Elemental analyses were performed in the Elemental Analysis Laboratory of this Department.

**Preparations of 2-Aryl-2-propyl Benzoates 1b-g and *p*-Nitrobenzoate 2f.** The substrates were prepared by using the one-pot procedure[9] from acetone, butyllithium, aryl halides, and benzoyl or *p*-nitrobenzoyl chloride on 30-mmol scale. The crude esters (50–60% yield) were recrystallized from hexanes to give pure compounds, mp: **1b**, oil;[11] **1c**, 80.5–81.5 °C; **1d**, oil; **1e**, 48–48.5 °C; **1f**, oil; **1g**, 67–67.5 °C; **2f**, 126–127 °C. Correct C and H analyses (<0.3%) were observed for all new compounds. Infrared and proton magnetic resonance spectra were in agreement with the assigned structures.

**Kinetic Measurements.** (a) Titrimetric method: A 0.005–0.01 M solution of the substrate in 80% acetone or in 70% acetone was prepared at about 25 °C, and aliquots of 2 mL were sealed under nitrogen. The ampules were removed from the thermostat at suitable time intervals and were titrated as described before.[15] All reactions were followed to about 2 half-lives with excellent first-order behavior (9–11 points, $r > 0.995$). (b) Conductimetric method: The sample was dissolved to make 10 mL of a $10^{-4}$ M solution, which was placed in a conductivity cell with platinum electrodes. The rates of solvolysis were monitored at 1-s intervals with an on-line conductivity amplifier[16] to 2 or more half-lives. Excellent linear correlation for a first-order plot was observed.

The rate constants and the calculated activation parameters are shown in Table I.

**Acknowledgment.** We are indebted to the National Science Council for financial support of this work.

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(16) The details about this instrument will be reported elsewhere.

**Table I. Competition Oxidation Rates of Bivalent Sulfides[a,b]**

| sulfides | competition oxidation rate | relative hydrolysis rate[c] |
|---|---|---|
| $(ClCH_2CH_2)_2S$ (**1**) | 1.0 | 1.0[d] |
| $C_2H_5SCH_2CH_2Cl$ (**1a**) | 4.8 | 5.9 |
| $(C_2H_5)_2S$ (**1b**) | 23 | |
| $(n\text{-}C_4H_9)_2S$ (**1c**) | 9.6 | |
| $(C_6H_5)_2S$ (**1d**) | 0.96 | |
| $C_6H_5SCH_2CH_2Cl$ (**1e**) | 0.92 | 0.095 |
| $C_6H_5SCH_2CH_2Br$ (**1f**) | 1.8 | 0.76 |
| $C_6H_5SCH_2CH_2OH$ (**1g**) | 4.0 | |
| $CH_3SCH_2CH_2Cl$ (**1h**) | 4.2 | 4.8 |
| $CH_3SCH_2CH_2OH$ (**1i**) | 10 | |
| $i\text{-}C_3H_7SCH_2CH_2Cl$ (**1j**) | 5.0 | 7.6 |
| $i\text{-}C_4H_9SCH_2CH_2Cl$ (**1k**) | 5.0 | *e* |
| $n\text{-}C_4H_9SCH_2CH_2Cl$ (**1l**) | 5.0 | 9.0 |
| $i\text{-}C_5H_{11}SCH_2CH_2Cl$ (**1m**) | 5.4 | *e* |

[a] The competition oxidation rate is the ratio of the sulfoxide products from the oxidation of two sulfides present in equal moles by a minimum amount of **2** in the reaction mixture. The accuracy of the reported competition oxidation rate is 5–10%. [b] The observed first-order rate of **1e** at 0.01 M excess **2** at 18 °C was measured to be 0.11 ± 0.01 $min^{-1}$. [c] Calculated from published first-order hydrolysis rate constants at 25 °C in the presence of 5–10 vol% ethanol, acetone, or acetonitrile (ref 7 and 8). [d] Based on the rate of displacement of the first chlorine in mustard, see ref 8. [e] The rate at 25 °C was too fast to be measured accurately.

## A Comparison of the Oxidative Reactivities of Mustard (2,2′-Dichlorodiethyl Sulfide) and Bivalent Sulfides

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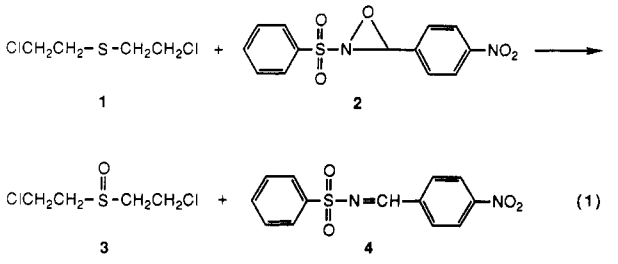
Mustard (**1**, 2,2′-dichlorodiethyl sulfide), a liquid vesicant, can be detoxified to the crystalline sulfoxide and sulfone by oxidation, although the sulfone has been reported to still exhibit some vesicant toxicity.[1,2] The sulfur in mustard is believed to be oxidatively less reactive than that in alkyl sulfides because of the presence of two large electron-withdrawing chlorine atoms. However, alkyl sulfides have often been used to simulate the oxidation of mustard.[3] Recently, *N*-sulfonyloxaziridine derivatives such as **2** were presented as a new class of neutral organic oxidants that selectively oxidize bivalent sulfides to sulfoxides in organic solvents.[4,5] In fact, the reaction rate was so fast that no rate coefficient could be measured at room temperature. In this study, the oxidation of mustard and a series of bivalent sulfides by **2** was examined, and the reaction rates were determined using NMR. Our purpose was to determine if mustard could be quickly detoxified by **2** via the same $S_N2$ mechanism previously reported for most sulfides (eq 1),[4,5] and to compare the oxidative reactivity of mustard with its monofunctional derivatives (i.e. simulants) as well as the alkyl and aryl sulfides (see list of compounds in Table I).




(1)

To a solution of 0.053 M mustard in $CDCl_3$ at 20 °C was added 0.1 M of **2**. In less than 2 min, $^{13}C$ NMR showed that all of the mustard (**1**) was converted to one product, mustard sulfoxide (**3**, $OSCH_2$, 55.1 ppm and $CH_2Cl$, 36.7 ppm), with half of the initial oxidant left unreacted. A second sample containing approximately 0.2 M **1** and 0.1 M **2** was examined. Immediate $^{13}C$ NMR analysis showed that 45% of **1** had reacted to produce **3**, and all of the initial **2** was reduced to **4**. Therefore, mustard was effectively detoxified by **2** in chloroform, and the stoichiometry shown in eq 1 was confirmed. The presence of chlorines did not provide any additional oxidation sites for reacting with **2**.

Subsequently, the oxidation of a series of bivalent sulfides by **2** was examined using $^{13}C$ or $^1H$ NMR in $CDCl_3$ at 0.05 to 0.1 M sulfide concentrations. All of the compounds reacted with the identical stoichiometry as that of mustard in less than 2 min. Thus, competition oxidation

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(4) Davis. F. A.; Jenkins, R. H., Jr.; Yocklovich, S. G. *Tetrahedron Lett.* **1978**, 5171–5174.
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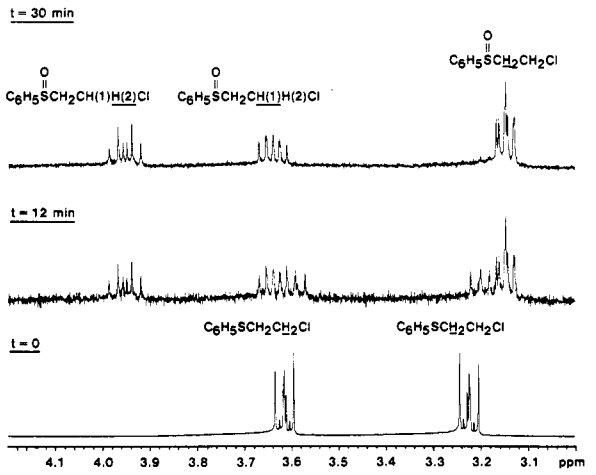


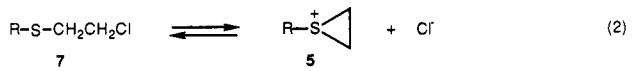

**Figure 1.** $^1H$ NMR spectra profile of the oxidation of **1e** by **2** in $CDCl_3$ at 18 °C.

rates for each of the sulfides with respect to mustard can be measured as follows: To a $CDCl_3$ solution containing equal moles of the sulfide and mustard was added a minimum amount of **2** to produce enough sulfoxide products for $^{13}C$ and/or $^1H$ NMR measurement (see Experimental Section). The final ratio of the two sulfoxide products was calculated as the competition rate of the sulfide to mustard. The NMR quantitation of the sulfoxides was more accurate than that based on the isolation of the sulfoxide products from the reaction mixtures in previous studies.[4,5] These rates are reported in Table I.

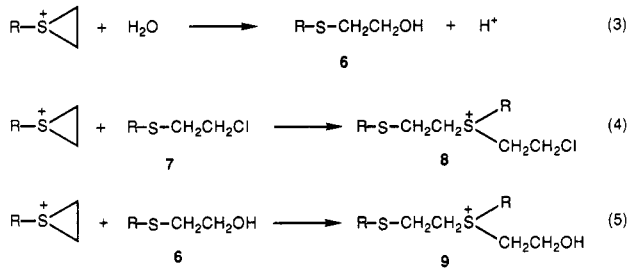
In addition to the competition rate, the first-order rate constant for **1e** in the presence of excess **2** was measured since **1e** was the least reactive sulfide (see Table I). The concentrations of both **1e** and **2** were kept to a minimum so that the rate of oxidation was sufficiently slow and could be followed accurately. $^1H$ NMR was used to monitor the disappearance of 0.0005 M **1e** in the presence of 0.01 M **2** in $CDCl_3$ (see Experimental Section and Figure 1 for the reaction profile). The observed first-order rate constant was determined to be 0.11 ± 0.01 $min^{-1}$ at 18 °C with a half-life of 6.5 ± 0.6 min. This is the first time an absolute first-order rate constant has been reported for the oxidation of any bivalent sulfide by **2** or its derivatives. On the basis of the competition rate of **1e** in Table I, mustard also reacts with the same rate constant. Thus, the first-order rate constants for all of the sulfides listed in Table I can be calculated from the competition rate data. The rate constants for most of the sulfides are indeed too fast to be determined at room temperature unless fast kinetic techniques are employed.

Since the reaction mechanism was an $S_N2$ nucleophilic attack by the sulfur on the oxygen of **2**,[5] the rate of oxidation should be dependent on the nucleophilicity of the sulfur. Both the electronic and steric effects of the substituent groups adjacent to the sulfur are important variables in determining the oxidative reactivity of the sulfide. When the first three compounds (**1**, **1a**, and **1b**) in Table I are compared, each electron-withdrawing chloroethyl group seems to reduce the oxidation rate of the sulfide by about 5-fold. Further, the alkyl sulfides (e.g. **1c**) oxidized faster than the aryl sulfides (**1e** and **1d**). The identical oxidation rate of **1**, **1d**, and **1e** seems also to indicate that both the phenyl ring and the 2-chloroethyl group have the same effect on the nucleophilicity of the adjacent sulfur. However, the steric effect of the large butyl groups in **1c** appears to have offset their electron-donating power, giving a lower competition rate than that of ethyl sulfide, **1b**. This phenomenon was further evidenced in the competition rates for a series of 2-chloroethyl sulfides: The oxidation reactivity was almost the same even though the alkyl group increased from C1 to C5 (**1h**, **1a**, and from **1j** to **1m**). It appears that the increase in electron-donating power from an additional $CH_2$ group in the above sulfide series was offset by the same degree of increase in steric hindrance. However, as the $\beta$ substituents changed from Cl to Br to OH, the electron-withdrawing power was significantly reduced. Consequently, the nucleophilicity (i.e. the oxidation reactivity) of the sulfide increased (e.g. **1e** vs **1f** and **1g**; or **1h** vs **1i**).

The hydrolysis of mustard and its derivatives has been extensively studied.[6] The first-order hydrolysis rate coefficients, as reported previously,[7,8] are controlled by the rate of the neighboring sulfur-assisted formation of the cyclic ethylenesulfonium ion intermediate **5** shown in eq 2. These rates, then, should also vary with the nucleophilicity of the sulfur and consequently should follow the same trend as the competition oxidation rates. This is demonstrated in Table I, as well. The same trend was observed, but the differences in the hydrolysis rates were greater. Perhaps the effect from an intramolecular nucleophile (e.g. sulfur) on the rate of an $S_N1$ hydrolysis is greater than that from an external nucleophile on the rate of an $S_N2$ oxidation. Furthermore, the steric effect discussed above does not affect the $S_N1$ hydrolysis rates of compounds **1h**, **1a**, **1j**, and **1l**. In this series, the hydrolysis rate increased with the size of the alkyl chain. Oxidation of bivalent sulfides, as shown in eq 1, follows a bimolecular mechanism. Unlike hydrolysis, it is believed that no ethylenesulfonium ion was ever present in the oxidation of the 2-chloroethyl sulfides because the reaction was too fast for any sulfonium ions to form in the $CDCl_3$ solvent.[9]




The data in Table I allow us to predict the formation of the dimeric sulfonium chlorides (**8** and **9** in eqs 4 and 5) resulting from reactions of **5** with the 2-hydroxyethyl and 2-chloroethyl sulfides (**6** and **7**). **9** predominates because, as shown in Table I, the sulfur in **6** (e.g. **1g** or **1i**) is a stronger nucleophile than that in **7** (e.g. **1e** or **1h**). As observed in our laboratory, more than 80% **9** was found in the final hydrolysis solution of 0.2 M **1h** in pure water, but no dimer was ever produced from **1e** under the same conditions. The lower nucleophilicity of the sulfur in **1** also suggests that it is more likely for mustard to react with

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(7) Yang, Y.-C.; Ward, J. R.; Luteran, T. *J. Org. Chem.* **1986**, *51*, 2756–2759.
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(9) In organic solvents in the presence of trace amounts of water, the production of sulfonium chloride **9** was indicative of the initial formation of the unstable intermediate **5**. However, **9** forms very slowly in solvents of low polarity. In a 0.2 M solution of **1h** in pure acetone, **9** (R = $CH_3$) was detected after 2 months; and in neat **1h**, **9** was detected after 1 year.

a competitive external nucleophile by an $S_N2$ mechanism in an aprotic solvent[10] than both **1a** and **1h**, which have been used as mustard simulants for substitution reactions.

## Experimental Section

The synthesis of mustard has been described previously;[1] it was prepared inhouse by the U.S. Army. *Caution*: The compound is a toxic vesicant and should only be used by trained professionals in properly equipped facilities. The rest of the sulfide substrates were obtained commercially either from Fairfield Chemical Company or from Aldrich. The oxaziridine compound was prepared at Drexel University.[4] All of the compounds used in this study were greater than 95% pure by $^1H$ and/or $^{13}C$ NMR and were used as received.

The competition rates were typically measured by $^1H$ NMR on a Varian XL200 FTNMR. The spectra of the reaction mixtures were obtained by using 1 pulse and a 90° flip angle. The concentrations of the two competing sulfides were equal at 0.1 M while the concentration of the *N*-sulfonyloxaziridine varied from 0.002 to 0.1 M and was typically 0.1 M. The competition rate was independent of the oxidant concentration within experimental error. However, the measured rates were more reproducible when the reactivity of the two sulfides was similar. For cases in which the sulfoxide yields were very small because the oxidant concentation was small, $^{13}C$ NMR was used since the $^1H$ NMR signals of the reaction mixture were too overlapped for accurate determinations of the sulfoxide peak areas.

The observed first-order rate was determined for **1e** in the presence of excess **2** by using $^1H$ NMR. The spectrum was recorded at 18 °C on a Varian VXR-400S FTNMR. The sweep width was narrowed to 1.6 ppm to observe only the methylene groups in **1e** (see Figure 1). Sixty-four transients were accumulated for each spectrum using a 90° pulse width and a repetition rate of 3.74 s. The progress of the reaction was monitored by measuring the simultaneous disappearance of the $CH_2$ resonances of the reactant and the appearance of the $CH_2$ rsonances of the sulfoxide product with time. The resonances were expanded and digitally integrated to obtain the peak areas.

**Registry No.** 1, 505-60-2; **1a**, 693-07-2; **1b**, 352-93-2; **1c**, 544-40-1; **1d**, 139-66-2; **1e**, 5535-49-9; **1f**, 4837-01-8; **1g**, 699-12-7; **1h**, 542-81-4; **1i**, 5271-38-5; **1j**, 4303-41-7; **1k**, 116037-20-8; **1l**, 4303-40-6; **1m**, 126823-30-1; **2**, 86428-23-1; **3**, 5819-08-9; **4**, 36176-89-3.

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## Eudistomidins B, C, and D: Novel Antileukemic Alkaloids from the Okinawan Marine Tunicate *Eudistoma glaucus*†

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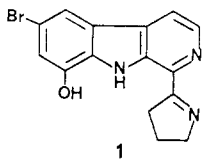
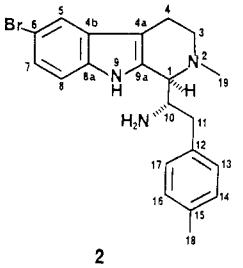
*Received January 10, 1990*

Marine tunicates have proven to be a rich source of intriguing structures and interesting biological activities.[2] In our continuing survey of bioactive compounds from Okinawan marine organisms,[3] we have reported a novel β-carboline, named eudistomidin A (**1**), with powerful calmodulin antagonistic activity from the Okinawan tunicate *Eudistoma glaucus*.[4] This paper describes the isolation and structure elucidation of eudistomidins B (**2**), C (**3**), and D (**4**), three new pharmacologically active components from this tunicate. The configuration at C-10 of eudistomidin C (**3**) was established by synthesis of 10-(*R*)-*O*-methyleudistomidin C. This tunicate also contained four known compounds, eudistomins D (**5**), E (**6**), H (**7**), and I (**8**), previously isolated from the Caribbean tunicate *Eudistoma olivaceum*.[5]



**1**



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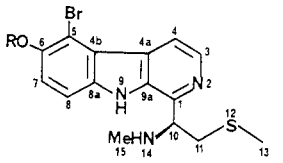
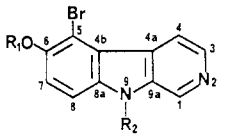
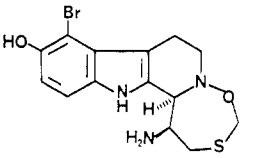


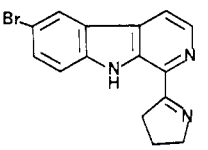
**3** R = H
**15** R = Me



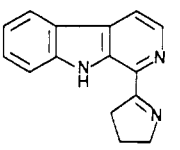
**4** $R_1$ = H $R_2$ = Me
**16** $R_1$ = $R_2$ = Me
**5** $R_1$ = $R_2$ = H



**6**



**7**



**8**

† This paper is dedicated to Professor Kenneth L. Rinehart, Jr., in honor of his 60th birthday.

(1) (a) Mitsubishi Kasei Institute of Life Sciences. (b) Tohoku University. (c) Kanazawa University. (d) Present address: Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan. (e) Present address: Faculty of Science and Technology, Keio University, Yokohama 223, Japan.

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