°.[16] Due to this fold the molecule has a substantial cleft and functional groups at C-2 and C-8 can be directed inward to converge at a common site. The structure is therefore ideally suited to the preparation of macrocycles, clathrates, or molecular clefts and helices.

This study establishes that functionalized analogs of Tröger's base can be easily prepared. The value of these structural units is that they are readily available in large scale at low cost, they are conformationally rigid and of known dimensions (Figure 1), and they are chiral. We are continuing to investigate the application of these concepts and materials in the area of host-guest chemistry.

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References and Notes.

1. Tröger's base, a chiral molecule of C_2 symmetry, is easily prepared in racemic form by the reaction of p-toluidine with formaldehyde according to the method of Goecke.[2] The structure was established by Spielman in 1935 and the base was first resolved into its enantiomeric forms in 1944 by Prelog.[3,4] Wagner and co-workers contributed much to our current understanding of such amine-formaldehyde condensations, and Farrar reexamined these reactions and identified several of the by-products generated in such syntheses.[5,6] Greenberg investigated the mechanism of the acid catalyzed racemization of the amine.[7]
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16. M_r =250.34, orthorhombic, Pccn (No. 56), Z=12, F(000)=1608, $\lambda(MoK_\alpha)$ = 0.71069 Å, 1738 reflections ($F \geq 4\sigma_F$) gave R = 0.066, a = 12.774(2), b = 30.290(5), c = 10.3859(19) Å, V = 4018.5 Å^3. 1.5 molecules per asymmetric unit.

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