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 $CF_3C{\equiv}CCF_3$. 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.* ($C_{33}H_{32}F_6N_6O_7S$) 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 $TsOH \cdot H_2O$ 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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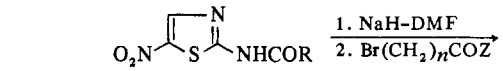
Various 2-(acyl- and alkoxycarbonylimino)-5-nitro-4-thiazoline-3-acetamides (III, Z = NR_1R_2; n = 1) and the corresponding 4-thiazoline-3-acetic acid esters (III, Z = alkoxy; n = 1) were prepared by alkylation of the sodium salt of the appropriate 2-acylamido-5-nitrothiazole or 5-nitro-2-thiazolecarbamic 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-5-nitrothiazole as potential schistosomicides[1] 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 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.[2]



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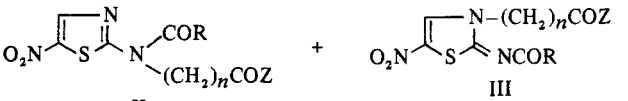
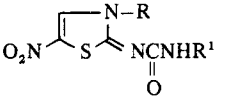


II III

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



IV

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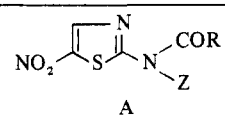
Table I. 2-(Substituted-imino)-5-nitro-3-substituted-4-thiazolines and 2-Amino-*N,N*-disubstituted-5-nitrothiazoles



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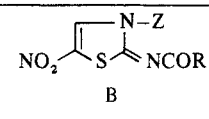


B

Compd	Type	R	Z	Mp, °C	Isoln procedure[a]	Recrystn solvent[b]	Reaction temp, °C	Yield, %	Formula
1	B	Me	CH_2CONH_2	211-213	*c*	A	25	37	$C_7H_8N_4O_4S$
2	B	Me	$CH_2CONHMe$	206-207		A	25	45	$C_8H_{10}N_4O_4S$
3	B	Me	CH_2CONMe_2	137-139	A	A	25	43	$C_9H_{12}N_4O_4S$[e]
4	B	Me	CH_2CONEt_2	140-141		A	25	66	$C_{11}H_{16}N_4O_4S$
5	B	Me	CH_2CONPr_2	127-128		A	25	47	$C_{13}H_{20}N_4O_4S$
6	B	Me	CH_2CONH-octyl	162-163	B	A, then B	25	2	$C_{15}H_{24}N_4O_4S$[f]
7	B	Me	$CH_2CONHCH_2Ph$	189-190		A	25	37	$C_{14}H_{14}N_4O_4S$[g]
8	B	Me	CH_2CO-pyrrolidino	161-163	B	A	60	48	$C_{11}H_{14}N_4O_4S$[h]
9	B	Me	CH_2CO-piperidino	165-166	B	A	80	7	$C_{12}H_{16}N_4O_4S$
10	B	Me	CH_2CO-morpholino	174.5-175.5	C	A	80	11	$C_{11}H_{14}N_4O_5S$
11	B	Me	$CH(Me)CONH_2$	225	D	A	25	4	$C_8H_{10}N_4O_4S$
12	A	Me	CH_2CO_2Et	109-111	E	A	25	13	$C_9H_{11}N_3O_5S$
13	B	Me	CH_2CO_2Et	159-160	F, G	A	25	17	$C_9H_{11}N_3O_5S$
14	B	Et	CH_2CONMe_2	163-164		A	25	25	$C_{10}H_{14}N_4O_4S$
15	B	Et	CH_2CONEt_2	151-153		A	25	41	$C_{12}H_{18}N_4O_4S$
16	B	Et	$CH_2CONHPr$	186-187		A	25	44	$C_{11}H_{16}N_4O_4S$
17	B	Et	CH_2CONBu_2	197-198		A	25	47	$C_{16}H_{26}N_4O_4S$
18	B	Et	$CH_2CONHCH_2Ph$	197-199		A	25	31	$C_{15}H_{16}N_4O_4S$
19	B	Et	CH_2CO-pyrrolidino	146-147	H	A	65	23	$C_{12}H_{16}N_4O_4S$
20	B	Et	CH_2CO-piperidino	159-160		A	80	43	$C_{13}H_{18}N_4O_4S$
21	B	Et	CH_2CO-morpholino	126-127	A	A	90	7	$C_{12}H_{16}N_4O_5S$
22	A	Et	CH_2CO_2Et	88-89	A, E	A	25	11	$C_{10}H_{13}N_3O_5S$
23	B	Et	CH_2CO_2Et	145-146	A, F	A	25	13	$C_{10}H_{13}N_3O_5S$
24	B	CMe_3	CH_2CONH_2	199-201 dec		A	75	46	$C_{10}H_{14}N_4O_4S$
25	B	CMe_3	CH_2CONMe_2	139-141		C	25 (0.5 hr), 40 (0.5 hr)	40	$C_{12}H_{18}N_4O_4S$
26	B	*c*-C_3H_5[i]	$CH_2CONHMe$	241-243	J	B, then D	65	6	$C_{10}H_{12}N_4O_4S$
27	B	*c*-C_3H_5	CH_2CONMe_2	172-174		B	25	18	$C_{11}H_{14}N_4O_4S$
28	B	*c*-C_3H_5	CH_2CONEt_2	154-157		B	25 (0.5 hr), 40 (0.5 hr)	55	$C_{13}H_{18}N_4O_4S$
29	B	*c*-C_3H_5	CH_2CONBu_2	99-102		B	25 (0.5 hr), 40 (0.5 hr)	41	$C_{17}H_{26}N_4O_4S$
30	B	*c*-C_3H_5	CH_2CO-piperidino	191-194		B	50	31	$C_{14}H_{18}N_4O_4S$
31	B	*c*-C_3H_5	CH_2CO_2Et	110-112	F	A	25 (0.5 hr), 40 (1 hr)	17	$C_{11}H_{13}N_3O_5S$
32	B	*c*-C_4H_7[i]	CH_2CONEt_2	97-99		A	25	25	$C_{14}H_{20}N_4O_4S$
33	B	*c*-C_4H_7	$CH_2CONHPr$	237-239		B	25	28	$C_{13}H_{18}N_4O_4S$
34	B	Ph	CH_2CONH_2	264-266 dec		E	95	50	$C_{12}H_{10}N_4O_4S$
35	B	Ph	CH_2CONMe_2	222-224		E	25	57	$C_{14}H_{14}N_4O_4S$
36	B	Ph	CH_2CONEt_2	207-209		E	120	58	$C_{16}H_{18}N_4O_4S$
37	B	Ph	CH_2CONPr_2	188-190		A	25 (1 hr), 50 (1 hr)	73	$C_{18}H_{22}N_4O_4S$
38	B	CCl_3	CH_2CONMe_2	124-126		A	25	13	$C_9H_9Cl_3N_4O_4S$
39	B	CMe_3	$CH_2CH_2CONH_2$	183-185		A	80	48	$C_{11}H_{16}N_4O_4S$
40	B	CMe_3	$CH_2CH_2CONEt_2$	114-115		A	80	54	$C_{15}H_{24}N_4O_4S$
41	B	CCl_3	$CH_2CH_2CONH_2$	162-165		A	80	28	$C_8H_7Cl_3N_4O_4S$
42	A	Me	$CH_2CH_2CH_2CN$	146-147		A	60	25	$C_9H_{10}N_4O_3S$
43	B	Me	$CH_2CH_2CH_2CN$	83-84		A	60	7	$C_9H_{10}N_4O_3S$
44	A	Me	$CH_2CH_2CH_2CONH_2$	144-145		F	*d*	34	$C_9H_{12}N_4O_4S$
45	B	Me	$CH_2CH_2CH_2CONH_2$	148-150		A	*d*	54	$C_9H_{12}N_4O_4S$
46	B	OEt	CH_2CONH_2	217-218 dec		A	25	26	$C_8H_{10}N_4O_5S$
47	B	OEt	$CH_2CONHMe$	215-216		A	25	11	$C_9H_{12}N_4O_5S$
48	B	OEt	CH_2CONMe_2	135-137		A	25	27	$C_{10}H_{14}N_4O_5S$
49	B	OEt	CH_2CONEt_2	132-134		A	25	54	$C_{12}H_{18}N_4O_5S$
50	B	OEt	CH_2CONPr_2	137-139		A	25	59	$C_{14}H_{22}N_4O_5S$
51	B	OEt	CH_2CONBu_2	130-132		A	25	65	$C_{16}H_{26}N_4O_5S$
52	A	OEt	CH_2CO_2Et	76-76.5	E	A	25 (0.5 hr), 45 (1.5 hr)	16	$C_{10}H_{13}N_3O_6S$
53	B	OEt	CH_2CO_2Et	128-129	F	A	25 (0.5 hr), 45 (1.5 hr)	26	$C_{10}H_{13}N_3O_6S$
54	B	OPh	CH_2CONMe_2	169-172		A	25	38	$C_{14}H_{14}N_4O_5S$
55	B	OPh	CH_2CONEt_2	153-155		A	25	44	$C_{16}H_{18}N_4O_5S$
56	B	OPh	CH_2CONPr_2	135-137		A	25	49	$C_{18}H_{22}N_4O_5S$
57	B	OPh	CH_2CONBu_2	97-99		A	25	31	$C_{20}H_{26}N_4O_5S$
58	B	OPh	CH_2CO-piperidino	148-149		A	60	24	$C_{17}H_{18}N_4O_5S$
59	A	OPh	CH_2CO_2Et	109-111	E	A	25	21	$C_{14}H_{13}N_3O_6S$
60	B	OPh	CH_2CO_2Et	129-131	F, G	A	25	25	$C_{14}H_{13}N_3O_6S$

[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_2O; F, compound insoluble in cold Et_2O; G, compound soluble in cold EtOAc; H, compound insoluble in cold EtOAc; J, compound insoluble in warm EtOAc. [b] A, EtOH; B, EtOAc; C, EtOAc-petroleum ether (bp 60-80°); D, MeOH; E, AcOH; F, *i*-PrOH. [c] Compound purified by recrystallization only. [d] Described in the Experimental Section. [e] C: calcd, 39.7; found, 40.2. [f] C: calcd, 50.5; found, 50.0. [g] N: calcd, 16.8; found, 17.3. [h] C: calcd, 44.3; found, 43.8. [i] *c*-C_3H_5 represents cyclopropyl, *c*-C_4H_7 represents cyclobutyl.

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

	Drug		Live schistosomes[c]	
Compd	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

[a] D represents drug–diet; G represents gavage; and S represents sc injection. [b] Represents a dose reduction based on percentage in diet. [c] 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^{-1} (Nujol) (=NCO–), and characteristic maxima at *ca.* λ 280 and 360 mμ (EtOH). Thiazoles II had maxima at *ca.* λ 235 and 340 mμ (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.

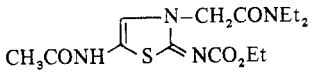
monkeys. Many of the thiazolines (III, $n = 1$) exhibited significant antischistosome activity in mice, and the most active of these are listed in Table II. Surprisingly thiazolines (III, $n = 2$ and 3) (**39**, **40**, **41**, **43**, and **45**) were all inactive in the mouse primary screen. With one 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 μg/ml, whereas the *N,N*-diethyl analog killed the worms within 15–67 hr at a concentration of 50 μg/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 gavage doses of 50–100 mg/kg per day for 10 days, but none was curative.[3]



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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‡

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.[4]

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_2 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_2O. Unless otherwise stated in Table I, the precipitated solid was filtered off, washed with H_2O, 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_2O (100 ml) and neutralized with $NaHCO_3$. Isolation with EtOAc afforded the product (**44**).

Similarly, hydrolysis of nitrile **43** afforded 2-(acetylimino)-5-nitro-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_2O (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.* ($C_{14}H_{22}N_4O_4S$) 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°, 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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‡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 ±0.4% of the theoretical values.