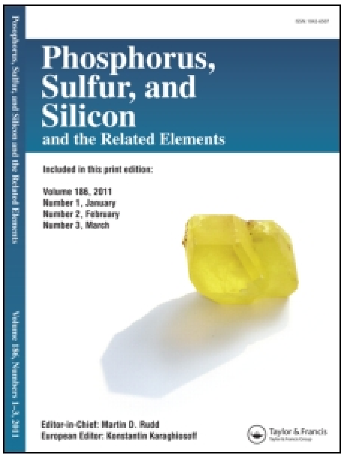

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ADDITION OF CYCLOHEXYLISOTHIOCYANATE TO O,O-DIETHYL-N,N'-ETHYLENE-BIS-PHENYL METHYL PHOSPHONATE. X-RAY STRUCTURE OF THE CONDENSATION PRODUCT

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ADDITION OF CYCLOHEXYLISOTHIOCYANATE TO O,O-DIETHYL-N,N'-ETHYLENE-BIS-PHENYL METHYL PHOSPHONATE. X-RAY STRUCTURE OF THE CONDENSATION PRODUCT

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The synthesis and the molecular structure of the title compound has been determined by single crystal X-ray analysis. $C_{38}H_{60}N_4O_6P_2S_2$ has a meso configuration, its crystal is monoclinic space group $P2_1/c$ with $a = 11.656(2)$, $b = 18.480(4)$, $c = 10.210(2)$, $\alpha = \gamma = 90°$, $\beta = 94.91(3)°$ and $Z = 2$. The refinement had a R-value 0.0537 for 2045 reflections. Bond distances and angles are quite normal and were within the expected range for all of the atoms. The torsion angle, N1-C8-C8A-N1A, is 180° so the molecule takes on a rather layered structure form one half to the other. There are a number of weak intermolecular interactions, but the strongest is between S1 and the hydrogens in C18 of the nearest neighbour molecule.

Keywords: Alkyl thioureas bearing phosphonic groups; ^{1}H-NMR and MS-FAB characterization; molecular geometry and configuration; *meso*-form

INTRODUCTION

Recently we reported on the functionalization of 1-amino-1-arylmethyl phosphonic acid diethyl esters at the NH group with isocyanates in order to produce alkyl ureas containing the phosphonate moieties in their structure[1]. The interest of such compounds, besides the potential use in agrochemistry and medicinal

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*Corresponding author. E-mail: sfailla@ic.ing.unict.it chemistry, lies in their ability to complex metal ions due to the presence of the ureido moiety.

Furthermore, the functionalization reaction choosen can be employed in order to prepare interesting macrocycles and/or polycondensates bearing the -P(O)(OR)$_2$ groups, when bifunctional substrates are used.

In order to exploit such functionalization reactions of the NH groups in our amino-phosphonates we tested, as electrophilic reagents, isothiocyanates with the aim of producing substituted thioureas and macromolecular systems possessing both the phosphonate and the thioureido moieties.

Therefore, having in mind the idea of preparing poly-thioureas and macrocyclic related systems, we caused to react O,O-diethyl-N,N′-ethylene-bis-phenyl methyl phosphonate (**1**) with mono-isothiocyanates in order to test the reactivity of the NH groups in such model reaction, and in order to fully characterize the condensation product obtained.

RESULTS AND DISCUSSION

When meso (**1**)[2,3] was caused to react with cycloexyl isothiocyanate in toluene at 80°C, compound **2** was obtained in moderate yield, according to reaction **I**.

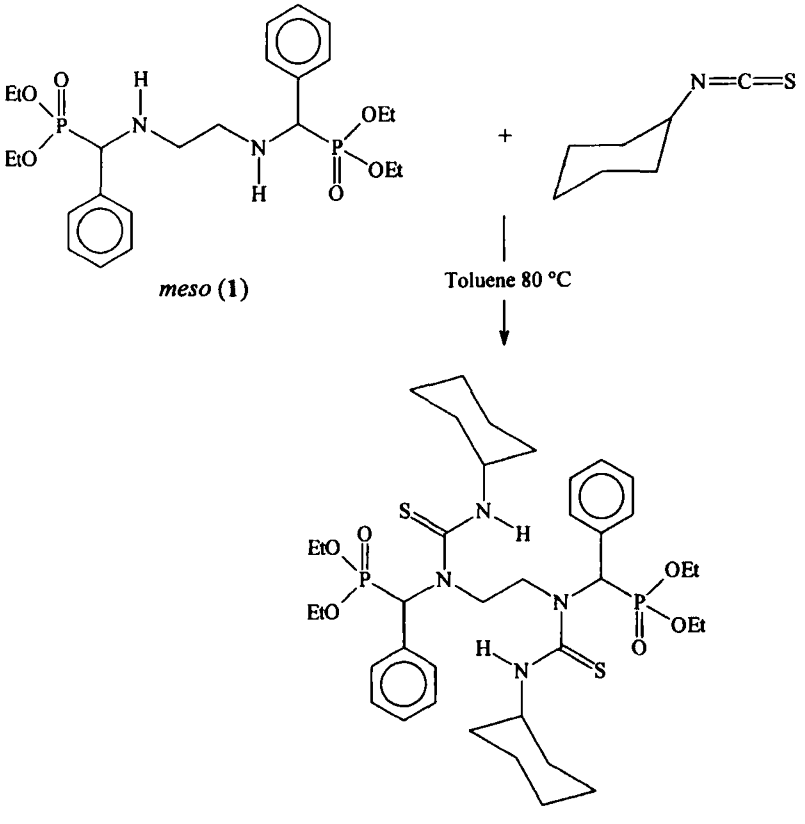
Meso (**2**), which possesses a sharp melting point (208°C), is a white crystalline solid soluble in most organic solvents. Contrary to the parent derivatives meso-(**1**)[2,3] and to the cognate ureido analog[1], compound **2** shows a very complex ^{1}H-NMR spectrum at 200 MHz in $CDCl_3$ as solvent (Figure 1). Three main spectral regions can be seen in this figure: the first one at δ 1.19–2.10 ppm where the cyclohexyl and the methyl protons of the ethoxy groups are confined; the central one at δ 3.59–4.48 ppm comprising the -N-CH$_2$- and the methylene protons of the ethoxy groups, and finally the low field region at δ 7.27–8.42 ppm where the aromatic, the -NH-C- and -CH-P protons resonate.

Thus the main conclusions which can be drawn from this spectrum are the following:

i) the fine structure (two sharp triplets) always present for these ethyl phosphonates esters[1,3] in the methyl region of the spectrum is now lost and only a very broad signal covered by the cyclohexyl protons is in evidence;

ii) the -CH-P- and the -NH-C- signals are shifted very much more downfield compared to the corresponding signals (6.41 and 7.08 ppm, respectively) of the cognate ureido analog[1];

iii) the extremely broad appearance of all these signals, which were highly diagnostic in all amino-phosphonate esters as well as in their functionalized



meso (**1**)

(I)

meso (**2**)

products[1], renders more intriguing the formula assignment and clearly speaks for a reduced conformational mobility of meso-**2** in solution, on the NMR time-scale. In fact, on increasing the probe temperature to 50°C the ethyl signals became sharper and the usual expected multiplicity could be seen.

Even the MS-FAB spectrum of 2 is quite different from the cognate ureido analog[1] and from the parent phosphonate derivatives. In fact, the MS-FAB spectrum of these two last families of compounds are rich in interesting and very diagnostic fragmentation pathways; i.e., loss of diethyl phosphite and isocyanate or diethyl phosphite molecules to gave the fragment ion corresponding to the Schiff base precursors. On the contrary, inspection of the MS-FAB spectrum of **2** reveals that a protonated molecular ion $[M + H]^+$ at m/z 795 is present, and the region at relatively low mass numbers is characterized by the presence of the

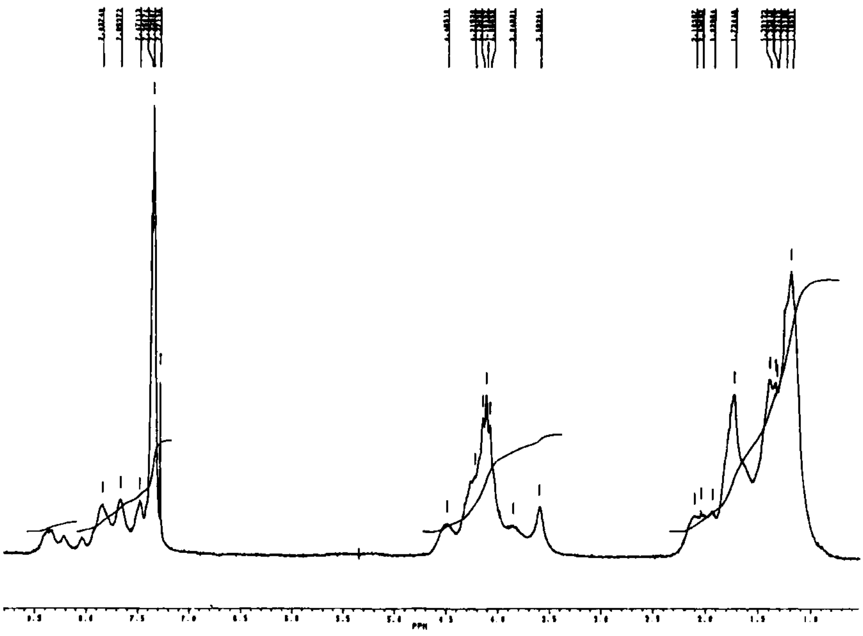
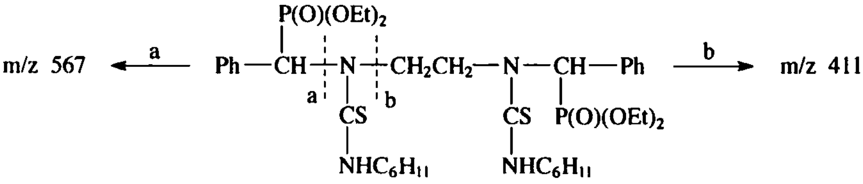


FIGURE 1 ^{1}H-NMR spectrum of compound **2** at 200 MHz in $CDCl_3$.

fragment ion at m/z 411, which constitutes the base peak in relative intensity. This fragment ion may originate from the protonated molecular ion by an α-scission to the nitrogen atoms of the molecular skeleton, which produces the two observed different fragment ions, at m/z = 567 and m/z = 441 respectively.



$$\text{m/z } 567 \xleftarrow{a} \text{Ph}-\overset{\text{P(O)(OEt)}_2}{\text{CH}}\underset{a}{\vdots}\underset{\substack{\text{CS}\\ \text{NHC}_6\text{H}_{11}}}{\text{N}}\underset{b}{\vdots}\text{CH}_2\text{CH}_2-\underset{\substack{\text{CS}\\ \text{NHC}_6\text{H}_{11}}}{\text{N}}-\underset{\text{P(O)(OEt)}_2}{\text{CH}}-\text{Ph} \xrightarrow{b} \text{m/z } 411$$

Therefore, in order to gain more precise information on the molecular formula and on the geometry of meso-**2** an X-ray structure determination of its molecular structure was undertaken.

X-RAY STRUCTURE OF MESO-2

The molecular conformation of **2** and the atomic numbering scheme are illustrated in Figure 2. The atomic coordinates are reported in Table I whereas Table II shows bond distances and bond angles for meso-**2**.

The molecule sits on a special position in space group $P2_1/c$ such that there is a center of symmetry between atoms C8 and C8A so the position of the atoms in only one-half of the molecule needed to be found, the others being related by symmetry operation. Bond distances and angles are quite normal and were within the expected range for all of the atoms. The torsion angle, N1-C8-C8A-N1A, is 180° so the molecule takes on a rather layered structure form one half

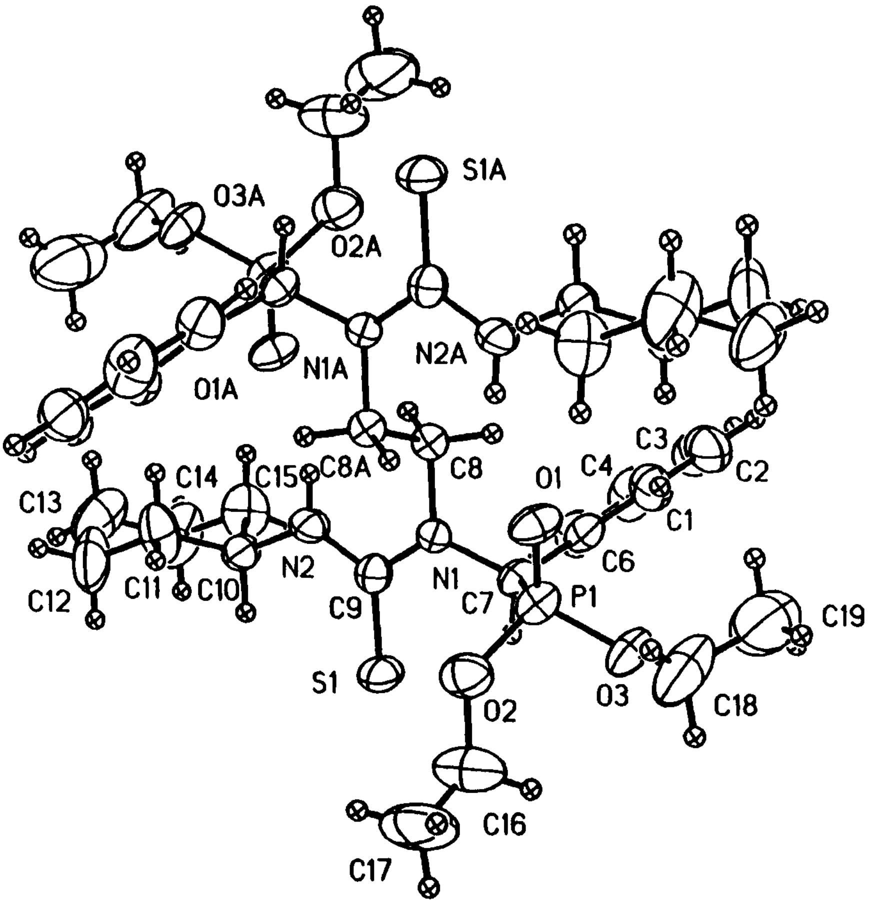


FIGURE 2 X-ray structure and atomic numbering scheme for meso-2.

TABLE I Atomic coordinates [$\times 10^4$] and equivalent isotropic displacement parameters [Å^2 $\times$ 10^3] for meso-2. U(eq) is defined as third of the trace of the ortogonalized U_{ij} tensor

	x	*y*	*z*	*U(eq)*
S(1)	7620(1)	10840(1)	−2415(2)	85(1)
P(1)	7760(2)	9353(1)	688(2)	71(1)
O(1)	6843(3)	8987(2)	1337(4)	77(1)
O(2)	7929(3)	8989(2)	−672(5)	94(2)
O(3)	8963(3)	9367(2)	1492(4)	83(1)
N(1)	6418(4)	10404(2)	−443(5)	56(1)
N(2)	5394(4)	10926(3)	−2220(5)	76(2)
C(1)	7596(5)	10607(4)	2806(10)	88(2)
C(2)	7699(6)	11106(6)	3802(9)	112(3)
C(3)	7787(7)	11822(6)	3526(11)	118(4)
C(4)	7787(6)	12035(5)	2251(11)	111(3)
C(5)	7717(5)	11542(5)	1253(7)	89(2)
C(6)	7626(5)	10814(4)	1510(8)	65(2)
C(7)	7518(5)	10302(3)	367(6)	57(2)
C(8)	5343(4)	10330(2)	266(5)	55(2)
C(9)	6422(5)	10717(3)	−1660(6)	66(2)
C(10)	5187(5)	11251(4)	−3515(6)	81(2)
C(11)	4274(7)	10840(3)	−4336(7)	113(3)
C(12)	4056(7)	11190(5)	−5675(8)	152(4)
C(13)	3658(7)	11959(5)	−5548(9)	150(4)
C(14)	4557(7)	12372(4)	−4740(9)	151(4)
C(15)	4815(6)	12023(4)	−3407(7)	104(3)
C(16)	8969(7)	9079(4)	−1358(8)	148(4)
C(17)	9082(7)	8561(5)	−2249(9)	289(8)
C(18)	9380(7)	8704(6)	2191(9)	168(5)
C(19)	9495(8)	8837(6)	3519(8)	243(7)

to the other. There are a number of weak intermolecular interactions, but the strongest is between S1 and the hydrogens in C18 of the nearest neighbour molecule.

EXPERIMENTAL

Cyclohexyl isothiocyanate, as well as solvents and other chemicals used, were high purity commercial products from Aldrich. All syntheses were performed under a dry N_2 atmosphere.

^{1}H-NMR spectra were recorded in $CDCl_3$, with TMS as an internal standard using a Bruker AC-200 instrument operating at 200 MHz. Mass spectra were obtained using a double focusing Kratos MS 50S instrument equipped with a standard FAB source and DS 90 data system. 3-Nitro-benzylalcohol was used as matrix. Melting points were determined on a Büchi 530 melting point apparatus

TABLE II Bond lengths [Å] and angles [°] for meso-**2**

S(1)-C(9)	1.666(5)	P(1)-O(1)	1.470(3)
P(1)-O(3)	1.563(4)	P(1)-O(2)	1.571(4)
P(1)-C(7)	1.801(5)	O(2)-C(16)	1.460(7)
O(3)-C(18)	1.478(8)	N(1)-C(9)	1.372(6)
N(1)-C(7)	1.478(6)	N(1)-C(8)	1.506(6)
N(2)-C(9)	1.339(6)	N(2)-C(10)	1.453(6)
N(2)-H(2)	0.86	C(1)-C(2)	1.371(8)
C(1)-C(6)	1.381(7)	C(1)-H(1)	0.93
C(2)-C(3)	1.359(9)	C(2)-H(2)	0.93
C(3)-C(4)	1.360(9)	C(3)-H(3)	0.93
C(4)-C(5)	1.364(8)	C(4)-H(4)	0.93
C(5)-C(6)	1.376(8)	C(5)-H(5)	0.93
C(6)-C(7)	1.499(7)	C(7)-H(7)	0.98
C(8)-C(8)#1	1.531(8)	C(8)-H(8A)	1.02
C(8)-H(8B)	1.04	C(10)-C(15)	1.498(7)
C(10)-C(11)	1.503(7)	C(10)-H(10)	0.98
C(11)-C(12)	1.515(8)	C(11)-H(11A)	0.97
C(11)-H(11B)	0.97	C(12)-C(13)	1.503(9)
C(12)-H(12A)	0.97	C(12)-H(12B)	0.97
C(13)-C(14)	1.488(9)	C(13)-H(13A)	0.97
C(13)-H(13B)	0.97	C(14)-C(15)	1.513(8)
C(14)-H(14A)	0.97	C(14)-H(14B)	0.97
C(15)-H(15A)	0.97	C(15)-H(15B)	0.97
C(16)-C(17)	1.334(8)	C(16)-H(16A)	0.97
C(16)-H(16B)	0.97	C(17)-H(17A)	0.96
C(17)-H(17B)	0.96	C(17)-H(17C)	0.96
C(18)-C(19)	1.373(10)	C(18)-H(18A)	0.97
C(18)-H(18B)	0.97	C(19)-H(19A)	0.96
C(19)-H(19B)	0.96	C(19)-H(19C)	0.96
O(1)-P(1)-O(3)	115.2(2)	O(1)-P(1)-O(2)	110.6(2)
O(3)-P(1)-O(2)	107.2(2)	O(1)-P(1)-C(7)	114.9(2)
O(3)-P(1)-C(7)	101.5(2)	O(2)-P(1)-C(7)	106.6(3)
C(16)-O(2)-P(1)	123.2(4)	C(18)-O(3)-P(1)	118.9(4)
C(9)-N(1)-C(7)	119.4(5)	C(9)-N(1)-C(8)	122.8(5)
C(7)-N(1)-C(8)	115.9(4)	C(9)-N(2)-C(10)	125.5(5)
C(9)-N(2)-H(2)	116.9(3)	C(10)-N(2)-H(2)	117.6(3)
C(2)-C(1)-C(6)	121.1(8)	C(2)-C(1)-H(1)	119.7(6)
C(6)-C(1)-H(1)	119.0(5)	C(3)-C(2)-C(1)	120.3(9)
C(3)-C(2)-H(2)	118.5(7)	C(1)-C(2)-H(2)	121.2(6)
C(2)-C(3)-C(4)	119.1(10)	C(2)-C(3)-H(3)	119.4(7)
C(4)-C(3)-H(3)	121.4(7)	C(3)-C(4)-C(5)	121.0(9)
C(3)-C(4)-H(4)	119.1(7)	C(5)-C(4)-H(4)	119.9(6)

and are uncorrected. The amino phosphonate diester precursor meso-**1** was prepared in high yield by adding diethylphosphite to the imine, as reported elsewhere[3].

Compound **2** was synthesized according to the following procedure:

TABLE II (Continued)

C(4)-C(5)-C(6)	120.8(8)	C(4)-C(5)-H(5)	120.1(6)
C(6)-C(5)-H(5)	119.1(5)	C(5)-C(6)-C(1)	117.5(7)
C(5)-C(6)-C(7)	118.2(8)	C(1)-C(6)-C(7)	124.3(8)
N(1)-C(7)-C(6)	111.4(5)	N(1)-C(7)-P(1)	109.9(4)
C(6)-C(7)-P(1)	118.2(5)	N(1)-C(7)-H(7)	105.8(3)
C(6)-C(7)-H(7)	104.9(3)	P(1)-C(7)-H(7)	105.6(2)
N(1)-C(8)-C(8)#1	109.4(5)	N(1)-C(8)-H(8A)	107.0(3)
C(8)#1-C(8)-H(8A)	110.7(4)	N(1)-C(8)-H(8B)	99.0(3)
C(8)#1-C(8)-H(8B)	108.2(4)	H(8A)-C(8)-H(8B)	121.5
N(2)-C(9)-N(1)	115.8(5)	N(2)-C(9)-S(1)	121.2(5)
N(1)-C(9)-S(1)	123.0(5)	N(2)-C(10)-C(15)	110.6(6)
N(2)-C(10)-C(11)	110.7(6)	C(15)-C(10)-C(11)	109.1(6)
N(2)-C(10)-H(10)	108.5(3)	C(15)-C(10)-H(10)	108.9(4)
C(11)-C(10)-H(10)	109.0(4)	C(10)-C(11)-C(12)	110.0(6)
C(10)-C(11)-H(11A)	109.5(4)	C(12)-C(11)-H(11A)	108.8(5)
C(10)-C(11)-H(11B)	109.3(4)	C(12)-C(11)-H(11B)	111.3(5)
H(11A)-C(11)-H(11B)	107.9	C(13)-C(12)-C(11)	110.8(8)
C(13)-C(12)-H(12A)	110.6(5)	C(11)-C(12)-H(12A)	107.8(5)
C(13)-C(12)-H(12B)	110.1(5)	C(11)-C(12)-H(12B)	109.3(5)
H(12A)-C(12)-H(12B)	108.2	C(14)-C(13)-C(12)	109.0(8)
C(14)-C(13)-H(13A)	110.0(5)	C(12)-C(13)-H(13A)	108.2(5)
C(14)-C(13)-H(13B)	111.6(5)	C(12)-C(13)-H(13B)	109.9(5)
H(13A)-C(13)-H(13B)	108.1	C(13)-C(14)-C(15)	110.8(7)
C(13)-C(14)-H(14A)	106.7(5)	C(15)-C(14)-H(14A)	109.6(5)
C(13)-C(14)-H(14B)	111.1(5)	C(15)-C(14)-H(14B)	110.6(4)
H(14A)-C(14)-H(14B)	108.0	C(10)-C(15)-C(14)	112.1(6)
C(10)-C(15)-H(15A)	109.6(4)	C(14)-C(15)-H(15A)	110.4(4)
C(10)-C(15)-H(15B)	109.0(4)	C(14)-C(15)-H(15B)	107.7(4)
H(15A)-C(15)-H(15B)	107.9	C(17)-C(16)-O(2)	112.3(8)
C(17)-C(16)-H(16A)	109.2(6)	O(2)-C(16)-H(16A)	108.3(4)
C(17)-C(16)-H(16B)	109.6(7)	O(2)-C(16)-H(16B)	109.3(4)
H(16A)-C(16)-H(16B)	108.0	C(16)-C(17)-H(17A)	109.4(6)
C(16)-C(17)-H(17B)	109.3(6)	H(17A)-C(17)-H(17B)	109.5
C(16)-C(17)-H(17C)	109.8(7)	H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5	C(19)-C(18)-O(3)	109.2(11)
C(19)-C(18)-H(18A)	109.0(7)	O(3)-C(18)-H(18A)	109.7(4)
C(19)-C(18)-H(18B)	111.1(7)	O(3)-C(18)-H(18B)	110.0(4)
H(18A)-C(18)-H(18B)	107.8	C(18)-C(19)-H(19A)	107.3(8)
C(18)-C(19)-H(19B)	111.6(6)	H(19A)-C(19)-H(19B)	109.5
C(18)-C(19)-H(19C)	109.5(7)	H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5		

Symmetry transformations used to generate equivalent atoms: #1 $-x + 1, -y + 2, -z$

To a solution of the amino phosphonate precursor 1.28 g (2.5 mmol) and a catalytic amount of Et_3N in dry toluene (20 ml) was added 1 ml (6.5 mmol) of cyclohexyl isothiocyanate and the solution heated to 80°C under a dry N_2 atmo sphere for three hours. The solvent was then evaporated and to the oily residue was added a few drops of ethylacetate. White crystal were formed on standing, which were collected by filtration and recrystallized from benzene to give pure meso-**2** (0.60 g, 0.75 mmol, 20%) m.p. 208°C. ^{1}H-NMR (see Figure 1); MS-FAB: 795 (M^+ 1), 567, 411 (base peak). Calcd for $C_{38}H_{60}N_4O_6P_2S_2$ (794.34), C 57.41, H 7.61, N 7.05; found C 57.51, H 7.68, N 7.10.

A suitable crystal of meso-**2** was mounted on a glass fiber, placed in a goniometer head on the Enraf-Nonius CAD4 diffractometer and centered optically. Lattice parameters were determined from 25 reflections ($18° < 2\theta < 22$). The crystal data are as follows: $C_{38}H_{60}N_4O_6P_2S_2$, fw = 794.96, monoclinic, P21/c, a = 11.656(2) Å, b = 18.480(4) Å, c = 10.210(2) Å, β = 94.91(3)°, Z = 2, D_x = 1.205 gcm^{-3}, V = 2191.2(7) Å^3, T = 293 K, μ = 2.40 cm^{-1}.

Intensity data for meso-2 were collected on a crystal measuring 0.25 × 0.20 × 0.18 mm using MoKα radiation (λ = 0.71073 Å). A total of 8176 reflections to 40.00° 2θ were measured in the ω–2θ mode and 2045 averaged, unique reflections (Rmerge = 0.0537) were used in the final refinements. Two representative reflections were monitored every 2 hrs as a check on instruments stability, and additional two reflections were monitored periodically for crystal orientation control. Lorenz, polarization, and decay corrections were applied to the data and the weighting scheme used during refinement was $1/\sigma^1$, based on counting statistics.

The structure was solved by the Direct methods using SHELXS-86[4], which revealed the position of most of the atoms. Any other non-hydrogen atoms were found by successive difference Fourier syntheses. Hydrogen atoms were placed their expected chemical positions using the HFIX comand in SHELXL-93[5] and were included in the final cycles of least squares with isotropic Uij's related to the atom's ridden upon. All other non-hydrogen atoms were refined anisotropically.

Scattering factors were taken from Cromer and Waber[6]. Anomalous dispersion corrections were those of Cromer[7]. All data processing was carried out on a DEC 3000 AXP computer using the Open MolEN system of programs[8]. Structure solution, refinement and preparation of figures and table for publication were carried out on PC's using SHELXS-86[4], SHELXL-93[5] and XP/PC[9].

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