Antiparasitic 5-Nitrothiazoles and 5-Nitro-4-thiazolines. 4[1]

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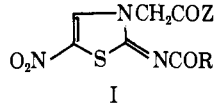
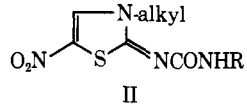
The synthesis and biological properties of some 2-heteroylimino-5-nitro-4-thiazoline-3-acetamides (I, R is heterocyclic) and some 1-(carbamoylmethyl)-1-(5-nitro-2-thiazolyl)ureas (IV, R is NHR_1) together with the corresponding ring N-substituted [3-(carbamoylmethyl)-5-nitro-4-thiazolin-2-ylidene]ureas (I, R is NHR_1) are described. I and/or IV are prepared by treatment of a DMF solution of the Na salt of the appropriate amide or urea III with several haloacetamides. Various I and some IV have significant antischistosome properties.

The synthesis of some schistosomicidal 2-acylimino-5-nitro-4-thiazoline-3-acetamides I in which R is alkyl, alkoxy, aryl, or aryloxy and Z is NR_1R_2 or alkoxy has been described earlier.[2] It was shown in this study that thiazolines I possessed very pronounced activity against the Puerto Rican strain of *Schistosoma mansoni* in experimentally infected mice. However, no compound appeared to be curative in *S. mansoni* infected rhesus monkeys, although slight to strong temporary egg suppression was observed when various I were administered in gavage doses of 50–100 mg/kg per day for 10 days. In addition, it was not found possible to draw any strict structure–activity relationships within the thiazoline series I.



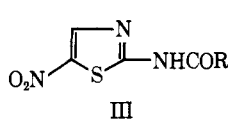
I



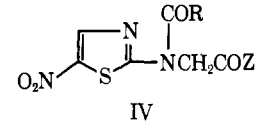
II

The present paper is concerned with the synthesis of thiazoline-3-acetamides I in which R is heterocyclic or NHR_1 (R_1 is Et or allyl). These compounds were prepared in order to attempt to delineate further structure–activity relationships existing in compounds of formula I and also hopefully to extend the potent antischistosome properties of I to primates. In particular, the preparation of ureas I in which R is NHR_1 was of interest, since it had been established that a wide variety of 1-alkyl-3-(3-alkyl-5-nitro-4-thiazolin-2-ylidene)ureas II possessed potent activities against *S. mansoni* both in mice and monkeys.[3]

Chemistry. Thiazolines I in which Z is NR_1R_2 or alkoxy (Table I, **1–7, 10–14, 16–22,** and **24–45**) and the analogs **8** and **15** were obtained in 6–74% yield by alkylation of a DMF solution of the sodium salt of the thiazolylamide or -urea III with the appropriate bromo or chloro compound. While alkylation of III (R is heterocyclic) appeared (from the ir spectra[2] of the crude reaction products) to afford little if any of the corresponding thiazole isomers IV, in most cases mixtures of ring N-alkylated ureas I (R is NHR_1) and exocyclic N-alkylated ureas IV (R is NHR_1) were formed on alkylation of the appropriate 1-(5-nitro-2-thiazolyl)ureas III (R is NHR_1) under similar conditions.



III



IV

Biology. The compounds described in the present communication were tested in mice against a Puerto Rican strain of *S. mansoni*† by Drs. P. E. Thompson and W. P. Stucki and coworkers of Parke, Davis and Co., Ann Arbor, Mich. Several of the most active thiazolines were evaluated further against *S. mansoni* in rhesus monkeys. As in previous work, drugs were administered in a powdered diet for 14 days or by gavage for 5 days, and compounds exhibiting antischistosome activity in mice are listed in Table II. It was found that thiazoline-3-acetamides **2, 5, 14, 21, 22, 25, 35, 37,** and **39** and the propionamide and butyramide analogs **15** and **9,** respectively, were inactive in the mouse primary screen. Although in general these results confirmed earlier work[2] [which showed that high antischistosome activity was confined to thiazolines I in which Z was alkoxy, NH_2, *N*-benzylamino, or *N,N*-[di(lower alkyl)amino], the lack of activity of primary amide **25** and the *N*-benzyl congener **35,** and the pyrrolidine and morpholine derivatives **37** and **39,** respectively, was a puzzling feature of the present series of compounds. Interestingly, thiazolines **43–45** derived from 1-allyl-3-(5-nitro-2-thiazolyl)urea also appeared to have no schistosomicidal activity.

While thiazole isomers of schistosomicidal 2-acylimino-5-nitro-4-thiazoline-3-acetamides I are generally inactive,[2] surprisingly in the present work thiazoles **24, 26,** and **27** were shown to cause slight but significant reductions (26–33%) in the live worm burden when administered to mice in the diet at 131–340 mg/kg per day for 14 days.

Some of the active thiazolines were administered to infected mice as a single sc injection of 100 mg/kg. When given by this route **6** and **13** lacked activity, although both these congeners possessed moderate to good efficacy when administered orally.

N,N-Dimethyl-5-nitro-2-(2-thenoylimino)-4-thiazoline-3-acetamide (**11**) was one of the most promising schistosomicides in mice, and it was selected for expanded chemotherapeutic evaluation. Against *S. mansoni* infections in rhesus monkeys, the drug caused only slight to temporary egg suppression when given in gavage doses of 50 mg/kg per day for 5 days. However, administered by a total of three separate intramuscular injections given every other day, and each of 200 mg/kg per day, **11** caused complete permanent suppression of egg production: the drug was only very slightly active though when administered similarly at 100 mg/kg per day. Another compound screened in rhesus monkeys was the sulfamic acid salt **23** of the active isonicotinoyl compound **18**; this was selected as an example of a water-soluble derivative of the thiazoline series I. However, when tested in monkeys by two intramuscular injections 4 days apart, and each of 200 mg/kg per day, **23** caused only slight to temporary suppression of egg production.

In conclusion, the available evidence suggests that although the 2-heteroylimino-5-nitro-4-thiazoline-3-acetamides I (R is heterocyclic) prepared in the present work are not curative in *S. mansoni* infected rhesus monkeys, they do possess enhanced antischistosome potency in this species. In addition, attempts to broaden the spectrum of schistosomicidal activity by the introduction of the 2-carbamoylimino moiety into thiazolines I failed; indeed, there appear to be few correlations in structure–activity terms between thiazoline-3-acetamides I and the 1-alkyl-3-(3-alkyl-5-nitro-4-thiazolin-2-ylidene)ureas II.

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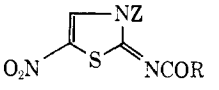
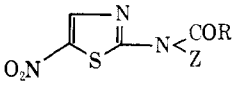
†For a description of test methods, see ref 4.

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



A



B

Compd	Type	R	Z	Mp, °C	Sepn[a] procedure	Recrystn solvent[b]	Yield, %	Formula
1	A	2-Furyl	CH_2CONH_2	266	*c*	A	26	$C_{10}H_8N_4O_5S$
2	A	2-Furyl	$CH_2CONHMe$	297–298 dec		B	37	$C_{11}H_{10}N_4O_5S$
3	A	2-Furyl	CH_2CONMe_2	218.5–220		A	47	$C_{12}H_{12}N_4O_5S$[d]
4	A	2-Furyl	CH_2CONEt_2	217–220		A	49	$C_{14}H_{16}N_4O_5S$
5	A	2-Furyl	$CH_2CONHPr$	283–284 dec		A	36	$C_{13}H_{14}N_4O_5S$
6	A	2-Furyl	CH_2CONPr_2	187–190		A	42	$C_{16}H_{20}N_4O_5S$
7	A	2-Furyl	CH_2CO_2Et	237–240		C	24	$C_{12}H_{11}N_3O_6S$
8	A	2-Furyl	$CH_2CH_2CH_2CN$	217–218		A	16	$C_{12}H_{10}N_4O_4S$
9	A	2-Furyl	$CH_2CH_2CH_2CONH_2$	208–210		C	69[e]	$C_{12}H_{12}N_4O_5S$
10	A	2-Thienyl	CH_2CONH_2	270–271		D	74[f]	$C_{10}H_8N_4O_4S_2$
11	A	2-Thienyl	CH_2CONMe_2	250–251		C	51	$C_{12}H_{12}N_4O_4S_2$[g]
12	A	2-Thienyl	CH_2CONEt_2	201–202		C	45	$C_{14}H_{16}N_4O_4S_2$
13	A	2-Thienyl	CH_2CONPr_2	194–195		C	59	$C_{16}H_{20}N_4O_4S_2$
14	A	2-Thienyl	CH_2CONBu_2	190–191		C	57	$C_{18}H_{24}N_4O_4S_2$
15	A	2-Thienyl	$CH_2CH_2CONH_2$	262–263 dec		B	36[h,i]	$C_{11}H_{10}N_4O_4S_2$
16	A	2-Pyridyl	CH_2CONMe_2	234–236 dec		A[j]	13[k]	$C_{13}H_{13}N_5O_4S$
17	A	3-Pyridyl	CH_2CONMe_2	246–247 dec		A	12	$C_{13}H_{13}N_5O_4S$
18	A	4-Pyridyl	CH_2CONMe_2	243–245 dec		E	23	$C_{13}H_{13}N_5O_4S$
19	A	4-Pyridyl	CH_2CONEt_2	194–196		C	17	$C_{15}H_{17}N_5O_4S$
20	A	4-Pyridyl	CH_2CONPr_2	188–190		C	18	$C_{17}H_{21}N_5O_4S$
21	A	4-Pyridyl	CH_2CONBu_2	209–211		C	49	$C_{19}H_{25}N_5O_4S$
22	A	4-Pyridyl	$CH_2CONH\text{-}C_6H_4\text{-}p\text{-}NO_2$	263–264 dec[l]		B	15	$C_{17}H_{12}N_6O_6S$
23	A	4-Pyridyl	CH_2CONMe_2	220–223 dec		D	59[e]	$C_{15}H_{13}N_5O_4S$ NH_2SO_3H
24	B	NHEt	CH_2CONH_2	206	A	A	15	$C_8H_{11}N_5O_4S$
25	A	NHEt	CH_2CONH_2	236 dec	B	C	10	$C_8H_{11}N_5O_4S$
26	B	NHEt	$CH_2CONHMe$	181–182		G	17	$C_9H_{13}N_5O_4S$[m]
27	B	NHEt	CH_2CONMe_2	168.5–169.5	C	C	10	$C_{10}H_{15}N_5O_4S$
28	B	NHEt	CH_2CONEt_2	182–183	C	C	10	$C_{12}H_{19}N_5O_4S$
29	A	NHEt	CH_2CONEt_2	202–203	D	C	14	$C_{12}H_{19}N_5O_4S$[n]
30	B	NHEt	$CH_2CONHPr$	184–185		G	6	$C_{11}H_{17}N_5O_4S$
31	B	NHEt	CH_2CONPr_2	175–176	C	C	10	$C_{14}H_{23}N_5O_4S$
32	A	NHEt	CH_2CONPr_2	175	D	C	10	$C_{14}H_{23}N_5O_4S$
33	B	NHEt	CH_2CONBu_2	154–155	C	C	16	$C_{16}H_{27}N_5O_4S$
34	A	NHEt	CH_2CONBu_2	174	D	C	20	$C_{16}H_{27}N_5O_4S$
35	B	NHEt	$CH_2CONHCH_2Ph$	184–185	C	C	10	$C_{15}H_{17}N_5O_4S$[o]
36	A	NHEt	$CH_2CONHCH_2Ph$	207–208	D	C	14	$C_{15}H_{17}N_5O_4S$
37	A	NHEt	$CH_2CO\text{-}c\text{-}NC_4H_8$	264 dec		C	9	$C_{12}H_{17}N_5O_4S$
38	A	NHEt	$CH_2CO\text{-}c\text{-}NC_5H_{10}$	241–242		C	22	$C_{13}H_{19}N_5O_4S$
39	A	NHEt	$CH_2CO\text{-}c\text{-}N(CH_2CH_2)_2O$	259–260		C	12	$C_{12}H_{17}N_5O_5S$
40	A	NHEt	$CH_2CONHCO_2Et$	219–220 dec	E	G	7	$C_{11}H_{15}N_5O_6S$
41	A	NHEt	$CH_2CON(Me)CO_2Et$	124–126		H	8	$C_{12}H_{17}N_5O_6S$
42	A	NHEt	$CH_2CONHCONH_2$	239–241 dec		I	12	$C_9H_{12}N_6O_5S$
43	A	$NHCH_2CH{=}CH_2$	$CH_2CONHCO_2Me$	212–214 dec		D	8	$C_{11}H_{13}N_5O_6S$ $0.5H_2O$
44	A	$NHCH_2CH{=}CH_2$	$CH_2CONHCO_2Et$	202–203 dec		J	11	$C_{12}H_{15}N_5O_6S$
45	A	$NHCH_2CH{=}CH_2$	$CH_2CONHCONH_2$	217–219 dec		I	20	$C_{10}H_{12}N_6O_5S$

[a] A, product insoluble in excess cold AcOH; B, product soluble in excess cold AcOH; C, product insoluble in excess cold EtOH; D, product soluble in excess cold EtOH; E, product insoluble in cold EtOAc. [b] A, AcOH; B, DMF; C, EtOH; D, MeOH; E, aqueous DMF; F, H_2O; G, EtOAc; H, C_6H_6, EtOAc, and then *i*-PrOH; I, aqueous DMF followed by hot H_2O wash; J, *i*-PrOH. [c] Purified by recrystallization only. [d] N: calcd, 17.8; found, 17.1. [e] Described in the Experimental Section. [f] Reaction temperature 60°. [g] N: calcd, 16.5; found, 16.0. [h] 3-Bromopropionamide added to a preheated (100°) solution of the Na Salt in DMF. [i] Reaction temperature 100°. [j] Crude product stirred with DMF (1 g in 10 ml) to remove insoluble starting material; recrystallized material washed with hot H_2O. [k] Reaction temperature 50°. [l] Varies with the rate of heating. [m] N: calcd, 24.4; found, 23.9. [n] N: calcd, 21.3; found, 20.8. [o] N: calcd, 19.3; found, 18.8.

Experimental Section‡

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

General Alkylation Procedure.[2] NaH (0.1 mol) was added in portions to a solution of the thiazolylamide (0.1 mol) in DMF at 0°, and the mixture was then stirred at room temperature until H_2 evolution ceased. The bromo- or chloro-alkylating agent[5] (0.11 mol) was added, and the mixture was stirred at room temperature until the pH reached 7.0. Dilution with ice-H_2O precipitated the crude product which was washed well with H_2O. The techniques used (when necessary) to separate thiazoline and thiazole isomers are given in Table I.

2-(2-Furoylimino)-5-nitro-4-thiazoline-3-butyramide (9). Nitrile **8** (1 g) was stirred with concentrated HCl (25 ml) for 2.5 hr at room temperature. The filtered solution was then diluted with H_2O (200 ml) to precipitate the product **9**.

Sulfamic Acid Salt (23) of *N*-[3-[(Dimethylcarbamoyl)-methyl]-5-nitro-4-thiazolin-2-ylidene]isonicotinamide. A solution of isonicotinamide **18** (9.8 g) in the minimum of boiling MeOH was charcoaled and filtered and then treated with a filtered hot solution of sulfamic acid (slight excess) in the minimum amount of MeOH. The mixture was cooled slowly, and the pre-

‡Melting points are corrected and were determined in capillary tubes. Analytical results were obtained for C, H, and N for all compounds, and, unless otherwise stated, were within ±0.4% of the theoretical values.

Table II. Effects of 5-Nitro-4-thiazolines **1–45** against *S. mansoni* in Mice

Compd	Drug		Live schistosomes[c]	
	Route × days[a]	mg/kg per day	% mice positive	% reduction
1	G × 5	400	87	21
3	D × 14	384	16	95
	S × 1	100	87	61
4	D × 14	345	33	93
	S × 1	100	12	99
6	D × 14	220	100	76
7	G × 5	400	57	53
10	G × 5	200	43	89
11	D × 14	372	0	100
	G × 5	50	87	84
	S × 1	100	90	87
12	D × 7, then D × 7	142, then 125[b]	60	86
13	D × 14	251	83	33
16	G × 5	200	25	91
	S × 1	100	37	87
17	G × 5	200	50	73
	S × 1	100	12	94
18	G × 5	200	25	91
	S × 1	100	100	69
19	D × 7, then D × 7	121, then 107[b]	50	72
20	D × 7, then D × 7	58, then 35[b]	100	29
24	D × 7, then D × 7	217, then 237[b]	100	31
26	D × 14	256	100	33
27	D × 7, then D × 7	340, then 131[b]	100	26
29	D × 14	396	33	94
	G × 5	400	75	63
32	D × 14	318	100	52
34	D × 14	229	100	23
38	D × 14	419	100	35
41	G × 5	400	100	88
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 six and eight animals, respectively, were used in the diet and gavage studies. The worm burden of the controls averaged 15 per mouse.

cipitated solid was washed with Et_2O and then recrystallized from MeOH.

N-(**5-Nitro-2-thiazolyl**)**picolinamide** (**46**). Freshly prepared picolinoyl chloride hydrochloride (from 98.4 g of picolinic acid) was added in portions to a suspension of 2-amino-5-nitrothiazole (87.0 g) in pyridine (500 ml) while the temperature was maintained below 30° (cooling). The mixture was then stirred 2 hr at room temperature and poured into H_2O. The product **46** (80%) was collected, washed well with H_2O, and dried; mp 268–274°. A small portion recrystallized from AcOH had mp 276–277°. *Anal.* ($C_9H_6N_4O_3S$) C, H, N.

N-(**5-Nitro-2-thiazolyl**)**isonicotinamide** (**47**). Prepared similarly to amide **46** above, the isonicotinamide analog **47** (42%) had mp 253–255° dec (from EtOAc). *Anal.* ($C_9H_6N_4O_3S$) C, H, N.

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