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# Antiparasitic 5-Nitrothiazoles and 5-Nitro-4-thiazolines. 2†

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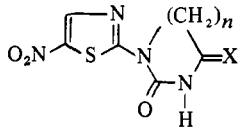
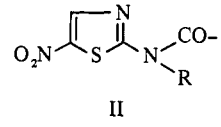
The synthesis of a wide variety of 3-[*N*-(5-nitro-2-thiazolyl)acylamino]propionamides IV and [1-(2-substituted ethyl)-1-(5-nitro-2-thiazolyl)-3-substituted]ureas V as potential antibacterial and antiparasitic agents is described. Treatment of 2-bromo-5-nitrothiazole with 3-aminopropionitrile afforded 3-[(5-nitro-2-thiazolyl)amino]propionitrile (**1**), the key intermediate. Some of the compounds prepared showed potent schistosomicidal, trichomonicidal, and/or antibacterial activities.

Many 2-amino-5-nitrothiazole derivatives have been shown to possess antiamebic,[2,3] antihistomonal,[4] and antitrichomonal[3,5] properties, and some have antischistosomal[3] activity. Thus, 1-(5-nitro-2-thiazolyl)-2-imidazolidinone (niridazole) (Ia) has been found to be effective in the treatment of human schistosomiasis and amebiasis and to give good results when used against dracunculiasis and strongyloidiasis. Recently the nitrothiazolylhydantoin Ib and -hydrouracil Ic have also been shown to possess antiparasitic activities.[6,7]

Whereas 2-(alkyl- and arylamino-)-5-nitrothiazoles are largely devoid of antischistosome activity,[8] many antiparasitic nitrothiazoles, including niridazole (Ia), 2-acetamido-5-nitrothiazole (aminitrozole), and 1-ethyl-3-(5-nitro-2-thiazolyl)urea (nithiazide), contain partial structure II in which R is H, $CH_2$, etc.

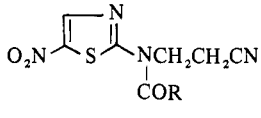


Ia, X = $H_2$; $n$ = 1
b, X = O; $n$ = 1
c, X = O; $n$ = 2



II

As part of a program to prepare novel chemotherapeutic agents, the synthesis of some 3-[*N*-(5-nitro-2-thiazolyl)acylamino]propionamides IV and [1-(2-substituted ethyl)-1-(5-nitro-2-thiazolyl)-3-substituted]ureas V was undertaken. Thiazoles IV contain partial structure II, in which R is



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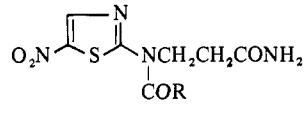
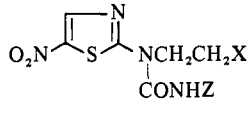


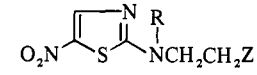
IV



V

$CH_2CH_2CONH_2$, and may be regarded as open-chain analogs of 1-(5-nitro-2-thiazolyl)hydrouracil (Ic). In particular, the preparation of 3-[*N*-(5-nitro-2-thiazolyl)acetamido]propionamide (**24**) was examined since this compound could be regarded as a possible metabolite of the known[6,7] active antischistosomal agent Ic.

**Chemistry.** The compounds described in the present work were derived from 3-[(5-nitro-2-thiazolyl)amino]propionitrile (**1**), which was prepared by treatment of 2-bromo-5-nitrothiazole with 3-aminopropionitrile in THF. Compounds **5–58** are listed in Tables I–III, and details of the synthesis of these and nitrothiazoles **1–4** and **59–61** are given in the Experimental Section.



| | Z | R | | Z | R |
|---|---|---|---|---|---|
| 1 | CN | H | 59 | $CO_2H$ | COMe |
| 2 | $CONH_2$ | H | 60 | $CONEt_2$ | COMe |
| 3 | $CO_2Et$ | H | 61 | $CONH(CH_2)_3NMe_2$ | COMe |
| 4 | $CO_2H$ | H | | | |

**Biological Activity.** The compounds described in this paper were tested against a Puerto Rican strain of *Schistosoma mansoni* in mice by Dr. Paul E. Thompson and coworkers of Parke, Davis and Co., Ann Arbor, Mich.‡ As in previous work, drugs were administered in a powdered diet for 14 days. Table IV lists the more active nitrothiazole derivatives, and it can be seen that schistosomicidal activity is present in a limited number of widely varying structural types. It was found that while 3-[*N*-(5-nitro-2-thiazolyl)-acetamido]propionamide (**24**) did possess moderate antischistome activity, the butyryl derivative **27** appeared to be the most potent propionamide IV. This latter compound effected an 85% kill of worms in mice when administered at *ca.* 305 mg/kg per day. While the formyl congener **23** possessed slight but significant schistosomicidal properties, somewhat surprisingly the chloroacetyl and propionyl analogs **25** and **26** were inactive in the mouse primary screen. Lengthening the carbon chain of the acyl group (RCO) in IV appeared to reduce efficacy (**28** and **29** and higher homologs), as did the use of cycloalkyl R moieties **35–37**. Alkyl substitution at the amide nitrogen apparently had little effect, since *N,N*-diethylamide **60** (corresponding to primary amide **24**) was also an active schistosomicide. However, the basic *N*-(dimethylamino)propylamide **61** had no activity in *S. mansoni* infected mice. Other propionamides IV, 3-[(5-nitro-2-thiazolyl)amino]propionamide (**2**), all nitriles III, and 3-[(5-nitro-2-thiazolyl)amino]propionitrile (**1**) were inactive in the mouse primary screen.

In the nitrothiazolylurea series V, surprisingly in view of

† For part 1 of this series, see ref 1.

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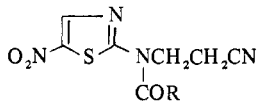
‡ For a description of test methods, see ref 9.

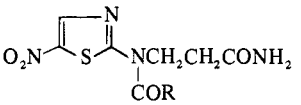
Table I. 3-[*N*-(5-Nitro-2-thiazolyl)acylamino]propionitriles

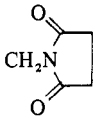


| Compd | R | Method | Reaction time, hr | % yield | Mp, °C | Recrystn solvent | Formula |
|---|---|---|---|---|---|---|---|
| 5 | Me | A | 1 | 56 | 182-184 | EtOH | $C_8H_8N_4O_3S$ |
| 6 | $CH_2Cl$ | B[a] | 3 | 53 | 175 | AcOH | $C_8H_7ClN_4O_3S$ |
| 7 | Et | A | 1 | 68 | 166-168 | EtOH | $C_9H_{10}N_4O_3S$ |
| 8 | *n*-Pr | A | 4[b] | 49 | 107-109 | *i*-PrOH | $C_{10}H_{12}N_4O_3S$ |
| 9 | *i*-Pr | A | 2.5[c] | 38 | 203-205 | EtOH | $C_{10}H_{12}N_4O_3S$ |
| 10 | *n*-Bu | B | 2.5 | 50 | 126-129 | EtOH | $C_{11}H_{14}N_4O_3S$ |
| 11 | *i*-Bu | B | 2 | 48 | 89-90.5 | *i*-PrOH | $C_{11}H_{14}N_4O_3S$ |
| 12 | $(CH_2)_4CH_3$ | B | 2.5 | 40 | 107-110 | EtOH | $C_{12}H_{16}N_4O_3S$ |
| 13 | $(CH_2)_6CH_3$ | B | 2.5 | 35 | 102-104 | EtOH | $C_{14}H_{20}N_4O_3S$ |
| 14 | $(CH_2)_8CH_3$ | B | 2.5 | 20 | 84-86 | *i*-PrOH, then EtOH | $C_{16}H_{24}N_4O_3S$ |
| 15 | $(CH_2)_{14}CH_3$ | B | 3 | 43 | 102-104 | EtOH | $C_{22}H_{36}N_4O_3S$ |
| 16 | c-$C_3H_5$[g] | B | 2 | 50 | 151-154 | EtOH | $C_{10}H_{10}N_4O_3S$ |
| 17 | c-$C_4H_7$[g] | B | 1.5 | 40 | 199-202 | EtOH | $C_{11}H_{12}N_4O_3S$ |
| 18 | c-$C_5H_9$[g] | B | 1.5 | 45 | 126-129 | EtOH | $C_{12}H_{14}N_4O_3S$ |
| 19 | $CH_2CH_2CO_2CH_3$ | B[d] | 1 | 31 | 115-117 | *i*-PrOH, then EtOAc | $C_{11}H_{12}N_4O_5S$ |
| 20 | $CH_2CH_2CO_2C_2H_5$ | B[d] | 2 | 18 | 77-79 | EtOH | $C_{12}H_{14}N_4O_5S$ |
| 21 | 4-Pyridyl | B[e] | 2 | 62 | 235-237 | AcOH | $C_{12}H_9N_5O_3S$ |
| 22 | 2-Furyl | B[d] | 2 | 38 | 171-173 | *i*-PrOH | $C_{11}H_8N_4O_4S$[f] |

[a]THF used instead of pyridine. [b]2 hr at 100°, then 2 hr at 125°. [c]2.5 hr at 130°. [d]Reaction effected using equal volumes of pyridine and $Me_2CO$. [e]Isonicotinoyl chloride hydrochloride used. [f]C: calcd, 45.2; found, 45.8. [g]c-$C_3H_5$ represents cyclopropyl, c-$C_4H_7$ represents cyclobutyl, and c-$C_5H_9$ represents cyclopentyl.

Table II. 3-[*N*-(5-Nitro-2-thiazolyl)acylamino]propionamides



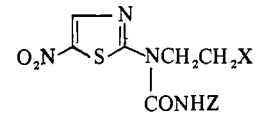
| Compd | R | Method | Reaction time, hr | Starting compd | % yield | Mp, °C | Recrystn solvent | Formula |
|---|---|---|---|---|---|---|---|---|
| 23 | H | A[a] | 1 | 2 | 63 | 210-211 | EtOH | $C_7H_8N_4O_4S$[f] |
| 24 | Me | A | 1.25 | 2 | 32 | 180-182 | EtOAc, then *i*-PrOH | $C_8H_{10}N_4O_4S$ |
| 25 | $CH_2Cl$ | C | 4 | 6 | 42 | 184 | EtOH | $C_8H_9ClN_4O_4S$ |
| 26 | Et | C | 0.75 | 7 | 42 | 158-160 | *i*-PrOH | $C_9H_{12}N_4O_4S$ |
| 27 | *n*-Pr | C | 0.75 | 8 | 68 | 160-162 | *i*-PrOH | $C_{10}H_{14}N_4O_4S$ |
| 28 | *i*-Pr | C | 0.75 | 9 | 33 | 164-167 | *i*-PrOH | $C_{10}H_{14}N_4O_4S$ |
| 29 | *n*-Bu | C | 0.75 | 10 | 48 | 161-163 | *i*-PrOH | $C_{11}H_{16}N_4O_4S$ |
| 30 | *i*-Bu | C | 0.75 | 11 | 67 | 159-161 | *i*-PrOH | $C_{11}H_{16}N_4O_4S$ |
| 31 | $(CH_2)_4CH_3$ | C | 3 | 12 | 31 | 138-140 | *i*-PrOH | $C_{12}H_{18}N_4O_4S$ |
| 32 | $(CH_2)_6CH_3$ | C | 20 | 13 | 50 | 121-123 | *i*-PrOH | $C_{14}H_{22}N_4O_4S$ |
| 33 | $(CH_2)_8CH_3$ | C | 20 | 14 | 52 | 136-138 | *i*-PrOH | $C_{16}H_{26}N_4O_4S$ |
| 34 | $(CH_2)_{14}CH_3$ | C | 22[d] | 15 | 32 | 123-125 | *e* | $C_{22}H_{38}N_4O_4S$[g] |
| 35 | c-$C_3H_5$[h] | C | 0.75 | 16 | 48 | 193-194 | *i*-PrOH | $C_{10}H_{12}N_4O_4S$ |
| 36 | c-$C_4H_7$[h] | C | 0.75 | 17 | 24 | 153-155 | *i*-PrOH | $C_{11}H_{14}N_4O_4S$ |
| 37 | c-$C_5H_9$[h] | C | 0.75 | 18 | 26 | 151-153 | *i*-PrOH | $C_{12}H_{16}N_4O_4S$ |
| 38 | $CH_2CH_2CO_2CH_3$ | B[b] | 2 | 2 | 22 | 146-147.5 | *i*-PrOH | $C_{11}H_{14}N_4O_6S$ |
| 39 | $CH_2CH_2CO_2C_2H_5$ | B[b] | 24 | 2 | 37 | 141-143 | *i*-PrOH | $C_{12}H_{16}N_4O_6S$ |
| 40 | 4-Pyridyl | C[c] | 0.75 | 21 | 29 | 220-221 | AcOH | $C_{12}H_{11}N_5O_4S$ |
| 41 | 2-Furyl | C | 0.75 | 22 | 32 | 202-204 | MeOH | $C_{11}H_{10}N_4O_5S$ |
| 42 |  | B[b] | 20 | 2 | 40 | 214-216 | AcOH | $C_{12}H_{13}N_5O_6S$ |

[a]Compd **2** heated at 100° with $HCO_2H$ and $Ac_2O$. [b]Used equal volumes of pyridine and $Me_2CO$. [c]Neutralized with $NaHCO_3$ after dilution with $H_2O$. [d]1 hr at 20°, 1 hr at 40°, and then 20 hr at 20°. [e]EtOH, then recrystallization of $NaHCO_3$-insoluble material from *i*-PrOH. [f]N: calcd, 23.0; found, 22.4. [g]N: calcd, 12.3; found, 11.7. [h]c-$C_3H_5$ represents cyclopropyl, c-$C_4H_7$ represents cyclobutyl, and c-$C_5H_9$ represents cyclopentyl.

the general lack of antischistosome activity of nitriles III compared with the corresponding active amides IV, 1-(2-cyanoethyl)-1-(5-nitro-2-thiazolyl)urea (**43**) was found to possess potent schistosomicidal activity, causing a 95% reduction in the live worm burden at 308 mg/kg per day. Interestingly, while amide **49** (the hydrolysis product of nitrile **43**) had no activity when tested by the same procedures, the *N*-acetyl derivative **44** of **43** possessed moderate antischistosome properties. Finally, ureas **46**, **48**, **53**, and **55** (not listed in Table IV) all showed slight but significant activity (less than 20% reduction in the worm burden at high dose levels).

In conclusion, several comments may be pertinent on the above results. While the *N*-acetyl- and *N*-butyrylpropion-

**Table III.** [1-(2-X-Ethyl)-1-(5-nitro-2-thiazolyl)-3-Z]ureas



| Compd | X | Z | Method | Reaction time, hr | Starting compd | % yield | Mp, °C | Recrystn solvent | Formula |
|---|---|---|---|---|---|---|---|---|---|
| **43** | CN | H | D | | 1 | 37 | 187-189 dec | EtOH | $C_7H_7N_5O_3S$ |
| **44** | CN | $COCH_3$ | E | 2 | 1 | 60 | 158-159 dec | EtOH | $C_9H_9N_5O_4S$ |
| **45** | CN | $COCH_2Br$ | E | 2.5 | 1 | 29 | 153-155 dec | EtOH | $C_9H_8BrN_5O_4S$ |
| **46** | CN | $COC_2H_5$ | E | 3.5 | 1 | 45 | 148-150 dec | EtOH | $C_{10}H_{11}N_5O_4S$ |
| **47** | CN | $COCH_2CH_2Br$ | E | 16 | 1 | 38 | 157-158 dec | EtOH | $C_{10}H_{10}BrN_5O_4S$ |
| **48** | CN | Et | E | 4.5[b] | 1 | 39 | 170-172 | *i*-PrOH | $C_9H_{11}N_5O_3S$ |
| **49** | $CONH_2$ | H | C[a] | 0.75 | **43** | 63 | 201-202 dec | AcOH | $C_7H_9N_5O_4S$ |
| **50** | $CONH_2$ | $COCH_3$ | E | 4 | 2 | 43 | 196-198 dec | Aqueous DMF | $C_9H_{11}N_5O_5S$ |
| 51 | $CONH_2$ | $COCH_2Cl$ | E | 4 | 2 | 63 | 173-175 dec | EtOAc-petrol[c] | $C_9H_{10}ClN_5O_5S$ |
| **52** | $CONH_2$ | $COCHCl_2$ | E | 4 | 2 | 69 | 165-166 dec | EtOAc-petrol[c] | $C_9H_9Cl_2N_5O_5S$[d] |
| **53** | $CONH_2$ | $COC_2H_5$ | E | 5 | 2 | 41 | 180-182 dec | EtOAc-petrol[c] | $C_{10}H_{13}N_5O_5S$ |
| **54** | $CONH_2$ | $COCH_2CH_2Br$ | E | 4 | 2 | 37 | 173-174 dec | EtOAc-petrol[c] | $C_{10}H_{12}BrN_5O_5S$ |
| **55** | $CONH_2$ | Et | C[a] | 0.75 | **48** | 27 | 185-186 | *i*-PrOH | $C_9H_{13}N_5O_4S$ |
| **56** | $CO_2C_2H_5$ | $COCH_2CH_2Br$ | E | 2 | 3 | 81 | 129-131 | EtOH | $C_{12}H_{15}BrN_4O_6S$ |
| **57** | $CO_2H$ | $COC_2H_5$ | E | 2 | **4** | 31 | 146-147 dec | EtOH | $C_{10}H_{12}N_4O_6S \cdot EtOH$ |
| **58** | $CO_2H$ | $COCH_2CH_2Br$ | E | 3 | **4** | 37 | 148-149 dec | EtOH | $C_{10}H_{11}BrN_4O_6S \cdot EtOH$ |

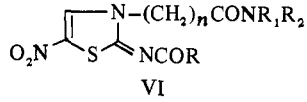
[a] Reaction mixture not diluted with $H_2O$. [b] Reaction effected in refluxing toluene. [c] Petroleum ether, bp 60-80°. [d] C: calcd, 29.2; found, 30.0.

**Table IV.** Effects of Nitrothiazoles 1-61 against *S. mansoni* in Mice

| Compd | Drug: Route × days[a] | Drug: mg/kg per day | % reduction in live schistosomes[c] |
|---|---|---|---|
| **23** | D × 14 | 347 | 20 |
| **24** | D × 7 then D × 7 | 118, then 238[b] | 59 |
| 27 | D × 14 | 305 | 85 |
| **28** | D × 14 | 305 | 5 |
| 29 | D × 14 | 426 | 39 |
| 35 | D × 7 then D × 7 | 160, then 238 | 15 |
| 37 | D × 14 | 360 | 25 |
| **43** | D × 14 | 308 | 95 |
| **44** | D × 7 then D × 7 | 167, then 198 | 33 |
| **60** | D × 14 | 339 | 49 |
| Niridazole | D × 14 | 249 | 99 |

[a] D represents drug-diet. [b] Represents a dose reduction based on percentage in diet. [c] Groups of six animals were used in the diet studies. The worm burden of the controls averaged 15 per mouse.

amides **24** and **27** did possess marked antischistosome properties, the degree of activity is somewhat less than that shown by the 5-nitro-4-thiazoline-3-acetamides (VI, $n = 1$) described earlier.[1] In the latter series of compounds, however, it was shown that analogs bearing the propionamide side chain (*i.e.*, VI, $n = 2$) were all inactive in the mouse primary screen. A more detailed comparison of the structure-



VI

activity relationships existing in the present series of compounds, other nitrothiazoles, and the 5-nitro-4-thiazolines described earlier[1] is given in the following paper.[10] However, it may not be inappropriate at this stage to point out that the discovery of schistosomicidal properties in propionamides IV is unexpected in view of the structure-specificity generally associated with analogs of niridazole (Ia).[11-13]

Compounds **1-61** were also evaluated against *Trichomonas vaginalis in vitro* and in mice.§ In the *in vitro* screen, many of the nitrothiazoles were trichomonicidal at concentrations of 1.56-6.25 μg/ml. When tested further against intraperitoneal *T. vaginalis* infections in mice, compounds **7**, **11**, **26**, and **30** were found to cure the infections when administered by gavage at 100 mg/kg twice daily for 3 days; compound **35** was effective at 50 mg/kg twice daily for 3 days; and thiazoles **24**, **27**, **31**, and **47** were curative at 25 mg/kg twice daily when administered similarly.

Nitrothiazoles **1-61** were also tested *in vitro* against a variety of bacteria according to procedures described previously.# The most active of these compounds (**24**, **51**, and **52**) had minimum inhibitory concentrations of 0.16, 0.31, and 0.31 μg/ml against *Streptococcus pyogenes* C203; 10, 5, and 5 μg/ml against *Salmonella typhimurium* V-31; and 20, 20, and 20 μg/ml against *Escherichia coli* Vogel, respectively. When tested against *S. pyogenes* infections in mice by oral (po) and subcutaneous (sc) administration, *N*-(2-carbamoylethyl)-*N*-(5-nitro-2-thiazolyl)butyramide (**27**) had $ED_{50}$ 8.2 (sc) and 9.6 mg/kg (po), and nitrothiazoles **24** and **52** had $ED_{50}$ <25 mg/kg (sc and po).

## Experimental Section**

The physical properties of most of the compounds prepared are collected in Tables I-III, and the experimental details below relate to these tables.

**3-[(5-Nitro-2-thiazolyl)amino]propionitrile (1).** 2-Bromo-5-nitrothiazole (121 g) was added in portions to a solution of 3-aminopropionitrile (86 g) in THF (1350 ml) at room temperature. The mixture was stirred 3.5 hr at room temperature and then the filtered solution was evaporated *in vacuo*. The residue was stirred with $H_2O$, and solid was collected and washed with $H_2O$, cold *i*-PrOH, and then $Et_2O$ to give the product (103.5 g), mp 155-157° dec after recrystallization from 50% EtOH. *Anal.* ($C_6H_6N_4O_2S$) C, H, N.

**3-[(5-Nitro-2-thiazolyl)amino]propionamide (2).** A mixture of nitrile 1 (10.0 g) and concentrated HCl (200 ml) was stirred until solid all dissolved (*ca.* 0.5 hr). Dilution with $H_2O$ (100 ml) and neutralization ($NaHCO_3$) precipitated the amide 2 (5.14 g), mp 190-191° (from EtOAc). *Anal.* ($C_6H_8N_4O_3S$) C, H, N.

***N*-(5-Nitro-2-thiazolyl)-β-alanine Ethyl Ester (3).** Nitrile 1 (12.0 g) was stirred 1 hr at room temperature with concentrated HCl

§ For a description of test methods, see ref 14.

# For the general *in vitro* and *in vivo* test procedures, see ref 15.

** 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.

(240 ml), and solution was evaporated *in vacuo* at 100°. Recrystallization of the residue from EtOH afforded the ester 3 (5.3 g), mp 135–137°. An analytical sample (recrystallized three times from EtOH) had mp 141–143°. *Anal.* ($C_8H_{11}N_3O_4S$) C, H, N.

*N*-(5-Nitro-2-thiazolyl)-β-alanine (4). A mixture of the nitrile 1 (5.0 g) and concentrated HCl (100 ml) was heated 1 hr at 100° and then cooled. Addition of $H_2O$ and isolation with EtOAc furnished the acid 4 (3.2 g), mp 162–163° [from EtOAc–petroleum ether (bp 60–80°)]. *Anal.* ($C_6H_7N_3O_4S$) C, H, N.

2-[*N*-(2-Cyanoethyl)acetamido]-5-nitrothiazole (5). Method A. A mixture of nitrile 1 (5.0 g), $Ac_2O$ (10 ml), and AcOH (10 ml) was heated at 100° (reaction time given) and cooled, and the solution was then poured slowly onto crushed ice. The oil that separated rapidly crystallized, and the solid was collected, washed well with $H_2O$, and recrystallized from EtOH to afford 5 (56%), mp 182–184°.

*N*-(2-Cyanoethyl)-3-methyl-*N*-(5-nitro-2-thiazolyl)butyramide (11). Method B. Isovaleryl chloride (10.88 g, 20% excess) was added dropwise to a solution of nitrile 1 (14.85 g) in pyridine (75 ml) at 10°. The mixture was stirred at room temperature (time given) and then poured into $H_2O$. The aqueous layer was decanted from the oil, which was then washed with $H_2O$ and triturated with *i*-PrOH. Several crops of material were obtained, and these were combined and recrystallized (twice) from *i*-PrOH (charcoal) to give 11 (48%), mp 89–90.5°.

*N*-(2-Carbamoylethyl)-*N*-(5-nitro-2-thiazolyl)propionamide (26). Method C. A suspension of *N*-(2-cyanoethyl)-*N*-(5-nitro-2-thiazolyl)-propionamide (7) (8.8 g) in concentrated HCl (88 ml) was stirred at room temperature (time given) and then poured into $H_2O$. Solid was collected, washed thoroughly with $H_2O$, dried, and recrystallized (charcoal) from *i*-PrOH. Amide 26 (42%) had mp 158–160°.

1-(2-Cyanoethyl)-1-(5-nitro-2-thiazolyl)urea (43). Method D. A solution of nitrile 1 (27.0 g) in THF (800 ml) was added over 0.75 hr to a stirred solution of $COCl_2$ in toluene (12.5% w/v, 900 ml), and the mixture was then stirred 3 hr at room temperature and 0.5 hr at 40°. Excess $COCl_2$ was removed with a stream of $N_2$, and the reaction mixture was left overnight at room temperature. The cooled (0°) vigorously stirred mixture was then saturated with $NH_3$ and evaporated *in vacuo*. The residue was stirred with $H_2O$ (*ca.* 800 ml), and the solid was collected, dried, and recrystallized from EtOH (charcoal) to give urea 43 (37%), mp 187–189° dec.

3-Acetyl-1-(2-cyanoethyl)-1-(5-nitro-2-thiazolyl)urea (44). Method E. Acetyl isocyanate (3.34 g, 20% excess) in THF (10 ml) was added dropwise to a solution of nitrile 1 (5.9 g) in THF (150 ml), and the mixture was then stirred at room temperature (reaction time given). A small amount of insoluble material was filtered off, and the filtrate was evaporated *in vacuo* to furnish urea 44 (60%), mp 158–159° dec (from EtOH).

*N*-Acetyl-*N*-(5-nitro-2-thiazolyl)-β-alanine (59). A mixture of acid 4 (13.29 g), $Ac_2O$ (40 ml), and AcOH (40 ml) was heated 2 hr at 100° and then poured into ice–$H_2O$ to give the *N*-acetyl derivative 59 of acid 4 (59%), mp 171–173° (from EtOAc). *Anal.* ($C_8H_9N_3O_5S$) C, H, N.

*N,N*-Diethyl-3-[*N*-(5-nitro-2-thiazolyl)acetamido]propionamide (60). Ethyl chloroformate (3.55 ml) was added to a solution of acid 59 (9.6 g) and $NEt_3$ (5.5 ml) in $CHCl_3$ (300 ml) at 0°, and the mixture was stirred 0.5 hr at 0°. Redistilled $NHEt_2$ (11.0 ml) was added dropwise at 0°, and the mixture was stirred 5 min at 0° and 1 hr at room temperature. The organic layer was washed with $H_2O$ (5 × 100 ml), dried ($MgSO_4$), and evaporated to provide the *N,N*-diethyl analog 60 of primary amide 24 (33%), mp 122–124° (from *i*-PrOH). *Anal.* ($C_{12}H_{18}N_4O_4S$) C, H, N.

*N*-[3-(Dimethylamino)propyl]-3-[*N*-(5-nitro-2-thiazolyl)acetamido]propionamide (61). Treatment of the mixed anhydride of acid 59 (from 7.1 g of acid) with 3-(dimethylamino)propylamine (8.3 g) at 0° (*cf.* preparation of 60) afforded the *N*-(dimethylamino)-propyl analog 61 of 24 (39%), mp 128–130° (from *i*-PrOH). *Anal.* ($C_{13}H_{21}N_5O_4S$) C, H, N.

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# Antiparasitic 5-Nitrothiazoles and 5-Nitro-4-thiazolines. 3[1]

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Alkylation of the sodium salt of 2-formamido-5-nitrothiazole in *N,N*-dimethylformamide with a variety of alkylating agents is shown to give exclusively exocyclic N-alkylated products IV. Removal of the *N*-formyl group was readily achieved with hydrazine hydrate or 1 equiv of sodium hydroxide, and the resulting aminothiazoles V were treated with several acid chlorides and isocyanates to give (acylamino)-thiazoles VI. Some of the nitrothiazoles IV, V, and VI exhibited moderate activity against *Schistosoma mansoni*, *Trichomonas vaginalis*, and a range of gram-positive and gram-negative bacteria.

The potent antischistosome activity of various 2-(acylimino)-5-nitro-4-thiazoline-3-acetamides I against *Schistosoma mansoni* infections in mice has been described recently.[2] Thiazolines I, in which R is alkyl, aryl, or alkoxy, etc., were prepared (together with varying amounts of the exocyclic N-alkylated thiazoles III) by alkylation of the sodium salt of the appropriate thiazolylamide II in DMF.

In the present work, it was found that alkylation of the sodium salt of 2-formamido-5-nitrothiazole under similar

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