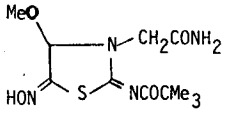
the oxime **1**, prepared by stannous chloride reduction of 2-(pivaloylimino)-5-nitro-4-thiazoline-3-acetamide **2**, is in fact a potent schistosomicidal agent in mice infected with *Schistosoma mansoni*.

Chemistry. Slow addition of anhydrous stannous chloride (0.5 moles) to a solution of the nitrothiazoline **2**[3a] (0.1 moles) and anhydrous sodium acetate (1 mole) in methanol at room temperature gave, after removal of inorganic salts, evaporation of solvent, and trituration with ethyl acetate, crude 5-(hydroxyimino)-4-methoxy-2-(pivaloylimino)thiazolidine-3-acetamide **1** (19%). Recrystallization (charcoal) from methanol afforded (poor recovery) pure **1**, m.p. 180–182 °C (found: C, 43.7; H, 6.1; N, 18.4. $C_{11}H_{18}N_4O_4S$ requires C, 43.7; H, 6.0; N, 18.5%); δ(DMSO-d_6), 1.11 (s, 9H, t-Bu), 3.25 (s, 3H, OMe), 3.97 and 4.36 (d, 2H, J 16.3 Hz, NCH_2), 5.66 (s, 1H, CH), 7.20 (s, 1H, amide NH), 7.57 (s, 1H, amide NH), and 12.25 (s, 1H, =NOH).



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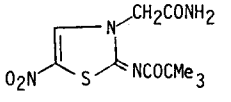
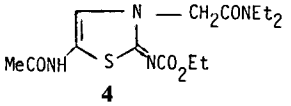


2

$Me_3CCONHCSNHCH_2CONH_2$ **3**



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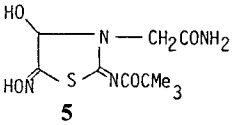

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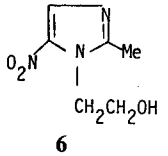

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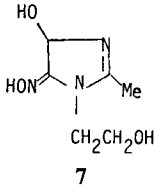

7

A by-product also isolated in low yield from the reaction mixture was shown to be the open-chain thiourea **3** (m.p. 157–159 °C from ethanol).

Biology. The oxime **1** was tested against 9-week mature infections of *S. mansoni* in Keeble or Charles River CD1 white mice by p.o. or s.c. administration and the results are presented in the table.

Discussion. Clearly, the table shows that the oxime **1** has good potency against *S. mansoni* in mice on both oral and parenteral administration. Indeed, the compound appears to be at least as potent as niridazole when given orally. This is in contrast with the only other reduced nitrothiazoline-3-acetamide (**4**) prepared to date[3a], which was inactive against *S. mansoni* although the parent nitro compound was active[3a].

Efficacy of **1** against *S. mansoni* in mice

Drug	Route × days	Dose (mg/kg/day)	%kill of *Schistosomes*
1	SC × 5	50	95
	PO × 5	50	78
	SC × 1	50	62
	PO × 1	50	16
Niridazole	PO × 1	50	0
	PO × 5	50	64
Praziquantel	PO × 1	50	13

As might be expected, the by-product thiourea **3** was not active in the mouse primary screen. It is postulated that this compound is formed from traces of water present in the reaction mixture through the intermediacy of the (probably highly reactive) hydroxy-oxime **5** (which could not be isolated). In confirmation of this, when the stannous chloride reduction of **2** was effected in aqueous tetrahydrofuran instead of methanol, greatly increased yields of **3** (and no **1**) were obtained.

When thiazoline **2** was administered to rats at single oral doses of 600 mg/kg, thiourea **3** was isolated from plasma as a major metabolite[4]. Again this compound could have been formed from **2** through the putative carbinolamine intermediate **5**.

Finally, although it is not known whether species such as **5** possess schistosomicidal properties, clearly the 'trapped' methyl ether **1** is active. It is tempting, however, to speculate on the relationship between the suggested novel intermediate **5**, and the nature of the biologically active (and cytotoxic), as yet unidentified, in vivo primary reduction products of nitroimidazoles such as metronidazole **6** and other antiparasitic nitroheterocyclics. Certainly, the known ring-opened metabolites of metronidazole [acetamide and N-(2-hydroxyethyl)oxamic acid[5,6]] could result from hydrolytic cleavage of a putative imidazoline-intermediate (**7**) corresponding to **5**. Further experiments are in hand to investigate the reduction of metronidazole using the conditions described for the synthesis of **1**.

1 Acknowledgments. The authors are grateful to Dr A. J. Everett and his staff for the physical chemistry measurements, and to Mr G. Dickerson for the antischistosome testing.

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The repression of siderophore synthesis by Mt. St. Helens' ash and silicate rock standards

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Summary. Mt. St. Helens' ash or U.S. Geological Survey silicate rock standards would replace $FeCl_3$ as the limiting nutrient and repress the synthesis of rhodotorulic acid in *Rhodotorulia pilimanae* cultures.

Key words. Siderophore; *Rhodotorula pilimanae;* rhodotorulic acid; Mt. St. Helens' ash.

To overcome the limited solubility of iron salts many microbes derepress the synthesis of ferric specific chelators (siderophores). These chelators are often excreted into the environment where following iron acquisition the complex is absorbed. Substantial information is known on siderophore biochemistry[2], but little is known on the sources or iron available to siderophores. The

Table 1. The affect of iron and rock samples on the production of rhodotorulic acid and packed cell volume of cultures of *Rhodotorula pilimanae*

Substance added to culture Identity	g/l or M[a]	Rhodotorulic acid (mM)	Packed cell vol. (%)
None	NA	7.30	1.6
Fe^{+3}	10^{-8}	6.84	1.7
Fe^{+3}	10^{-7}	5.79	3.8
Fe^{+3}	10^{-6}	2.38	5.3
Fe^{+3}	10^{-5}	0.83	6.8
Fe^{+3}	10^{-4}	0.06	6.7
Fe^{+3}	10^{-3}	0.00	7.0
Mt. St. Helens' ash	40	0.17	6.6
(May 18, 1980)	5	1.62	5.5
	0.1*	4.38	3.4
Mt. St. Helens' ash	40	0.06	6.6
(June 12, 1980)	5	1.83	5.1
	0.1*	4.56	3.3
Sand	40	0.09	6.8
	5	1.82	5.5
	0.1*	2.70	4.5
Andesite	5	0.07	6.7
AGV-1	0.1*	2.02	5.4
Basalt	5	0.29	6.7
BCR-1	0.1*	1.85	5.4
Granite	5	0.92	6.5
G-2	0.1*	2.96	3.9
Grandoiorite	5	0.41	6.7
GSP-1	0.1*	2.64	4.2
Peridotite	5	0.18	6.8
PCC-1	0.1*	1.27	4.9

[a] The exponential numbers are molar while the asterisked numbers represent 300 ml cultures (see text).

purified siderophore, rhodotorulic acid, is capable of leaching iron from rock samples, but no studies have been presented on the effect of the presence of rock on siderophores production[3].

Materials and methods. The United States Geological Survey silicate rock standards[4], Mt. St. Helens' ash (May 18 and June 12, 1980, eruptions), and a local sand sample were obtained and prepared as described earlier[3]. To determine the effect of rock samples on the siderophore production by cultures of the yeast *Rhodotorula pilimanae* (ATCC 26423), weighed rock samples were autoclaved in 250 (or 2000) ml Erlenmeyer flasks, then combined with 30 (or 300) ml of sterile iron-free medium[5]. A second series of flasks contained iron added as ferric chloride. The flasks were inoculated with 2 (or 20) ml of full-grown, iron-free culture. Following incubation with shaking (200 one-inch gyrations/min) at room temperature for 14 days the packed cell volume was determined by centrifugation (15 min, 2000 × g) with graduated sedimentation tubes. The resulting supernatants were examined spectrophotometrically for the presence of rhodotorulic acid[4].

Results and discussion. The affect of iron and rock samples on the production of rhodotorulic acid and packed cell volume of cultures of *R. pilimanae* is presented in the table. Rhodotorulic acid biosynthesis is repressed in *R. pilimanae* at iron concentrations greater than micromolar levels (table and Atkin et al.[5]). Judging from the packed cell volumes, iron is the limiting nutrient in cultures containing less than micromolar concentrations of this element. An examination of the cell volume figures shows the rock samples will replace $FeCl_3$ as the limiting nutrient; in addition, increasing amounts of rock samples will repress the synthesis of rhodotorulic acid. The amounts of ash or rock required to repress the formation of rhodotorulic acid are inversely related to the amounts of iron leached by rhodotorulic acid from these rocks[3]. The lack of this latter inverse relationship with the amounts of iron leached by rhodotorulic acid-free controls[3] indicates the rhodotorulic acid is actually involved in the dissolution of the rock samples.

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Latrunculin-A, ichthyotoxic constituent of the nudibranch *Chromodoris elisabethina*

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Summary. Latrunculin-A, an ichthyotoxin previously described from a Red Sea sponge, *Latrunculia magnifica*, has been isolated from a Pacific nudibranch, *Chromodoris elisabethina*, for which it serves as a defense allomone.
Key words. Nudibranch; latrunculin-A; sponge; *Chromodoris elisabethina;* defense allomone.

In 1980 Kashman et al.[1] reported the structure of latrunculin-A (**1**), isolated from a Red Sea sponge, which in its natural habitat is not predated by fishes. Subsequent biological evaluation of latrunculin-A (**1**) revealed[2] that the compound disrupts microfilament organization in cultured cells. This activity is analogous, albeit at far lower concentrations, to that of the mold derived cytochalasins.

Nudibranchs are opisthobranch mollusks that lack a shell and hence obvious physical defenses. Numerous investigations in recent years[3] have shown that these marine invertebrates owe their survival to various chemical defensive strategies. In many instances the responsible agents originate in the nudibranchs' selective diet, predominantly sponges and cnidarians, and are sequestered and stored near the body surface.

The variably colored striped *Chromodoris elisabethina* were collected on Guam and later at Enewetak in the Marshall islands, where the animals were observed while feeding on a sponge, *Heteronema* sp.[4]. The nudibranchs were either extracted with isopropyl alcohol immediately (Enewetak) or they were first frozen, then extracted (Guam). TLC of the alcoholic residue indicated a single major organic constituent. Successive solvent partition (hexanes/10% aq MeOH; CCL_4/20% aq MeOH; and $CHCl_3$/40% aq MeOH) furnished the principal metabolite in the carbon tetrachloride fraction. HPLC (Si-60, Knauer-Unimetrics, petroleum ether/EtOAc, 1:1) of this fraction led to a colorless oil of composition $C_{22}H_{31}NO_5S$ by high resolution mass spectrometry. UV (λ_{max}^{MeOH} 219 nm, ε 18,700), IR ($\nu_{max}^{CH_2Cl_2}$ 3670, 3560, 3400, 1690 br cm^{-1}) and initial ^{13}C-NMR data provided few structural clues. The richly detailed ^1H-NMR spectrum in chloroform-d and benzene-d_6, decoupling experiments of the diene portion of the molecule, and particularly a COSY plot[5] made it apparent that we were dealing with a compound that either was closely related or identical to latrunculin-A (**1**). A ^1H-NMR spectrum of **1**, kindly provided by Professor Kashman, confirmed identity.

In our antimicrobial screen latrunculin-A showed strong activity