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Synthesis and Molecular Structure of Heterocyclic Tröger's Bases Derived from *C*-Amino Heterocycles

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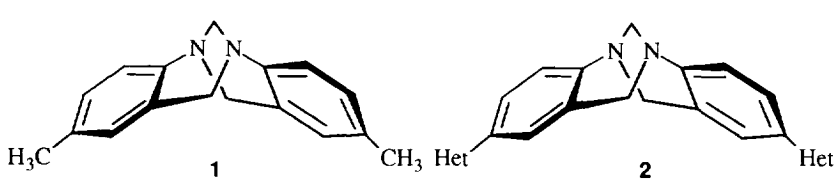
Abstract.— Fourteen amino heterocycles were allowed to react in the different experimental conditions of formation of Tröger's bases. Amino-azoles and -benzazoles yielded the corresponding Tröger's bases while amino-azines and -benzazines failed to react. The exception was 6-aminoquinoline which yielded the corresponding Tröger's base. When there are two positions of cyclisation the reaction is always regioselective. Tröger's base analogues with pentagonal aromatic frameworks, **6b** and **7b**, have been synthesized for the first time and the X-ray molecular structure of **7b** has been determined.

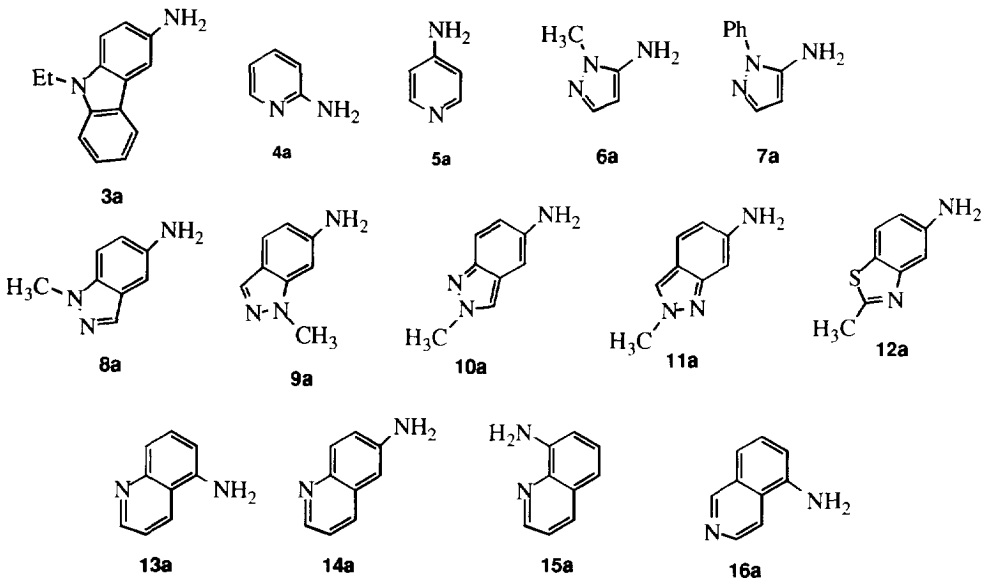
INTRODUCTION

Tröger's base **1**, a concave chiral molecule, was first synthesized by Tröger in 1887.[1] Tröger's base analogues provide relatively rigid chiral armatures for the construction of chelating and biomimetic systems;[2] recently the catalytic activity of metal complexes of **1** has been reported.[3] We have described the synthesis, from heterocyclic substituted anilines, of the first Tröger's base analogues **2** containing azole rings (Het = azolyl) as substituents on the phenyl rings.[4]



The aim of the present work is to explore the reactivity of amino heterocycles as precursors in the synthesis of a new family of Tröger's bases bearing heterocyclic rings instead of phenyl ones in their aromatic part. Because only some anilines yield Tröger's bases,[5] and since the heteroatoms could interfere, it was by no means evident

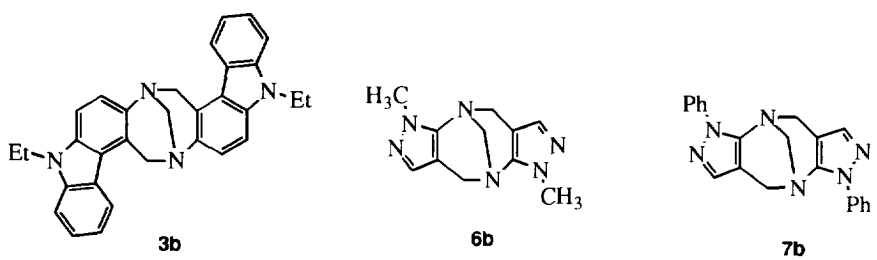
that amino heterocycles could be used as precursors for Tröger's base analogues. Thus, fourteen *C*-amino-heterocycles **3a-16a** with different structural characteristics (Scheme 1) were allowed to react with aqueous formaldehyde and hydrochloric acid (method **A**),[5] and with hexamethylenetetramine in trifluoroacetic acid (method **B**).[2g] These two methods represent the most widely used experimental conditions for the preparation of Tröger's bases.

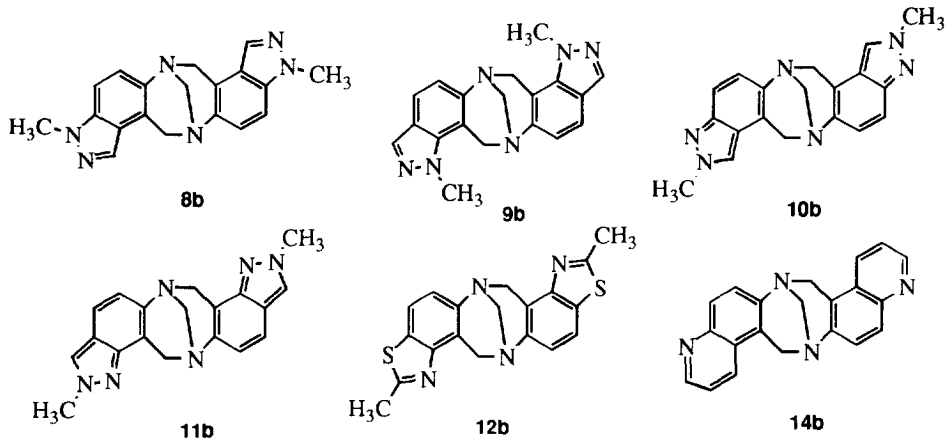


Scheme 1

RESULTS AND DISCUSSION

Analogues of Tröger's Base. In Table 1 we have summarized the results obtained with amino heterocycles and the yields of the corresponding Tröger's bases represented in Scheme 2. These bases have been identified by spectroscopic methods (either ^{1}H-NMR plus high resolution mass spectrometry or microanalysis), and besides the X-ray structure of base **7b** has been determined (Figure 1).





Scheme 2

Table 1. Synthesis of Tröger's Base Analogues

heterocycle	Tröger's base	method	yield %[a]
3-amino-9-ethylcarbazole **3a**	**3b**	**A**	18[b]
idem	-	**B**	-
2-aminopyridine **4a**	-	**A, B**	-
4-aminopyridine **5a**	-	**A, B**	-
5-amino-1-methylpyrazole **6a**	**6b**	**B**	6
idem	-	**A**	-
5-amino-1-phenylpyrazole **7a**	**7b**	**A**	30
idem	-	**B**	-
1-methyl-5-aminoindazole **8a**	**8b**	**A**	46
idem	**8b**	**B**	*c*
1-methyl-6-aminoindazole **9a**	**9b**	**A**	51
idem	**9b**	**B**	*c*
2-methyl-5-aminoindazole **10a**	**10b**	**A**	42
idem	**10b**	**B**	*c*
2-methyl-6-aminoindazole **11a**	**11b**	**A**	36
idem	**11b**	**B**	*c*
2-methyl-5-aminobenzothiazole[d] **12a**	**12b**	**A**	*c*
idem	**12b**	**B**	52
5-aminoquinoline **13a**	-	**A, B**	-
6-aminoquinoline **14a**	**14b**	**A**	27
idem	**14b**	**B**	*c*
8-aminoquinoline **15a**	-	**A, B**	-
5-aminoisoquinoline **16a**	-	**A, B**	-

[a]Isolated yield. [b]56% Yield estimated by ^{1}H-NMR in the reaction crude. [c]Complex reaction mixture with lower yield in Tröger's base than with the alternative method. [d]Hydrochloride.

Amines which do not react following either experimental methods are incapable of reacting under more drastic conditions, such as higher temperatures, longer reaction times or more acidic media.[4] 2-Amino **4a** and 4-aminopyridine **5a** were always recovered unchanged from all experiments, while 5-aminoquinoline **13a**, 8-amino-quinoline **15a** and 5-aminoisoquinoline **16a** led to complex reaction mixtures, where only traces of the corres-ponding Tröger's bases could be detected by ^{1}H-NMR. Yields of Tröger's bases estimated by ^{1}H-NMR in the reaction mixtures, using picric acid as internal standard, were sensibly higher than yields of isolated pure products probably due to the difficulty of eluting these new Tröger's bases in column chromatography. For example, in the case of base **3b** the yield estimated by ^{1}H-NMR was 56% (see Table 1) while only 18% of pure compound was isolated. In order to find improved conditions, 6-aminoquinoline **14a** was treated in one experiment with hexamethylenetetramine in twice the quantity of trifluoroacetic acid with regard to the quantity used in method **B**, and in another experiment, with methylal and methanesulfonic acid, a method that has been recently reported[6] to be excellent for preparing Tröger's bases. In the first case a complex reaction mixture was obtained in which base **14b** was present in lower yield than in the standard reaction. Reaction of 6-aminoquinoline **14a** with methylal and methanesulfonic acid afforded a reaction mixture where no base **15b** was detected by ^{1}H-NMR.

The amino heterocycles can be divided first into azoles (π-excessive heterocycles) and azines (π-deficient heterocycles)[7,8] and then into monocyclic compounds, which bear the amino group directly bonded to the heterocycle, and the benzo condensed derivatives where the amino group is bonded to the carbocycle.

For monocyclic azoles, **6a** and **7a**, considering that pyrazole reacts at position 4 with formaldehyde to yield 4-hydroxymethylpyrazoles and 4,4'-bispyrazolylmethanes,[8] this reactivity is expected to be enhanced by the amino group. Thus 5-aminopyrazoles lead to bases **6b** and **7b**, the first Tröger's base analogues having a pentagonal aromatic ring in their framework instead of the usual benzene ring. On the other hand, monocyclic azines like 2-amino **4a** and 4-aminopyridine **5a** were always recovered unchanged, corresponding to the lower reactivity of the pyridine ring and other π-deficient heterocycles towards electrophilic attack at carbon atoms.[7]

The benzo condensed heterocycles derived from azoles, **3a**, **8a-12a**, yield the corresponding Tröger's bases while in the case of benzo condensed azines only 6-aminoquinoline **14a** yields a Tröger's base. The cyclization is always regioselective and occurs towards the *ortho* position contiguous to the heterocyclic ring, the more reactive site towards electrophilic reagents in 5-aminoindazoles[8] and in benzazines.[7] When the amino group is bonded to C-5 or C-8 in derivatives of quinoline, **13a** and **15a**, and isoquinoline, **16a**, only traces of the corresponding Tröger's bases were detected, owing to the lower reactivity towards electrophiles of the C-6 and C-7 positions in these heterocycles.

X-ray Diffraction Studies. The crystal structure of compound **7b** (Figures 1a and 1b) was determined[14] in order to know the influence of the replacement of a six-membered benzene ring (structures **1** and **2**) by a five-membered aromatic ring (pyrazole). Concerning the main aspect of the 'armature' of Tröger's bases,[5] *i.e.* the dihedral angle between aromatic rings, θ, Wilcox reported the following values: 92.9°, 97.4°, 102.2°, 92.7°, 104.1°, 89.7° and 88.6°.[5] In the case of compound **7b** the dihedral angle θ (dihedral angle between C5a, N6, N7, C8, C8a and C10a, N1, N2, C3, C3a planes) amounts to 96.4(4)°. It appears that the eight membered ring in Tröger's bases is flexible enough to accommodate both 6-8-6 and 5-8-5 ring fusions without any significant difference in the 'armature'. Concerning the molecular packing of **7b** (Figure 2) there are stacking interactions between the *N*-phenyl rings of two adjacent molecules.

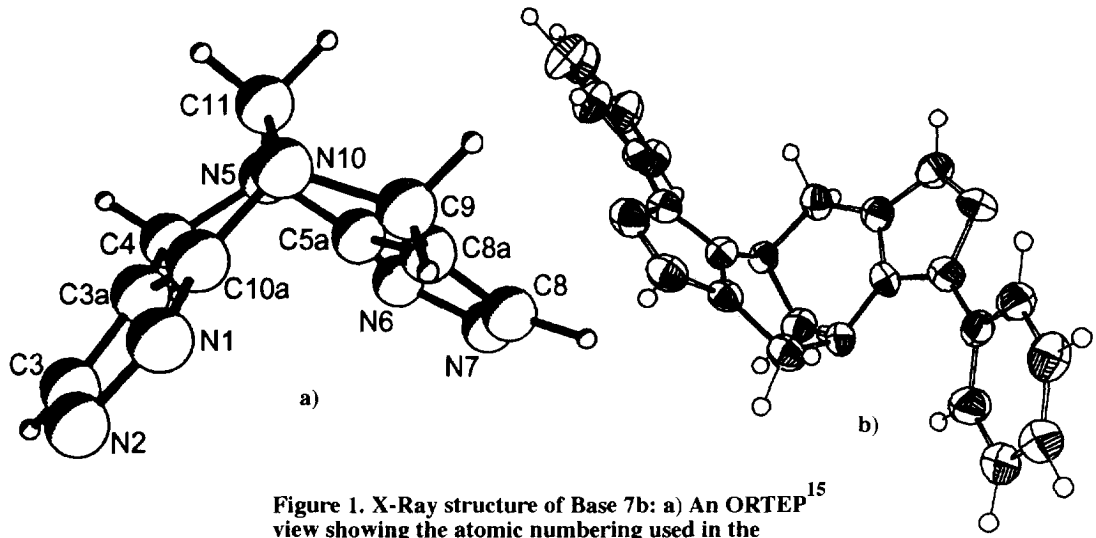


Figure 1. X-Ray structure of Base 7b: a) An ORTEP[15] view showing the atomic numbering used in the present crystallographic work; b) a PLUTO[16] drawing without the N-phenyl rings on N-1 and N-6

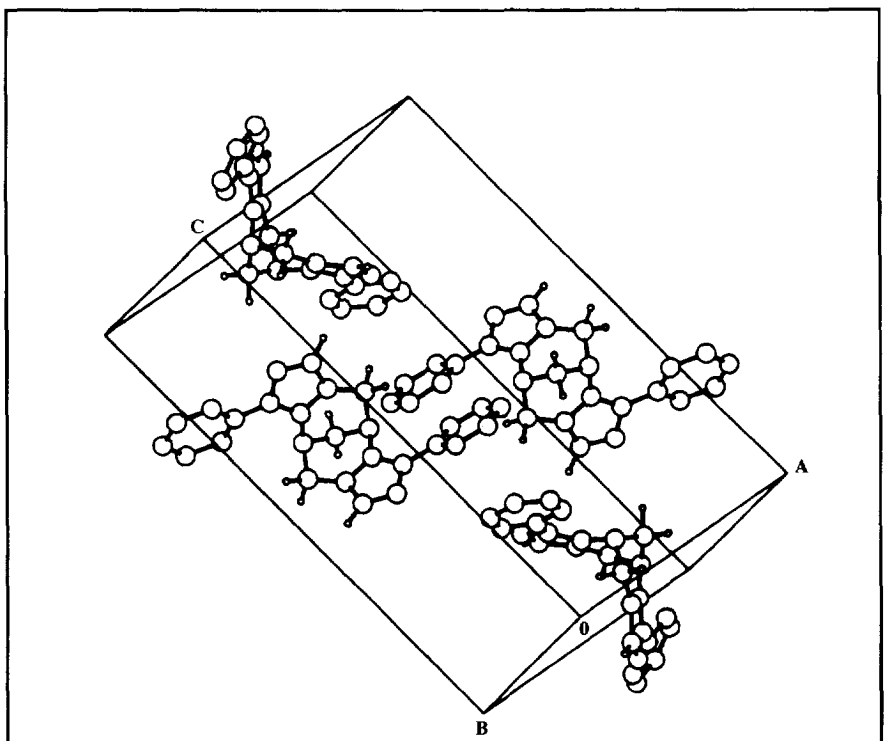
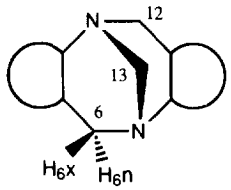


Figure 2. A view of the unit cell of Tröger's Base 7b

EXPERIMENTAL SECTION

Synthesis.- Melting points were determined on a Buchi 510 apparatus and are uncorrected. ^{1}H FT-NMR spectra were recorded in dilute solutions (*ca.* 0.3%) in $CDCl_3$ at 300 MHz on a Varian VXR-300S spectrometer. The chemical shifts were measured relative to TMS. The complicated problem of assignment of aliphatic protons in heterocyclic Tröger's bases has been addressed elsewhere;[9] otherwise, the aromatic part of pairs of compounds **a** and **b** is very similar excepting for the proton which disappears on cyclization. High resolution mass spectra were recorded using a VG Autospec spectrometer.

Heterocyclic Tröger's base analogues were obtained as pale yellow solids using the following methods. All the starting amino heterocycles used in Table 1 are commercial products.



Positions 6 and 12 are equivalent by symmetry

Method A. To a stirred mixture of 3 mmol of the amino heterocycle in 3.5 mL of 95% ethanol under argon was added 1.5 mL of 35-40% aqueous formalin (17-20 mmol of formaldehyde). The mixture was cooled to 0° C, 1.3 mL of concentrated HCl were added and the solution was stirred at 60° C under argon for 24 h. The reaction mixture at room temperature was then diluted with 45 mL of water, basified to p*H* 8-9 with concentrated NH_4OH and extracted with CH_2Cl_2 (4x25mL). The organic phase was successively washed with 65 mL of saturated $NaHCO_3$ solution and with 65 mL of saturated NaCl solution, and then dried over anhydrous $MgSO_4$. The solvent was eliminated under reduced pressure and the residue was purified by flash chromatography over silicagel.

Method B. A mixture of 5 mmol of the amino heterocycle and 5 mmol of hexamethylenetetramine in 10 mL of TFA was stirred at room temperature under argon for 24 h. Then the TFA was removed under vacuum and the residue was diluted with 5 mL of H_2O, basified to p*H* = 8-9 with concentrated NH_4OH, extracted with CH_2Cl_2 (4 x 25 mL) and the organic phase dried over anhydrous $MgSO_4$. The solvent was eliminated under reduced pressure and the residue was purified by flash chromatography over silicagel.

3b: eluted with hexane/ethyl acetate (6/4); mp 271-273°C; HRMS (EI): calcd for $C_{31}H_{28}N_4$: 456.231397. Found: 456.231450; TLC: Rf = 0.39 (silicagel, hexane/ethyl acetate: 1/1). ^{1}H-NMR ($CDCl_3$) δ = 4.98 (H-6$_{endo}$, ^2J = 16.7 Hz), 5.32 (H-6$_{exo}$, 2J = 16.7 Hz), 4.69 (H-13).

6b: eluted with dichloromethane/methanol (98/2); mp 161-162°C; Anal. Calcd. for $C_{11}H_{14}N_6$: C, 57.38; H, 6.13; N, 36.50. Found: C, 57.25; H, 6.28; N, 36.61. ^{1}H-NMR ($CDCl_3$) δ = 4.17 (H-6$_{endo}$, ^2J = 15.6 Hz), 4.39 (H-6$_{exo}$, ^2J = 15.6 Hz), 4.23 (H-13).

7b: eluted with toluene/ethanol (99/1); mp 216-218°C; Anal. Calcd. for $C_{21}H_{18}N_6$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.47; H, 5.26; N, 23.82. ^{1}H-NMR ($CDCl_3$) δ = 3.74 (H-6$_{endo}$, ^2J = 15.9 Hz), 4.23 (H-6$_{exo}$, ^2J = 15.9 Hz), 4.31 (H-13).

8b: eluted with dichloromethane/methanol (19/0.4); mp 284-286°C; Anal. Calcd. for $C_{19}H_{18}N_6$: C, 69.07; H, 5.49; N, 25.44. Found: C, 69.12; ; H, 5.41; N, 25.52. ^{1}H-NMR ($CDCl_3$) δ = 4.45 (H-6$_{endo}$, ^2J = 16.8 Hz), 4.89 (H-6$_{exo}$, 2J = 16.8 Hz), 4.48 (H-13).

9b: eluted with dichloromethane/methanol (19/0.4); mp 275-277°C; Anal. Calcd. for $C_{19}H_{18}N_6$: C, 69.07; H, 5.49, N, 25.44. Found: C, 68.80; H, 5.56; N, 25.45. ^{1}H-NMR ($CDCl_3$) δ = 4.82 (H-6_{endo}, ^2J = 16.2 Hz), 5.12 (H-6_{exo}, ^2J = 16.2 Hz), 4.40 (H-13).

10b: eluted with dichloromethane/methanol (19/0.5); mp 287-289°C; Anal. Calcd. for $C_{19}H_{18}N_6$: C, 69.07; H, 5.49; N, 25.44. Found: C, 68.99; H, 5.66; N, 25.45. ^{1}H-NMR ($CDCl_3$) δ = 4.30 (H-6_{endo}, ^2J = 16.8 Hz), 4.76 (H-6_{exo}, ^2J = 16.8 Hz), 4.47 (H-13).

11b: eluted with dichloromethane/methanol (19/0.5); mp 251-253°C; Anal. Calcd. for $C_{19}H_{18}N_6$: C, 69.07; H, 5.49; N, 25.44. Found: C, 69.02; H, 5.54; N, 25.43. ^{1}H-NMR ($CDCl_3$) δ = 4.63 (H-6_{endo}, ^2J = 17.4 Hz), 4.88 (H-6_{exo}, ^2J = 17.4 Hz), 4.51 (H-13).

12b: eluted with toluene/ethanol (98/2); mp 285-287°C; Anal. Calcd. for $C_{19}H_{16}N_4S_2$: C, 62.61; H, 4.42; N, 15.37: Found C, 62.53; H, 4.73; N, 15.39. ^{1}H-NMR ($CDCl_3$) δ = 4.81 (H-6_{endo}, ^2J = 17.4 Hz), 5.02 (H-6_{exo}, ^2J = 17.4 Hz), 4.48 (H-13).

14b: eluted with dichloromethane/methanol (19/1); mp 252-254°C; HRMS (EI) Calcd. for $C_{21}H_{16}N_4$: 324.137497. Found: 324.136810; TLC: Rf = 0.19 (silicagel, dichloromethane/methanol: 19/1). ^{1}H-NMR ($CDCl_3$) δ = 4.73 (H-6_{endo}, ^2J = 16.8 Hz), 5.04 (H-6_{exo}, ^2J = 16.8 Hz), 4.51 (H-13).

Crystal Structure of Compound ***7b***.- A summary of the fundamental crystal data is given in Table 2. A colourless prismatic crystal was mounted in a kappa diffractometer. The cell dimensions were refined by lest-squares fitting the θ values of the 25 reflections with 2θ range of 9 - 22°. The intensities were corrected for Lorentz and polarization effects. Scattering factors for neutral atoms were taken from the *International Tables for X-Ray Crystallography*.[10] The structure was solved by Multan[11] and Fourier methods. An empirical absorption correction[12] was applied at the end of the isotropic refinements. Final mixed refinement was undertaken with weights w = 1/(a+b|Fo|^2), where a = 2.75, b = 0.03 if |Fo| < 8, a = 5.78, b = 0.32 if 8 < |Fo| < 16 and a = 0.77 and b = 0.01 if 16< |Fo| < 161 calculated by PESOS.[13] The hydrogen atoms were included with fixed isotropic contributions at their calculated positions. Final difference synthesis showed no significantly electron density. Most of the calculations were carried out with the *X-Ray 80 System*.[14]

Table 2. Crystal and Refinement Data for Tröger's Base **7b**[17]

formula		$C_{21}H_{18}N_6$
formula wt		354.4
crystal system		monoclinic
space group		$P2_1/n$
cell dimensions		
	a, Å	13.017(5)
	b, Å	6.959(2)
	c, Å	19.401(8)
	β, °	98.01(3)
Z		4
V, Å		1740(1)
D_{calcd}, g cm^{-3}		1.35
F(000)		744
temp, °C		22
diffractometer		Enraf-Nonius CAD4

radiation	graphited-monochromated Mo $K\alpha$ (λ = 0.71069 Å)
μ(Mo $K\alpha$), cm^{-1}	0.79
crystal dimensions, mm	0.3 x 0.2 x 0.07
θ range, °	1-25
scan technique	$\omega/2\theta$
data collected	(-15, 0, 0) to (15, 8, 23)
unique data	3062
observed reflexions $I > 2s(I)$	983
decay	≤1%
R_{int}, %	1.8
$R = \Sigma \lvert\Delta F\rvert / \Sigma \lvert F_o\rvert$	5.5
$R_w = (\Sigma w \Delta^2 F / \Sigma w \lvert F_o\rvert^2)^{1/2}$	4.7
maximum shift/error	0.04
average shift/error	0.009
absorption correction range	0.65 - 1.18

Acknowledgements

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