triene (12). The acetate (75 mg) was dissolved in anhydrous methanol (5 ml) under a nitrogen atmosphere. The solution was cooled to 0 °C using an alcohol–ice bath. Methanolic potassium hydroxide solution (1%, 1 ml) was added and the solution stirred for 1 h. The reaction mixture was poured into ether, then washed with 5% hydrochloric acid. The ether layer was dried over sodium sulfate to a residue. The residue was chromatographed on silica plates (20 × 20 × 0.15 cm) prepared from EM silica gel PF-254 which were developed with 25% ether in hexane to obtain the alcohol **12** (40 mg): R_f 0.25; λ_{max} (CCl_4) 260 nm; ir 3600 cm^{-1}; NMR (CCl_4/Me_4Si) δ 1.75 (s, 3 H), 4.31 (s, 2 H), 4.51 (d, 1 H, J = 9 Hz), 5.26 (d, 1 H, J = 10 Hz), 5.39 (d, 1 H, J = 17 Hz), 6.05 (dd, 1 H, J = 17, 10 Hz), 6.05 (dd, 1 H, J = 16, 9 Hz), 6.32 (s, 1 H), 6.70 (d, 1 H, J = 16 Hz); mass spectrum *m/e* 165, 167, 169 ($C_6H_7OCl_2^+$), base peak 129, 131 ($C_6H_6OCl^+$), 89, 91 ($C_4H_6Cl^+$); high-resolution mass measurement M^+ 254.0031, $C_{10}H_{13}OCl_3{}^{35}$ requires 254.0032.

7-Formyl-3-methyl-3,4,8-trichloro-1,5,7-octatriene (14). The alcohol (39 mg) and manganese dioxide were stirred in hexane at room temperature for 24 h. The solution was filtered through Whatman paper to remove solids. The hexane was evaporated in vacuo to a residue. The residue was chromatographed on silica plates (20 × 20 × 0.15 cm) prepared from EM silica gel PF-254. Development with 25% ether in hexane gave the pure aldehyde (15 mg): R_f 0.3; λ_{max} (CCl_4) 264 nm; NMR (CCl_4/Me_4Si) δ 1.74 (s, 3 H), 4.46 (d, 1 H, J = 9 Hz), 5.24 (d, 1 H, J = 10 Hz), 5.40 (d, 1 H, J = 16 Hz), 6.05 (dd, 1 H, J = 16, 10 Hz), 6.49 (dd, 1 H, J = 15, 2 Hz), 7.02 (s, 1 H), 7.11 (dd, 1 H, J = 15, 9 Hz), 9.52 (d, 1 H, J = 2 Hz); mass spectrum *m/e* 252, 254, 256, 258 (M^+), 217, 219, 221 (M^+ − Cl), 181, 183 ($C_{10}H_{10}OCl^+$), base peak 89, 91 ($C_4H_6OCl^+$); high-resolution mass measurement M^+ 251.9875, $C_{10}H_{11}OCl_3{}^{35}$ requires 251.9875.

Acknowledgments. We thank the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—**1**, 55304-01-3; **2**, 35671-09-1; **5**, 55035-53-5; **6**, 58967-05-8; **7**, 58967-06-9; **11**, 58967-07-0; **12**, 53915-35-8; **14**, 58967-08-1.

Supplementary Material Available. A listing of fractional coordinates, bond distances, bond angles, and observed and calculated structure factors (9 pages). Ordering information is given on any current masthead page.

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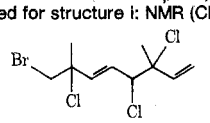

i

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(15) The aldehyde **12** undergoes an autocatalytic decomposition, with loss of hydrogen chloride, to give a tetraene (uv 328 nm) which rapidly decomposes to a complex mixture of products.
(16) *Laurencia johnstonii*, the major source of johnstonol (**2**) and prepacifenol epoxide (**1**), is found in the Gulf of California. Prepacifenol epoxide (**1**) has not been isolated from *L. pacifica*, although this local species is known to contain johnstonol (**2**).
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Cyclic Polysulfides from the Red Alga *Chondria californica*

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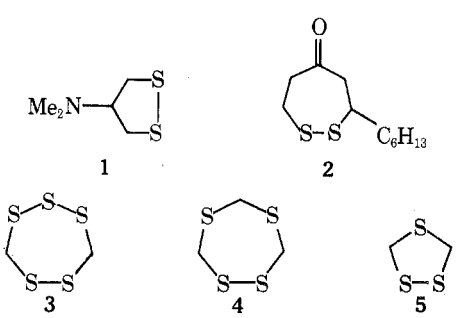
The antibiotic activity of the red alga *Chondria californica* is due to a mixture of cyclic polysulfides and their oxidation products. We have identified 1,2,4-trithiolane, 1,2,4,6-tetrathiepane, 1,2,3,5,6-pentathiepane, 1-oxo-1,2,4-trithiolane, 4-oxo-1,2,4-trithiolane, 4-dioxo-1,2,4,6-tetrathiepane, and a 12-membered heterocycle containing eight sulfur atoms.

Cyclic polysulfides are relatively uncommon in nature, but those compounds which have been described have usually exhibited interesting biological activities.[1] Marine organisms have provided two interesting examples of cyclic disulfides. The annelid worm *Lumbriconereis heteropoda* contains nereistoxin (**1**), a simple compound having insecticidal activity.[2] Two brown algae of the genus *Dictyopteris* have been shown to contain a cyclic disulfide **2**, together with acyclic mono-, di-, and trisulfides.[3] Among examples of cyclic polysulfides attributed to terrestrial organisms are two antibiotics, 1,2,3,5,6-pentathiepane (lenthionine, **3**) and 1,2,4,6-tetra-

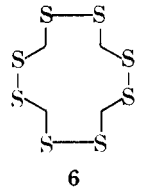


thiepane (4), obtained from the mushroom *Lentinus edodes*.[4,5] We wish to describe the isolation and structural elucidation of seven sulfur-containing heterocycles, including the antibiotics 3 and 4, from the red alga *Chondria californica*.

Fresh *Chondria californica*, collected at Isla San Jose, Mexico, in April 1975, possessed a strong "sulfur" odor. Crude extracts of the alga exhibited antimicrobial activity against *Vibrio anguillarium*. Chromatography of combined extracts of *C. californica* on Florisil afforded column fractions containing three distinct bands of antimicrobial activity, designated A, B, and C in order of increasing eluent polarity.

Careful chromatography of the combined fractions of band A on silica gel plates, using hexane as eluent, afforded two antibacterial components. The minor compound (0.06% of extractable oil) could be sublimed or recrystallized to obtain long needles of 1,2,4,6-tetrathiepane (4), mp 78–79 °C, identical in all respects with a synthetic sample prepared by the method of Morita and Kobayashi.[5] The major component (0.9%), obtained as white crystals, mp 56–57 °C, from 10% dichloromethane in ether, was shown to have identical spectral data with that published for lenthionine (3) (lit. mp 60–61 °C).[4] Vapor phase chromatography showed that the material contained approximately 95% lenthionine (3) contaminated with 1,2,4-trithiolane (5) and traces of two unidentified isomers of tetrathiane ($C_2H_4S_4$). The identities of lenthionine (3) and 1,2,4-trithiolane (5) were confirmed by coinjection of authentic samples.[5]

When the combined fractions of band A were allowed to stand prior to chromatography, a white powder was precipitated. The white powder was recrystallized from 30% chloroform in carbon disulfide to obtain white needles (0.02%), mp 177–178 °C, having the molecular formula $C_4H_8S_8$. The NMR spectrum of the octasulfide consisted of a single signal at δ 4.33 ppm, indicating the presence of four symmetrically arranged methylene groups, each flanked by two sulfur atoms. There are only two structures, 6 and 7, which satisfy these require-



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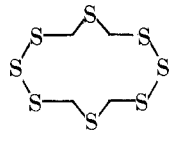

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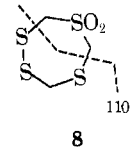
ments. We favor structure 6, but only on the basis of negative evidence. Structure 7 might be expected to give an ion at *m/e* 96, due to the S_3^+ fragment, which has been observed in the low-resolution mass spectrum of lenthionine (3).[4] The major peaks in the low-resolution mass spectrum could be assigned to fragments derived from either structure 6 or structure 7, but the absence of a peak at *m/e* 96 sways the balance in favor of structure 6.

The combined fractions of antibacterial band B were triturated under ether to obtain a solid (17.5%) which crystallized from chloroform as colorless prisms, mp 154–155 °C, having the molecular formula $C_3H_6O_2S_4$. The infrared spectrum contained signals at 1330, 1125, and 1120 cm^{-1} which could be assigned to either sulfone or thiolsulfonate groups.[6] The NMR spectrum consisted of three two-proton singlets at δ 4.18, 4.43, and 4.56 ppm which were assigned to three methylene groups, each flanked by heteroatoms. The data are consistent with two structures, a sulfone 8 and a thiolsulfonate 9. High-resolution mass measurement of the peak at *m/e* 110



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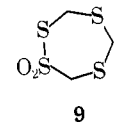

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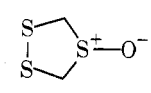
showed that the signal was due to a $CH_2S_3^+$ fragment, which can result from simple cleavage of the sulfone 8 as shown. Thiolsulfonates are reported to react rapidly with mercaptans to obtain a disulfide and a sulfinic acid.[7] The unknown molecule was recovered unchanged after treatment for >12 h with either propyl mercaptan in chloroform or cysteine in aqueous acetone, indicating that it was 4-dioxo-1,2,4,6-tetrathiepane (8).

Careful chromatography of the combined fractions of antibacterial band C allowed the separation of two isomeric compounds 10 and 11, both having the molecular formula



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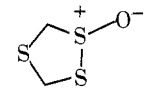

11

$C_2H_4OS_3$. The NMR spectrum of the more polar compound 10 (1%), obtained as white needles, mp 76–77 °C, consisted of an AB quartet at δ 3.97 and 4.25 ppm (J = 12 Hz) which was assigned to two identical methylene groups in which the geminal protons are nonequivalent, owing to the asymmetry of the sulfoxide group (ir 1105, 1043 cm^{-1}). The NMR spectrum of the less polar compound 11 (0.6%), isolated as an oil, contained two AB quartets at δ 3.99 and 4.64 (J = 12 Hz) and 4.40 and 4.73 ppm (J = 10 Hz), which were assigned to two different methylene groups in which the geminal protons were again nonequivalent. The infrared spectrum of 11 contained signals at 1120, 1087, and 1065 cm^{-1} which are appropriate for a thiolsulfinate.[8] Reduction of 1-oxo-1,2,4-trithiolane (11) with triphenylphosphine[9] in chloroform at room temperature gave a quantitative yield of 1,2,4-trithiolane (5) identical in all respects with an authentic sample.[5] Under identical conditions, 4-oxo-1,2,4-trithiolane (10) gave less than 10% reduction to 1,2,4-trithiolane (5), a result which is consistent with published data.[10] We were able to synthesize a mixture of the 4-oxo-1,2,4-trithiolane (10) and 1-oxo-1,2,4-trithiolane (11) by oxidation of 1,2,4-trithiolane (5) with sodium periodate in aqueous acetone.[11] The natural and synthetic materials were identical in all respects except for the optical activity.

Although 4-oxo-1,2,4-trithiolane (10) possesses a plane of symmetry, 1-oxo-1,2,4-trithiolane (11) is capable of exhibiting optical activity. We could not detect an optical rotation at 589 nm. However, the circular dichroism spectrum in the range of 200–400 nm exhibited two negative ($[\theta]_{258}$ −100, $[\theta]_{341}$ −130) and one broad positive ($[\theta]_{300}$ +20) Cotton effects having very small molecular ellipticity maxima. We cannot assign an absolute configuration from this data.

By screening the pure compounds, we have shown that the cyclic polysulfides, particularly 4-dioxo-1,2,4,6-tetrathiepane (8), are responsible for the antibiotic activity of *Chondria californica*. Analysis of *C. californica* specimens from La Jolla, Calif., indicated the presence of the same metabolites, suggesting that they occur throughout the range of the alga. We have examined samples of *C. nidifica* and *C. coerulescens* but were unable to detect either antibacterial activity or cyclic polysulfides. A search for terpenoids in *C. californica* yielded only steroids and *trans*-phytol (1%).

Experimental Section

^1H NMR spectra were recorded on a Varian HR-220 spectrometer, ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer, and infrared spectra were recorded on a Perkin-Elmer Model 700 spectrophotometer. Low-resolution mass spectra were recorded at 70 eV on a Hewlett-Packard 5930A mass spectrometer; high-resolution mass measurements were supplied by the Chemistry Department, UCLA. The circular dichroism spectrum was recorded on a Cary 61 spectrophotometer. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Vapor phase chromatographic (VPC) analyses were performed on a Hewlett-

Packard 402 chromatograph, using a 6 ft × 2 mm column packed with 3% SP2250 on Supelcoport.

Collection and Extraction of *Chondria californica*. *Chondria californica* was collected at Isla San Jose (−2 m) in the Gulf of California (24°53'N, 110°35'W) in April 1975. The alga was drained of excess water and frozen immediately. After approximately 1 month, the alga was thawed and homogenized under ethyl acetate (1 l.) in a Waring blender. The solids (500 g) were removed by filtration and extracted with chloroform (2 × 2 l.) in a Soxhlet apparatus. The ethyl acetate filtrate was separated from the aqueous phase and dried over sodium sulfate. All organic extracts were combined and the solvents removed to obtain a viscous green oil (8.1 g, 1.6% of dry weight).

Chromatographic Separations. The combined extracts (8.1 g) were applied to a column of 100–200 mesh Florisil (Floridin) (318 g) and eluted with solvents of increasing polarity from hexane to methanol. Each fraction was screened against *Vibrio anguillarium* to reveal three bands of antibiotic activity. Fractions 3–9 were combined as band A (110 mg), fractions 21–24 were combined as band B (2.511 g), and fractions 27 and 28 were combined as band C (320 mg).

1,2,4,6-Tetrathiepane (4) and 1,2,3,5,6-Pentathiepane (3). The semisolid material of band A was rechromatographed on preparative silica gel GF plates (20 cm × 20 cm × 1.5 mm) using hexane as eluent to obtain two bands at R_f 0.4 (minor) and 0.3 (major). The minor component was extracted and crystallized from *p*-dioxane to obtain colorless needles of 1,2,4,6-tetrathiepane, mp 78–79 °C, identical in all respects with authentic material prepared by the method of Morita and Kobayashi. Yield 5 mg (0.06% of extractable oil); NMR ($CDCl_3$) δ 4.22 (s, 2 H) and 4.26 ppm (s, 4 H). The major component was extracted and crystallized from 10% dichloromethane in diethyl ether to obtain white crystals of 1,2,3,5,6-pentathiepane (**3**), mp 56–57 °C (lit. mp 60–61 °C). Yield 75 mg (0.9% of extractable oil); NMR ($CDCl_3$) δ 4.33 ppm (s, 4 H). Analysis of the sample by GC and combined GC–mass spectrometry showed that the melting point depression was caused by small quantities (<5% total) of two isomers of tetrathiane and 1,2,4-trithiolane (**5**), identified by coinjection of an authentic sample.[5]

Octasulfide 6 or 7. The combined fractions of band A were allowed to stand as a concentrated oil prior to rechromatography. A white solid which precipitated was collected and recrystallized from 30% chloroform in carbon disulfide to obtain white needles of the octasulfide, mp 177–178 °C. Yield 2 mg (0.025% of extractable oil); NMR ($CDCl_3$) δ 4.33 ppm (s); mass spectrum *m/e* (rel intensity) 312 (3), 188 (3), 156 (7), 142 (16), 124 (40), 110 (31), 78 (45), 64 (13), 46 (65), 45 (100) with appropriate ^{34}S peaks; high-resolution mass measurement, observed 311.8392, $C_4H_8S_8$ requires 311.8392.

4-Dioxo-1,2,4,6-tetrathiepane (8). The combined fractions of band B (2.511 g) were triturated under diethyl ether (3 × 50 ml) to obtain a white powder (1.70 g) which was crystallized from chloroform to obtain 4-dioxo-1,2,4,6-tetrathiepane (**8**) as prisms, mp 154–155 °C. Yield 1.42 g (17.5% of extractable oil); ir ($CHCl_3$) 1330, 1125, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.18 (s, 2 H), 4.43 (s, 2 H), 4.56 (s, 2 H); ^{13}C NMR (Me_2SO-d_6) 43.8, 54.1, 63.3 ppm; mass spectrum *m/e* (rel intensity) 202 (33), 138 (16), 124 (8), 110 (9), 92 (20), 64 (30), 46 (97), 45 (100) with appropriate ^{34}S peaks; high-resolution mass measurement, observed 201.9257, $C_3H_6O_2S_4$ requires 201.9251, observed 109.9319, $CH_2S_3^+$ requires 109.9319.

4-Oxo-1,2,4-trithiolane (10) and 1-Oxo-1,2,4-trithiolane (11). The combined fractions of band C were rechromatographed on preparative silica gel plates using diethyl ether as eluent to obtain two bands, visualized with iodine, at R_f 0.40 and 0.25. The band at R_f 0.25 was extracted to obtain a solid which crystallized from 10% chloroform in hexane to obtain white needles of 4-oxo-1,2,4-trithiolane (**10**), mp 76–77 °C. Yield 83 mg (1.0% of extractable oil); ir ($CDCl_3$) 1105, 1043 cm^{-1}; NMR ($CDCl_3$) δ 3.97 (d, 2 H, J = 12 Hz), 4.25 ppm (d, 2 H, J = 12 Hz); mass spectrum *m/e* (rel intensity) 140 (60), 124 (5), 110 (42), 78 (66), 64 (12), 62 (50), 46 (96), 45 (100) with appropriate ^{34}S peaks; high-resolution mass measurement, observed 139.9422, $C_2H_4OS_3$ requires 139.9424.

The band at R_f 0.4 was extracted to obtain 1-oxo-1,2,4-trithiolane (**11**) as an oil. Yield 50 mg (0.6% of extractable oil); ir ($CHCl_3$) 1120, 1087, 1065 cm^{-1}; uv λ_{max} (ϵ) 335 (70), 210 (2700); CD (MeOH) $[\theta]_{258}$ −100, $[\theta]_{300}$ +20, $[\theta]_{341}$ −130; NMR ($CDCl_3$) δ 3.99 (d, 1 H, J = 12 Hz), 4.40 (d, 1 H, J = 10 Hz), 4.64 (d, 1 H, J = 12 Hz), 4.73 ppm (d, 1 H, J = 10 Hz); mass spectrum *m/e* (rel intensity) 140 (44), 124 (10), 110 (22), 94 (26), 78 (20), 60 (36), 46 (77), 45 (100) with appropriate ^{34}S peaks; high-resolution mass measurement, observed 139.9424, $C_2H_4OS_3$ requires 139.9424.

Synthesis of 4-Oxo-1,2,4-trithiolane (10) and 1-Oxo-1,2,4-trithiolane (11). A solution of sodium periodate (306 mg, 1.33 mmol) in distilled water (2 ml) was added dropwise over 5 min to a cooled (0 °C), stirred solution of 1,2,4-trithiolane (165 mg, 1.33 mmol) in acetone (10 ml). The solution was stirred at 0–5 °C for 3 h and at room temperature for 21 h. The resulting solution was extracted with chloroform (2 × 25 ml), the extracts were dried over magnesium sulfate, and the solvent was evaporated to yield a yellow oil. Chromatography of the oil on preparative silica gel plates gave 4-oxo-1,2,4-trithiolane (**10**), mp 75–75 °C (50 mg, 27% theoretical), and 1-oxo-1,2,4-trithiolane (**11**) (49 mg, 26% theoretical).

Reduction of 1-Oxo-1,2,4-trithiolane (11). A solution of 1-oxo-1,2,4-trithiolane (14 mg, 0.1 mmol) and triphenylphosphine (26 mg, 0.1 mmol) in chloroform (1 ml) was stirred under a nitrogen atmosphere at room temperature for 24 h. The solvent was removed and the product mixture examined by NMR and GC. Both analyses indicated a quantitative reduction of 1-oxo-1,2,4-trithiolane to 1,2,4-trithiolane (**5**), which was not isolated from the mixture with triphenylphosphine oxide.

Acknowledgments. We wish to thank Dr. G. Blunden for a gift of *C. coerulescens*. The algae used in this study were identified by Drs. R. Lewin, J. Stewart, and J. Norris. Antibiotic screening was performed by M. S. Wolfe in our laboratory. The circular dichroism spectrum was measured by Dr. W. Radding in the laboratory of Dr. M. Goodman. Collections of *C. californica* were made during a cruise of R/V Dolphin funded by the National Science Foundation (BMS75-07659). This research was supported by an NIH grant (AI-11969). S. J. W. wishes to thank the National Science Foundation for a graduate fellowship.

Registry No.—**3**, 292-46-6; **4**, 292-45-5; **5**, 289-16-7; **6**, 58966-88-4; **8**, 58966-89-5; **10**, 58966-90-8; **11**, 58966-91-9.

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