Synthesis of a Troger's Base Analogue *via* Stereoselective Reductive Coupling of *N*-Phenylpiperazine to Norbornane-2,5-dione

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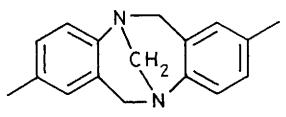
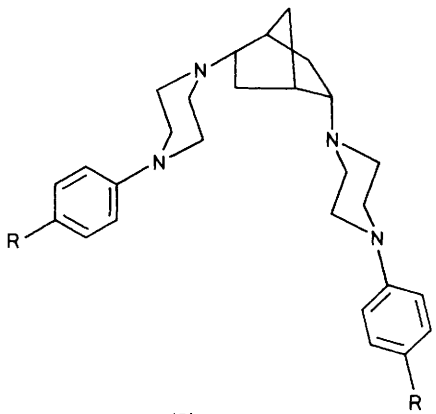
The reaction of *N*-phenylpiperazines with norbornane-2,5-dione and $NaCNBH_3$ gives the *endo–endo* dipiperazinyl norbornanes, which define a right triangular cavity potentially useful in host–guest chemistry as determined by *X*-ray crystallography and dipole moment measurements.

Much recent host–guest chemistry has focused on molecules with concave binding surfaces, where shape and hydrophobicity play dominant roles in determining binding efficiency.[1] Many of these molecules are macrocyclic and macropolycyclic hosts whose syntheses rely on high dilution techniques or on favourable equilibration among products of various sizes. Also, concave acyclic hosts have been under increasing consideration.[2] While some of the latter compounds are derived from syntheses at least as elaborate as those required for many macrocycles, a few have been prepared *via* much simpler routes. Among the most intensively studied compounds are derivatives of Troger's base, (**1**), whose synthesis dates back to the 19th century.[3] These derivatives form inclusion compounds with a variety of organic guests, both in aqueous solution and in the solid state,[4] and are easily functionalized to provide better defined binders.[5] In this communication, we report the synthesis and crystal structure of a Troger's base analogue, (**2**)† derived from the norbornane skeleton, as well as solution phase characterization of the dinitro derivative (**3**).



(**1**)



(**2**) R = H

(**3**) R = NO_2

The compounds of interest were obtained in single steps from norbornane-2,5-dione[6] and the corresponding, commercially available *N*-phenylpiperazines under typical reductive coupling conditions[7] (4 equiv. of H– as $NaCNBH_3$ per equiv. of dione, 40 ml of MeOH per g of dione, pH 6 maintained with ethereal HCl, room temperature, 6 days).

Compound (**2**) was isolated by diluting the reaction mixture with aqueous HCl, washing with ether, basifying the aqueous layer, and collecting the solids. Trituration with hot 1,2-dichloroethane gave pure material. Product (**3**) was obtained by diluting the reaction mixture to 110% of its original volume

† *Crystal data* for (**2**): monoclinic, space group $P2_1/c$-C_{2h}^5, a = 25.258(5), b = 6.207(1), c = 17.356(4) Å, β = 122.66(1)°, $\alpha = \gamma = 90°$, U = 2291(1) Å^3, Z = 4, D_c = 1.208 g cm^{-3}, linear absorption coefficient 0.52 mm^{-1}, $F(000)$ = 904, Nicolet CAD four-circle diffractometer with graphite-monochromated Cu-K_α radiation, θ–2θ scan, λ = 1.54184 Å, μ(Cu-K_α) = 0.52 mm^{-1}. 3153 Unique reflections with $I > 3\sigma(I)$ were used in the refinement. The non-hydrogen atoms were located using SHELXT Direct Methods programs. Hydrogen atoms were located by difference Fourier techniques and included in the structure factor calculations as idealized atoms riding on their respective carbon atoms. The structure was refined by cascade block diagonal matrix least-squares, $\Sigma w(|F_o| - |F_c|)^2$, $w = 1/\sigma_F^2$, final R = 0.044 and R_w = 0.055, GOF = 1.27. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

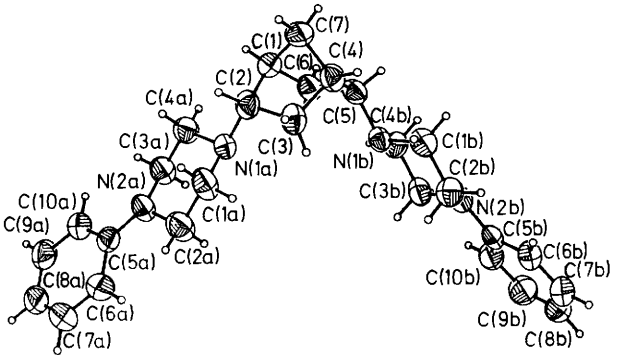


Figure 1. Perspective drawing of (**2**) with nonhydrogen atoms represented by 50% thermal vibration ellipsoids and H atoms by arbitrarily small spheres.

with H_2O, collecting the yellow precipitate, dissolving it in CH_2Cl_2, converting unreacted nitrophenylpiperazine to its acetamide with AcCl, and extracting the product into aqueous HCl and then back into CH_2Cl_2 under basic conditions. The unoptimized yields of the two reactions were 60 and 40%, respectively, with most of the material loss due to half-reacted norbornanone precipitating prematurely from the reaction mixture (NMR and TLC evidence).

Preliminary stereochemical assignments were made using NMR spectroscopy.‡ The ^{13}C NMR spectra indicated only one isomer present for each compound, possessing C_2 symmetry, and thus ruling out the *exo–endo* isomer. Analysis of the ^1H–^1H couplings‡ suggested that the isomers were *endo–endo*. These suppositions were confirmed by an *X*-ray structural analysis performed on (**2**), with the result shown in Figure 1. The phenylpiperazinyl groups define an approximately right triangular space, atop which the more basic nitrogen lone pairs converge. Molecular models and previous calculations[8] indicate that this is the most favoured conformation in solution as well, since it minimizes the *gauche* interactions at the norbornane–piperazine bonds. The dipole moment of (**3**) is 8.9 D in dioxane, which is within experimental error of $\sqrt{2}$ times the value for *N*,*N*-dimethyl-*p*-nitroaniline, 6.8 D, under identical conditions. This measurement is consistent with the 90° angle of the flanking groups shown in the *X*-ray structure of (**2**).

The norbornyl amines of (**3**) are sufficiently basic and sterically unencumbered to form salts with phosphonic and carboxylic acids, an adduct with $MeSnCl_3$, and a hydrogen-bonded complex with *p*-nitrobenzenesulphonamide, as observed by ^1H and ^{31}P NMR. Although the detailed structures of these aggregates were not determined, an AC conductometric titration of (**3**) with n-octylphosphonic acid in dioxane showed a slight but reproducible increase in incremental conductivity after the addition of 1 equivalent of acid beyond that required to protonate basic sites on the capacitor, indicating some distinction of the 1 : 1 complex from the 2 : 1 salt. When the titration was performed with *p*-nitro-*N*-phenylpiperazine itself, precipitation was observed before the addition of 1 equivalent of titrant. Molecular models indicate that the two basic nitrogens of (**2**) or (**3**) may simultaneously hydrogen-bond to a phosphonic or phosphoric acid group.

Compound (**2**) resembles the Troger's bases in that its 'sides' are at roughly 90° angles, the cavity is chiral, and the molecule is electron rich. The synthetic route would be amenable to incorporation of many functional groups, including acid- and base-sensitive ones. Thus, it may well be useful as a complementary structural unit to Troger's base in the construction of basic, hydrophobic hosts.

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‡ *Spectroscopic data* for (**2**): ^1H NMR ($CDCl_3$) δ 1.46 (s, 2, H-7), 1.53 (m, 2, H-3,6 *endo*), 1.68 (dd, 2, H-3,6 *exo*, *J* 5, 12 Hz), 2.32 (br. s, 2, H-1,4), 2.36 (dd, 2, H-2,5, *J* 5, 12 Hz), 2.5 and 2.6 (m, 8, pip-H), 3.2 (m, 8, pip-H), 6.8 (t, 2, ArH), 6.9 (m, 4, ArH), 7.2 (m, 4, ArH). ^{13}C NMR ($CDCl_3$) δ 26.1, 37.2, 39.0, 48.9, 52.5, 68.4, 116.0, 119.5, 129.0 and 151.4. For (**3**), essentially the same as (**2**) except ArH at 6.8 and 8.1, ArC at 112.5, 125.9, 138.4, and 154.9. For comparison to norbornanols, see K.-T. Liu, *Tetrahedron Lett.*, 1973, 2747.

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