1-Alkyl-3-(3-alkyl-5-nitro-4-thiazolin-2-ylidene)ureas and Related Compounds as Schistosomicides

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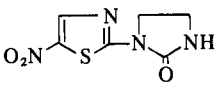
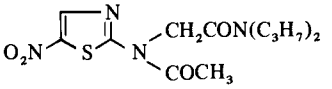
A wide variety of 1-alkyl-3-(3-alkyl-5-nitro-4-thiazolin-2-ylidene)ureas, 1-alkyl-3-(3-aralkyl-5-nitro-4-thiazolin-2-ylidene)ureas (IV), and related compounds have been prepared. The two main preparative routes involved nitration of a urea, obtained from an isocyanate and a 3-substituted-2-iminothiazoline, and alkylation of a 1-alkyl-3-(5-nitro-2-thiazolyl)urea with the desired halide in the presence of NaH. Activity against *Schistosoma mansoni* infections is widespread among these compounds both in mice and monkeys. Structure-activity relationships are discussed.

Activity among structures related to the schistosomicide niridazole (I) has been shown to be quite limited. Even minor modifications completely eliminate activity against the parasite.[1] In extending our studies to still other structures bearing some similarity to the niridazole molecule, it was found surprisingly that although II had little activity the isomeric 2-(acetylimino)-5-nitro-*N,N*-dipropyl-4-thi-

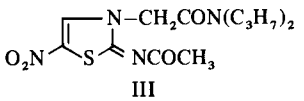


I

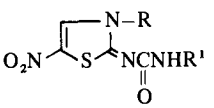


II

azoline-3-acetamide (III) was highly active against *Schistosoma mansoni* infections.[2] Follow-up of this exciting lead revealed rapidly that unlike the niridazole types potent activity was widespread among the thiazolines, notwithstanding a wide variety of structural modifications. Work on the analogs of III has been described in the accompanying article.[3] In this paper we describe the extension of this work to a series of nitrothiazoline urea derivatives (IV).[4]



III



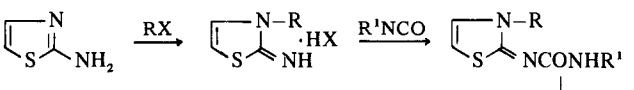
IV

Chemistry. Two routes were used to prepare the majority of these compounds, and they are depicted below. In procedure A, 2-aminothiazole, which is known to alkylate on the ring nitrogen, was treated with an alkyl halide to provide the 3-alkyl-2-iminothiazoline. The urea was then prepared by the action of an isocyanate on this material, and nitration provided the desired nitrothiazoline urea IV. To prepare some tertiary ureas a dialkylaminocarbamoyl chloride could be substituted for the isocyanate in procedure A. In those cases where the carbamoyl chloride was not readily available tertiary ureas could also be obtained by the fusion of an amine with phenyl 3-ethyl-4-thiazoline-$\Delta^{2,N}$-carbamate prepared from 3-ethyl-2-iminothiazoline and phenyl chloroformate.†

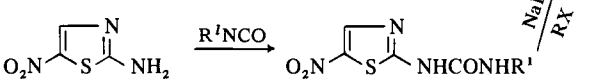
It is of interest to note that in the attempt to prepare 1-(3-ethyl-5-nitro-4-thiazolin-2-ylidene)-3,3-diisopropylurea *via* nitration of the corresponding urea only 1-(3-ethyl-5-nitro-4-thiazolin-2-ylidine)-3-isopropylurea resulting from the loss of one of the isopropyl groups could be isolated.

†This procedure was developed by D. B. Capps and will be the subject of a separate communication.

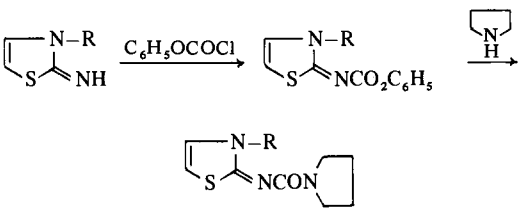
Procedure A



Procedure B

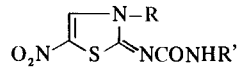


Procedure B involved formation of the 1-alkyl-3-(5-nitro-2-thiazolyl)ureas by the reaction of an isocyanate with 2-amino-5-nitrothiazole, followed by alkylation with an alkyl halide of the urea anion formed by the action of NaH. This method affords the possibility of obtaining three isomeric products resulting from alkylation on the ring N, the N in the 2 position of the thiazole ring, or the terminal urea N.



In many cases low yields were obtained, and, in several instances, isomeric materials were isolated in addition to IV, thus confirming the presence of several reactive sites. In most cases, however, it was possible to obtain the desired product without difficulty simply by recrystallization. The structure of the isomer isolated in this procedure was confirmed in several cases by demonstrating the identity of the products obtained in procedures A and B. In those cases where both routes were not utilized, the structure could be confirmed readily spectroscopically. Thus the nmr spectra of type IV reveal the singlet for the thiazoline ring proton shifted downfield to 8.9-9.1 ppm (in DMSO) in contrast to the isomeric aromatic compounds wherein this ring proton appears at 8.5 ppm. The ultraviolet spectra are also diagnostic for type IV since these compounds exhibit a pronounced hypsochromic shift in methanol in the presence of base (OH^-). The isomeric aromatic compounds containing a proton on the N in the 2 position of the thiazole, *i.e.*, resulting from alkylation on the terminal N, exhibited a striking bathochromic shift in basic methanol. Alkylation at the 2-N however gave products whose spectra did not

Table I. 1-Alkyl-3-(3-alkyl-5-nitro-4-thiazolin-2-ylidene)ureas



No.	R	R'	Mp, °C	Yield purified, %	Procedure	Purifn solvent	Formula	Analyses	Activity *vs. S. mansoni* in mice[g] Drug: Route X days	Drug: mg/kg per day	Live worms: % mice positive	Live worms: % reduction
1	Et	H	231–233	9	B	MeCN	$C_6H_8N_4O_3S$	C, H; N[a]	G X 5	400	75	85
2	Et	Me	244–245	47	B	*i*-PrOH	$C_7H_{10}N_4O_3S$	C, H, N	D X 14	307	0	100
									G X 5	400	14	99
									G X 5	100	100	69
3	$CH_2C{\equiv}CH$	Me	201–202	39	B	*i*-PrOH	$C_8H_8N_4O_3S$	C, H, N	G X 5	400	0	100
									G X 5	100	100	74
4	$CH_2CH{=}CHCl$	Me	155–158	9	B	MeOH	$C_8H_9ClN_4O_3S$	C, H, N	G X 5	200	0	100
									G X 5	50	100	17
5	$CH_2C(CH_3){=}CCl_2$	Me	160–162	40	B	MeOH	$C_9H_7Cl_2N_4O_3S$	C, H, N	G X 5	200	62	83
6	$CH_2C(CH_3){=}CH_2$	Me	135–136	25	B	MeOH	$C_9H_{13}N_4O_3S$	C, H, N	G X 5	200	63	89
7	Me	Et	188–190	26	A	*i*-PrOH	$C_7H_{10}N_4O_3S$	C, H, N	G X 5	400	75	84
									G X 5	100	100	0
8	CH_2SCH_3	Et	151–153	6	B-1	*i*-PrOH	$C_8H_{12}N_4O_3S_2$	C, H, N	G X 5	400	25	98
									G X 5	100	100	0
9	Et	Et	176–178	23	A	EtOAc	$C_8H_{12}N_4O_3S$	C, H, N	G X 5	400	0	100
									G X 5	100	87	15
									D X 14	279	100	27
10	$HOCH_2CH_2$	Et	241–243	12	B-1	MeCN	$C_8H_{12}N_4O_4S$	C, H, N	D X 14	332	83	76
									G X 5	400	86	47
									G X 5	100	100	0
11	$CH_2CH_2SCH_3$	Et	144–146	16	B-1	*i*-PrOH	$C_9H_{14}N_4O_3S_2$	C, H, N	G X 5	400	75	85
12	$(CH_2)_2SCH_2CH_3$	Et	114–116	16	B-1	*i*-PrOH	$C_{10}H_{16}N_4O_3S_2$	C, H, N	G X 5	400	37	92
13	$(CH_2)_2OCH_2CH_3$	Et	131.5–135	15	B-1	*i*-PrOH	$C_{10}H_{16}N_4O_4S$	C, H, N	G X 5	400	14	98
									G X 5	100	100	0
14	Pr	Et	156–158	17	A	*i*-PrOH	$C_9H_{14}N_4O_3S$	C, H, N	G X 5	200	16	97
									G X 5	100	100	17
15	$CH_2CH{=}CH_2$	Et	151–153	20	B	MeCN	$C_9H_{12}N_4O_3S$	C, H, N	D X 14	306	0	100
									G X 5	400	14	99
									G X 5	100	100	22
16	$CH_2C{\equiv}CH$	Et	171–173	23	B	*i*-PrOH	$C_9H_{10}N_4O_3S$	C, H, N	D X 14	252	0	100
									G X 5	400	0	100
									G X 5	100	50	89
17	$CH_2CH{=}CHCl$	Et	134–138	14	B	EtOAc–petr ether	$C_9H_{11}ClN_4O_3S$	C, H, N	G X 5	400	0	100
									G X 5	100	12	99
									G X 5	50	100	47
18	$CH_2C(CH_3){=}CH_2$	Et	163–165	8	B	MeOH	$C_{10}H_{14}N_4O_3S$	C, H, N	G X 5	200	100	49
19	$CH_2C(CH_3){=}CCl_2$	Et	156–159	44	B	EtOAc	$C_{10}H_{12}Cl_2N_4O_3S$	C, H, N	G X 5	200	28	95
									G X 5	50	100	35
20	$CH_2CHBrCH_2Br$	Et	156–157	38	D	EtOH	$C_9H_{12}Br_2N_4O_3S$	C, H, N	G X 5	400	12	97
									G X 5	100	100	53
21	$CH(CH_3)_2$	Et	167–170	26	B	*i*-PrOH	$C_9H_{14}N_4O_3S$	C, H, N	D X 14	334	84	84
									G X 5	400	87	71
22	Bu	Et	137–139	28	A	*i*-PrOH	$C_{10}H_{16}N_4O_3S$	C, H; N[b]	D X 7	278	0	100
									D X 7	270		
23	$CH_2CH(CH_3)_2$	Et	148–151	14	B-1	*i*-PrOH	$C_{10}H_{16}N_4O_3S$	C, H, N	D X 14	302	83	85
									G X 5	400	88	50

24	$CH_2CH(CH_2)_2$	Et	156–158	27	B-1	*i*-PrOH	$C_{10}H_{14}N_4O_3S$	C, H, N	G X 5	200	75	92
25	$(CH_2)_4CH_3$	Et	114–117	23	B-1	*n*-Heptane	$C_{11}H_{18}N_4O_3S$	C, H, N	G X 5	400	0	100
									G X 5	100	75	72
26	$(CH_2)_6CH_3$	Et	99–101	37	B-1	*i*-PrOH–H_2O	$C_{13}H_{22}N_4O_3S$	C, H, N	G X 5	400	75	85
27	$(CH_2)_7CH_3$	Et	97–100	31	B-1	isooctane	$C_{14}H_{24}N_4O_3S$	C, H, N	D X 14	322	100	0
									G X 5	400	100	0
28	$CH_2C_6H_{11}$	Et	201–202	26	B-1	*i*-PrOH	$C_{13}H_{20}N_4O_3S$	C, H, N	D X 14	312	100	16
									G X 5	400	100	12
29	$(CH_2)_2C_6H_{11}$	Et	160–163	33	B-1	*i*-PrOH	$C_{14}H_{22}N_4O_3S$	C, H, N	D X 14	336	33	92
									G X 5	400	100	38
30	Et	$CH_2CH=CH_2$	141–143.5	29	B	*i*-PrOH	$C_9H_{12}N_4O_3S$	C, H, N	D X 14	270	50	90
									G X 5	400	57	91
									G X 5	100	100	0
31	$HOCH_2CH_2$	$CH_2CH=CH_2$	186–187	41	B	*i*-PrOH	$C_9H_{12}N_4O_4S$	C, H, N	G X 5	400	20	98
									G X 5	100	86	8
32	$CH_2CH_2OCH_3$	$CH_2CH=CH_2$	103–105	3.5	B-1	MeCN–H_2O	$C_{10}H_{14}N_4O_4S$	C, H, N	D X 14	259	0	100
									D X 14	91	83	58
33	$CH_2CH=CH_2$	$CH_2CH=CH_2$	118–121	30	B	MeOH	$C_{10}H_{12}N_4O_3S$	C, H, N	G X 5	200	87	62
34	$CH_2C\equiv CH$	$CH_2CH=CH_2$	144.5–147.5	30	B	MeOH	$C_{10}H_{10}N_4O_3S$	C, H, N	G X 5	200	16	99
									G X 5	50	100	0
35	$CH_2CH=CHCl$	$CH_2CH=CH_2$	141–143	7	B	EtOAc–petr ether	$C_{10}H_{11}ClN_4O_3S$	C, H, N	G X 5	200	12	99
									G X 5	50	100	26
36	$CH_2C(CH_3)=CH_2$	$CH_2CH=CH_2$	112–115	34	B	EtOH	$C_{11}H_{14}N_4O_3S$	C, H, N	G X 5	200	100	10
37	$CH_2C(CH_3)=CCl_2$	$CH_2CH=CH_2$	141–143	40	B	MeOH	$C_{11}H_{12}Cl_2N_4O_3S$	C, H, N	G X 5	200	63	53
38	Et	$CH(CH_3)_2$	163–166	12	A	EtOH–H_2O	$C_9H_{14}N_4O_3S$	C, H, N	G X 5	400	100	44
39	Et	Bu	111–115	48	A	*i*-PrOH	$C_{10}H_{16}N_4O_3S$	C, H, N	D X 14	347	66	90
									G X 5	400	87	70
40	Et	$C(CH_3)_3$	134–136	20	B-1	*i*-Pr_2O	$C_{10}H_{16}N_4O_3S$	C, H, N	G X 5	400	100	9
41	Et	C_8H_{17}	111–113	28	A	*i*-PrOH	$C_{13}H_{20}N_4O_3S$	C, H, N	D X 14	355	100	0
									G X 5	400	100	35
					1-(Alkyl)-3-(3-aralkyl-5-nitro-4-thiazolin-2-ylidene)ureas							
42	$CH_2C_6H_5$	Me	188.5–190	49	B-1	*i*-PrOH	$C_{12}H_{12}N_4O_3S$	C, H, N	G X 5	200	0	100
									G X 5	50	100	0
43	$CH_2C_6H_5$	Et	148–150	41	B-1	*i*-PrOH	$C_{13}H_{14}N_4O_3S$	C, H, N	D X 14	285	0	100
									G X 5	100	0	100
									G X 5	50	37	70
44	$CH_2C_6H_4$-3-Br	Et	156–159	38	B-1	*i*-PrOH	$C_{13}H_{13}BrN_4O_3S$	C, H, N	G X 5	400	0	100
									G X 5	100	37	95
45	$CH_2C_6H_4$-4-Br	Et	164–166.5	5	B-1	*i*-PrOH	$C_{13}H_{13}BrN_4O_3S$	C, H, N	G X 5	100	0	100
									G X 5	50	87	73
46	$CH_2C_6H_4$-2-Cl	Et	126–127[h]	44	B-1	*i*-PrOH	$C_{13}H_{13}ClN_4O_3S$	C, H, N	G X 5	400	0	100
									G X 5	100	75	86
47	$CH_2C_6H_4$-3-Cl	Et	158.5–161.5	17	B-1	EtOAc–iso-octane	$C_{13}H_{13}ClN_4O_3S$	C, H, N	G X 5	400	25	94
									G X 5	50	75	31
48	$CH_2C_6H_4$-4-Cl	Et	142–142.5[i]	37	B-1	EtOH	$C_{13}H_{13}ClN_4O_3S$	C, H, N	D X 14	286	0	100
									G X 5	400	0	100
									G X 5	50	25	94
49	$CH_2C_6H_4$-3-F	Et	161–163	18	B-1	*i*-PrOH	$C_{13}H_{13}FN_4O_3S$	C, H, N	G X 5	400	0	100
									G X 5	50	100	54
50	$CH_2C_6H_3$-2,4-Cl_2	Et	156.5–159.5	35	B-1	*i*-PrOH	$C_{13}H_{12}Cl_2N_4O_3S$	C, H, N	G X 5	400	57	91
51	$CH_2C_6H_3$-3,4-Cl_2	Et	202–206	46	B-1	MeCN	$C_{13}H_{12}Cl_2N_4O_3S$	C, H, N	D X 14	335	84	83
									G X 5	400	100	37
52	$CH_2C_6H_3$-2,6-Cl_2	Et	190–191	89	B-1		$C_{13}H_{12}Cl_2N_4O_3S$	C, H, N	G X 5	400	100	16

Table I *(Continued)*

No.	R	R'	Mp, °C	Yield purified, %	Procedure	Purifn solvent	Formula	Analyses	Activity *vs. S. mansoni* in in mice[g] Drug Route X days	Drug mg/kg per day	Live worms % mice positive	Live worms % reduction
53	$CH_2C_6H_4$-4-NO_2	Et	171–172	20	A	*i*-PrOH	$C_{13}H_{13}N_5O_5S$	C, H, N	D X 14	328	0	100
									G X 5	200	12	99
									G X 5	50	100	17
54	$CH_2C_6H_3$-4-NO_2-2-OH	Et	195–197	13	B-1	*i*-PrOH	$C_{13}H_{13}N_5O_6S \cdot C_3H_8O$	C, H; N[c]	G X 5	400	100	0
55	$CH_2C_6H_4$-2-Me	Et	183–185	41	B-1	EtOH	$C_{14}H_{16}N_4O_3S$	C, H, N	G X 5	400	37	94
56	$CH_2C_6H_4$-3-Me	Et	128–131	26	B-1	*i*-PrOH	$C_{14}H_{16}N_4O_3S$	C, H, N	G X 5	400	12	99
									G X 5	100	100	0
57	$CH_2C_6H_4$-4-Me	Et	169.5–171.5	48	B-1	MeCN	$C_{14}H_{16}N_4O_3S$	C, H, N	D X 14	304	0	100
									G X 5	400	100	27
58	$CH_2C_6H_4$-2-CN	Et	175–178	23	B-1	EtOAc	$C_{14}H_{13}N_5O_3S$	C, H, N	G X 5	200	0	100
									G X 5	50	75	88
59	$CH_2C_6H_4$-3-CN	Et	195–198	44	B-1	MeCN	$C_{14}H_{13}N_5O_3S$	C, H, N	G X 5	200	0	100
									G X 5	50	100	68
60	$CH_2C_6H_4$-4-CN	Et	178–182	10	B-1	*i*-PrOH	$C_{14}H_{13}N_5O_3S$	C, H, N	G X 5	400	0	100
									G X 5	100	25	96
61	$CH_2C_6H_4$-4-OMe	Et	175–178	45	B-1	*i*-PrOH	$C_{14}H_{16}N_4O_4S$	C, H, N	G X 5	400	86	0
62	$CH_2C_6H_3$-2,4-Me_2	Et	156–159	42	B-1	*i*-PrOH	$C_{15}H_{18}N_4O_3S$	C, H, N	D X 14	308	0	100
									G X 5	400	100	30
63	$CH_2C_6H_3$-3,4-Me_2	Et	156–158	24	B-I	*i*-PrOH	$C_{15}H_{18}N_4O_3S$	C, H, N	G X 5	400	100	7
64	$CH_2C_6H_4$-3-CO_2Me	Et	209–211.5	37	B-1	MeCN	$C_{15}H_{16}N_4O_5S$	C, H, N	G X 5	400	100	0
65	$CH_2C_6H_2$-2-Cl-3,4(OCH_2O)	Et	180–182	51	B-1	EtOAc–iso-octane	$C_{14}H_{13}ClN_4O_5S$	C, H, N	G X 5	400	100	0
66	$CH_2C_6H_2$-2,4,6-Me_3	Et	226.5–230	35	B-1	MeCN	$C_{16}H_{20}N_4O_3S$	C, H, N	G X 5	400	100	0
67	$CH_2C_6H_4$-3-OiPr	Et	170.5–173.5	45	B-1	*i*-PrOH	$C_{16}H_{20}N_4O_4S$	C, H, N	G X 5	400	100	0
68	$CH_2C_6H_4$-4-$OCH_2C_6H_5$	Et	144–145.5	44	B-1	EtOH	$C_{20}H_{20}N_4O_4S$	C, H, N	D X 14	302	100	15
									G X 5	400	86	11
69	$CH(CH_3)C_6H_5$	Et	179–181	23	B-1	*i*-PrOH	$C_{14}H_{16}N_4O_3S$	C, H, N	G X 5	400	25	91
70	CH_2-α-naphthyl	Et	170.5–174	42	B	EtOH	$C_{17}H_{16}N_4O_3S$	C, H, N	G X 5	400	86	28
71	$CH_2C_6H_5$	$CH_2CH{=}CH_2$	115.5–117	31	B-1	EtOH	$C_{14}H_{14}N_4O_3S$	C, H, N	G X 5	400	0	100
									G X 5	50	87	67
72	$CH_2C_6H_4$-2-Cl	$CH_2CH{=}CH_2$	94–96	11	B	C_6H_6	$C_{14}H_{13}ClN_4O_3S$	C, H, N	G X 5	400	0	100
									G X 5	100	86	47
73	$CH_2C_6H_4$-3-Cl	$CH_2CH{=}CH_2$	99–102	22	B	C_6H_6	$C_{14}H_{13}ClN_4O_3S$	C, H, N	G X 5	200	43	85
74	$CH_2C_6H_4$-4-Cl	$CH_2CH{=}CH_2$	165.5–167.5	17	B	C_6H_6	$C_{14}H_{13}ClN_4O_3S$	C, H, N	G X 5	400	87	65
75	$CH_2C_6H_4$-2-NO_2	$CH_2CH{=}CH_2$	114–115	10	B	EtOAc	$C_{14}H_{13}N_5O_5S$	C, H, N	G X 5	400	12	99
									G X 5	100	100	64
76	$CH_2C_6H_4$-3-NO_2	$CH_2CH{=}CH_2$	163–164	28	B	EtOAc	$C_{14}H_{13}N_5O_5S$	H; C, N[d]	G X 5	400	0	100
									G X 5	100	57	87
77	$CH_2C_6H_4$-4-NO_2	$CH_2CH{=}CH_2$	148–150	23	B	EtOAc	$C_{14}H_{13}N_5O_5S$	H; C, N[e]	G X 5	400	37	93
78	$CH_2C_6H_5$	CH_2-c-$CHCH_2O$	161–164	42		EtOH	$C_{14}H_{14}N_4O_4S$	C, H, N	G X 5	200	100	13
79	$CH_2C_6H_5$	$CH_2CHOHCH_2OH$	145–149	16		MeOH	$C_{14}H_{16}N_4O_5S$	C, H, N	G X 5	400	100	20
80	$CH_2C_6H_5$	$CH_2CHBrCH_2Br$	136–138	58	D	EtOH	$C_{14}H_{14}Br_2N_4O_3S$	C, H, N	G X 5	400	100	16
81	$CH_2C_6H_5$	$(CH_2)_3OCH_3$	139–141	37	C	*i*-PrOH	$C_{15}H_{18}N_4O_4S$	C, H, N	G X 5	400	100	0
82	$CH_2C_6H_5$	$(CH_2)_3SCH_3$	135.5–137.5	75	C	*i*-PrOH	$C_{15}H_{18}N_4O_3S_2$	H, N, S; C[f]	G X 5	400	100	3
83	$CH_2C_6H_5$	$CH(CH_3)_2$	167–169	43	B-1	*i*-PrOH	$C_{14}H_{16}N_4O_3S$	C, H, N	G X 5	100	87	48
84	$CH_2C_6H_4$-4-NO_2	$(CH_2)_3CH_3$	122–125	23	B-1	C_6H_6	$C_{15}H_{17}N_5O_5S$	C, H, N	G X 5	400	37	89
85	$CH_2C_6H_5$	$C(CH_3)_3$	186–186.5	15	B-1	*i*-PrOH	$C_{15}H_{18}N_4O_3S$	C, H, N	G X 5	400	100	0
86	$CH_2C_6H_5$	$(CH_2)_5CH_3$	104–105	27	B-1	*i*-PrOH	$C_{17}H_{22}N_4O_3S$	C, H, N	G X 5	400	87	5

87	$CH_2C_6H_5$	$(CH_2)_{11}CH_3$	85–86	17	B-1	*i*-PrOH	$C_{23}H_{34}N_4O_3S$	C, H, N	D X 14	353	100	16
88	$CH_2C_6H_5$	$CH_2CO_2C_2H_5$	133–136	69	C	*i*-PrOH	$C_{15}H_{16}N_4O_5S$	C, H, N	G X 5	400	100	0
					Miscellaneous Ureas							
89	Et	*c*-$C_3H_3C_6H_5$[j]	195–197	26	B	*i*-PrOH	$C_{15}H_{16}N_4O_3S$	C, H, N	D X 14	297	100	0
									G X 5	400	100	30
90	Et	C_6H_5	179–180	17	B-1	*i*-PrOH	$C_{12}H_{12}N_4O_3S$	C, H, N	D X 14	314	100	0
									G X 5	400	100	0
91	Et	C_6H_{11}	158–160	25	A	*i*-PrOH	$C_{12}H_{18}N_4O_3S$	C, H, N	D X 14	329	0	100
									G X 5	400	75	84
92	$CH_2C_6H_5$	C_6H_5	210–212	32	B-1	*i*-PrOH	$C_{17}H_{14}N_4O_3S$	C, H, N	D X 14	345	100	7
									G X 5	400	87	38
93	$CH_2C_6H_5$	C_6H_{11}	203.5–206	42	B-1	EtOH	$C_{17}H_{20}N_4O_3S$	C, H, N	D X 14	300	83	72
									G X 5	400	100	29
94	$CH_2C_6H_5$	$CH_2C_6H_5$	124–127	48	C	*i*-PrOH	$C_{18}H_{16}N_4O_3S$	C, H, N	G X 5	400	100	0
95	$CH_2C_6H_5$	$(CH_2)_2C_6H_5$	183–185	42	C	MeCN	$C_{19}H_{18}N_4O_3S$	C, H, N	G X 5	400	100	0
96	$(CH_2)_2C_6H_5$	Et	135.5–138.5	25	B-1	*i*-PrOH	$C_{14}H_{16}N_4O_3S$	C, H, N	D X 14	356	83	68
									G X 5	400	100	54
97	$(CH_2)_3OC_6H_5$	Et	135.5–138	23	B-1	*i*-PrOH	$C_{15}H_{18}N_4O_4S$	C, H, N	D X 14	413	100	68
98	$(CH_2)_2OCH_2C_6H_5$	Et	117–120.5	3	B-1	*i*-PrOH	$C_{15}H_{18}N_4O_4S$	C, H, N	G X 5	400	86	35
99	$(CH_2)_2O(CH_2)_2OC_6H_5$	Et	152.5–154	7	B-1	*i*-PrOH	$C_{16}H_{20}N_4O_5S$	C, H, N	G X 5	400	75	50
100	$CH_2C_6H_5$	$SO_2C_6H_4$-4-CH_3	232–233.5	15	C	MeCN	$C_{18}H_{16}N_4O_5S_2$	C, H, N	G X 5	400	100	0
	Niridazole								D X 14	249	17	99
									G X 5	100	100	53

[a] N: calcd, 25.91; found, 26.40. [b] N: calcd, 20.57; found, 21.06. [c] N: calcd, 16.40; found, 15.98. [d] C: calcd, 46.3; found, 45.8. N: calcd, 19.3; found, 18.8. [e] C: calcd, 46.3; found, 45.8. N: calcd, 19.3; found, 18.8. [f] C: calcd, 49.18; found, 49.60. S: calcd, 17.50; found, 17.48. [g] 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. [h] Resolidifies and remelts 152–154°. [i] Resolidifies and remelts 162.5–164°. [j] *c*-$C_3H_3C_6H_5$ represents 2-phenylcyclopropyl.

shift upon changing from acid to basic methanol, although on occasion it appeared that these tertiary derivatives were unstable in basic methanol as evidenced by the rapid development of a band at high wavelength.

In those instances where the isocyanate was in short supply, it was found convenient to utilize a 3-alkyl-2-imino-5-nitro-4-thiazoline as the starting material (procedure C).

Procedure C

Thus acid hydrolysis of *N*-(3-ethyl-5-nitro-4-thiazolin-2-ylidene)-2,2-dimethylpropionamide[5] afforded 3-ethyl-2-imino-5-nitro-4-thiazoline (V) isolated as the hydrochloride salt. Treatment with an isocyanate then provided the desired urea. These intermediates also allowed the synthesis of bis urea VI (**108**) as well as the sulfonyl urea VII (**100**).

VI

VII

Using the functionalities provided by these general synthetic routes we were able to prepare still other structural variations. Thus bromination of 1-allyl-3-(3-benzyl-5-nitro-4-thiazolin-2-ylidene)urea (procedure D) provided the dibromo derivative VIII, and its treatment with *m*-chloroperbenzoic acid provided epoxide IX from which the corresponding 2,3-dihydroxy derivative was obtained. From 1-ethyl-3-[3-(2-hydroxyethyl)-5-nitro-4-thiazolin-2-ylidene]-urea obtained by the alkylation procedure were prepared the chloro derivative X by treatment with $SOCl_2$ and the acetate (XI) and caproate esters by treatment with acetic anhydride and hexanoyl chloride.

VIII

IX

X

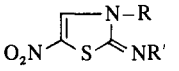
XI

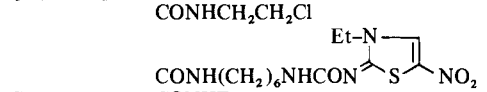
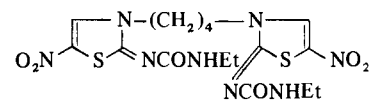
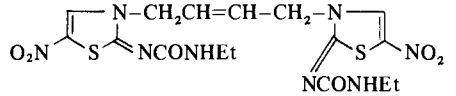
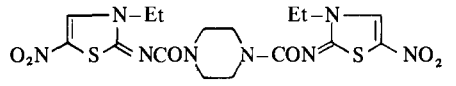
An attempt to prepare the nitroso analog of the active series failed when nitrosation of 1-ethyl-3-(3-ethyl-4-thiazolin-2-ylidene)urea provided instead the *N*-nitroso derivative XII.

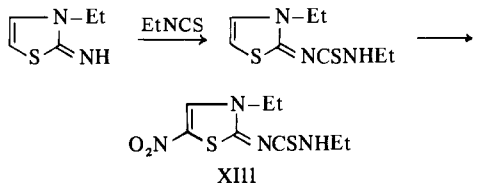
XII

It was of interest to examine the corresponding thiourea (XIII). This was prepared by nitration of 1-ethyl-3-(3-ethyl-

Table II. Miscellaneous Structures. Activity *vs. S. mansoni* in Mice



No.	R	R'	Drug: Route X days	Drug: mg/kg per day	Live worms: % mice positive	Live worms: % reduction
101	Et	$CONMe_2$	G X 5	400	0	100
				50	100	27
102	Et	$CONEt_2$	G X 5	100	87	59
103	Et	CO-morpholino	G X 5	400	0	100
				100	87	19
104	Et	$CON(CH_2)_4$	G X 5	200	100	36
105	Et	$CONPr_2$	G X 5	200	100	21
106	$CH_2COC_6H_4$-3-NO_2	CONHEt	G X 5	400	87	26
107	Et	$CONHCH_2CH_2Cl$	G X 5	200	87	29
108	Et		G X 5	400	100	0
109	CH_2CH_2Cl	CONHEt	G X 5	400	0	100
				100	100	38
110	$CH_2CH_2OCOCH_3$	CONHEt	G X 5	400	25	93
111	$CH_2CH_2OCOC_6H_{13}$	CONHEt	G X 5	400	100	6
112	Et	CONHEt (4Me)	D X 14	376	100	0
			G X 5	400	62	48
113			D X 14	332	100	24
114			D X 14	300	100	0
115			G X 5	400	100	0
116	Et	CSNHEt	G X 5	400	100	0
	Niridazole		D X 14	249	17	99
			G X 5	100	100	53



XIII

4-thiazolin-2-ylidene)-2-thiourea which was obtained through the reaction of ethyl isothiocyanate with 3-ethyl-2-iminothiazoline.

Biology. The compounds described herein were supplied to Dr. Paul E. Thompson and coworkers of these laboratories for evaluation against a Puerto Rican strain of *S. mansoni* in mice.‡ As in previous work, drugs were administered in a powdered diet (D) for 14 days or by gavage (G) in 10 mg/kg of aqueous 1% hydroxyethyl or carboxymethyl cellulose for 3–10 days. The data are summarized in Tables I and II and it is seen that schistosomicidal activity is widespread among the ureas. Two of the 1-(alkyl)-3-(3-benzyl-5-nitro-4-thiazolin-2-ylidene)ureas (compounds **43**, **45**) were the most potent substances examined, completely eliminating live schistosomes from infected mice at a gavage dose of 100 mg/kg daily for 5 days. Compounds **2**, **3**, **4**, **9**, **15**, **16**, **17**, **22**, **25**, **32**, **42**, **44**, **46**, **47**, **49**, **53**, **57**, **58**, **59**, **60**, **62**, **71**, **72**, **76**, **91**, **101**, **103**, and **109** also cured all of the mice at somewhat higher dose levels ranging from 200 to 400 mg/kg daily by gavage for 5 days or from 252 to 328 mg/kg daily for 14 days by drug-diet. Many other analogs, although not curative, effected a marked reduction in live schistosomes at similar gavage or daily diet doses.§

One cannot deduce strict structure-activity relationships from the available data, however, several comments may be pertinent. Thus among the alkyl derivatives, simple alkyl or olefinic groups on either the urea or thiazole nitrogens retained activity while drastic lengthening of the carbon chain or excessive branching severely reduced activity. Among the 3-benzyl derivatives a variety of monosubstituted derivatives retained strong activity while multiple substitution was dystherapeutic. Once again branching of the substituent on the urea N or lengthening the chain decreased activity. More drastic structural variations also tended to diminish activity (*i.e.*, VI, VII, XIII). Bis substitution on the urea N with alkyl groups retained activity as long as the group was small. Bis analogs of the active compounds, however, exhibited little or no activity. It is interesting that a haloalkyl substituent on the ring N retained activity while the same grouping on the urea N (**107**) was essentially inactive. The only compound prepared (**112**) with a substituent at the 4 position of the thiazoline nucleus had very little activity and this avenue was not explored further. The thio analog XIII (**116**) also was inactive.

‡For a description of test methods see ref 6.

§P. E. Thompson and R. E. Voigtman, unpublished results, Parke, Davis and Company, Ann Arbor, Mich.

Twelve compounds (**9**, **17**, **16**, **24**, **25**, **43**, **46**, **48**, **49**, **53**, **58**, and **102**) were examined against the Puerto Rican strain of *S. mansoni* in rhesus monkeys, and 9 of them (**9**, **43**, **46**, **16**, **17**, **24**, **25**, **58**, and **102**) showed significant antischistosomal activity in this host. Drugs were given orally by gavage twice daily 5 days a week for 1 or 2 weeks. Compounds **9**, **43**, **25**, and **102** furthermore were curative at well-tolerated doses of 50–100 mg/kg per day for 5–10 days. In dogs, however, at doses double the therapeutically effective level in monkeys, intolerance variably reflected by emesis, convulsions, incoordination, and death was observed, and further studies on this series were abandoned.

Experimental Section#

Procedure A. 1-Ethyl-3-(3-ethyl-5-nitro-4-thiazolin-2-ylidene)urea (9). 3-Ethyl-2-iminothiazoline Hydriodide.[7] A solution of 100 g (1.0 mole) of 2-aminothiazole and 200 g (1.28 moles) of EtI in 800 ml of *i*-PrOH was heated under reflux for 24 hr, cooled, and filtered to give 182 g (74%) of the product as a tan solid, mp 106–110°.

1-Ethyl-3-(3-ethyl-4-thiazolin-2-ylidene)urea Hydrochloride. To a solution of 50 g (0.2 mole) of 3-ethyl-2-iminothiazoline hydriodide in 85 ml of C_5H_5N was added 14.2 g (0.2 mole) of ethyl isocyanate, and the mixture was heated on the steam bath for 2 hr. The mixture was cooled and filtered to remove $C_5H_5N \cdot HI$. Ether was added to the filtrate, and the mixture was filtered to remove additional $C_5H_5N \cdot HI$. The solvents were removed *in vacuo*, and the residual oil was washed with H_2O, taken up in Et_2O, dried, and treated with *i*-PrOH saturated with HCl gas. The resulting solid was collected and recrystd first from *i*-PrOH and then from EtOH to give 21.6 g of the product (46%), mp 192–195°. *Anal.* ($C_8H_{13}N_3OS \cdot HCl$) C, H, N.

1-Ethyl-3-(3-ethyl-5-nitro-4-thiazolin-2-ylidene)urea (9). To 15 ml of concd H_2SO_4 at 0–10° was added in portions 6 g (0.0255 mole) of 1-ethyl-3-(3-ethyl-4-thiazolin-2-ylidene)urea hydrochloride. The solution was maintained at 0–10° and 1.6 g (0.0255 mole) of red fuming HNO_3 was added dropwise. The mixture was allowed to stir in the cold for 1 hr, was then allowed to warm to room temp, and was poured into about 250 ml of iced H_2O. The yellow solid was collected and recrystd from *i*-PrOH and then from EtOAc to give 1.4 g of the product (23%), mp 176–178°.

3-Alkyl-2-imino-4-thiazolines. The following intermediates were prepared similarly to 3-ethyl-2-imino-4-thiazoline described above: 3-butyl-2-imino-4-thiazoline hydrobromide, mp 115–118°, in 40% yield after recrystallization from EtOH–Et_2O, used as is; 2-imino-3-(*p*-nitrobenzyl)-4-thiazoline hydrobromide;[8] 3-methyl-2-imino-4-thiazoline hydriodide, mp 181–184°;[7] and 2-imino-3-propyl-4-thiazoline, used crude after removing the solvent from the reaction mixture.

1-Alkyl-3-(3-alkyl-4-thiazolin-2-ylidene)ureas. The following intermediates were prepared similarly to 1-ethyl-3-(3-ethyl-4-thiazolin-2-ylidene)urea described above: 1-butyl-3-(3-ethyl-4-thiazolin-2-ylidene)urea hydrochloride, mp 109–111°, in 46% yield after recrystallization from toluene [*Anal.* ($C_{10}H_{17}N_3OS \cdot HCl$) C, H, N]; 1-cyclohexyl-3-(3-ethyl-4-thiazolin-2-ylidene)urea hydrochloride, mp 124–126°, in 26% yield after recrystallization from H_2O [*Anal.* ($C_{12}H_{19}N_3OS \cdot HCl$) C, H, N]; 1-(3-ethyl-4-thiazolin-2-ylidene)-3-octylurea hydrochloride $\cdot 0.33H_2O$, mp 84–89°, in 45% yield after recrystallization from *i*-PrOH–Et_2O [*Anal.* ($C_{14}H_{25}N_3OS \cdot HCl \cdot 0.33H_2O$) H, N. C: calcd, 51.59; found, 50.98. H_2O: calcd, 1.84; found, 1.20]; 1-(3-butyl-4-thiazolin-2-ylidene)-3-ethylurea, mp 68–70°, in 58% yield after recrystallization from EtOAc–isooctane [*Anal.* ($C_{10}H_{17}N_3OS$) C, H, N]; 1-ethyl-3-(3-methyl-4-thiazolin-2-ylidene)urea hydrochloride, mp 224–229° dec, in 69% yield after recrystallization from *i*-PrOH (Material was not analytically pure and was nitrated as is.); 1-ethyl-3-[3-(*p*-nitrobenzyl)-4-thiazolin-2-ylidene]urea, mp 109–111.5°, in 65% yield after recrystallization from dil EtOH [*Anal.* ($C_{13}H_{14}N_4O_3S$) C, H, N]; and 1-ethyl-3-(3-propyl-4-thiazolin-2-ylidene)urea, mp 74–78°, in 63.4% yield used after reprecipitation from Me_2CO with petr ether.

3-(3-Ethyl-5-nitro-4-thiazolin-2-ylidene)-1,1-dimethylurea (101). To a solution of 12.8 g (0.05 mole) of 3-ethyl-2-imino-4-thiazoline hydriodide in 50 ml of C_5H_5N was added 6 g (0.056 mole) of dimethylcarbamoyl chloride, and the mixture was heated on the steam bath for 5 hr. The solvent was removed *in vacuo*, and the residue was dissolved in a small volume of H_2O and extracted with Et_2O. The extracts were dried, and the solvent was removed *in vacuo* to provide 6.2 g (62%) of 3-(3-ethyl-4-thiazolin-2-ylidene)-1,1-dimethylurea as a tan-orange solid which could not be readily purified further. This material was added in portions to 15 ml of concd H_2SO_4 at 10°. To this solution at 0–5° was added dropwise 2.0 g (0.031 mole) of red fuming HNO_3. The mixture was allowed to warm to room temp, stirred for 3 hr, and poured into iced H_2O. The solid was collected and recrystd from *i*-PrOH to give 0.4 g (6%) of the product, mp 195–198°. *Anal.* ($C_8H_{12}N_4O_3S$) N. C: calcd, 39.34; found, 38.91. H: calcd, 4.95; found, 4.53.

1,1-Diethyl-3-(3-ethyl-5-nitro-4-thiazolin-2-ylidene)urea (102). To 25.6 g (0.1 mole) of 3-ethyl-2-imino-4-thiazoline hydriodide in 100 ml of C_5H_5N was added 14.5 g (0.107 mole) of diethylcarbamoyl chloride, and the mixture was heated on the steam bath for 5 hr. The solvent was removed *in vacuo*, and the residue was triturated with H_2O. The solid was collected and dried in air to give 18 g (79%) of 1,1-diethyl-3-(3-ethyl-4-thiazolin-2-ylidene)urea, mp 76–78.5°, as an orange-rust solid. This material (13.0 g, 0.061 mole) was added in portions to 40 ml of concd H_2SO_4 at 10°. To this cold solution was added dropwise 3.8 g (0.061 mole) of red fuming HNO_3. The reaction mixture was stirred for 0.5 hr at 0–10°, allowed to warm to room temp, stirred an additional 0.5 hr, and poured into 400 ml of iced H_2O. The sticky red precipitate was collected and recrystd twice from *i*-PrOH to give 2.1 g (13%) of the product as gold crystals, mp 140–142°. *Anal.* ($C_{10}H_{16}N_4O_3S$) C, H, N.

***N*-(3-Ethyl-5-nitro-4-thiazolin-2-ylidene)-4-morpholinecarboxamide (103)** was prepared similarly from *N*-(3-ethyl-4-thiazolin-2-ylidene)-4-morpholinecarboxamide in 66% yield after recrystallization from *i*-PrOH, mp 215–219°. *Anal.* ($C_{10}H_{14}N_4O_4S$) C, H, N.

***N*-(3-Ethyl-5-nitro-4-thiazolin-2-ylidene)-1-pyrrolidinecarboxamide (104)** was prepared similarly from *N*-(3-ethyl-4-thiazolin-2-ylidene)-1-pyrrolidinecarboxamide in 25% yield, mp 245–248° after recrystallization from *i*-PrOH. *Anal.* ($C_{10}H_{14}N_4O_3S$) C, H, N.

Phenyl 3-Ethyl-4-thiazoline-$\Delta^{2,N}$-carbamate. To a solution of 102 g (0.65 mole) of phenyl chloroformate in 1 l. of THF cooled to 15° was added a solution of 81 g (0.63 mole) of 3-ethyl-2-iminothiazoline and 91 ml (0.65 mole) of triethylamine in about 200 ml of THF. The resulting solid was collected and washed with ether, the filtrate was added to the original reaction mixture, and the solvents were removed *in vacuo*. The residue was washed with H_2O and recrystd from dil EtOH to give 146.5 g (94%) of the product, mp 108.5–111.5°. *Anal.* ($C_{12}H_{12}N_2O_2S$) C, H, N.

***N*-(3-Ethyl-4-thiazolin-2-ylidene)-4-morpholinecarboxamide.** A mixture of 10.0 g (0.04 mole) of phenyl 3-ethyl-4-thiazoline-$\Delta^{2,N}$-carbamate and 4.0 ml (0.046 mole) of morpholine was heated for 50 min at 145–150°. The cooled mixture was taken up in 300 ml of C_6H_6 and extracted with 60 ml of 1 *N* NaOH. The aqueous extract was extracted with 100 ml of C_6H_6, the combined C_6H_6 extracts were washed twice with 5-ml portions of satd NaCl solution and dried, and the solvent was removed *in vacuo*. The residual oil was dissolved in 30 ml of C_6H_6, 300 ml of warm cyclohexane was added, and the mixture was chilled. The solid was collected and recrystd from H_2O and then from a mixture of toluene and cyclohexane to give 6.1 g (63%) of the product, mp 144–146.5°. *Anal.* ($C_{10}H_{15}N_3O_2S$) C, H, N.

***N*-(3-Ethyl-4-thiazolin-2-ylidene)-1-pyrrolidinecarboxamide.** This was prepared similarly to the morpholine analog described above except that it was heated for 1 hr at 102°. Recrystallization from cyclohexane gave 83% of the product, mp 94–95°. *Anal.* ($C_{10}H_{15}N_3SO$) C, H, N.

3-(3-Ethyl-5-nitro-4-thiazolin-2-ylidene)-1,1-dipropylurea (105). To 25.6 g (0.1 mole) of 3-ethyl-2-imino-4-thiazoline hydriodide in 100 ml of C_5H_5N was added 17 g of dipropylcarbamoyl chloride, and the mixture was heated on the steam bath for 5 hr. The solvent was removed *in vacuo*, and the semisolid residue was triturated with H_2O and allowed to remain overnight. The dark oil which was present was extracted with ether. The extracts were washed with water and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residual dark oil (18.4 g) was used as is in the next step. The 3-(3-ethyl-4-thiazolin-2-ylidene)-1,1-dipropylurea (18 g, 0.0705 mole) was added dropwise to 25 ml of concd H_2SO_4, cooled in an ice bath. To this cold solution (0–10°) was added dropwise 4.4 g of red fuming HNO_3. The mixture was stirred cold for 20 min and poured into 250 ml of iced water. The yellow solid was collected and recrystd from *i*-PrOH to give 5.8 g (28%) of the product, mp 161–165°. *Anal.* ($C_{12}H_{20}N_4O_3S$) C, H, N.

#Melting points (corrected) were taken on a Thomas-Hoover capillary melting point apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of theoretical values. Nmr data were obtained on a Varian A-60 instrument.

1-(3-Ethyl-5-nitro-4-thiazolin-2-ylidene)-3-isopropylurea (38). To 15 ml of concd H_2SO_4, cooled in an ice bath, was added 8.8 g (0.0344 mole) of 1-(3-ethyl-4-thiazolin-2-ylidene)-3,3-diisopropylurea. To this soln at 0–10° was added 2.2 g of red fuming HNO_3. The mixture was stirred cold briefly and filtered. The solid was recrystd from 2-PrOH to give 2.0 g of a yellow solid, mp 144–145°. This material was dissolved in EtOH and made basic by the addition of 1 *N* NaOH. The yellow ppt was collected and dried to give 1.1 g (12%) of the product, mp 163–166°. *Anal.* ($C_9H_{14}N_4O_3S$) C, H, N.

3-(3-Ethyl-4-thiazolin-2-ylidene)-1,1-diisopropylurea. To a soln of 25.6 g (0.1 mole) of 3-ethyl-2-imino-4-thiazoline hydriodide in 100 ml of pyridine was added 17 g (0.104 mole) of diisopropylcarbamoyl chloride. The mixture was heated on the steam bath for 4.5 hr, and the solvent was removed *in vacuo*. The residue was triturated with water and filtered to give 15 g of a yellow-brown solid. This was taken up in Et_2O and dried, and the solvent was allowed to evaporate to provide 9 g (35%) of the product, mp 82–84°. *Anal.* ($C_{12}H_{21}N_3OS$) C, H, N.

1-Ethyl-3-[5-nitro-3-(*m*-nitrophenacyl)-4-thiazolin-2-ylidene]urea (106). To 25 ml of concd H_2SO_4 at 15–20° was added slowly 7.25 g (0.025 mole) of 1-ethyl-3-[3-phenacyl-4-thiazolin-2-ylidene]urea, and to the resulting solution 1.6 g (0.05 mole) of red fuming HNO_3 was added. The mixture was stirred cold for 1 hr, allowed to warm to room temp, stirred an additional 2 hr, and poured into 200 ml of iced H_2O. The solid was collected and recrystd from MeCN and then twice from *i*-PrOH to give 1.2 g (13%) of the product, mp 217–218° dec. *Anal.* ($C_{14}H_{13}N_5O_6S$) C, H, N.

1-Ethyl-3-(2-thiazolyl)urea. A mixture of 100 g (1.0 mole) of 2-aminothiazole and 75 g (1.05 mole) of ethyl isocyanate in 500 ml of MeCN was heated under reflux for 5 hr. A solid formed, the mixture was filtered hot, and the solid was washed with additional solvent and dried to give 141 g (82%) of the product, mp 177–180° *Anal.* ($C_6H_9N_3OS$) C, H, N.

1-Ethyl-3-(3-phenacyl-4-thiazolin-2-ylidene)urea. A mixture of 8.6 g (0.05 mole) of 1-ethyl-3-(2-thiazolyl)urea and 10 g (0.05 mole) of phenacyl bromide in 250 ml of *i*-PrOH was heated under reflux for 3 hr. The solution was allowed to cool to room temp, and the solid that formed was collected, washed with Me_2CO, and recrystd twice from MeCN to yield 3.7 g (20%) of the product as the hydrobromide salt, mp 218–219°. *Anal.* ($C_{14}H_{16}BrN_3O_2S$) C, H, N.

To a suspension of 42.5 g (0.115 mole) of the salt in 200 ml of hot EtOH was added 1 *N* NaOH until all the solid had dissolved, and the solution was slightly basic. The solution was cooled, 300 ml of H_2O was added, and the white solid was collected and dried to yield 32 g (96%) of the base, mp 133–135°. *Anal.* ($C_{14}H_{15}N_3O_2S$) C, H, N.

Procedure B. 1-Ethyl-3-(3-ethyl-5-nitro-4-thiazolin-2-ylidene)-urea (9). To a stirred mixture of 21.6 g (0.1 mole) of 1-ethyl-3-(5-nitro-2-thiazolyl)urea in 150 ml of DMF was added 4.7 g of a 53% dispersion of NaH in mineral oil (0.1 mole). The resulting solution was warmed to 60°, 17.2 g (0.11 mole) of EtI was added slowly, and the mixture was then heated at 60–65° for 2 hr. The mixture was allowed to cool and was poured into 600 ml of iced H_2O. The solid was collected, dried, and recrystd once from EtOAc and then three times from *i*-PrOH to give 5.1 g (21%) of the product, mp 175–177°, identical with the material prepared by procedure A above.

1-Ethyl-3-(5-nitro-2-thiazolyl)urea.[9] To a suspension of 290 g (2.0 moles) of 2-amino-5-nitrothiazole in 2 l. of toluene was added 200 g (2.8 moles) of ethyl isocyanate. The mixture was heated under reflux for 24 hr and filtered hot to give a quantitative yield of the product, mp 232–233°.

1-Alkyl-3-(5-nitro-2-thiazolyl)ureas. The following intermediates were prepared similarly to 1-ethyl-3-(5-nitro-2-thiazolyl)urea described above: 1-allyl-3-(5-nitro-2-thiazolyl)urea, mp 176–180°, in 35% yield after recrystn from EtOH–H_2O [*Anal.* ($C_7H_8N_4O_3S$) C, H, N]; 1-(3-nitro-2-thiazolyl)-3-(2-phenylcyclopropyl)urea, mp 202–205.5° dec, in 70% yield after recrystn from EtOH [*Anal.* ($C_{13}H_{12}N_4O_3S$) C, H, N]; 1-(*n*-dodecyl)-3-(5-nitro-2-thiazolyl)urea, mp 142–144°, in 38% yield after recrystn from EtOAc (This material was not obtained analytically pure and was used as is.); 1-cyclohexyl-3-(5-nitro-2-thiazolyl)urea, mp 209–214° (resolidifies and decomposes by 222°), in 64% yield after recrystn from MeCN [*Anal.* ($C_{10}H_{14}N_4O_3S$) C, H, N]; 1-(*n*-hexyl)-3-(5-nitro-2-thiazolyl)urea, mp 165–168°, in 23% yield after recrystn from EtOAc [*Anal.* ($C_{10}H_{16}N_4O_3S$) H, N. C: calcd, 44.10; found, 44.70)]; 1-*tert*-butyl-3-(5-nitro-2-thiazolyl)urea, mp >290°, in 65% yield after recrystn from EtOH–H_2O [*Anal.* ($C_8H_{12}N_4O_3S$) C, H. N: calcd, 22.94; found, 23.44)].

Literature preparations were available for 1-methyl-3-(5-nitro-2-thiazolyl)urea,[9] 1-butyl-3-(5-nitro-2-thiazolyl)urea, 1-isopropyl-3-(5-nitro-2-thiazolyl)urea, 1-(5-nitro-2-thiazolyl)-3-phenylurea,[10] and 1-(5-nitro-2-thiazolyl)urea.[11]

Procedure B-1. 1-Ethyl-3-(5-nitro-3-pentyl-4-thiazolin-2-ylidene)urea (25). To a suspension of 21.6 g (0.1 mole) of 1-ethyl-3-(5-nitro-2-thiazolyl)urea in 150 ml of DMF at 10–15° was added in portions 4.4 g of a 55% dispersion in oil of NaH. The mixture was allowed to warm to room temp and heated to 80–85°, and 21.8 g (0.11 mole) of *n*-amyl iodide was added in portions. The mixture was heated at 85–90° for 3.5 hr and cooled to room temp, and an equal volume of toluene was added. The mixture was washed twice with H_2O, and the organic layer was dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue was recrystd from EtOAc–isooctane to give 9.6 g of yellow solid, mp 109–119°. Recrystn from about 2 l. of *n*-heptane gave 6.6 g of the product, mp 114–117°.

Procedure C. 3-Benzyl-2-imino-5-nitro-4-thiazoline Hydrochloride. A mixture of 108.5 g (0.34 mole) of *N*-(3-benzyl-5-nitro-4-thiazolin-2-ylidene)-2,2-dimethylpropionamide[5] and 58.2 ml (0.68 mole) of concd HCl in 2 l. of MeOH was heated under reflux for 4 hr. The solvent was removed *in vacuo*, and the residue was treated with 1 l. of cold *i*-PrOH. The liquid was decanted and upon standing deposited 19.1 g of a yellow powder, mp 217–218°. The undissolved gummy residue was triturated with an additional 1 l. of *i*-PrOH. The gum solidified, and the solid was collected, ground thoroughly in a mortar, and dried to give an additional 49.9 g of the product, mp 216–218°, total yield 75%. This material was used as is in the next step.

1-Benzyl-3-(3-benzyl-5-nitro-4-thiazolin-2-ylidene)urea (94). To 10 g (0.0368 mole) of 3-benzyl-2-imino-5-nitrothiazoline hydrochloride in 200 ml of Me_2CO was added 3.73 g (0.0368 mole) of triethylamine and 4.9 g (0.0368 mole) of benzyl isocyanate. The mixture was heated under reflux for 4 hr, cooled, and filtered. The filtrate was evaporated to dryness *in vacuo*, and the yellow oil was triturated with about 50 ml of cold H_2O. The H_2O was decanted, and the residue which solidified upon standing overnight was recrystd from about 100 ml of *i*-PrOH to give 6.5 g of the product (48%), mp 124–127°.

1-(2-Chloroethyl)-3-(3-ethyl-5-nitro-4-thiazolin-2-ylidene)urea (107). To a suspension of 1 g (0.0048 mole) of 3-ethyl-2-imino-5-nitrothiazoline hydrochloride in 40 ml of Me_2CO containing 0.48 g (0.0048 mole) of Et_3N was added 0.503 g (0.0048 mole) of 2-chloroethyl isocyanate. The mixture was heated under reflux for 4.5 hr and filtered hot. The filtrate was cooled and refiltered, and then evapd to dryness *in vacuo*. The residue was recrystd twice from *i*-PrOH to give 0.7 g (52%) of the product, mp 148–149°. *Anal.* ($C_8H_{11}ClN_4O_3S$) C, H, N.

3-Ethyl-2-imino-5-nitro-4-thiazoline Hydrochloride. To a soln of 12.2 g (0.0474 mole) of *N*-(3-ethyl-5-nitro-4-thiazolin-2-ylidene)-2,2-dimethylpropionamide[5] in 250 ml of MeOH was added 8.15 ml of concd HCl (0.0948 mole), and the mixture was heated under reflux for 5 hr. The solvent was removed *in vacuo*, and the residue was recrystd from 500 ml of EtOH to give 4.3 g (43%) of the product as white crystals, mp 235°. *Anal.* ($C_5H_8ClN_3O_2S$) C, H, N.

1,1'-Hexamethylenebis[3-(3-ethyl-5-nitro-4-thiazolin-2-ylidene)-urea]·1.33CH_3CN (108). A mixture of 21.0 g (0.1 mole) of 3-ethyl-2-imino-5-nitro-4-thiazoline hydrochloride and 8.4 g (0.05 mole) of hexamethylene diisocyanate in 400 ml of Me_2CO containing 10.1 g (0.1 mole) of triethylamine was heated under reflux for 3 hr and allowed to cool to room temp. The solid was collected and triturated with H_2O. The undissolved material was recrystd from 1400 ml of MeCN to give 23.4 g (82%) of the product, mp 217–219°. *Anal.* ($C_{18}H_{26}N_8O_6S_2$·1.33CH_3CN) C, H, N. The nmr spectrum confirmed the presence of MeCN.

Procedure D. 1-(3-Benzyl-5-nitro-4-thiazolin-2-ylidene)-3-(2,3-dibromopropyl)urea (80). To a stirred solution of 5.0 g (0.0157 mole) of 1-allyl-3-(3-benzyl-5-nitro-4-thiazolin-2-ylidene)urea in 200 ml of $CHCl_3$ at 0° was added dropwise a solution of 0.81 ml of Br_2 in 10 ml of $CHCl_3$. The mixture was stirred at room temp for 0.5 hr and concd to dryness. The residue was recrystd twice from EtAc and then from 95% EtOH to give 4.4 g (58%) of the product, mp 136–138°.

1-(3-Benzyl-5-nitro-4-thiazolin-2-ylidene)-3-(2,3-epoxypropyl)-urea (78). A mixture of 25 g (0.079 mole) of 1-allyl-3-(3-benzyl-5-nitro-4-thiazolin-2-ylidene)urea and 15.7 g (0.091 mole) of *m*-chloroperbenzoic acid in 250 ml of $CHCl_3$ was allowed to remain at *ca.* 0° for 60 hr. The mixture was filtered, and the excess peracid was destroyed with 5% aqueous sodium sulfite. The organic layer was washed several times with 10% aqueous $NaHCO_3$, dried, and evaporated to half-volume. The solid was collected and recrystd from EtOH to give 3.5 g (14%) of the product, mp 161–164°.

1-(3-Benzyl-5-nitro-4-thiazolin-2-ylidene)-3-(2,3-dihydroxypro-

pyl)urea (79). A mixture of 4.2 g (0.0126 mole) of 1-(3-benzyl-5-nitro-4-thiazolin-2-ylidene)-3-(2,3-epoxypropyl)urea and 42 ml of HCO_2H was heated under reflux for 1 hr and evapd to dryness *in vacuo*. The residue was heated under reflux with 42 ml of 2 *N* HCl, and the aqueous layer was decanted from a brown gum. The gum was triturated with MeOH, and the solid that formed was recrystd from MeOH to give 1 g (23%) of the product, mp 145–149°

1-[3-(2-Chloroethyl)-5-nitro-4-thiazolin-2-ylidene)-3-ethylurea (109). A mixture of 6.1 g (0.0235 mole) of 1-ethyl-3-[3-(2-hydroxyethyl)-5-nitro-4-thiazolin-2-ylidene]urea (10) and 65 ml of $SOCl_2$ was heated at 50–60° for 6 hr and cooled, and the $SOCl_2$ was removed *in vacuo*. The residue was recrystallized twice from *i*-PrOH, then from C_6H_6, and once again from *i*-PrOH to give 2.1 g (32%) of the product, mp 131–133°. *Anal.* ($C_8H_{11}ClN_4O_3S$) C, H, N.

1-Ethyl-3-[3-(2-hydroxyethyl)-5-nitro-4-thiazolin-2-ylidene]urea Acetate Ester (110). A mixture of 5.3 g (0.028 mole) of 1-ethyl-3-[3-(2-hydroxyethyl)-5-nitro-4-thiazolin-2-ylidene]urea in 50 ml of HOAc and 50 ml of acetic anhydride was heated on the steam bath for 2.5 hr and evapd to dryness *in vacuo*. The residue was triturated with Et_2O and then recrystd from *i*-PrOH to give 3.7 g of the product (44%), mp 135–137°. *Anal.* ($C_{10}H_{14}N_4O_5S$) C, H, N.

1-Ethyl-3-[3-(2-hydroxyethyl)-5-nitro-4-thiazolin-2-ylidene]urea Caproate Ester (111). To a solution of 4.4 g (0.0169 mole) of 1-ethyl-3-[3-(2-hydroxyethyl)-5-nitro-4-thiazolin-2-ylidene]urea in DMF was added 2.8 g (0.0208 mole) of hexanoyl chloride. When the exothermic reaction had abated, the mixture was heated on the steam bath for 2.5 hr and poured into iced H_2O. The solid was recrystd from toluene to give 3.4 g (56%) of the product, mp 93.5–98°. *Anal.* ($C_{14}H_{22}N_4O_5S$) C, H, N.

3-Ethyl-2-imino-4-methyl-4-thiazoline Hydriodide. A solution of 100 g (0.876 mole) of 2-amino-4-methylthiazole and 140 g (0.897 mole) of EtI in 500 ml of *i*-PrOH was heated under reflux for 24 hr and allowed to cool to room temp. The solid was collected and recrystd from about 1 l. of MeCN to give 101.8 g (43%), mp 159–164°. An analytical sample was prepared by recrystallizing 10 g from MeCN again to give 7.9 g, mp 162–165°. *Anal.* ($C_6H_{11}IN_2S$) C, H, N.

1-Ethyl-3-(3-ethyl-4-methyl-4-thiazolin-2-ylidene)urea. To a solution of 27 g (0.1 mole) of 3-ethyl-2-imino-4-methyl-4-thiazoline hydriodide in 95 ml of C_5H_5N was added 8 g (0.11 mole) of EtNCO. The solution was heated on the steam bath for 2.5 hr and filtered. The filtrate was concd to dryness *in vacuo* and triturated with warm H_2O. Initially most of the material dissolved, but upon scratching a copious ppt formed. The solid was collected and recrystd from about 1100 ml of *n*-heptane to give 11.9 g (56%) of the product, mp 117.5–121°. *Anal.* ($C_9H_{15}N_3OS$) C, H, N.

1-Ethyl-3-(3-ethyl-4-methyl-5-nitro-4-thiazolin-2-ylidene)urea (112). 1-Ethyl-3-(3-ethyl-4-methyl-4-thiazolin-2-ylidene)urea, 8.8 g (0.0437 mole), was added in portions to 15 ml of concd H_2SO_4 at 0–10°. To the cold solution was added dropwise 2.75 g (0.0437 mole) of red fuming HNO_3. The cold mixture was stirred for 15 min, allowed to come to room temp, and stirred for 4 hr. It was then poured into 300 ml of iced H_2O. The solid was collected and recrystd from *i*-PrOH to give 3.3 g (29%) of the product, mp 188–190°. *Anal.* ($C_9H_{14}N_4O_3S$) C, H, N.

1,1'-[Tetramethylenebis(5-nitro-4-thiazolin-3-yl-2-ylidene)]-bis(3-ethylurea) (113). To a solution of 21.6 g (0.1 mole) of 1-ethyl-3-(5-nitro-2-thiazolyl)urea in 150 ml of DMF maintained at about 20° was added in portions 4.4 g of a 55% dispersion of NaH in oil. The mixture was warmed to 70°, and 19 g (0.11 mole) of 1-bromo-4-chlorobutane was added. The mixture was heated at 70–80° for 2 hr, cooled, and poured into iced H_2O. The sticky solid was collected and triturated with hot *i*-PrOH to give 4.7 g of a yellow solid. Recrystallization from a mixture of DMF and EtOH gave 2.3 g (9.5%) of the product, mp >300°. *Anal.* ($C_{16}H_{22}N_8O_6S_2$) C, H, N.

1,1'-[2-Butenylenebis(5-nitro-2-thiazolin-3-yl-2-ylidene)]bis-(3-ethylurea) (114). The sodium salt of 10.8 g (0.05 mole) of 1-ethyl-3-(5-nitro-2-thiazolyl)urea was prepd in the usual manner from NaH in 60 ml of DMF. To this was added 3.5 ml of $ClCH_2CH{=}CHCH_2Cl$, and the mixture was stirred at 80° for 2.75 hr and poured into H_2O. The crude product was collected and recrystd from HOAc to give 1.7 g (7%) of the product, mp 275° dec. *Anal.* ($C_{16}H_{20}N_8O_6S_2$) C, H, N.

N,N'-Bis(3-ethyl-5-nitro-4-thiazolin-2-ylidene)-1,4-piperazinedicarboxamide Monohydrate (115). To 15 ml of concd H_2SO_4 at 0–10° was added in portions 5.8 g (0.0147 mole) of *N,N'*-bis(3-ethyl-4-thiazolin-2-ylidene)-1,4-piperazinedicarboxamide. To the cold solution was added 1.85 g (0.0294 mole) of red fuming HNO_3 dropwise. The mixture was stirred cold for 15 min and then poured into 200 ml of iced water. The solid was collected, triturated with hot EtOH, and slurried with ether to give 5.0 g (68%) of the product, mp 316° dec. *Anal.* ($C_{16}H_{20}N_8O_6S_2 \cdot H_2O$) C, H, N, H_2O.

N,N'-Bis(3-ethyl-4-thiazolin-2-ylidine)-1,4-piperazinedicarboxamide. A mixture of 10 g (0.04 mole) of phenyl 3-ethyl-4-thiazoline-$\Delta^{2,N}$-carbamate and 1.8 g (0.02 mole) of piperazine was heated at 140–150° for 1 hr, cooled, and diluted with 50 ml of Me_2CO, and the solid was collected (6.5 g). Recrystallization from a mixture of DMF and MeCN provided 5.8 g (73%) of the product, mp 270–277°. *Anal.* ($C_{16}H_{22}N_6O_2S_2$) C, H, N.

1-Ethyl-3-(3-ethyl-4-thiazolin-2-ylidene)-1-nitrosourea. To 11.8 g (0.05 mole) of 1-ethyl-3-(3-ethyl-4-thiazolin-2-ylidene)urea hydrochloride in H_2O containing 4.28 ml (0.05 mole) of concd HCl was added dropwise at 15–20° an aqueous solution of 3.45 g (0.05 mole) of $NaNO_2$. The mixture was stirred at 20° for 2 hr and filtered. The solid was recrystd from *i*-PrOH to give 5.8 g (51%) of the product, mp 106–109°. *Anal.* ($C_8H_{12}N_4O_2S$) C, H, N.

1-Ethyl-3-(3-ethyl-5-nitro-4-thiazolin-2-ylidene)-2-thiourea (116). To 15 ml of concd H_2SO_4, cooled in an ice bath, was added in portions 8.0 g (0.0372 mole) of 1-ethyl-3-(3-ethyl-4-thiazolin-2-ylidene)-2-thiourea. To the cold soln was added dropwise 2.3 g (0.0372 mole) of red fuming HNO_3. The mixture was stirred for 20 min and poured into 200 ml of iced H_2O. The yellow solid that resulted was collected and recrystd from 1100 ml of *i*-PrOH to give 2.5 g (27%) of the product, mp 237–239°. *Anal.* ($C_8H_{12}N_4O_2S_2$) C, H, N.

1-Ethyl-3-(3-ethyl-4-thiazolin-2-ylidene)-2-thiourea. To 25.6 g (0.1 mole) of 3-ethyl-2-imino-4-thiazoline hydriodide and 10.1 g (0.1 mole) of triethylamine in 200 ml of Me_2CO was added 8.7 g (0.1 mole) of ethyl isothiocyanate. The mixture was heated under reflux for 2 hr, and the solvent was removed *in vacuo*. The residue was triturated with 200 ml of H_2O, and the solid was collected and recrystd from MeCN to give 10.6 g (49%) of the product, mp 95–98°. *Anal.* ($C_8H_{13}N_3S_2$) C, H, N.

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