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Synthesis of Novel Mercapto Analogues of Tröger's Base

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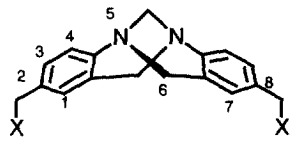
Abstract: *Synthesis of 2,8-bis(mercaptomethyl)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (2) and its derivatization to 7 and 8 have been reported.*

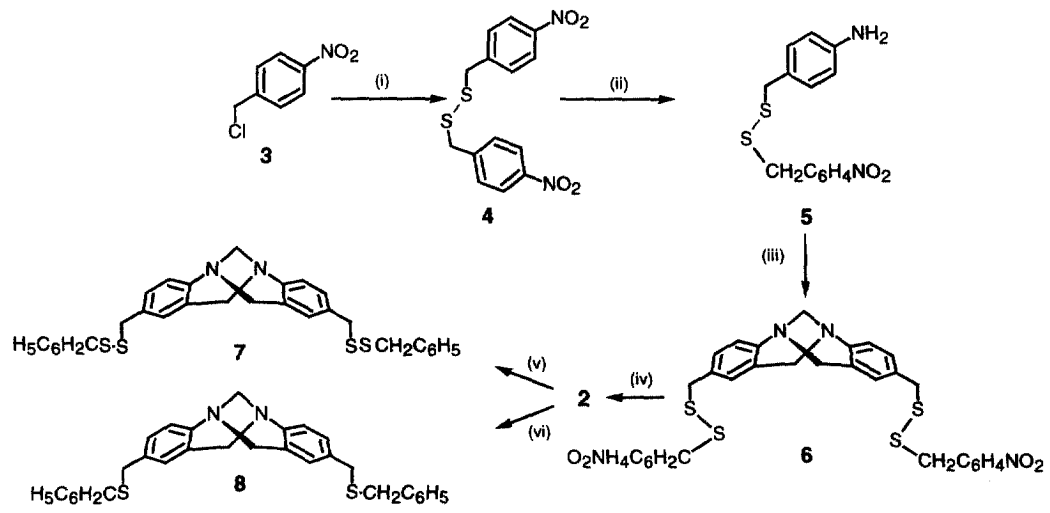
Tröger's base **1**, first synthesized by Julius Tröger[1], was the first amine to be resolved[2] where the chirality was solely due to a very high inversion barrier around 'N'-atoms. The molecule with a rigid 'V' shaped geometry and its analogues have found interest in recent years in the design of molecular receptors, clathrate hosts, chiral solvating agents and DNA intercalators[1b-d].



1: X = H

2: X = SH

For the design of a novel replicating system[3] based on Tröger's base analogues[4] we required 2,8-bis(mercaptomethyl)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine (**2**)[5]. However, to our surprise, there are no reports in the literature for the synthesis of mercapto analogues of Tröger's base, inspite of the potential of such compounds for the synthesis of derivatives via alkylation and disulfide exchange reaction. In this communication, we report the synthesis of the mercapto analogue of Tröger's base **2** and its facile derivatization to thia and dithia analogues **7** and **8**.



Reagents and Conditions: (i) a: $Na_2S_2O_3$, $5H_2O$, b: dil. H_2SO_4, c: I_2/ethanol, 76%[6]; (ii) $SnCl_2$, $2H_2O$, ethyl acetate, 70°C, 50 min, 52%[7]; (iii) CH_2O in H_2O (37% w/w), HCl, THF/ethanol/H_2O (14:10:1), 50°C, 24 h, 35%; (iv) Dithiothreitol/triethylamine/chloroform, 85%; (v) $PhCH_2SSPy$/chloroform, room temperature, 24 h, 74%; (vi) $PhCH_2Br$, C_6H_6/ethanol/KOH, 1 h, 83%.

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Bis-(4-nitrophenylmethyl)disulfide (**4**) was synthesized from cheap and readily available 4-nitrobenzyl chloride in two steps in 76% overall yield[6]. Reduction of compound **4** with $SnCl_2.2H_2O$ yielded a mixture of mono- and bis-amino compounds along with some unchanged material from which the mono-amine **5** with a protected disulfide bond was obtained in 52% isolated yield[7]. Acid catalyzed condensation of the amine with formaldehyde in a mixture of tetrahydrofuran, ethanol and water as solvent afforded the Tröger's base analogue **6** in 35% yield. The two disulfide linkages of compound **6** were cleaved using DTT as the reducing agent[8] to afford compound **2** in 85% isolated yield[9].

The presence of two thiol groups in compound **2** makes it very attractive for an entry to the thia- and dithia analogues of Tröger's base. As a test, when compound **2** was stirred at room temperature with $PhCH_2SSPy$, the dithia analogue **7** was produced by disulfide exchange reaction[10] in 74% isolated yield. Alkylation with benzyl bromide[11] in benzene/ethanol yielded compound **8** in 83% isolated yield. Facile derivatization of compound **2** and also the biological importance of S-H group[12] in it, makes it very useful in organic and bioorganic chemistry research, some of which are being pursued in this laboratory and will be reported in due course.

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