

Synthesis of Methyl-2,4-bis(cyclohexane)dispiro-1,2,3,4,4a,5,6,7-octahydro-(1*H*,3*H*)quinazoline-8-carbodithioate Derived from Cyclohexanone in One Step

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The new compound Methyl-2,4-bis(cyclohexane)dispiro-1,2,3,4,4a,5,6,7-octahydro-(1*H*,3*H*)-quinazoline-8-carbodithioate has been synthesized from cyclohexanone and carbon disulfide. It has been characterized by uv-visible, FTIR, mass spectra and a complete structure proposed based on ¹H and ¹³C NMR spectroscopy.

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Introduction.

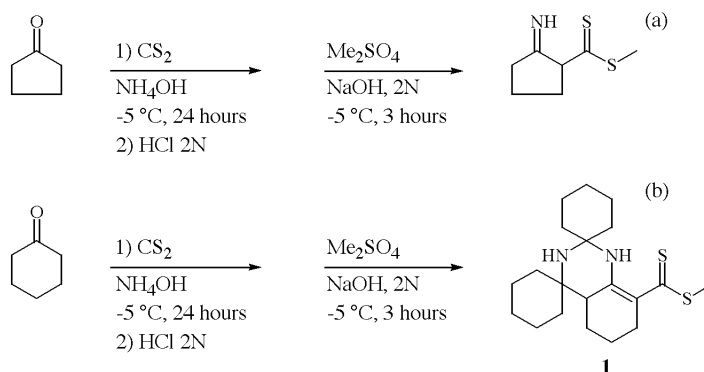
Due to the complexity of the problems to be studied in bioinorganic chemistry [1] frequently it is necessary to develop models that allow us to better understand the metal's role in biological processes. Thus bioinorganic has developed an area called biomimetics, focused on the synthesis of low molecular weight molecules that mimic the properties of metallic sites in metallobiomolecules of significant interest [2]. There have been numerous efforts in this area and a variety of models have been developed. Particularly, several works [3] have tried to simulate the pseudotetrahedral coordination sphere of two nitrogens and two sulfurs that nature uses as the metal's coordination site [4] in a variety of cases such as: Cu(II) in blue copper proteins like the plastocyanines, Ni(II) in nickel hydrogenases, Zn(II) in "Zn fingers" proteins involved in DNA activation and transcript regulation. The first model was proposed using methyl-*N,N'*-alkylbis(2-amino-1-cyclopentencarbodithioate) type ligands derived from cyclopentanone [5]. In order to introduce a ligand structural

modification that favors a greater site distortion and approach the entatic state characteristic of the metal systems mentioned above, in this work was developed a bidentate ligand, dispirotetracyclo nitrogen-sulfur, by changing cyclopentanone to cyclohexanone, modifying the reaction conditions described by Bordás (Scheme 1a) [6]. Metal complexes with ligands that have β -dithio-carboxy methyl enamine chelation sites, like the one synthesized, has been previously reported [7]. These complexes, in which a pseudotetrahedral coordination sphere was attained, represents an important advance in the biomimetic studies of metallobiomolecules.

Results and Discussion.

In the synthesis process of Methyl-2,4-bis(cyclohexane)dispiro-1,2,3,4,4a,5,6,7-octahydro-(1*H*,3*H*)-quinazoline-8-carbodithioate (Scheme 1b), to a solution of ammonium hidroxide with cyclohexanone at -5 °C carbon disulfide was slowly added, the resulting solution was stirred for 24 hour. The crude acid was methylated with dimethyl sulfate. The methyl ester was obtained as a yellow

Scheme 1



(a) Product found by Bordás [14] synthesized from cyclopentanone. (b) Synthesized ligand from cyclohexanone: Methyl-2,4-bis(cyclohexane)dispiro-1,2,3,4,4a,5,6,7-octahydro-(1*H*,3*H*)-quinazoline-8-carbodithioate.

Table 1
 ^1H and ^{13}C Spectra Data. HMQC Correlation

	$\delta\text{-}^{13}\text{C}$ (ppm)	$\delta\text{-}^1\text{H}$ (ppm)	Conf	m	J_1 -(Hz)	J_2 -(Hz)	^1H	Conf	m	J_1 -(Hz)	J_2 -(Hz)
-CS ₂ Me	196.3	-	-	-	-	-	-	-	-	-	-
C _{8'}	160.3	-	-	-	-	-	-	-	-	-	-
C ₈	114.3	-	-	-	-	-	-	-	-	-	-
C ₂	68.4	-	-	-	-	-	-	-	-	-	-
C ₄	53.6	-	-	-	-	-	-	-	-	-	-
C _{4'}	48.5	2.18	ax	dd	11.8	5.0	-	-	-	-	-
C ₁ -Sp ₂	42.4	1.65	-	m	-	-	1.65	-	m	-	-
C ₅ -Sp ₂	40.6	1.85	-	m	-	-	1.70	-	m	-	-
C ₁ -Sp ₄	38.1	1.75	-	m	-	-	1.25	-	m	-	-
C ₅ -Sp ₄	29.1	1.50	eq	m	-	-	1.25	-	m	-	-
C ₇	28.6	2.91	eq	dd	14.6	4.2	2.48	ax	td	14.6	2.6
C ₃ -Sp ₄	26.2	1.70	eq	m	-	-	1.10	ax	ct	-	-
C ₃ -Sp ₂	24.9	1.55	-	m	-	-	1.35	-	m	-	-
C ₆	22.9	1.95	-	m	-	-	1.25	-	m	-	-
C ₂ -Sp ₂	22.4	1.85	eq	m	-	-	1.50	ax	m	-	-
C ₄ -Sp ₂	22.2	1.85	eq	m	-	-	1.37	ax	m	-	-
C ₅	22.0	1.80	eq	m	-	-	1.45	ax	m	-	-
C ₂ -Sp ₄	21.1	1.85	eq	m	-	-	1.50	ax	m	-	-
C ₄ -Sp ₄	20.9	1.70	eq	m	-	-	1.37	ax	m	-	-
-SCH ₃	17.5	2.54	-	s	-	-	-	-	-	-	-

dd = doublet of doublets, td = triplet of doublets, m = multiplet, eq = equatorial, ax = axial, Sp₂ and Sp₄ = spiro at C₂ and C₄ of the quinazolizone system respectively.

solid, in 20% overall yield after recrystallization in dioxane. The structure of this compound was established using uv, ir, nmr and ms. Figure 1a shows the numbering system for the reported compound, and Table 1 gives the ^1H and ^{13}C nmr broad band spectral data. The ^1H nmr spectrum shows the presence of a proton at very low field, 14.84 ppm, indicating hydrogen bonding between the N₁-H and the thiocarbonyl moiety. It is also important to mention here the presence of three significant signals which were the basis for determining the structure; these signals correlated to several carbons through two or more bonds. The first signal appears at 2.91 ppm as a doublet of doublets associated with the equatorial proton at C₇, while its geminal proton gives signal at 2.54 ppm as a triplet of doublets. (See Figure 1b) The last signal is the allylic proton C_{4'}-H which resonates at 2.18 ppm as a doublet of doublets. The carbon-13 spectrum shows 20 well differentiated signals, three of them at low field: 196.3 ppm, -(C=S)SCH₃, at 160.3 ppm, HN-C=C, and at 114.3

ppm due to the β -carbon of the enamine system, HN-C=C-. The DEPT-135 [8], spectrum helps to identify the unique C-H, 48.5 and -CH₃, 17.5, and the two quaternary carbons C₂, 68.4 and C₄, 53.6 ppm. The remaining -CH₂ signals were identified with aid of HMQC and HMBC spectra.

Conclusions.

A simple one-step synthesis of the bidentate nitrogen-sulfur ligand Methyl-2,4-bis(cyclohexane)dispiro-1,2,3,4,4a,5,6,7-octahydro-(1*H*,3*H*)-quinazoline-8-carbodithioate was developed. The versatility of this kind of ligands enables them to coordinate a wide scope of metals, that opens up new possibilities in catalytic, electrochemical and medical properties for these new compounds, presently being explored in our research group.

EXPERIMENTAL

Spectra uv-visible were taken in a LAMBDA 3 Perkin-Elmer spectrophotometer, in chloroform solutions. Vibrational spectra (5000 - 400 cm⁻¹) were taken in a FTIR Perkin-Elmer 1725X spectrophotometer, in KBr pellets. The ^1H and ^{13}C NMR spectra were taken in a Bruker Advance DRX 400 spectrometer, in CDCl₃ solutions;. Mass spectra were taken in a Hewlett-Packard System 5988A spectrometer.

Synthesis of the Methyl-2,4-bis(cyclohexane)dispiro-1,2,3,4,4a,5,6,7-octahydro-(1*H*,3*H*)-quinazoline-8-carbodithioate (1).

To 100 mL of ammonium hydroxide (29% by volume) in a 250 mL beaker, 25 mL (0.24 mole) of cyclohexanone and 28 mL (0.49 mole) of carbon disulfide were added; stirring for 24 hour at -5 °C. After this time a reddish solid was recovered by suction

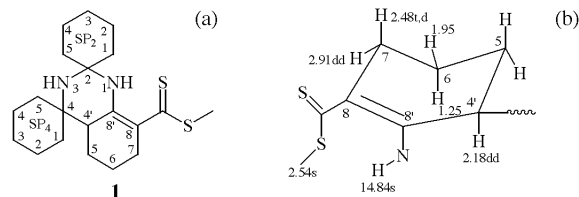


Figure 1. (a) Numbering system for the reported compound. (b) Proposed stereochemistry of the substituted cyclohexene ring.

filtration. The solid was transferred to a beaker, distilled water was added and stirred to obtain a suspension; sufficient 2 M HCl was added to reach pH = 4. The solid was separated by suction filtration, washed with abundant water and with a minimum amount of diethyl ether. The crude acid was placed in a beaker containing a 100 mL solution of 2 N NaOH, and allowed to stir for 24 hours to get a suspension. Dimethyl sulfate, 4.2 mL (0.044 mole), was added dropwise, and the mixture stirred for 3 hour at -5 °C. A brown-yellow solid was collected by suction. 5.6 g (0.015 mole) of the ester product was placed in a beaker with 100 mL of methanol, and stirred for 24 hour. A yellow solid is collected by suction, washed with methanol and vacuum dried. The product was recrystallized in dioxane, giving a 20 % overall yield, mp 177 - 180 °C [9]; ir: ν 3448 (N-H), 3288 (N-H-free), 1589 (C=C + ν C=N) cm^{-1} ; uv: λ_{max} (ϵ , $\text{M}^{-1}\text{cm}^{-1}$) 239 (15590), 315 (40382), 408 (26403); ms: m/z M^+ , 364.4(6); M^+ -CH₃, 349.3(10); M^+ -CH₃S₂, 273.1(8).

Anal. Calcd. For C₂₀H₃₂N₂S₂: C, 65.88; H, 8.85; N, 7.68; S, 17.59. Found: C, 65.53; H, 8.68; N, 7.81; S, 17.48 [10].

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- [8] DEPT-135: Distortionless Enhancement by Polarization Transfer. HMQC: Heteronuclear Multiple Quantum Correlation. HMBC: Heteronuclear Multiple Bond Correlation.
- [9] All reactions must be carried out under the hood in closed vessels. All reaction residues must be stored for proper disposal.
- [10] Microanalysis Laboratory, Department of Chemistry, Bristol University, U.K.