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SYNTHESIS AND STRUCTURAL CHARACTERIZATION OF OCTAETHYL-17-THIOCHLORIN AND OCTAETHYL-7,17-DITHIOISOBACTERIOCHLORIN

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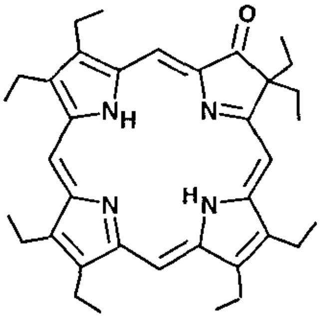
Abstract - Conversion of the octaethyl-17-oxochlorin and octaethyl-7,17-dioxoisobacteriochlorin into their thio and dithio analogs using Lawesson's reagent is reported. Spectroscopic data, along with X-ray crystallographic data for the dithio compound and its dioxo precursor, are reported.

Porphyrins and porphyrin derivatives bearing sulfur containing substituents are rare.[1-3] In order to have modified porphyrins to compare spectroscopically with sulfmyoglobin, an inactivated form of myoglobin formed by addition of sulfide to oxidized (ferryl) myoglobin,[4-5] we undertook to convert the oxo and dioxo porphyrins **1** and **2** into their thio counterparts **3** and **4**. Because the unusual electronic absorption spectra found for **3** and **4** cast some doubt on their identification, we have performed the detailed characterization reported here.



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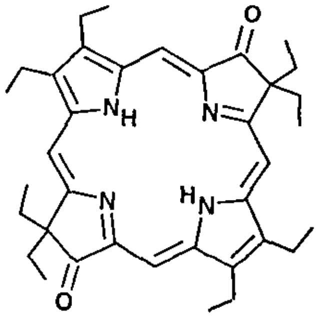

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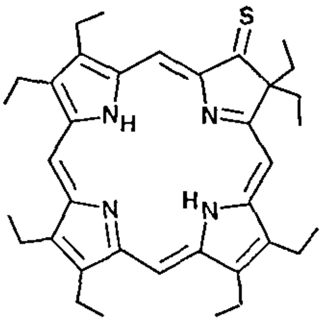

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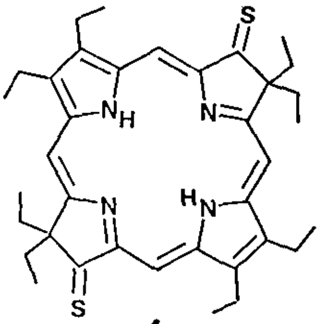

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RESULTS AND DISCUSSION

Treatment of 1 or 2 with Lawesson's reagent,[6] 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide, yields the corresponding thio compounds 3 and 4 in modest and variable yields between 30 and 40% after chromatography on dry silica gel. The electronic absorption spectra of the purified, bright green products are compared with their precursors in Figure 1. As is readily apparent, the spectra of 3 and 4 are much more complex than their oxo analogs. Three or four bands are seen in the Soret region and the low energy region is also more complex. The spectral complexity, which deserves theoretical attention, must result from coupling of the thioketo and porphyrin chromophores. Other spectroscopic data on 3 and 4, however, support their formulation. In the infrared spectra the characteristic ketonic absorptions of 1 and 2 are lost on conversion, and 3 and 4 show new absorptions at 1116 and 1123 cm^{-1}, respectively, which are assigned to ν (C=S). The ^{1}H nmr spectra are consistent with the structural assignments. The spectrum of 3 shows two NH resonances and four meso resonances while that of 4 shows only a single NH resonance and two meso resonances. In each case the resonances of the geminal ethyl groups resonate to lower frequency than the other ethyl groups. Intensity data

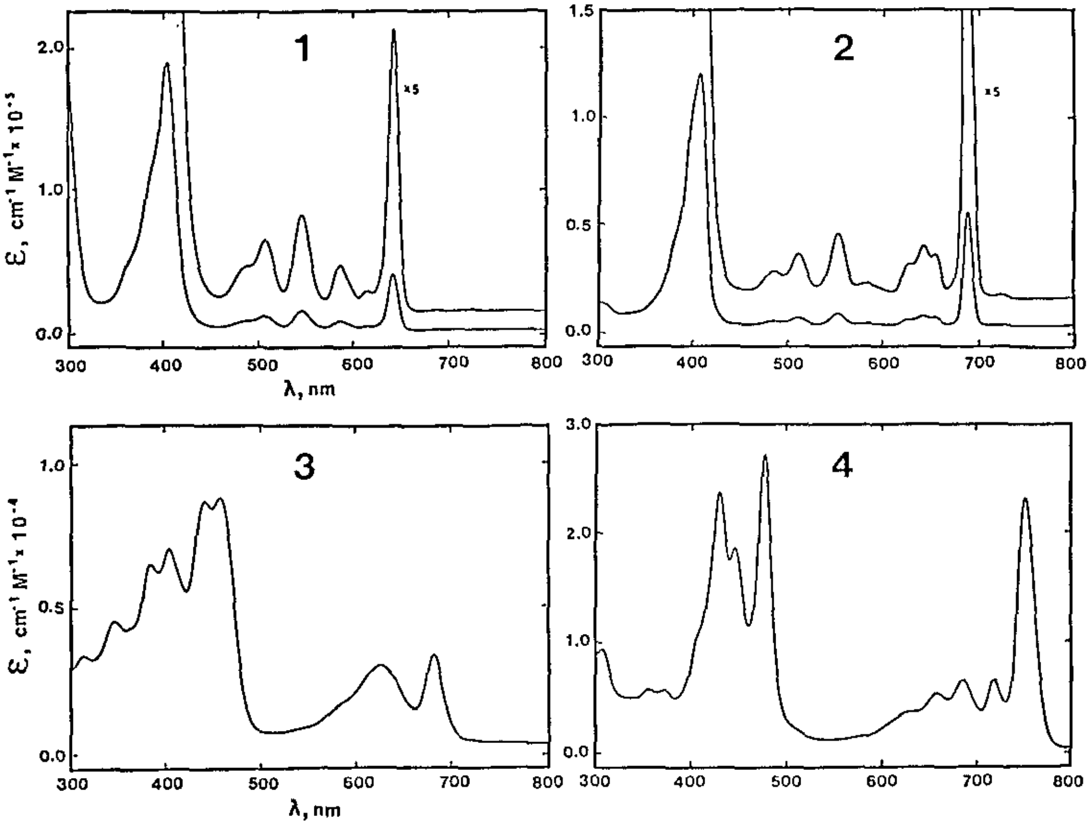

Figure 1. The electronic spectra of compounds 1 - 4 in dichloromethane solution. Notice that the spectra of thio compounds 3 and 4 are broader and less intense than the oxo counterparts.

and decoupling experiments clearly establish the assignment of these resonances to these ethyl groups. The methylene groups of these geminal ethyl groups are particularly distinctive. Since they are diastereotopic, the two methylene protons of each ethyl group have distinct chemical shifts whereas the in-plane, ethyl methylene protons are magnetically equivalent and appear as simple quartets. The composition of 3 and 4 is verified by mass spectral results. In order to unambiguously identify a representative example, the X-ray crystal structure of 4 was obtained. For comparison the structure of its precursor, 2, was also determined by X-ray diffraction. The structure of 2 is shown in Figure 2 with some dimensions, while that of 4 is given in Figure 3. Positional parameters are given in Table I (for 2) and in Table II (for 4). Both molecules are packed about a center of symmetry. They contain a planar isobacteriochlorin core with the C=O and C=S units in that plane as expected from observations on nickel(II)octaethyl-17-oxochlorin.[7] There is almost no puckering of the modified pyrrole rings. The methyl groups and, of course, the geminal ethyl groups, lie out of that plane. The C=S bond distance (1.629(12) A) is within the range normally found for carbon-sulfur double bonds.[8,9] The crystallographic data were not of sufficient quality to experimentally locate the N-H proton of 2, but it was located for 4.

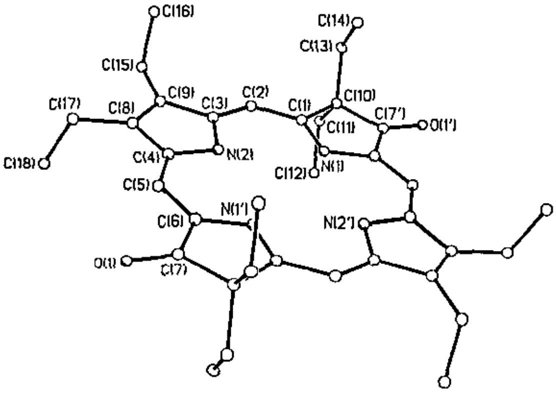

Figure 2. A perspective drawing of 2.
The C(7)-O(1) distance is 1.251(13) A.

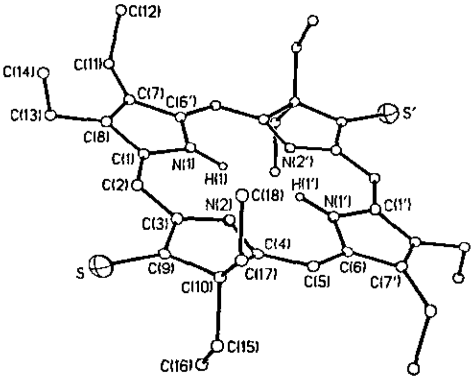

Figure 3. A perspective drawing of 4.
The C(9)-S distance is 1.629(12) Å.

EXPERIMENTAL

Materials. Octaethylporphyrin and Lawesson's reagent were purchased from Aldrich Chemical Co. Oxo compounds 1 and 2 were prepared using osmium tetroxide as described in the literature.[10,11] Toluene was dried by distillation from sodium.

Preparation of 3 and 4. Compounds 3 and 4 were prepared from the corresponding oxo compounds 1 and 2 through reaction with Lawesson's reagent. A solution of 60 mg (0.1 mmole) of 1 or 2 in anhydrous toluene (20 ml) was treated with Lawesson's reagent (25 mg, 0.06 mmole) and the mixture heated under reflux under argon for 3 h. Moisture was strictly excluded during the entire operation. The reaction mixture was then allowed to cool to room temperature and the solvent removed under vacuum. The resulting green residue was dissolved in 10 ml of dichloromethane and applied to a dry silica gel column (1 x 8"). Elution with dichloromethane/petroleum-ether (1:1) produced the desired bright green product as the first fraction. The solvent was removed under reduced pressure, and recrystallization of the resulting solids from dichloromethane/methanol produced 12.4 mg of 3, (0.022 mmole, 21.9%) and 22.9 mg of 4, (0.038 mmole, 38.3%). It has been our observation that the yields were variable.

Octaethyl-17-thiochlorin, 3. ^{1}H nmr ($CDCl_3$), δ(ppm): -2.43, -2.36 (br, 1 H each, NH); 0.05 (t, 6H, gem-CH_2CH_3); 1.8 (m, 18H, CH_3); 2.70, 2.96 (m, 2H each, gem-CH_2CH_3); 3.85, 4.02 (m, 12H, CH_2); 9.09, 9.68, 9.77, 10.31 (1H each, meso-H). UV-Vis, λ_{max} (CH_2Cl_2), nm (10^{-4} E_m, $M^{-1}cm^{-1}$): 313 (0.33), 345 (0.45), 383 (0.65), 404 (0.70), 442 (0.86), 458 (0.88), 626 (0.30, br), 682 (0.34). Mass spectrum (EI), M/e (amu): 566 (M^+), 538, 523. IR (NaCl), ν, cm^{-1}: 3344 (NH), 2960, 2934, 2873 (CH), 1116 (C=S).

Octaethyl-7,17-dithioisobacteriochlorin, 4. ^{1}H nmr ($CDCl_3$), δ (ppm): -1.66 (br, 2H, NH); 0.14 (t, 12H, gem-CH_2CH_3); 1.78, 1.83 (t, 6H each, CH_3); 2.68, 2.90 (m, 4H each, gem-CH_2CH_3); 3.92 (m, 8H, CH_2); 8.90, 10.03 (2H each, meso-H). UV-Vis, λ_{max} (CH_2Cl_2), nm (10^{-4} E_m, $M^{-1}cm^{-1}$): 428 (2.39), 446 (1.89), 478 (2.74), 656 (0.55), 686 (0.66), 718 (0.67), 752 (2.34). Mass spectrum (EI), M/e (amu): 598 (M^+), 582, 566, 554, 541, 525, 508, 299 (M^{2+}). IR (NaCl), ν, cm^{-1}: 3372 (NH), 2961, 2926, 2879 (CH), 1123 (C=S).

Physical measurements. The ^{1}H nmr spectra were recorded at 360 and 300 MHz using Nicolet NT 360 or General Electric QE 300 Fourier transform spectrometer. Electronic spectra were obtained using a Hewlett-Packard 8456A spectrometer. Infrared spectra were recorded using a IR/32 FTIR spectrometer. Mass spectra were obtained on a VG Analytical ZAB-HS double-focusing mass spectrometer.

X-ray crystallography. Suitable crystals of 2 and 4 were grown from a concentrated solution of the compound in dichloromethane. The solution was placed in the bottom of a glass tube (8mm x 25 cm) and heptane was layered over this solution. After standing for a few days at 23°C, suitable crystals had grown at the interface of the two solvents. Crystals of 2 were black parallelepipeds while those of the dithio derivative, 4, were dark blue needles. The diffracted intensity in both cases was rather poor and dropped off rapidly in 2θ, an effect which could be blamed on the presence of loosely held solvent molecules (particularly n-

Table I. Atomic coordinated (x10^4) and isotropic thermal parameters (Å^{2}x10^3) for **2**.

	x	y	z	U
N(1)	4672(11)	-56(7)	4021(4)	21(2)
N(2)	6073(10)	1592(6)	4915(4)	21(2)
O(1)	6523(10)	1397(6)	7408(4)	40(2)
C(1)	5101(14)	734(9)	3586(5)	24(3)
C(2)	5856(14)	1759(9)	3754(5)	26(3)
C(3)	6308(13)	2161(8)	4337(5)	26(3)
C(4)	6661(14)	2248(8)	5412(5)	25(3)
C(5)	6618(14)	1934(9)	6046(5)	28(3)
C(6)	6003(14)	957(8)	6312(5)	25(3)
C(7)	6027(14)	744(9)	6980(5)	28(3)
C(8)	7310(13)	3256(8)	5142(5)	23(3)
C(9)	7095(14)	3213(9)	4495(5)	25(3)
C(10)	4718(16)	398(10)	2911(6)	38(3)
C(11)	3477(16)	1215(11)	2581(6)	47(4)
C(12)	1878(19)	1338(13)	2937(8)	74(5)
C(13)	6244(15)	365(10)	2488(6)	44(4)
C(14)	7582(16)	-391(11)	2776(7)	54(4)
C(15)	7585(14)	4062(9)	3997(5)	27(3)
C(16)	9165(16)	3732(11)	3673(6)	50(4)
C(17)	7977(14)	4232(8)	5518(5)	25(3)
C(18)	6621(15)	5067(10)	5714(6)	37(3)
C(19)	2188(35)	2713(24)	5420(15)	46(8)
C(20)	1453(38)	1625(26)	5596(14)	53(8)
C(21)	682(30)	891(21)	5031(13)	29(6)
C(22)	-114(38)	-226(25)	5203(12)	50(8)
C(23)	-844(37)	-915(26)	4591(16)	52(8)
C(24)	-1614(43)	-2023(30)	4809(17)	74(10)
C(25)	-2237(43)	-2637(28)	4203(18)	70(10)

Table II. Atomic coordinates ($\times 10^4$) and isotropic thermal parameters ($Å^2 \times 10^3$) for **4**.

	x	y	z	U
S	-52(3)	2846(4)	2503(2)	33(1)*
N(1)	757(8)	2321(13)	-23(4)	23(3)
N(2)	-161(8)	288(12)	956(4)	22(3)
C(1)	952(10)	3379(14)	492(5)	21(3)
C(2)	655(9)	3042(14)	1087(5)	21(3)
C(3)	123(9)	1627(14)	1302(5)	14(3)
C(4)	-619(10)	-808(15)	1329(5)	23(3)
C(5)	-1057(9)	-2340(15)	1140(5)	24(3)
C(6)	-1163(9)	-3045(14)	549(5)	23(3)
C(7)	1668(9)	4609(14)	-365(5)	21(3)
C(8)	1552(9)	4765(14)	271(5)	17(3)
C(9)	-174(10)	1487(14)	1947(5)	17(3)
C(10)	-622(9)	-206(14)	2008(5)	18(3)
C(11)	2275(10)	5685(15)	-787(5)	29(4)
C(12)	3560(9)	5169(16)	-875(5)	36(4)
C(13)	1966(10)	6171(14)	674(5)	25(3)
C(14)	3161(10)	5810(17)	1055(5)	44(4)
C(15)	-1890(9)	-221(15)	2238(5)	28(3)
C(16)	-2807(10)	703(16)	1810(5)	37(4)
C(17)	205(10)	-1239(14)	2456(5)	26(3)
C(18)	1485(10)	-1265(16)	2302(6)	39(4)
Cl(1)	1287(10)	5761(15)	3773(5)	42(3)
Cl(2)	1606(13)	5025(19)	5023(7)	78(5)
C(19)	1000	6532	4513	18(11)
C(20)	-168	6000	4907	67(14)
C(21)	920	5891	5009	26(10)
C(22)	1465	5922	4568	102(20)
C(23)	1611	5374	4145	47(12)

* Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor.

Table III. Crystal Data and Summary of Data Collection and Refinement.

Compound	**2**·C_7H_{16}	**4**·$0.6CH_2Cl_2$·$0.7C_7H_{16}$
formula	$C_{43}H_{60}N_4O_2$	$C_{41.5}H_{56.4}Cl_{1.2}N_4S_2$
Formula weight	664.99	718.01
crystal size, mm	0.125 x 0.30 x 0.475	0.05 x 0.05 x 0.42
space group	$P2_1/c$	$P2_1/n$
a, Å	8.184(5)	11.293(5)
b, Å	11.811(6)	8.218(4)
c, Å	21.080(14)	21.425(15)
β, deg	90.84(5)	95.21(4)
V, $Å^3$	2037(2)	1980(2)
Z	2	2
T, K	140 K	130 K
d_{exptl}, gcm^{-3}	1.08	1.20
μ(Mo Kα), cm^{-1}	0.68	2.2
$2\theta_{max}$, deg	45	42
diffractometer	$P2_1$	$P2_1$
λ (Å)	0.71069	0.71069
total reflections	3030	2478
unique reflections	2661	2127
observed reflections	996 ($I>2.5\sigma(I)$)	1102 ($I>2\sigma(I)$)
weighting scheme	$1/\sigma^2(F_o)$	$1/\sigma^2(F_o)$
no. parameters	125	116
R	0.096	0.092
R_w	0.102	0.075
ave Δ/esd	0.016	0.007
min and max peaks in final diff map, $eÅ^{-3}$	-0.29, +1.09	-0.39, +0.57

heptane) in the structures. The crystals were cooled during data collection in part to retard the loss of this solvent. Crystal data and data collection parameters are given in Table III. No decay in the intensities of two standard reflections was observed. Intensities were measured using a ω scan technique. The structures were solved by direct methods. Hydrogen atoms were included in the refinement using positions calculated from a riding model with C-H of 0.96 Å and $U_H = 1.2\ U_C$. The rigid body refinement of methyl groups requires three refined parameters per group. The unique hydrogen on nitrogen was located in **4** and included at the position found in the difference map with a free isotropic U value. In **2**, the molecule of n-heptane is disordered with respect to a center of symmetry and therefore the carbon atoms were refined at 0.5 occupancy. In **4**, peak intensities in the difference map, together with bond distances and angles, were used to construct a model of 0.30 CH_2Cl_2 and 0.35 n-heptane, although three of the heptane carbon atoms were not located. In order to reach convergence it was necessary to fix the carbon atom positions of the n-heptane; their isotropic thermal parameters were allowed to freely refine and gave reasonable values for this model. Due to the low number of observed reflections, all atoms were refined isotropically in both structures except for the sulfur atom of **4**. Crystallographic programs were those of SHELXTL (Nicolet Analytical X-ray Instruments, Madison, Wisconsin). Atomic scattering factors were taken from a standard source.[12]

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