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Novel Functionalised Tröger's Bases: Synthesis of a New Class of Tröger's Base Analogues Containing Dicarboxyl Functionality

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Abstract: The synthesis of three new Tröger's base analogues, each functionalized with two carboxyl groups, is described. Copyright © 1996 Elsevier Science Ltd

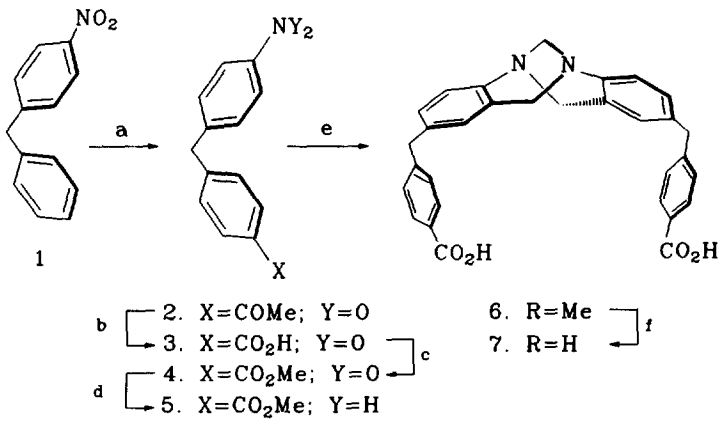
Since its synthesis a century ago,[1] Tröger's base has persisted to be a molecule of interest. Analogues of this molecule have been used in diverse applications since the early eighties. The "V"-shaped Tröger's base unit was extensively used by Wilcox *et al.* for designing molecular receptors.[2] The quaternized form of this molecule has been reported to form clathrates and inclusion compounds.[3] A Tröger's base-derived DNA intercalater[4] and a heterocycle-appended Tröger's base analogues have also been described.[5]

Along with the increased functions performed by the Tröger's base unit, many reports on the synthesis of various derivatized forms of this versatile molecule have recently appeared in the literature. A *bis*-$RhCl_3$ complex of Trögers base has been synthesized and used by Alper *et al.* for the hydrosilylation of alkynes.[6] An unusual synthesis of a highly 'electron deficient' Tröger's base was reported by Becker *et al.*[7] Lhomme *et al.* have synthesised and studied the mechanism of formation of an acridine-Tröger's base conjugate.[8] A novel porphyrin-containing Tröger's base has been prepared and its binding with several α,ω diamines studied.[9]

A few years ago we reported the first diastereoselective synthesis of the Tröger's base moiety using 7-deoxycholic acid as a chiral template.[10] In this communication we report the design and synthesis of three Tröger's base analogues, **7**, **11** and **16**, from readily available starting materials, each possssing a pair of carboxyl-appended phenyl rings.

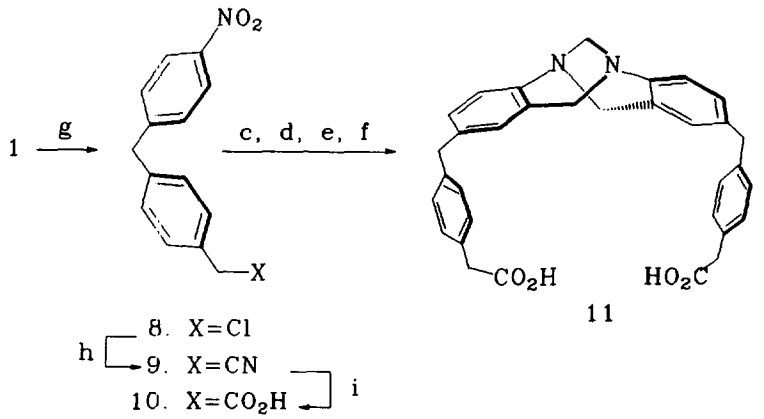
The nitro-acids **3**, **10** and **15** were the key components in the synthesis. We used the Kröhnke method[11] to synthesise acid **3** from compound **2** in moderate yields (*Scheme 1*). Acid **10** was obtained in three steps from nitrodiphenylmethane, following chloromethylation,[12] cyanation and hydrolysis (*Scheme 2*). After esterification with methanol, compounds **3** and **10** were converted to the Tröger's base diacids following reported procedures.[13]

It was at this stage that the extreme insolubility of these Tröger's bases in ethyl acetate, and particularly in chloroform, prompted us to synthesize compound **16**. We thought that the lipophilic cyclohexanes would make it soluble in common organic solvents, e.g., ethyl acetate, $CHCl_3$ and CH_2Cl_2. Diphenylcyclohexane was prepared from cyclopentanone following reported procedures.[14] A selective



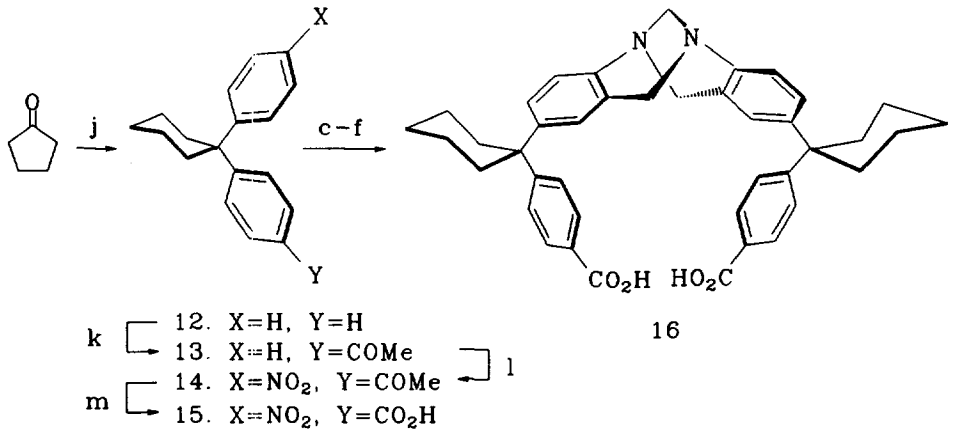
a. $AcCl/AlCl_3/CH_2Cl_2$ (56%); b. Br_2–AcOH; Pyr; NaOH; c. $MeOH/H_2SO_4$ (50%)
d. $SnCl_2$–$2H_2O$/EtOAc; e. Urotropine/TFA (45%); f. $LiOH/MeOH/H_2O$ (80%)

Scheme 1



g. $ClCH_2OMe/AlCl_3$; h. KCN/EtOH (60%); i. $H_2SO_4/AcOH/H_2O$
c. (68%); d, e. (40%); f. (80%)

Scheme 2



j. *ref* 13; k. 1 eq $AcCl/AlCl_3/CH_2Cl_2$ (35%); l. fuming HNO_3 (45%)
m. aq NaOCl (92%); c. (87%); d. (81%); e, f. (38%)

Scheme 3

Friedel-Crafts acetylation,[15] nitration and haloform reaction yielded acid **15** *(Scheme 3)*. The nitro-acid was taken to the required Tröger's base by the usual way and it was found that **16** *was indeed soluble in common organic solvents* like chloroform, ethyl acetate etc. It was possible to record the ^1H and ^{13}C NMR resonance spectra of the compound in $CDCl_3$.[16]

We have thus been able to synthesise three Tröger's bases each funtionalized with a pair of carboxylic acid groups. We have designed compound **16** to overcome the 'insolubility' associated with diacids **7** and **11**. The positioning of the additional phenyl rings in these compounds makes it possible to use them in supramolecular chemistry. The synthesis of other fascinating analogues of Tröger's base are being pursued in this laboratory and the results from these studies will be reported elsewhere.

Acknowledgments

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References

1. Troger, J.; *J. Prakt. Chem.*, **1887**, *36*, 225.

2. (a) Cowart, M.D.; Sucholeiki, I.; Bukowinik, R.R.; Wilcox, C.S. *J. Am. Chem. Soc.*, **1988**, *110*, 6204. (b) Adrian, J.C. Jr.; WIlcox, C.S. *J. Am. Chem. Soc.*, **1989**, *111*, 8055. (c) Webb, T.H.; Suh, H.; Wilcox, C.S. *J. Am. Chem. Soc.*, **1991**, *113*, 8554.
3. Bond, D.R.; Scott, J.L. *J. Chem. Soc., Perkin Trans. 2.*, **1991**, 47.
4. Yashima, E.; Akashi, M.; Miyauchi, N. *Chem. Lett.*, **1991**, 1017.
5. Cerrada, L.; Cudero, J.; Elguero, J.; Pardo, C. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 2049.
6. Goldberg, Y.; Alper, H. *Tetrahedron Lett.*, **1995**, *36*, 369.
7. Becker, D.P.; Finnegan, P.M; Collins, P.W. *Tetrahedron Lett.*, **1993**, *34*, 1889.
8. Salez, H.; Wardani, A.; Demeunynck, M.; Tatibouet, A.; Lhomme, J. *Tetrahedron Lett.*, **1995**, *36*, 1271.
9. Crossley, M.J.; Hambley, T.W.; Mackay, L.G.; Try, A.C.; Walton, R. *J. Chem. Soc., Chem. Commun.*, **1995**, 1077.
10. Maitra, U., Bag, B.G. *J. Org. Chem.*, **1992**, *57*, 6<x9.
11. Kröhnke, F. *Ber.*, **1933**, *66*, 604.
12. Taylor, L.D.; Davis, R.V. *J. Org. Chem.*, **1963**, *28*, 1713.
13. Bag, B.G; Maitra, U. *Synth. Commun.*, **1995**, *25*, 1849, and references cited therein.
14. Fortin, C.J.; Forest, M.; Vaziri, C.; Gravel, D.; Rousseau Y. *Can. J. Chem.*, **1973**, *51*, 3445.
15. Cram, D.J.; Antar, M.F.; *J. Am. Chem. Soc.*, **1958**, *80*, 3103.
16. *All Tröger's base dimethyl esters were purified by column chromatography on silica gel. After hydrolysis and acidification, the pure precipitated diacids were extracted with a large volume of ethyl acetate and characterised spectroscopically.*
***2,8-Bis(4-carboxybenzyl)-6H,12H-5,11-methanodibenzo [b,f][1,5] diazocine* 7**: **^{1}H-NMR, 270 MHz, DMSO-d_6, δ**: 3.82 (s, 4H), 3.95 (d, 2H, *J* 16.2 Hz), 4.11 (s, 2H), 4.51 (d, 2H, *J* 16.2 Hz), 6.74 (s, 2H), 6.96 (s, 4H), 7.27 (d, 4H,*J* 8.1 Hz), 7.81 (d, 4H, *J* 8.1 Hz); **^{13}C-NMR, 100 MHz, DMSO-d_6, δ:** 41.2, 58.8, 66.9, 125.6, 127.6, 128.2, 128.7, 129.3, 129.6, 130.3, 136.5, 146.9, 147.3, 168.2; **Mp:** 305°C(d); **IR (nujol):** 1669, 1590, 1255 cm^{-1}; **LRMS:** 490 (M^+, 100%). ***2,8-Bis((4-carboxymethyl)benzyl)-6H,12H-5,11-methano-dibenzo[b,f][1,5]diazocine* 11**: **^{1}H-NMR,270 MHz, DMSO-d_6, δ:** 3.41 (s, 4H), 3.69 (s, 4H), 3.97 (d, 2H, *J* 16.2 Hz), 4.12 (s, 2H, 4.49 (d, 2H, *J* 16.2 Hz), 6.61 (s, 2H), 6.89-6.90 (m, 4H), 7.27 (d, 4H, *J* 8.1 Hz), 7.81 (d, 4H, *J* 8.1 Hz); **^{13}C-NMR, 100 MHz, DMSO-d_6, δ:** 40.18, 40.22, 58.0, 66.2, 124.7, 126.6, 127.2, 127.9, 128.5, 129.3, 132.5, 136.3, 139.5, 146.1, 172.7; **Mp:** 241°C; **IR (nujol):** 1707 cm^{-1}; **LRMS:** 518 (M^+, 100%), 500 (M^+-H_2O, 30%). ***2,8-Bis((4-carboxyphenyl)cyclohexyl)-6H,12H-5,11-methano-dibenzo[b,f][1,5] diazocine* 16**: **^{1}H-NMR, 270 MHz, $CDCl_3$, δ:** 1.49 (s, 12H), 2.21 (s, 8H), 4.19 (d, 2H, *J* 17 Hz), 4.59 (s, 2H), 4.86 (d, 2H, *J* 16.2 Hz), 6.89 (s, 2H), 7.19-7.27 (m, 8H), 7.95 (d, 4H, *J* 8.1 Hz); **^{13}C-NMR, 100 MHz $CDCl_3$**, δ: 22.7, 26.1, 36.8, 46.3, 57.2, 66.4, 124.6, 124.9, 125.0, 125.5, 127.3, 130.4, 139.3, 139.5, 147.5, 153.6, 171.0; **Mp:** 178°C(d); **IR (neat):** 3500-2300, 2900, 2820, 1670, 1160 cm^{-1}; **LRMS:** 626 (M^+, 100%).

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