tion was carried out as described for compd 10 from 1.80 g (0.003 mole) of XI and 1.62 g (0.010 mole) of CF<sub>3</sub>C=CCF<sub>3</sub>. After heating at 80° for 5 hr, the reaction was complete (tlc). The reaction mixt was cooled, and the cryst ppt was collected by filtration. There was obtained 1.82 g (79%) of the triazole ester (XIII), mp 167-168°; ir and nmr were consistent. Anal. (C<sub>33</sub>H<sub>32</sub>F<sub>6</sub>N<sub>6</sub>O<sub>7</sub>S) C, H, N.

The ester, 0.5 g, was dissolved in 20 ml of CF<sub>3</sub>COOH contg 1 drop of anisole. The soln was stirred at 0-10° for 1 hr and then poured into a mixt of 20:70 Et<sub>2</sub>O-Skellysolve B. The ppt was collected by filtration to yield 0.332 g of crude 20. This was purified in the following manner. The material was suspended in 20 ml of H<sub>2</sub>O and heated to 60°. Then 0.19 g of TsOH H<sub>2</sub>O was added, and the clear soln was filtered and cooled. The cryst ppt was collected by filtration. This solid was dissolved in a small vol of H<sub>2</sub>O at 70° and filtered, and the pH adjusted to 4.1 with Et<sub>3</sub>N. On cooling, a cryst ppt of 20 was formed which was collected and dried, 0.170 g (44.3%), mp 158-161°; ir and nmr were consistent.

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### References

- (1) D. Willner, C. T. Holdrege, S. R. Baker, and L. C. Cheney, J. Antibiot., 25, 64 (1972).
- (2) J. A. Webber, G. W. Huffman, R. E. Koehler, C. F. Murphy, C. W. Ryan, E. M. Van Heyningen, and R. T. Vasileff, J. Med.

# Schistosomicidal 5-Nitro-4-thiazolines

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Various 2-(acyl- and alkoxycarbonylimino)-5-nitro-4-thiazoline-3-acetamides (III,  $Z = NR_1R_2$ ; n = 1) and the corresponding 4-thiazoline-3-acetic acid esters (III, Z = alkoxy; n = 1) were prepared by alkylation of the sodium salt of the appropriate 2-acylamido-5-nitrothiazole or 5-nitro-2-thiazolecarbamic acid ester with a 2-bromoacetamide or bromoacetate in N,N-dimethylformamide. Many of these 5-nitro-4-thiazolines showed potent schistosomicidal activity, effecting a 50-100% reduction of adult Schistosoma mansoni in mice at daily doses of less than 400 mg/kg for 14 days.

Continuing our investigations on derivatives of 2-amino-5nitrothiazole as potential schistosomicides<sup>1</sup> the alkylation of 2-acetamido-5-nitrothiazole with substituted bromoacetamides was examined. In contrast with previous work with 2-formamido-5-nitrothiazole wherein alkylation took place almost exclusively on the amide nitrogen to give derivatives of type II, similar treatment of 2-acetamido-5nitrothiazole provided iminothiazolines (III) as a result of alkylation on the thiazole ring nitrogen. Surprisingly, it was found that, in contrast to the minimal activity of II, the iminothiazolines III were extremely potent against *Schistosoma mansoni* infections in experimental animals.

The present communication presents the results of the investigation of this novel lead and describes the preparation of various 2-(acyl- and alkoxycarbonylimino)-5-nitro-4-thiazoline-3-acetamides (III,  $Z = NR_1R_2$ ; n = 1) and the corresponding 4-thiazoline-3-acetic acid esters (III, Z = alkoxy; n = 1), together with several of the analogs (III, n = 2 and 3). Extension of this series to the related system IV is described in the subsequent paper.<sup>2</sup>

Chem., 14, 113 (1971), and references cited therein.

- (3) P. A. S. Smith, "The Chemistry of Open Chain Organic Nitrogen Compounds," Vol. II, W. A. Benjamin, Inc., New York, N. Y., 1966, pp 211-268.
- (4) G. L'abbe, Chem. Rev., 69, 345 (1969).
- (5) G. L'abbe, Belg. Chem. Ind., 34, 519 (1969).
- (6) M. D. Barker, G. A. Somerfield, and V. Arkley, British Patent 1,057,883 (1967).
- (7) J. D. Cocker, B. R. Cowley, J. S. G. Cox, S. Eardley, G. I. Gregory, J. K. Lazenby, A. G. Long, J. C. P. Sly, and G. A. Somerfield, J. Chem. Soc., 5015 (1965).
- (8) B. R. Cowley, G. I. Gregory, and A. G. Long, British Patent 1,211,694 (1970).
- (9) L. A. Wetherill, W. Graham, and M. J. Covil, British Patent 1,104,938 (1968).
- (10) H. G. Viehe, Ed., "Chemistry of Acetylenes," Marcel Dekker, New York, N. Y., 1969, pp 471-473, 802.
- (11) K. Ohno and J. Tsuji, J. Amer. Chem. Soc., 90, 99 (1968).
- (11) R. Onlo and J. Isali, J. Inder. Chem. Box, 96, 99 (1966)
  (12) "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, p 813.
- (13) B. Fechtig, H. Peter, H. Bickel, and E. Vischer, Helv. Chim. Acta, 51, 1108 (1968).
- (14) H. W. O. Weissenberger and M. G. Van Der Hoeven, *Recl. Trav. Chim. Pays-Bas*, 89, 1081 (1970).
- (15) J. L. Spencer, E. H. Flynn, R. W. Roeske, F. Y. Siu, and R. R. Chauvette, J. Med. Chem., 9, 746 (1966).
- (16) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, J. Amer. Chem. Soc., 77, 6269 (1955).

 $O_{2}N \xrightarrow{N} N HCOR \xrightarrow{1. \text{ NaH-DMF}} O_{2}N \xrightarrow{N} N HCOR \xrightarrow{1. \text{ NaH-DMF}} O_{2}N \xrightarrow{N} O_$ 

**Chemistry.** Thiazolines (III, n = 1) (1-10, 13-21, 23-38, 46-51, 53-58, and 60, Table I) and the  $\alpha$ -methyl analog 11 were obtained in 2-73% yield by alkylation of a DMF solution of the sodium salt of the appropriate amide or carbamic acid ester I with a bromoacetamide or bromoacetate. The alkylation process gave varying amounts of thiazoline III together with the thiazole isomer II; however, the required thiazolines were obtained in a pure state relatively easily in most cases by fractional crystallization (accompanying thiazoles II were not purified in most cases).

$$O_2N \xrightarrow{I}_{O_2N} N-R \\ NCNHR^4 \\ O \\ IV$$

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$ \begin{array}{cccccccccccccccccccccccccccccccccccc$				CH <sub>2</sub> CONMe <sub>2</sub>						
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	28	в	$c$ - $C_3H_5$	CH <sub>2</sub> CONEt <sub>2</sub>	154-157		В		55	$C_{13}H_{18}N_4O_4S$
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$\begin{array}{cccccccccccccccccccccccccccccccccccc$			с-С4H7	CH <sub>2</sub> CONHPr					28	C13H18N4O4S
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	60	<u>B</u>	OPh	CH <sub>2</sub> CO <sub>2</sub> Et	129-131	F, G	A	25	25	$C_{14}H_{13}N_{3}O_{6}S$

 $^{a}$ A, isolation by extraction of the aqueous layer with EtOAc; B, compound soluble in cold EtOH; C, compound soluble in AcOH; D, isolation by extraction of the filtered aqueous layer with EtOAc; E, compound soluble in cold Et<sub>2</sub>O; F, compound insoluble in AcOH; D, isolation by extraction of the filtered aqueous layer with EtOAc; E, compound soluble in cold Et<sub>2</sub>O; F, compound insoluble in cold EtOAc; G, compound soluble in cold EtOAc; H, compound insoluble in cold EtOAc; C, EtOAc-petroleum ether (bp 60-80°); D, MeOH; E, AcOH; F, *i*-PrOH. <sup>c</sup>Compound purified by recrystallization only. <sup>d</sup>Described in the Experimental Section. <sup>e</sup>C: calcd, 39.7; found, 40.2. <sup>f</sup>C: calcd, 50.5; found, 50.0. <sup>g</sup>N: calcd, 16.8; found, 17.3. <sup>h</sup>C: calcd, 44.3; found, 43.8. <sup>i</sup>c-C<sub>3</sub>H<sub>5</sub> represents cyclopropyl, c-C<sub>4</sub>H<sub>7</sub> represents cyclobutyl.

Table II. Effects of 2-(Acylimino)-5-nitro-4-thiazoline-3-acetamides and Analogs against S. man	ansoni in Mice
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	Dru	g	Live schistosomes <sup>c</sup>		
Compd	Route $\times days^a$	mg/kg per day	% mice positive	% reduction	
1	D X 14	151	100	31	
	G × 5	200	12	97	
3	D X 14	348	100	55	
5	D X 14	65	50	77	
	<b>S</b> ×1	100	33	96	
7	D × 14	299	50	80	
8	D × 14	246	66	74	
9	$D \times 7$ then $D \times 7$	134 then 183 <sup>b</sup>	16	95	
	$S \times 1$	100	87	74	
10	$D \times 7$ then $D \times 7$	149 then 193 <sup>b</sup>	16	84	
11	$D \times 7$ then $D \times 7$	166 then 238 <sup>b</sup>	66	71	
13	D X 14	236	66	65	
14	$D \times 17$ then $D \times 7$	140 then 209 <sup>b</sup>	66	61	
15	D × 14	77	50	78	
10	S ×1	100	14	95	
17	$D \times 7$ then $D \times 7$	$100$ 89 then $85^{b}$	80	65	
17	S ×1	100	100	66	
18	$D \times 14$	358	83	62	
1 <b>9</b>	$D \times 14$ D × 14	314	33	86	
20	$D \times 14$ D × 14	345	50	73	
20	$S \times 1$	100	100	79	
<b>2</b> 1	$D \times 7$ then $D \times 7$	100 104 then $117^{b}$	50	88	
<b>2</b> 3		162 then $229^{b}$	83	60	
23	$D \times 7$ then $D \times 7$		_		
	S ×1	100	100	28	
24	GX 5	25	75	58	
25	S ×1	12.5	43	83	
25	G×5	200	62	50	
27	$D \times 7$ then $D \times 7$	294 then $232^b$	16	95	
••	$S \times 1$	100	75	70	
28	$D \times 7$ then $D \times 7$	117 then $173^{b}$	20	97	
	$S \times 1$	100	28	93	
29	D × 14	287	16	97	
30	$D \times 7$ then $D \times 7$	340 then 294 <sup>b</sup>	60	81	
32	$D \times 7$ then $D \times 7$	102 then 176 <sup>b</sup>	83	72	
34	D × 14	387	0	100	
	S ×1	100	100	29	
35	G X 5	200	62	79	
36	D × 14	68	83	69	
38	G X 5	100	75	39	
48	$D \times 7$ then $D \times 7$	137 then 183 <sup>b</sup>	33	91	
	S ×1	100	100	32	
49	$D \times 7$ then $D \times 7$	84 then 87 <sup>b</sup>	60	68	
50	$D \times 7$ then $D \times 7$	128 then 142 b	66	61	
51	$D \times 7$ then $D \times 7$	115 then 176 b	83	56	
53	D × 14	496	100	80	
54	D × 14	341	100	49	
60	D× 14	288	100	54	
Niridazole	D × 14	249	17	99	
_	GX 5	100	100	53	

<sup>a</sup>D represents drug-diet; G represents gavage; and S represents sc injection. <sup>b</sup>Represents a dose reduction based on percentage in diet. <sup>c</sup>Groups of 6 and 8 animals, respectively, were used in the diet and gavage studies. The worm burden of the controls averaged 15 per mouse.

The two isomeric forms II and III were distinguished readily by means of their ir and uv spectra. Thus thiazolines III had two bands at *ca.* 1610 and 1580 cm<sup>-1</sup> (Nujol) (=NCO-), and characteristic maxima at *ca.*  $\lambda$  280 and 360 m $\mu$  (EtOH). Thiazoles II had maxima at *ca.*  $\lambda$  235 and 340 m $\mu$  (EtOH).

Thiazolines (III, n = 2) (39-41) were prepared similarly, except that the 3-bromopropionamide was added to a preheated (80°) DMF solution of the sodium salt of the thiazole I. When the alkylating agent was added to the sodium salt at room temperature and the reaction was allowed to proceed to neutrality at room temperature or at 80°, starting thiazole I was recovered in high yield (*i.e.*, under these conditions, elimination of HBr occurred before alkylation took place).

2-(Acetylimino)-5-nitro-4-thiazoline-3-butyramide (45) and the corresponding thiazole (44) were prepared indirectly by hydrolysis of the respective nitriles 43 and 42 (readily separated by fractional crystallization of the crude isomer mixture from EtOH).

The amount of thiazoline produced in the alkylation was found to depend on the nature of groups R and Z. Thus when R was relatively bulky (aromatic or *tert*-Bu) the crude product appeared (from the ir spectrum) to contain greater amounts of the thiazoline. Thiazole formation appeared to be promoted by use of bromoacetic acid esters.

**Biology.** The compounds described in the present work were tested in mice against a Puerto Rican strain of *S. mansoni* by Dr. Paul E. Thompson and coworkers of these laboratories.<sup>†</sup> As in previous work, drugs were administered in a powdered diet (D) for 14 days or by gavage (G) in 10 ml/kg of aqueous 1% hydroxyethyl or carboxymethyl cellulose for 3-10 days. Several of the most active thiazolines were tested further against *S. mansoni in vitro* or in rhesus

+For a description of test methods see ref 3.

monkeys. Many of the thiazolines (III, n = 1) exhibited significant antischistosome activity in mice, and the most active of these are listed in Table II. Surprisingly thiazolines (III, n = 2 and 3) (39, 40, 41, 43, and 45) were all inactive in the mouse primary screen. With one exception, all the thiazole isomers isolated were found to be inactive. Thiazole 44, however, caused a 13% reduction in worm burden when administered in the diet at 326 mg/kg for 14 days; the corresponding thiazoline 45 was inactive under the same conditions.

Thiazolines 2, 6, 26, 33, 37, 55, 56, and 57 were inactive in the mouse test, and it appeared that one requirement for high activity in III, n = 1, was  $Z = NH_2$  or N,N-disubstituted amino (although the N-benzylamino compounds 7 and 18 both possessed strong schistosomicidal activity). In the series III, Z = N,N-dialkylamino, in general, activity tended to fall off as the size of the alkyl groups was increased. This effect was most pronounced in thiazolines (III, R = OPh), where only the N,N-dimethyl derivative 54 was active.

Several of the more potent schistosomicidal thiazolines were administered to infected mice as a single sc injection of 100 mg/kg. Thiazolines 5, 9, 15, 17, 20, 23, 24, 27, 28, 34, and 48 caused a 28-96% reduction in the live worm burden under these conditions, and the most active compound, 5-nitro-2-(pivaloylimino)-4-thiazoline-3-acetamide (24), killed 83% of the worms when administered as a single sc injection of 12.5 mg/kg. Surprisingly, thiazolines 1, 3, 38, 51, and 53 were inactive when given parenterally, even though they were active when administered in the diet or by gavage and were close analogs of other compounds active by injection.

2-(Acetylimino)-5-nitro-4-thiazoline-3-acetamide (1) and N,N-diethyl-5-nitro-2-(propionylimino)-4-thiazoline-3-acetamide (15) were also tested *in vitro* against 10-week-old male and female *S. mansoni*. Thiazoline 1 was inactive when tested at 50  $\mu$ g/ml, whereas the N,N-diethyl analog killed the worms within 15-67 hr at a concentration of 50  $\mu$ g/ml. This somewhat surprising result would seem to indicate the need for an active metabolite for 1 but not necessarily for 15.

Against S. mansoni infections in rhesus monkeys, thiazolines 1, 7, 10, 14, 15, 19, 20, 23, 51, and 53 caused slight to strong temporary egg suppression when administered in gav..ge doses of 50-100 mg/kg per day for 10 days, but none was curative.<sup>3</sup>

Finally, the 5-acetamido compound 61 (prepared as a potential metabolite of the active 49) was shown to be inactive in the mouse primary screen.

#### Experimental Section<sup>‡</sup>

The physical properties of most of the compounds prepared are collected in Table I.

Chloroacetylpiperidine, -pyrrolidine, and -morpholine and the bromoacetamides and -propionamides were prepared by literature methods.<sup>4</sup>

General Alkylation Procedure. NaH (50% dispersion in mineral oil) (0.1 mole) was added in portions to a solution of the appropriate I (0.1 mole) in DMF at 0°, and the mixture was then stirred at room temp until H<sub>2</sub> evolution ceased. The alkylating agent (0.11 mole) was then added at room temp (at 80° for alkylation with 3-bromopropionamides), and the mixture was stirred (reaction temperature given) until the pH reached 7.0 and then poured into iced H<sub>2</sub>O. Unless otherwise stated in Table I, the precipitated solid was filtered off, washed with H<sub>2</sub>O, and dried. The product was then either recrystd from the stated solvent, or separated from accompanying thiazole isomer by one of the listed procedures and then recrystd.

4-[N-(5-Nitro-2-thiazolyl)acetamido] butyramide (44). Nitrile 42 (1.0 g) was stirred with concd HCl (20 ml) at room temp for 1.5 hr, and the solution was then diluted with H<sub>2</sub>O (100 ml) and neutralized with NaHCO<sub>3</sub>. Isolation with EtOAc afforded the product (44).

Similarly, hydrolysis of nitrile 43 afforded 2-(acetylimino)-5nitro-4-thiazoline-3-butyramide (45).

5-Acetamido-3-[(diethylcarbamoyl)methyl]-4-thiazoline- $\Delta^{2,N}$ carbamic Acid Ethyl Ester (61). Zn dust (7 g) was added in portions to a suspension of 49 (3.5 g) in AcOH (12 ml) and Ac<sub>2</sub>O (7 ml) while the temp was maintained at <40° (intermittent ice cooling). The mixture was stirred 2 hr at room temp, and the filtered solution was evaporated *in vacuo* to provide 61 (11%), mp 223-224° (from EtOH). Anal. (C<sub>14</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub>S) C, H, N.

5-Nitro-2-thiazolecarbamic Acid Phenyl Ester (62). Phenyl chloroformate (75.2 g) was added to a stirred, ice-cooled suspension of 2-amino-5-nitrothiazole (48 g) in  $C_5H_5N$  (200 ml) at such a rate that the internal temp remained at  $<50^{\circ}$ , and the mixture was then left overnight. Solid was collected, washed thoroughly with  $H_2O$  and 2 N HCl, and then recrystd from  $C_6H_6$ -DMF to give (62) (48%), mp 254-255° dec. Anal. ( $C_{10}H_7N_3O_4S$ ) C, H, N.

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#### **References**

- (1) L. M. Werbel and J. R. Battaglia, J. Med. Chem., 14, 10 (1971).
- (2) L. M. Werbel, M. B. Degnan, G. F. Harger, D. B. Capps, P. J. Islip, and M. Closier, J. Med. Chem., 15, 955 (1972).
- (3) P. E. Thompson, J. E. Meisenhelder, and H. Najarian, Amer. J. Trop. Med. Hyg., 11, 31 (1962).
- (4) W. E. Weaver and W. M. Whaley, J. Amer. Chem. Soc., 69, 515 (1947); S. Kushner, R. I. Cassell, J. Morton, II, and J. H. Williams, J. Org. Chem., 16, 1283 (1951); U. S. Patent 2,768,202 (Oct 23, 1956); and J. E. Gearien and K. J. Liska, J. Amer. Chem. Soc., 76, 3554 (1954).

 $<sup>\</sup>pm$ Melting points are corrected and were determined in a capillary tube. Analytical results were obtained for C, H, and N for all compounds, and, unless otherwise stated, were within  $\pm 0.4\%$  of the theoretical values.