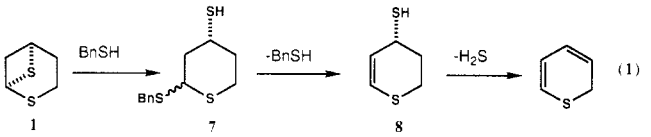
1). The ease by which this type of trans-sulfurization occurs may be an important contributing factor to the



(1)

antimicrobial activity that we have observed with certain strained disulfides.[9a] Even though **1** is not an S–S bonded disulfide, the strained dithiaketal functionality, nonetheless, permits trans-sulfurization to occur. Unfortunately, no antimicrobial activity against several of the common bacterial or viral strains could be noted.[9b] Further, the compound is also void of any platelet aggregating properties as well as lipoxygenase inhibition.[9b] Since the fully elaborated congener[4a] is active, it suggests that the side chains of TXA_2 are also important for biochemical activity.

Experimental Section[8b]

2-[[2-[(Menthyloxy)carbonyl]ethyl]thio]thiacyclohexan-4-one [(−)-5a]. To a solution of dihydrothiin-4-one (0.627 g, 5.5 mmol) and *l*-3-menthyl mercaptopropionate (4.026 g, 16.5 mmol) in dry DMF (18 mL) was added 0.19 mL (1.1 equiv) of *i*-$PrNEt_2$ under an atmosphere of argon. After stirring for 15 h, the solvent was removed under reduced pressure, and the residue was chromatographed on silica (1:5 EtOAc/hexanes) to give 1.8 g of a colorless oil. The oil was dissolved in hexanes and placed in the freezer (−20 °C). After 2 days, the crystals formed were collected and recrystallized to give 0.23 g (25% yield) of (−)-**5a**: R_f (13% EtOAc/hexanes) 0.18; mp 49–50 °C; $[\alpha]^{23}_D$ −225.16° (*c* = 0.89, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.7–0.9 (18 H, m), 2.1–3.0 (10 H, m), 4.4 (1 H, dd, *J* = 5.0 Hz), 4.7 (1 H, dt, J_1 = 10.56 and J_2 = 4.4 Hz); ^{13}C NMR ($CDCl_3$) δ 204.9, 170.7, 74.3, 49.1, 48.0, 46.6, 42.8, 40.6, 34.5, 33.9, 31.0, 27.0, 26.0, 25.8, 23.2, 21.7, 20.4, 16.1. Enantiomer (+)-**5a** was similarly obtained from *d*-menthol: mp 50–51 °C; $[\alpha]^{23}_D$ +223.58° (*c* = 1.0, EtOH).

2-[[2-[(Menthyloxy)carbonyl]ethyl]thio]thiacyclohexan-4-ol [(−)-6a]. To a solution of (−)-**5a** (0.25 g, 0.7 mmol) in dry THF (20 mL) kept at −78 °C under an atmosphere of argon was added dropwise 1.3 equiv of a 1 M THF solution of LS-Selectride. The mixture was stirred at −78 °C for 2 h and then quenched with 10 mL of a saturated aqueous solution of NH_4Cl. Ethyl acetate (30 mL) was added at ambient temperature, and the mixture was transferred to a separatory funnel. The organic phase was separated, washed with 2 × 20 mL of brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica (1:6 EtOAc/toluene) to give an 80% overall yield of the two isomeric alcohols, (−)-**6a** and (−)-**6b**. (−)-**6a**: R_f (1:7 EtOAc/benzene) 0.18; mp 66–67 °C; $[\alpha]^{23}_D$ −213.56° (*c* = 0.5, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.7–2.20 (23 H, m), 2.63–3.08 (6 H, m), 4.0–4.15 (1 H, m), 4.18–4.30 (1 H, dd, *J* = 4.84 Hz), 4.50–4.80 (1 H, dt, J_1 = 10.56 and J_2 = 4.4 Hz). (−)-**6b**: R_f (1:7 EtOAc/benzene) 0.11; mp 81–82 °C; $[\alpha]^{23}_D$ −95.4° (*c* = 0.50, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.72–2.20 (23 H, m), 2.63–2.99 (6 H, m), 3.6–3.79 (1 H, m), 3.83–3.98 (1 H, dd, *J* = 10.27 Hz), 4.68–4.83 (1 H, dt, J_1 = 10.56 and J_2 = 4.4 Hz). Similarly, using the *d*-menthol mercapto ester ((+)-4),[8b] (+)-**6a** [mp 66–67 °C; $[\alpha]^{23}_D$ −211.40° (*c* = 0.50, EtOH)] and (+)-**6b** [mp 79–80 °C; $[\alpha]^{23}_D$ +92.74° (*c* = 0.5, EtOH)] were obtained.

2-[[2-[(Menthyloxy)carbonyl]ethyl]thio]-4-thiacyclohexane Mesylate. A mixture of 1.0 g (2.77 mmol) of (−)-**6a**, 1.2 mL (3 equiv) of Et_3N, and freshly distilled mesyl chloride (0.45 mL, 2 equiv) was stirred in 25 mL of dry CH_2Cl_2 under an atmosphere of argon at 0 °C. After 1 h, the mixture was transferred to a separatory funnel and washed with brine. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. The resulting residue was chromatographed on silica (1:6 EtOAc/toluene) to give the mesylate (95% yield) as a colorless oil: R_f (1:6 EtOAc/toluene) 0.43; $[\alpha]^{23}_D$ −95.40° (*c* = 0.50, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.72–2.17 (18 H, m), 2.63–2.99 (10 H, m), 3.03 (3 H, s), 4.21–4.32 (1 H, q), and 4.95–5.08 (1 H, m). From *d*-menthol, the corresponding (+) enantiomer was similarly obtained.

2,6-Dithiabicyclo[3.1.1]heptane [(+)-1].[4a] To a solution of the above mesylate (0.6 g, 1.8 mmol) in dry THF (20 mL) kept under an atmosphere of argon and at 60 °C was added dropwise 3.75 mL (3.75 mmol) of a 1 M THF solution of lithium hexamethyldisilazane. The reaction mixture was then refluxed for 2 h and allowed to reach ambient temperature, and the solvent was removed by rotary evaporation. The resulting residue was chromatographed on silica (1:9 ether/pentane) to give 0.09 g (37% yield) of a white solid, which was further purified by sublimation on to a cold finger (40 °C, 24 mmHg): R_f (10% ether/pentane) 0.42; mp 44–45 °C; $[\alpha]^{23}_D$ +84.8° (*c* = 0.24, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.24 (1 H, dd, *J* = 5.9 Hz), 4.03 (1 H, m), 3.84 (1 H, dt, J_1 = 9.6 and J_2 = 6.6 Hz), 3.45 (1 H, m), 2.93 (1 H, dd, *J* = 12.6 Hz), 2.52 (1 H, m), 2.3–2.4 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 23.06, 30.92, 44.65, 49.75, 50.56. The corresponding enantiomer was similarly obtained from *d*-menthol: mp 42–43 °C; $[\alpha]^{23}_D$ −101.5° (*c* = 2.64, $CHCl_3$).

Acknowledgment. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Natural Sciences and Engineering Research Council of Canada for support of this work.

(9) (a) Stinson, S. *Chem. Eng. News* **1987**, February 9th, 23. (b) Racemic material was used. We would like to thank Drs. David Thomson and Geoffrey K. Richards of The Montreal General Hospital and Dr. Roy Johnson (Upjohn) for these results.

Renieramycins E and F from the Sponge *Reniera* sp.: Reassignment of the Stereochemistry of the Renieramycins

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A bright blue sponge of the genus *Reniera*, which has been found both at Isla Grande, Mexico, and some 14 200 km distant, in an obscure marine lake in Palau, Western Caroline Islands, was shown to contain a series of alkaloids that included renierone (**1**), mimosamycin (**2**), *N*-formyl-1,2-dihydrorenierone (**3**), the isoindole **4**, and renieramycins A-D (**5–8**).[1] A similar suite of metabolites that include mimosamycin (**2**), mimocin (**9**), and saframycins A (**10**), B (**11**), C (**12**), and S (**13**) were isolated after treatment of the culture medium of a streptothricin-producing strain of *Streptomyces lavendulae* no. 314 with sodium cyanide.[2] Striking similarities between renierone (**1**) and mimocin (**9**) and between the renieramycins **5–8** and saframycins **10–13** were noted. However, the stereochemistry assigned to the renieramycins **5–8**[1b] differed from that determined by X-ray analysis[2c] of saframycin C (**12**) at C-1, the point of attachment of the side chain.[3] In this paper we report

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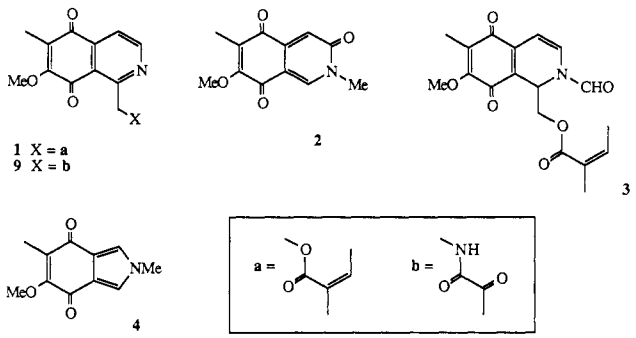
(3) The absolute configuration of the renieramycins is unknown: they have been redrawn with the opposite absolute configuration to that in ref 1b in order to correspond with the saframycins.

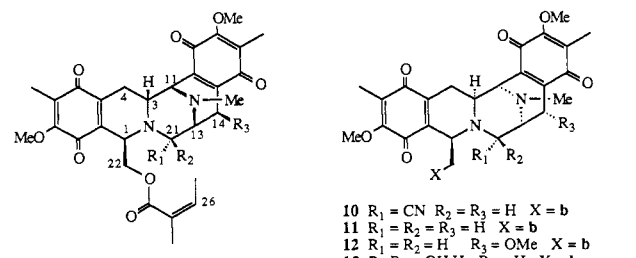
0022-3263/89/1954-5822$01.50/0

Table I. ^{1}H NMR Data (360 MHz, $CDCl_3$) for Renieramycins E (14), F (15), and A (16)[1b] and Saframycin A (10)[2c] [Chemical Shift (Multiplicity, Integral, Coupling Constants, Hz)]

H no.	14	15	16	10
1	4.44 (m, 1 H)	4.43 (m, 1 H)	3.60 (br s, 1 H)	3.98 (m, 1 H, 4, 3, 1.5)
3	3.16 (dt, 1 H, 11.5, 2.5)	3.11 (br d, 1 H, 11)	2.64 (dt, 1 H, 11, 2.5)	3.14 (dt, 1 H, 11, 3)
4α	2.75 (dd, 1 H, 16.9, 2.5)	2.75 (dd, 1 H, 16.8, 2.5)	2.75 (dd, 1 H, 17, 2.5)	2.87 (dd, 1 H, 17, 3)
4β	1.31 (ddd, 1 H, 16.9, 11.5, 2.9)	1.20 (dd, 1 H, 16.8, 11.5, 2.9)	1.26 (dd, 1 H, 17, 11, 3)	1.28 (ddd, 1 H, 17, 11, 3)
11	3.92 (br d, 1 H, 2.5)	4.00 (m, 1 H)	4.04 (br d, 1 H, 2.5)	4.06 (dd, 1 H, 3, 2.5)
13	3.21 (br d, 1 H, 7.6)	3.29 (br d, 1 H, 2.2)	3.18 (br s, 1 H)	3.44 (br d, 1 H, 7.5)
14α	2.66 (dd, 1 H, 20.9, 7.6)			2.83 (dd, 1 H, 20.5, 7.5)
14β	2.21 (d, 1 H, 20.9)	3.76 (s, 1 H)	4.44 (br s, 1 H)	2.30 (d, 1 H, 20.5)
21α			2.71 (dd, 1 H, 11, 3.5)	
21β	4.44 (m, 1 H)	4.57 (br d, 1 H, 10.1)	3.18 (br d, 1 H, 11)	3.99 (d, 1 H, 2.5)
22	4.45 (dd, 1 H, 11.2, 3.2)	4.28 (dd, 1 H, 11.2, 2.5)	4.49 (dd, 1 H, 11.5, 3)	3.84 (ddd, 1 H, 14, 9.5, 1.5)
22	4.15 (dd, 1 H, 11.2, 1.8)	4.20 (dd, 1 H, 11.2, 3)	4.19 (dd, 1 H, 11.5, 2)	3.26 (dt, 1 H, 14, 4)
Me (25)	1.57 (m, 3 H, 1.4)	1.57 (m, 3 H, 1.4)	1.55 (br s, 3 H)	
26	5.92 (qq, 1 H, 7.2, 1.4)	5.94 (qq, 1 H, 7.2, 1.4)	5.92 (br q, 1 H, 7)	
Me (26)	1.79 (dq, 3 H, 7.2, 1.4)	1.80 (dq, 3 H, 7.2, 1.4)	1.78 (br d, 3 H, 7)	
ArMe	1.91 (s, 3 H)	1.90 (s, 3 H)	1.91 (s, 3 H)	1.93 (s, 3 H)
ArMe	1.91 (s, 3 H)	1.94 (s, 3 H)	1.92 (s, 3 H)	1.99 (s, 3 H)
ArOMe	3.98 (s, 3 H)	3.97 (s, 3 H)	4.00 (s, 3 H)	4.02 (s, 3 H)
ArOMe	4.00 (s, 3 H)	4.00 (s, 3 H)	4.01 (s, 3 H)	4.03 (s, 3 H)
OMe		3.53 (s, 3 H)		
NMe	2.25 (s, 3 H)	2.46 (s, 3 H)	2.43 (s, 3 H)	2.32 (s, 3 H)
NH				6.70 (dd, 1 H, 9.5, 4)
OH	D_2O exchanged	D_2O exchanged		

the isolation of two very unstable compounds, renieramycins E (14) and F (15), and propose that the structures of renieramycins A–D (5–8) be reassigned to 16–19, in which the stereochemistry is identical with that of the saframycins.





The sponge *Reniera* sp. was recollected in January 1988 from the same marine lake at Palau at which the previous collection had been obtained. The sponge was immediately frozen, and, unlike previous collections, a small portion of the sponge was examined within a few days of collection. The ^{1}H NMR spectrum of the crude ethyl acetate extract did not contain signals due to renierone (1) or mimosamycin (2), which had dominated the spectra of previous extracts but instead indicated that a dimeric renieramycin was the major constituent of the crude extract. Chromatography of a portion of the ethyl acetate soluble material from a methanol extract of the sponge on silica gel caused a great deal of decomposition and, after reversed-phase HPLC separation, renierone (1), mimosamycin (2), and a small quantity of renieramycin E (14) were obtained. Chromatography of the remaining extract on Sephadex LH-20 resulted in less decomposition, and, after HPLC separation, renieramycin E (14, 0.027% dry wt total), renieramycin F (15, 0.008% dry wt), and renierone (1) were isolated.

Renieramycin E (14) was obtained as an unstable amorphous yellow powder. High-resolution mass measurement of the $(M + H - H_2O)^+$ ion at m/z 549.2247 and observation of the $(M + H)^+$ ion at m/z 567 indicated a molecular formula of $C_{30}H_{34}N_2O_9$, which is identical with that of renieramycin A (16). The IR and UV spectra of renieramycin E (14) were similar but not identical with those of renieramycin A. The ^{1}H NMR spectra of renieramycin E and renieramycin A were clearly different (Table I), although they shared many features such as the number and multiplicity of signals. Each spectrum contained two methoxyl signals, a *N*-methyl signal, two aromatic methyl signals, and the three signals due to the angelate ester. Decoupling studies indicated that the remaining signals in 14 could be divided into three isolated spin systems, two of which (H-1, H-22 and H-4, H-3, H-11) were easily assigned by comparison with the spectrum of 16. The signals at δ 2.21 (d, 1 H, J = 20.9 Hz) and 2.26 (dd, 1 H, J = 20.9, 7.6 Hz), assigned to a methylene group adjacent to a quinone ring, were coupled to a signal at δ 3.21 (br d, 1 H, J = 7.6 Hz) that was in turn coupled to a signal at δ 4.44 (m, 1 H). In acetone solution, this latter signal appeared at δ 4.53 (dd, 1 H, J = 6.5, 1.4 Hz) and was coupled to a D_2O exchangeable signal at δ 4.35 (d, 1 H, J = 6.5 Hz). These data required the presence of a carbinolamine group at C-21. The ^{13}C NMR spectrum of renieramycin E (14) could not be recorded because of the inherent instability of the molecule.

NMR experiments indicated that the stereochemistry of renieramycin E (14) is exactly the same as that of the saframycins. The unusual high-field position of the H-4 signal at δ 1.31, the close correspondence of the coupling constants of renieramycin E and saframycin A (Table I), and the observed nuclear Overhauser enhancements clearly define the stereochemistry. In particular, the observed enhancement of the H-1 signal on irradiation of the H-3 signal indicated that the two hydrogens were on the same side of the ring. The large homoallylic coupling constant

(J = 2.7 Hz) between H-1 and H-4 also requires the geometry at C-1 to be the same as that in the saframycins. Although we were unable to obtain new samples of renieramycins A–D (**16–19**), we are now convinced that the stereochemistry of *all* renieramycins is the same as the stereochemistry of saframycin C, which was determined by X-ray analysis.[2c] There is good reason to believe that during the structural elucidation of renieramycins A–D[1b] the crucial NOEDS experiment, in which irradiation of H-14 resulted in enhancement of H-1, was performed with too high a power level so that both H-14 and H-22 were irradiated.[4] Professor T. Fukuyama has independently reached the same conclusion while studying the synthesis of saframycins[5] and renieramycins.[6]

The structure of renieramycin F (**15**) was deduced by comparison of spectra data with those of renieramycins E (**14**) and B (**17**).[1b] High-resolution mass measurement of the $(M + H - H_2O)^+$ peak at m/z 579.2285 and the presence of the $(M + H)^+$ peak at m/z 597 suggested a molecular formula of $C_{31}H_{36}N_2O_{10}$. The ^1H NMR spectrum contained a methoxyl signal at δ 3.53 (s, 3 H) and a signal at δ 3.76 (s, 1 H) that was assigned to an H-14 proton that is orthogonal to the H-13 proton. These data, together with the almost identical chemical shifts and coupling constants for the remaining signals, allowed the structure of renieramycin F (**15**) to be proposed.

During the entire period that this research was being conducted, renieramycins E (**14**) and F (**15**) were observed to be decomposing. The decomposition was fastest in chloroform solutions exposed to the air and during column chromatography and was significantly slower during HPLC and when the compounds were stored as dry powders under nitrogen. Among the observed degradation products were renierone (**1**) and mimosamycin (**2**), which together suggest that renieramycins E and F undergo an oxidative cleavage reaction. Considering that the ^1H NMR spectrum of the fresh crude extract of *Reniera* sp. appeared to be relatively clean and contained only those peaks later attributed to renieramycins E (**14**) and F (**15**) and contained no signals below δ 6.0, one must entertain the possibility that the "monomeric" products isolated previously are all artifacts of the isolation and chromatographic procedures employed.

Experimental Section

Collection and Isolation Procedures. The blue sponge *Reniera* sp. (59.1 g dry weight) was collected in shallow water (−2 m) at a small marine lake on Urukthapel Island, Palau, Western Caroline Islands. The sponge was frozen, and after <2 weeks, it was twice extracted for 2 days with methanol (2 × 1 L). The extracts were evaporated, and the aqueous residue (ca. 400 mL) was extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were dried over sodium sulfate, and the solvent was evaporated to obtain a black tar-like oil (400 mg). Half of the oil was chromatographed on silica gel using a solvent gradient from hexane to ethyl acetate. The more polar fractions were combined, and the solvent was evaporated to yield a greenish-yellow powder (23 mg) that was separated by reversed-phase HPLC on C-18 Partisil using 9:1 methanol–water as eluant to obtain renierone (**1**, 3.5 mg, 0.006% dry weight), mimosamycin (**2**, 2.1 mg, 0.0035% dry weight), and renieramycin E (**14**, 5.0 mg, 0.0085% dry weight). The second portion of the black oil was chromatographed on Sephadex LH-20 using methanol as eluant. Those fractions that gave ^1H NMR spectra containing diagnostic methoxyl signals were combined to yield a green powder (25 mg) that was again subjected to reversed-phase HPLC separation to obtain renierone (**1**, 2.0 mg, 0.0035% dry weight) and a mixture of renieramycins (18.5 mg). The mixture was separated by HPLC on silica gel using 4:1 ethyl acetate–hexane as eluant to obtain renieramycin E (**14**, 10.8 mg, 0.018% dry weight) and renieramycin F (**15**, 4.5 mg, 0.008% dry weight).

Renieramycin E (14): amorphous yellow powder, unstable; UV (MeOH) 266 nm (ϵ 17 000); IR ($CHCl_3$) 3390, 1700, 1655, 1615 cm^{-1}; ^1H NMR ($CDCl_3$), see Table I; ^1H NMR (acetone-d_6) δ 1.35 (ddd, 1 H, J = 16.5, 11.2, 2.7 Hz), 1.56 (br s, 3 H), 1.74 (dq, 3 H, J = 7.2, 1.4 Hz), 1.85 (s, 3 H), 1.87 (s, 3 H), 2.27 (s, 3 H), 2.32 (d, 1 H, J = 21 Hz), 2.66 (dd, 1 H, J = 21, 7.2 Hz), 2.72 (dd, 1 H, J = 16.5, 2.5 Hz), 3.26 (m, 2 H), 3.89 (br d, 1 H, J = 1.8 Hz), 3.94 (s, 3 H), 3.99 (s, 3 H), 4.25 (dd, 1 H, J = 11.2, 1.8 Hz), 4.35 (d, OH, J = 6.5 Hz), 4.42 (m, 1 H), 4.45 (dd, 1 H, J = 11.2, 2.7 Hz), 4.53 (dd, 1 H, J = 6.5, 1.4 Hz), 5.99 (qq, 1 H, J = 7.2, 1.4 Hz); FABMS (m/z) 567 (2, M + H), 551 (44, M + 3H − H_2O), 549 (100, M + H − H_2O); HRMS m/z 549.2247, $C_{30}H_{33}N_2O_8$ requires 549.2237.

Renieramycin F (15): amorphous yellow powder, unstable; UV (MeOH) 265 nm (ϵ 12 000); IR ($CHCl_3$) 3300, 1710, 1660, 1615 cm^{-1}; ^1H NMR ($CDCl_3$), see Table I; ^1H NMR (acetone-d_6) δ 1.24 (ddd, 1 H, J = 17, 11.5, 2.5 Hz), 1.56 (br s, 3 H), 1.75 (dq, 3 H, J = 7.2, 1.4 Hz), 1.83 (s, 3 H), 1.90 (s, 3 H), 2.43 (s, 3 H), 2.68 (dd, 1 H, J = 17, 2.5 Hz), 3.20 (dt, 1 H, J = 11.5, 2.5 Hz), 3.31 (br d, 1 H, J = 2.2 Hz), 3.50 (s, 3 H), 3.87 (s, 1 H), 3.95 (s, 3 H), 3.97 (m, 1 H), 3.98 (s, 3 H), 4.25 (dd, 1 H, J = 11.2, 3 Hz), 4.31 (dd, 1 H, J = 11.2, 2.5 Hz), 4.40 (d, OH, J = 10.3 Hz), 4.42 (m, 1 H), 4.71 (dd, 1 H, J = 10.3, 2.5 Hz), 5.97 (qq, 1 H, J = 7.2, 1.4 Hz); FABMS (m/z) 597 (4, M + H), 581 (100, M + 3H − H_2O), 579 (52, M + H − H_2O); HRMS m/z 579.2285, $C_{31}H_{35}N_2O_9$ requires 579.2342.

Acknowledgment. We thank the Government and people of the Republic of Palau for facilitating the field research. This research was supported by a grant from the National Institutes of Health (CA49084-15) and a student Fellowship from Smith, Kline and French.

(4) We have been unable to repeat this experiment on renieramycin A because none of the original sample remains and it was not reisolated.
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Synthesis of 1,2,5-Thiadiazolidin-3-one 1,1-Dioxides: X-ray Structure Determination of 4,4-Diphenyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide

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Hydantoins, 1,3-imidazolidine-2,4-diones (**1**), are well known for their anticonvulsant activity.[1,2] In particular, 5,5-diphenylhydantoin (DPH, **1**, R = C_6H_5), is widely prescribed for control of generalized tonic–clonic (grand mal) epileptic seizures. The exact nature of the molecular mechanism is not known, but one theory relates activity to the hydrogen bonding ability of the drug to the receptor site (e.g. adenine of nucleic acids).[3]

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