

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 $\text{CF}_3\text{C}\equiv\text{CCF}_3$. 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.* ($\text{C}_{13}\text{H}_9\text{F}_6\text{N}_3\text{O}_5\text{S}$) C, H, N.

The ester, 0.5 g, was dissolved in 20 ml of CF_3COOH 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_2O -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_2O and heated to 60°. Then 0.19 g of $\text{TsOH}\cdot\text{H}_2\text{O}$ 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_2O at 70° and filtered, and the pH adjusted to 4.1 with Et_3N . 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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Schistosomicidal 5-Nitro-4-thiazolines

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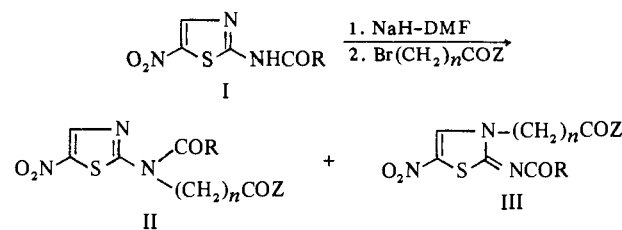
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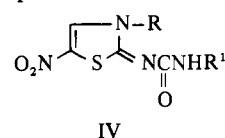
Various 2-(acyl- and alkoxy-carbonylimino)-5-nitro-4-thiazoline-3-acetamides (III, $\text{Z} = \text{NR}_1\text{R}_2$; $n = 1$) and the corresponding 4-thiazoline-3-acetic acid esters (III, $\text{Z} = \text{alkoxy}$; $n = 1$) were prepared by alkylation of the sodium salt of the appropriate 2-acylamido-5-nitrothiazole 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-5-nitrothiazole as potential schistosomicides¹ 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-5-nitrothiazole 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 alkoxy-carbonylimino)-5-nitro-4-thiazoline-3-acetamides (III, $\text{Z} = \text{NR}_1\text{R}_2$; $n = 1$) and the corresponding 4-thiazoline-3-acetic acid esters (III, $\text{Z} = \text{alkoxy}$; $n = 1$), 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.²



Chemistry. Thiazolines (III, $n = 1$) (1-10, 13-21, 23-38, 46-51, 53-58, and 60, Table I) and the α -methyl analog II 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).



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Table I. 2-(Substituted-imino)-5-nitro-3-substituted-4-thiazolines and 2-Amino-*N,N*-disubstituted-5-nitrothiazoles

Compd	Type	R	Z	Mp, °C	Isoln procedure ^a	Recrystn solvent ^b	Reaction temp, °C	Yield, %	Formula	Chemical Structure	
										A	B
1	B	Me	CH ₂ CONH ₂	211-213	<i>c</i>	A	25	37	C ₇ H ₈ N ₄ O ₄ S		
2	B	Me	CH ₂ CONHMe	206-207		A	25	45	C ₈ H ₁₀ N ₄ O ₄ S		
3	B	Me	CH ₂ CONMe ₂	137-139	A	A	25	43	C ₉ H ₁₂ N ₄ O ₄ S ^e		
4	B	Me	CH ₂ CONEt ₂	140-141		A	25	66	C ₁₁ H ₁₆ N ₄ O ₄ S		
5	B	Me	CH ₂ CONPr ₂	127-128		A	25	47	C ₁₃ H ₂₀ N ₄ O ₄ S		
6	B	Me	CH ₂ CONH-octyl	162-163	B	A, then B	25	2	C ₁₅ H ₂₄ N ₄ O ₄ S ^f		
7	B	Me	CH ₂ CONHCH ₂ Ph	189-190		A	25	37	C ₁₄ H ₁₄ N ₄ O ₄ S ^g		
8	B	Me	CH ₂ CO-pyrrolidino	161-163	B	A	60	48	C ₁₁ H ₁₄ N ₄ O ₄ S ^h		
9	B	Me	CH ₂ CO-piperidino	165-166	B	A	80	7	C ₁₂ H ₁₆ N ₄ O ₄ S		
10	B	Me	CH ₂ CO-morpholino	174.5-175.5	C	A	80	11	C ₁₁ H ₁₄ N ₄ O ₅ S		
11	B	Me	CH(Me)CONH ₂	225	D	A	25	4	C ₈ H ₁₀ N ₄ O ₄ S		
12	A	Me	CH ₂ CO ₂ Et	109-111	E	A	25	13	C ₉ H ₁₁ N ₃ O ₅ S		
13	B	Me	CH ₂ CO ₂ Et	159-160	F, G	A	25	17	C ₉ H ₁₁ N ₃ O ₅ S		
14	B	Et	CH ₂ CONMe ₂	163-164		A	25	25	C ₁₀ H ₁₄ N ₄ O ₄ S		
15	B	Et	CH ₂ CONEt ₂	151-153		A	25	41	C ₁₂ H ₁₈ N ₄ O ₄ S		
16	B	Et	CH ₂ CONHPr	186-187		A	25	44	C ₁₁ H ₁₆ N ₄ O ₄ S		
17	B	Et	CH ₂ CONBu ₂	197-198		A	25	47	C ₁₆ H ₂₆ N ₄ O ₄ S		
18	B	Et	CH ₂ CONHCH ₂ Ph	197-199		A	25	31	C ₁₅ H ₁₆ N ₄ O ₄ S		
19	B	Et	CH ₂ CO-pyrrolidino	146-147	H	A	65	23	C ₁₂ H ₁₆ N ₄ O ₄ S		
20	B	Et	CH ₂ CO-piperidino	159-160		A	80	43	C ₁₃ H ₁₈ N ₄ O ₄ S		
21	B	Et	CH ₂ CO-morpholino	126-127	A	A	90	7	C ₁₂ H ₁₆ N ₄ O ₅ S		
22	A	Et	CH ₂ CO ₂ Et	88-89	A, E	A	25	11	C ₁₀ H ₁₃ N ₃ O ₅ S		
23	B	Et	CH ₂ CO ₂ Et	145-146	A, F	A	25	13	C ₁₀ H ₁₃ N ₃ O ₅ S		
24	B	CMe ₃	CH ₂ CONH ₂	199-201 dec		A	75	46	C ₁₀ H ₁₄ N ₄ O ₄ S		
25	B	CMe ₃	CH ₂ CONMe ₂	139-141		C	25 (0.5 hr), 40 (0.5 hr)	40	C ₁₂ H ₁₈ N ₄ O ₄ S		
26	B	<i>c</i> -C ₃ H ₅ ⁱ	CH ₂ CONHMe	241-243	J	B, then D	65	6	C ₁₀ H ₁₂ N ₄ O ₄ S		
27	B	<i>c</i> -C ₃ H ₅	CH ₂ CONMe ₂	172-174		B	25	18	C ₁₁ H ₁₄ N ₄ O ₄ S		
28	B	<i>c</i> -C ₃ H ₅	CH ₂ CONEt ₂	154-157		B	25 (0.5 hr), 40 (0.5 hr)	55	C ₁₃ H ₁₈ N ₄ O ₄ S		
29	B	<i>c</i> -C ₃ H ₅	CH ₂ CONBu ₂	99-102		B	25 (0.5 hr), 40 (0.5 hr)	41	C ₁₇ H ₂₆ N ₄ O ₄ S		
30	B	<i>c</i> -C ₃ H ₅	CH ₂ CO-piperidino	191-194		B	50	31	C ₁₄ H ₁₈ N ₄ O ₄ S		
31	B	<i>c</i> -C ₃ H ₅	CH ₂ CO ₂ Et ₂	110-112	F	A	25 (0.5 hr), 40 (1 hr)	17	C ₁₁ H ₁₃ N ₃ O ₅ S		
32	B	<i>c</i> -C ₄ H ₇ ⁱ	CH ₂ CONEt ₂	97-99		A	25	25	C ₁₄ H ₂₀ N ₄ O ₄ S		
33	B	<i>c</i> -C ₄ H ₇	CH ₂ CONHPr	237-239		B	25	28	C ₁₃ H ₁₈ N ₄ O ₄ S		
34	B	Ph	CH ₂ CONH ₂	264-266 dec		E	95	50	C ₁₂ H ₁₀ N ₄ O ₄ S		
35	B	Ph	CH ₂ CONMe ₂	222-224		E	25	57	C ₁₄ H ₁₄ N ₄ O ₄ S		
36	B	Ph	CH ₂ CONEt ₂	207-209		E	120	58	C ₁₆ H ₁₈ N ₄ O ₄ S		
37	B	Ph	CH ₂ CONPr ₂	188-190		A	25 (1 hr), 50 (1 hr)	73	C ₁₈ H ₂₂ N ₄ O ₄ S		
38	B	CCl ₃	CH ₂ CONMe ₂	124-126		A	25	13	C ₉ H ₉ Cl ₃ N ₄ O ₄ S		
39	B	CMe ₃	CH ₂ CH ₂ CONH ₂	183-185		A	80	48	C ₁₁ H ₁₆ N ₄ O ₄ S		
40	B	CMe ₃	CH ₂ CH ₂ CONEt ₂	114-115		A	80	54	C ₁₅ H ₂₄ N ₄ O ₄ S		
41	B	CCl ₃	CH ₂ CH ₂ CONH ₂	162-165		A	80	28	C ₈ H ₇ Cl ₃ N ₄ O ₄ S		
42	A	Me	CH ₂ CH ₂ CH ₂ CN	146-147		A	60	25	C ₉ H ₁₀ N ₄ O ₃ S		
43	B	Me	CH ₂ CH ₂ CH ₂ CN	83-84		A	60	7	C ₉ H ₁₀ N ₄ O ₃ S		
44	A	Me	CH ₂ CH ₂ CH ₂ CONH ₂	144-145		F	<i>d</i>	34	C ₉ H ₁₂ N ₄ O ₄ S		
45	B	Me	CH ₂ CH ₂ CH ₂ CONH ₂	148-150		A	<i>d</i>	54	C ₉ H ₁₂ N ₄ O ₄ S		
46	B	OEt	CH ₂ CONH ₂	217-218 dec		A	25	26	C ₈ H ₁₀ N ₄ O ₅ S		
47	B	OEt	CH ₂ CONHMe	215-216		A	25	11	C ₉ H ₁₂ N ₄ O ₄ S		
48	B	OEt	CH ₂ CONMe ₂	135-137		A	25	27	C ₁₀ H ₁₄ N ₄ O ₅ S		
49	B	OEt	CH ₂ CONEt ₂	132-134		A	25	54	C ₁₂ H ₁₈ N ₄ O ₅ S		
50	B	OEt	CH ₂ CONPr ₂	137-139		A	25	59	C ₁₄ H ₂₂ N ₄ O ₅ S		
51	B	OEt	CH ₂ CONBu ₂	130-132		A	25	65	C ₁₆ H ₂₆ N ₄ O ₅ S		
52	A	OEt	CH ₂ CO ₂ Et	76-76.5	E	A	25 (0.5 hr), 45 (1.5 hr)	16	C ₁₀ H ₁₃ N ₃ O ₆ S		
53	B	OEt	CH ₂ CO ₂ Et	128-129	F	A	25 (0.5 hr), 45 (1.5 hr)	26	C ₁₀ H ₁₃ N ₃ O ₆ S		
54	B	OPh	CH ₂ CONMe ₂	169-172		A	25	38	C ₁₄ H ₁₄ N ₄ O ₅ S		
55	B	OPh	CH ₂ CONEt ₂	153-155		A	25	44	C ₁₆ H ₁₈ N ₄ O ₅ S		
56	B	OPh	CH ₂ CONPr ₂	135-137		A	25	49	C ₁₈ H ₂₂ N ₄ O ₅ S		
57	B	OPh	CH ₂ CONBu ₂	97-99		A	25	31	C ₂₀ H ₂₆ N ₄ O ₅ S		
58	B	OPh	CH ₂ CO-piperidino	148-149		A	60	24	C ₁₇ H ₁₈ N ₄ O ₅ S		
59	A	OPh	CH ₂ CO ₂ Et	109-111	E	A	25	21	C ₁₄ H ₁₃ N ₃ O ₆ S		
60	B	OPh	CH ₂ CO ₂ Et	129-131	F, G	A	25	25	C ₁₄ H ₁₃ N ₃ O ₆ S		

^aA, 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 Et₂O; F, compound insoluble in cold Et₂O; G, compound soluble in cold EtOAc; H, compound insoluble in cold EtOAc; J, compound insoluble in warm EtOAc. ^bA, EtOH; B, EtOAc; C, EtOAc-petroleum ether (bp 60-80°); D, MeOH; E, AcOH; F, *i*-PrOH. ^cCompound purified by recrystallization only. ^dDescribed in the Experimental Section. ^eC: calcd, 39.7; found, 40.2. ^fC: calcd, 50.5; found, 50.0. ^gN: calcd, 16.8; found, 17.3. ^hC: calcd, 44.3; found, 43.8. ⁱ*c*-C₃H₅ represents cyclopropyl, *c*-C₄H₇ represents cyclobutyl.

Table II. Effects of 2-(Acylimino)-5-nitro-4-thiazoline-3-acetamides and Analogs against *S. mansoni* in Mice

Compd	Drug		Live schistosomes ^c	
	Route × days ^a	mg/kg per day	% mice positive	% reduction
1	D × 14	151	100	31
	G × 5	200	12	97
3	D × 14	348	100	55
5	D × 14	65	50	77
	S × 1	100	33	96
7	D × 14	299	50	80
8	D × 14	246	66	74
9	D × 7 then D × 7	134 then 183 ^b	16	95
	S × 1	100	87	74
10	D × 7 then D × 7	149 then 193 ^b	16	84
11	D × 7 then D × 7	166 then 238 ^b	66	71
13	D × 14	236	66	65
14	D × 17 then D × 7	140 then 209 ^b	66	61
15	D × 14	77	50	78
	S × 1	100	14	95
17	D × 7 then D × 7	89 then 85 ^b	80	65
	S × 1	100	100	66
18	D × 14	358	83	62
19	D × 14	314	33	86
20	D × 14	345	50	73
	S × 1	100	100	79
21	D × 7 then D × 7	104 then 117 ^b	50	88
23	D × 7 then D × 7	162 then 229 ^b	83	60
	S × 1	100	100	28
24	G × 5	25	75	58
	S × 1	12.5	43	83
25	G × 5	200	62	50
27	D × 7 then D × 7	294 then 232 ^b	16	95
	S × 1	100	75	70
28	D × 7 then D × 7	117 then 173 ^b	20	97
	S × 1	100	28	93
29	D × 14	287	16	97
30	D × 7 then D × 7	340 then 294 ^b	60	81
32	D × 7 then D × 7	102 then 176 ^b	83	72
34	D × 14	387	0	100
	S × 1	100	100	29
35	G × 5	200	62	79
36	D × 14	68	83	69
38	G × 5	100	75	39
48	D × 7 then D × 7	137 then 183 ^b	33	91
	S × 1	100	100	32
49	D × 7 then D × 7	84 then 87 ^b	60	68
50	D × 7 then D × 7	128 then 142 ^b	66	61
51	D × 7 then D × 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
	G × 5	100	100	53

^aD represents drug-diet; G represents gavage; and S represents sc injection. ^bRepresents a dose reduction based on percentage in diet.

^cGroups 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^{-1} (Nujol) (=NCO-), and characteristic maxima at *ca.* λ 280 and 360 $\text{m}\mu$ (EtOH). Thiazoles II had maxima at *ca.* λ 235 and 340 $\text{m}\mu$ (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.† 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.

