Derivatives of 2-Amino-5-nitrothiazole as Potential Schistosomicides

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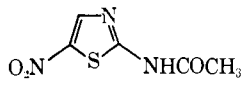
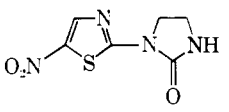
A variety of derivatives of 2-amino-5-nitrothiazole and 2-hydrazino-5-nitrothiazole were prepared as potential schistosomicides. The general lack of activity over a wide range of structural types serves to emphasize the specificity surrounding the highly active 1-(5-nitro-2-thiazolyl)-2-imidazolidinone (II).

A variety of nitro heterocyclic systems have been demonstrated to possess useful therapeutic properties. Nitrofurans for example have been extensively investigated[1] and several are useful clinically in man. More recently nitroimidazoles[2] have found a place in the treatment of protozoan infections. Derivatives of nitrothiazole have remained relatively unexplored. It has been known for some time that simple analogs of 2-amino-5-nitrothiazole are effective against trichomonad infections. In 1955 the activity of acetamide (I) against



I

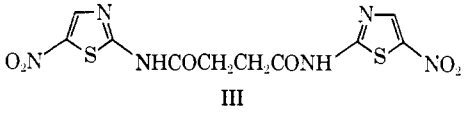


II

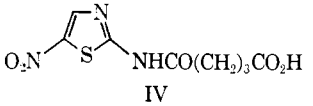
experimental infections of *Schistosoma mansoni* in mice was demonstrated.[3] Several years ago Lambert, Wilhelm, and coworkers[4-7] reported their success in the modification of this system culminating in the introduction of a new clinical agent for schistosomiasis, niridazole (II).

We report here some investigations into the chemistry of 2-amino-5-nitrothiazole which have been proceeding in our laboratories during the past several years, and the activities of the products of this work as antiparasitic agents.

Treatment of 2-amino-5-nitrothiazole (ANT) with simple dicarboxylic acid anhydrides led to bisamides or half-amide–half-acids. Thus succinic anhydride, glutaric anhydride, 1,2-cyclohexanedicarboxylic anhydride, and *cis*-4-cyclohexene-1,2-dicarboxylic anhydride provided III–VI. 1,2,4,5-Benzenetetracarboxylic anhydride gave a product which appears to be VII or the isomeric VIII. This material which exhibits a strong ester carbonyl at 1730 cm^{-1} is apparently formed from the imide during the purification from ethanol. Phthalic anhydride provided only the imide IX in poor yield.



III



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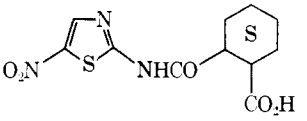
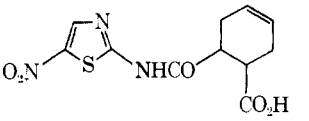


V



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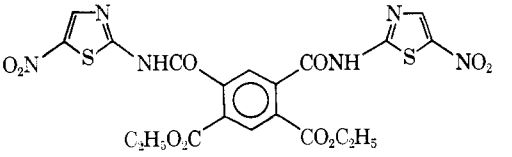
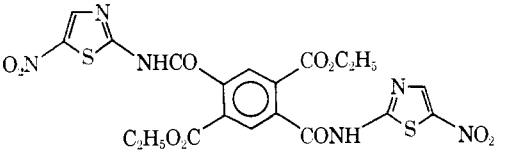
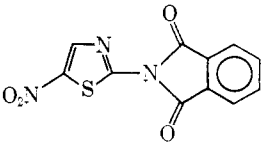


VII



VIII

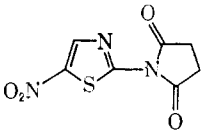
Treatment of ANT with oxalyl chloride in pyridine gave the bisamide X. The use of longer chain dicarboxylic acid chlorides led directly to the desired imides.



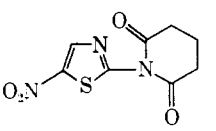
IX

X

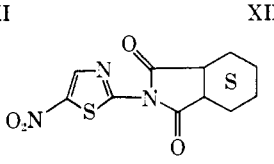
Succinyl chloride and glutaryl chloride afforded, respectively, XI and XII. The half-amide–half-acids



XI



XII



XIII

* To whom correspondence should be addressed.

(1) For an extensive review see K. Miura and H. K. Reckendorf, *Progr. Med. Chem.*, **5**, 320 (1967).

(2) R. M. Michaels, *Advan. Chemother.*, **3**, 39 (1968).

(3) A. C. Cuckler, A. B. Kupferberg, and N. Millman, *Antibiot. Chemother.*, **5**, 540 (1955).

(4) C. R. Lambert, N. Wilhelm, H. Striebel, F. Kradolfer, and P. Schmidt, *Experientia*, **20**, 452 (1964).

(5) C. R. Lambert, *Ann. Trop. Med. Parasitol.*, **58**, 292 (1964).

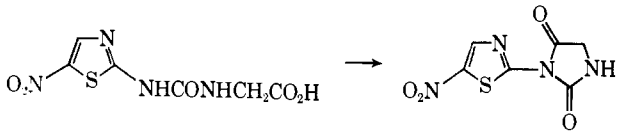
(6) P. Schmidt and M. Wilhelm, *Angew. Chem., Int. Ed. Engl.*, **5**, 857 (1966).

(7) M. Wilhelm, F. H. Marquardt, K. Meier, and P. Schmidt, *Helv. Chim. Acta*, **49**, 2443 (1966).

could also be chlorinated with $SOCl_2$ and cyclized to the imides. In this manner XIII was formed from V. These imide analogs of II were uniformly inactive against *S. mansoni* infections in mice.[8]

The hydantoin XIV, which is more closely related structurally to II, was prepared by treatment of ANT with carbethoxyethyl isocyanate to give ethyl 5-(5-

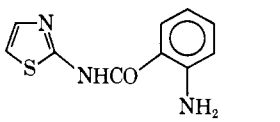
XV



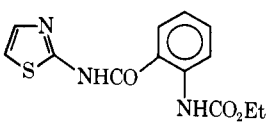
XIV

nitro-2-thiazolyl)hydantoate (XV), acid hydrolysis to the hydantoic acid, chlorination with $SOCl_2$, and cyclization in C_6H_6. This material is also inactive against *S. mansoni* infections. These results appear to preclude activity in those derivatives of ANT with CO functions flanking both sides of the amine.

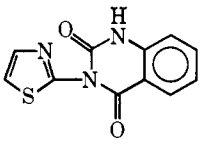
An attempt was also made to prepare the benzene analog of XIV. Thus 2-aminothiazole was condensed with isatoic anhydride to give *o*-amino-*N*-2-thiazolylbenzamide (XVI). Although reaction with ethyl chloroformate led only to ethyl *o*-(2-thiazolylcarbamoyl)carbanilate (XVII), treatment with $COCl_2$ provided the desired 3-(2-thiazolyl)-2,4(1*H*,3*H*)-quinazolinedione (XVIII).



XVI

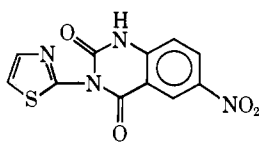


XVII

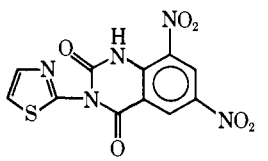


XVIII

Nitration in H_2SO_4 at 0° attacked only the Ph ring leading to XIX which is assigned the 6-nitro structure. Nitration of XVIII using excess HNO_3 once again left



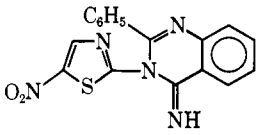
XIX



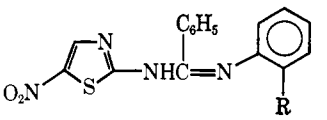
XX

the thiazole ring untouched, confirmed by the presence of the unsubstituted thiazole pair of AB doublets in the nmr spectrum, and led only to the dinitrophenyl derivative XX.

Preparation of a similar ring system (XXI) was also



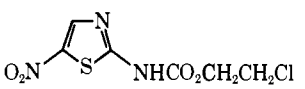
XXI



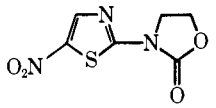
XXII

envisioned. Thus the condensation of ANT with *N*-(α-chlorobenzylidene)anthranilonitrile in pyridine provided *N'*-(*o*-cyanophenyl)-*N*-(5-nitro-2-thiazolyl)-benzamidine (XXII, R = CN). However the attempted cyclization to XXI with $BF_3 \cdot Et_2O$ led to isolation only of (XXII, R = $CONH_2$).

Treatment of ANT with chloroethyl chloroformate gave the chloroethyl carbamate XXIII. Mild treatment with dil KOH yielded oxazolidinone XXIV, the O isostere of niridazole (II), which was inactive against *S. mansoni* in the mouse. This material proved to be

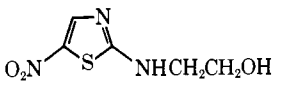


XXIII

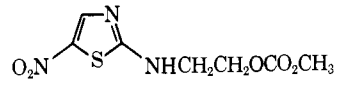


XXIV

extremely labile to base, and this is a possible reason for its lack of activity *in vivo*. Treatment of XXIV with aq base gave 2-[(5-nitro-2-thiazolyl)amino]ethanol (XXV), while treatment of XXIV with methanolic base provided the corresponding carbonate XXVI.



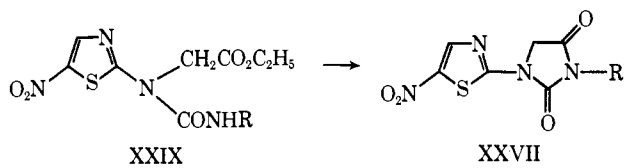
XXV



XXVI

The hydantoin analogs XXVII of niridazole (II) were reported recently[9] to have schistosomicidal activity. It was of interest to us to prepare some open chain analogs

XXVIII



XXIX XXVII

of II by the reaction of ethyl *N*-(5-nitro-2-thiazolyl)-glycinate (XXVIII) with isocyanates. We found, however, that upon treating XXVIII in DMF with alkyl isocyanates, the expected intermediate XXIX was not isolated, but facile cyclization led directly to the substituted hydantoins XXVII (R = CH_3, C_2H_5, CH_2CH_2Cl). We have confirmed the high activity of these materials in mice against *S. mansoni* infections.

To prepare the required ethyl *N*-(5-nitro-2-thiazolyl)-glycinate[10] 2-formamido-5-nitrothiazole was alkylated

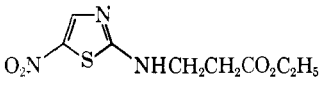
(8) Results described in this communication were obtained from tests in mice against a Puerto Rican strain of *S. mansoni* by Dr. Paul E. Thompson and coworkers of these laboratories. Drugs were given in a powdered diet for 14 days or by gavage in 10 ml/kg of aqueous 1% hydroxyethyl or carboxymethyl cellulose for 5 or 10 days. Activity is assessed on the basis of the degree of elimination of live schistosomes from infected mice. For a description of test methods see P. E. Thompson, J. E. Meisenhelder, and H. Najarian, *Amer. J. Trop. Med. Hyg.*, **11**, 31 (1962).

(9) Ciba Ltd., Netherlands Patent 6,505,226, Oct 25, 1965.

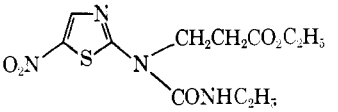
(10) The procedure for the preparation of ethyl *N*-formyl-*N*-(5-nitro-2-thiazolyl)glycinate, and its hydrolysis to *N*-(5-nitro-2-thiazolyl)glycine was provided by Dr. P. J. Islip of our Hounslow, England, laboratories.

in DMF with ethyl bromoacetate using NaH. The vagaries of this reaction which leads either directly to XXVIII or the *N*-formyl derivative depending upon the conditions are discussed in the Experimental Section.

Interestingly the 6-membered ring was not formed with such facility. Thus ethyl *N*-(5-nitro-2-thiazolyl)-β-alaninate (XXX), prepared by the reaction of 2-bromo-5-nitrothiazole with ethyl β-alaninate, treated with ethyl isocyanate in DMF led only to ethyl *N*-(ethylcarbamoyl)-*N*-(5-nitro-2-thiazolyl)-β-alaninate (XXXI).

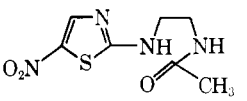


XXX



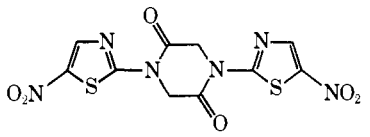
XXXI

An additional open chain analog of II was prepared by the condensation of 2-bromo-5-nitrothiazole with *N*-acetylethylenediamine. This material (XXXII) was also ineffective against *S. mansoni* infections in mice.

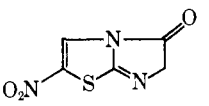


XXXII

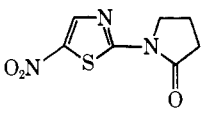
The action of $SOCl_2$ on *N*-(5-nitro-2-thiazolyl) glycine gave the bislactam XXXIII. The alternate structure XXXIV is eliminated by the mass spectrum which contains a peak for the molecular ion at 370 mass units, the molecular weight of the dimeric structure XXXIII. Simple lactam analogs of II such as XXXV have been reported to have antischistosomal properties.[11] The analog (XXXIII) was inactive.



XXXIII

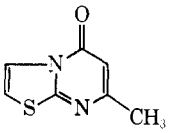


XXXIV

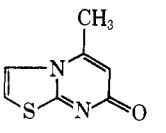


XXXV

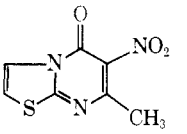
In order to investigate the effect of incorporation of the thiazole ring into a bicyclic system, the work of Antaki and Petrow[12] was repeated. Thus the fusion of 2-aminothiazole with ethyl β-aminocrotonate yielded a material, mp 122–123°, which according to tlc contained two components. This material could not be purified by crystallization, and is presumed to be a mixture of the two possible condensation products XXXVI and XXXVII. Nitration of this mixture afforded a single homogeneous material, mp 159–160°, presumably identical with the X-nitro derivative reported by Antaki and Petrow, mp 165°. The nmr spectrum of this material revealed that nitration had taken place in the pyrimidinone ring since the pair of thiazole AB doublets was still intact. The compound obtained is thus XXXVIII or XXXIX, and not unexpectedly was inactive against *S. mansoni* infections.



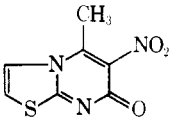
XXXVI



XXXVII

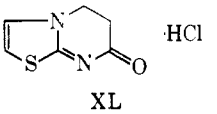


XXXVIII

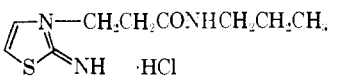


XXXIX

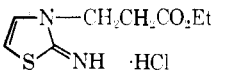
3-Chloro-*N*-2-thiazolylpropionamide upon heating above its melting point underwent cyclization to 5,6-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one monohydrochloride (XL). Nitration of this intermediate was not feasible since it underwent facile cleavage even upon mild treatment with amines or alcohols to form imino-thiazolines XLI and XLII. Similar ring closures have been reported recently in the benzthiazole system,[13] but the resulting ring systems appear to be considerably more stable since the cyclizations were effected in base (OH^- or R_2NH).



XL



XLI



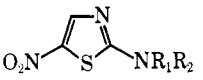
XLII

It was also of interest to examine some analogous cyclic derivatives wherein one of the ring C atoms was replaced by N. These formally may be considered as derivatives of 2-hydrazino-5-nitrothiazole. Recently a series of 2,2′-hydrazobis(5-nitrothiazoles) was shown to have limited antiprotozoal activity.[14]

The benzalhydrazone of 2-hydrazino-5-nitrothiazole could be prepared by the method of Graner[15] consisting of the reaction between preformed benzaldehyde hydrazone and 2-bromo-5-nitrothiazole in EtOH. It was found that 2-hydrazino-5-nitrothiazole could be prepared directly by addition of hydrazine to a soln of 2-bromo-5-nitrothiazole in THF at room temperature. This material was not subjected to microanalysis as a result of the reports[15] of its instability and resistance to all attempts at purification. Similarly ethyl carbazate provided XLIII, and (2-hydroxyethyl)hydrazine afforded XLIV. This structure (XLIV) is preferred to the alternative XLV because of the known propensity of alkyl hydrazines to undergo alkylation on the substi-

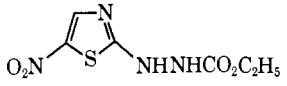
(11) Parke, Davis and Co., U. S. Patent 3,311,614, 1967.
(12) H. Antaki and V. Petrow, *J. Chem. Soc.*, 551 (1951).
(13) G. Tsatsas and E. Costakis, *Chem. Commun.*, **19**, 991 (1967).
(14) M. Avramoff, S. Adler, and A. Foner, *J. Med. Chem.*, **10**, 1138 (1967).
(15) R. F. Graner, *Rev. Real. Acad. Cienc. Exactas Fis. Natur. Madrid*, **56**, 623 (1962) [*Chem. Abstr.*, **59**, 1614 (1963)].

TABLE I

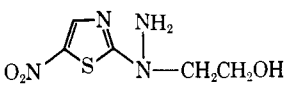


NR_1R_2[a]	λ_{max}, mμ	ε × 10³	λ_{max}, mμ	ε × 10³	λ_{max}, mμ	ε × 10³
NHC_2H_5	445	20.6	228.5	6.4		
$NHNH_2$	445	15.0	240	7.1		
$N(CH_3)_2$	392	9.2	282	6.4	245	7.7
$N(C_2H_5)_2$	400	8.9	281	7.1	248	~8.2
$N(NH_2)CH_2CH_2OH$	392	11.5	280	5.9	242	6.1

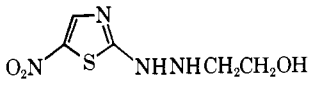
[a] All curves run in MeOH containing 1 drop of 2 *N* NaOH/3.5-ml cell.



XLIII



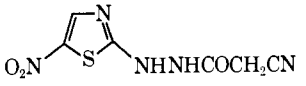
XLIV



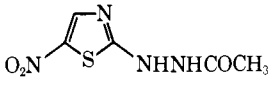
XLV

tuted N. Uv comparison of selected analogs (Table I) in basic MeOH further confirms this structure assignment. A compound containing tertiary N at the 2 position of the thiazole ring is seen to absorb at 280 and 400 mμ while a secondary N as the anion in basic medium absorbs at about 230 and 445 mμ.

The cyanoacethydrazide derivative XLVI had been reported previously by Graner. The acethydrazide XLVII was prepared similarly. Treatment of XLVII

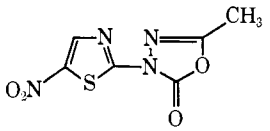


XLVI

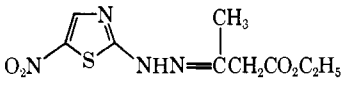


XLVII

with $COCl_2$ gave 2-methyl-4-(5-nitro-2-thiazolyl)-Δ^2-1,3,4-oxadiazolin-5-one (XLVIII). Treatment of 2-hydrazino-5-nitrothiazole with ethyl acetoacetate gave

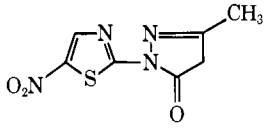


XLVIII

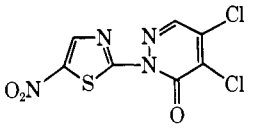


XLIX

the hydrazone (XLIX) which was cyclized with $POCl_3$ to provide the analogous 3-methyl-1-(5-nitro-2-thiazolyl)-2-pyrazolin-5-one (L), while mucochloric acid afforded 4,5-dichloro-2-(5-nitro-2-thiazolyl)-3(2*H*)-pyridazinone (LI).

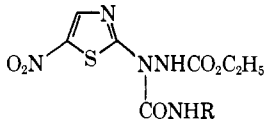


L

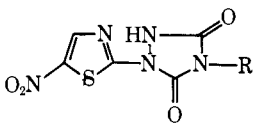


LI

Ethyl 3-(5-nitro-2-thiazolyl)carbazate (XLIII) reacts with isocyanates to form the expected ureas LII (R = CH_3, $CH_2CH{=}CH_2$, CH_2CH_2Cl). Unlike the glycine ester XXVIII there is no apparent propensity for cyclization to the 4-alkyl-2-(5-nitro-2-thiazolyl)-1,2,4-triazolidine-3,5-dione LIII. It is interesting that without the opportunity to ring close on the 2-amino N, urea LII (R = CH_2CH_2Cl) is completely devoid of antischistosome activity. On the other hand LII (R = CH_3) does possess a low order of activity.

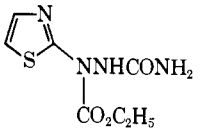


LII

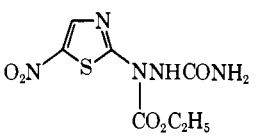


LIII

The reaction of 2-thiobiurea with 1,2-dichloroethyl ethyl ether gives 1-(2-thiazolyl)semicarbazide,[16] which upon treatment with ethyl chloroformate provided LIV. Nitration then afforded ethyl 3-carbamoyl-3-(5-nitro-2-thiazolyl)carbazate (LV). Efforts to ring close this material were unsuccessful.



LIV



LV

Treatment of 2-hydrazino-5-nitrothiazole with 2-chloroethyl isocyanate provided a material presumed to be LVI, although condensation on the other N cannot be excluded.

LVI

The hydrazine analogs of 2-amino-5-nitrothiazole described were uniformly ineffective against *S. mansoni* infections in mice.

Various of these materials were screened also against experimental infections of amebiasis,[17] trichomoniasis,[17] intestinal helminthiases,[18] trypanosomiasis (*Trypanosoma cruzi*),[19] and a variety of bacteria. The following were cidal at the indicated concentrations (μl/ml) against *T. vaginalis in vitro:* IV (25), V (25), VI (25), X (0.78), XI (25), XIII (25), XXII (R = CN) (1.56), XXIII (0.78), XXIV (0.2), XXVI (1.56), XXXII (25), XLIV (25), LII (R = $CH_2CH{=}CH_2$) (6.25), LII (R = CH_2CH_2Cl) (6.25), LVI (1.56). Against *Entamoeba histolytica (in vitro)* the following were cidal at the indicated concentrations (μl/ml): XI (40), XXIII (80), XXIV (40), XXVI (20). Compound IX showed some activity *vs.* infections of *Nematospiroides dubius* and

(16) H. Beyer and W. Schindler, *Chem. Ber.*, **86**, 1410 (1953).

(17) For a description of test methods see P. E. Thompson, A. Bayles, S. F. Herbst, B. Olszewski, and J. E. Meisenhelder, *Antibiot. Chemother.*, **9**, 618 (1959).

(18) For a description of test methods see H. G. Sheffield, J. E. Meisenhelder, and P. E. Thompson, *J. Parasitol.*, **45**, 653 (1959).

(19) For a description of test methods see A. Bayles, J. Waitz, and P. E. Thompson, *J. Protozool.*, **13**, 110 (1966).

Hymenolepis nana in mice. Compounds XXIII and XXVI showed activity *vs. Escherichia coli* (Vogel) at 20 μl/ml and *E. coli* (Vogel), *Klebsiella pneumoniae* (MGH-2), and *Salmonella typhimurium* (V-31) at 20 μl/ml, respectively.

Experimental Section[20]

***N,N'*-Bis(5-nitro-2-thiazolyl)succinamide (III).**—A mixture of 14.5 g (0.1 mole) of 2-amino-5-nitrothiazole (ANT) and 10 g (0.1 mole) of succinic anhydride in DMF was heated at 125° for 6 hr, cooled to room temp, and filtered. The white solid was recrystd from DMF and washed with MeOH to give 2.7 g (14.5%) of the product, mp 288° dec with charring from 280°. *Anal.* ($C_{10}H_8N_6O_6S_2$) C, H, N.

***N*-(5-Nitro-2-thiazolyl)glutaramic Acid (IV).**—A soln of 14.5 g (0.1 mole) of ANT and 12.4 g (0.1 mole) of glutaric anhydride in DMF was heated at 100° for 4 hr. The cooled reaction mixture was poured into H_2O. The solid which formed was collected and triturated thoroughly with Et_2O. The insol portion was recrystd from DMF–H_2O to give the product (2.5 g, 10%), mp 239–240°. A large amount of unchanged ANT could be recovered from the Et_2O filtrate. *Anal.* ($C_8H_9N_3O_5S$) C, H, N.

2-[(5-Nitro-2-thiazolyl)carbamoyl]cyclohexanecarboxylic Acid (V).—A soln of 14.5 g (0.1 mole) of ANT and 15.2 g (0.1 mole) of 1,2-cylohexane dicarboxylic anhydride in DMF was heated at 100° for 4 hr, cooled, and filtered. The solid was recrystd from MeCN to give 9 g (30%) of the product, mp 195–196°. *Anal.* ($C_{11}H_{13}N_4O_5S$) C, H, N.

6-[(5-Nitro-2-thiazolyl)carbamoyl]-3-cyclohexene-1-carboxylic Acid (VI).—A soln of 14.5 g (0.1 mole) of ANT and 15.0 g (0.1 mole) of *cis*-4-cyclohexene-1,2-dicarboxylic anhydride in DMF was heated at 100° for 4 hr. The cooled soln was poured into iced water and the precipitate recrystd 3 times from MeCN to give 2.6 (8.8%) of the product, mp 200–201°. *Anal.* ($C_{11}H_{11}N_3O_5S$) C, H, N.

Diethyl 4,6-Bis[(5-nitro-2-thiazolyl)carbamoyl]isophthalate (VII or VIII).—A soln of 14.5 g (0.1 mole) of ANT and 21.8 g (0.1 mole) of 1,2,4,5-benzenetetracarboxylic anhydride in DMF was heated at 100° for 4 hr. The solid which formed in the hot mixture was removed by filtration and recrystd from dil EtOH twice to give 8.7 g (30.8%) of the product which melted above 260°. *Anal.* ($C_{20}H_{16}N_6S_2O_{10}$) C, H, N.

***N*-(5-Nitro-2-thiazolyl)phthalimide (IX).**—A soln of 14.5 g (0.1 mole) of ANT and 14.8 g (0.1 mole) of phthalic anhydride in DMF was heated at 125° for 6 hr. The soln was cooled, and the solid that formed was collected and recrystd from DMF to give 3.5 g (12.7%) of the product, mp 267–268.5°. *Anal.* ($C_{11}H_5N_3O_4S$) C, H, N.

***N,N'*-Bis(5-nitro-2-thiazolyl)oxamide·DMF (X).**—To a soln of 14.5 g (0.1 mole) of ANT in DMF containing 11 g of Et_3N was added an Et_2O soln (about 30 ml) of 6.4 g (0.05 mole) of oxalyl chloride. An exothermic reaction took place and the mixture was cooled in ice water to maintain the temp just above room temp. After 1 hr the mixture was filtered. The solid was stirred with warm H_2O and the insol portion was collected and recrystd from DMF to give 3 g (14.5%) of the product, mp > 300°. *Anal.* [$C_8H_3N_6O_6S_2 \cdot (CH_3)_2NCHO$] C, H, N.

***N*-(5-Nitro-2-thiazolyl)succinimide (XI).**—To an Et_2O–DMF soln of 7.2 g (0.05 mole) of succinyl chloride was added dropwise a DMF soln of 14.5 g (0.1 mole) of ANT containing 8.7 g (0.11 mole) of pyridine. After the mildly exothermic reaction had subsided the reaction mixture was stirred at room temp overnight. Filtration yielded 1.0 g of solid. Et_2O was removed from the filtrate *in vacuo* and the resulting soln was poured into H_2O. The solid obtained was combined with the 1 g of material obtained previously and recrystd twice from MeCN to provide 2.4 g (21%) of the product which softened at 224° and melted to 229.5°. *Anal.* ($C_7H_5N_3O_4S$) C, H, N.

***N*-(5-Nitro-2-thiazolyl)glutarimide (XII).**—To a soln of 8.5 g (0.05 mole) of glutaryl chloride in a mixture of Et_2O and DMF was added dropwise a soln of 14.5 g (0.1 mole) of ANT in DMF containing 8.7 g (0.11 mole) of pyridine. The mixture was allowed to stir at room temp overnight. The Et_2O was removed *in vacuo* and the residual liquid poured into H_2O. The solid which formed was recrystd twice from EtOH to give 1.8 g (15%) of the product, mp 161.5–164°. *Anal.* ($C_8H_7N_3O_4S$), C, H, N.

***N*-(5-Nitro-2-thiazolyl)-1,2-cyclohexanedicarboximide (XIII).**—A soln of 4 g (0.017 mole) of 2-[(5-nitro-2-thiazolyl)carbamoyl]-cyclohexanecarboxylic acid and 4.1 g (0.034 mole) of $SOCl_2$ in 150 ml of C_6H_6 was heated under reflux for 5 hr. Upon cooling a solid was deposited which was removed and recrystd from EtOH to give 1.6 g (33%) of the product, mp 157°. *Anal.* ($C_{11}H_{11}N_3O_4S$) C, H, N.

3-(5-Nitro-2-thiazolyl)hydantoin (XIV).—Ethyl 5-(5-nitro-2-thiazolyl)hydantoate (5 g, 0.018 mole) was heated under reflux for 1 hr with 40 ml of 6 *N* HCl. The cooled mixture was filtered to yield 3 g of crude 5-(5-nitro-2-thiazolyl)hydantoic acid, mp 198° dec. This material (0.016 mole) in 100 ml of C_6H_6 and 3 ml of THF was heated under reflux with 4 g (0.034 mole) of $SOCl_2$ for 5 hr. The cooled soln deposited a solid which was recrystd first from MeCN and then from DMF to give 0.7 g (19%) of the product, mp 252–253°. *Anal.* ($C_6H_4N_4O_4S$) C, H, N.

Ethyl 5-(5-Nitro-2-thiazolyl)hydantoate (XV).—A soln of 14.5 g of ANT (0.1 mole) and 14 g (0.11 mole) of ethyl isocyanatoacetate in DMF was heated at 100° for 4 hr. The reaction mixture was cooled and poured into H_2O. The solid which resulted was recrystd twice from MeCN–H_2O to give 12 g (43%) of the product, mp 194–195°. *Anal.* ($C_8H_{10}N_4O_5S$) C, H, N.

***o*-Amino-*N*-2-thiazolylbenzamide (XVI).**—To a soln of 10 g (0.1 mole) of 2-aminothiazole in about 200 ml of DMF maintained at 50° was added in portions 11.4 g (0.07 mole) of isatoic anhydride. The soln was heated at 100° for 8 hr, cooled, and poured into iced water. The solid which formed was collected and recrystd from *i*-PrOH to give 9 g (46%) of the product, mp 151–153°. *Anal.* ($C_{10}H_9N_3OS$) C, H, N.

Ethyl *o*-(2-Thiazolylcarbamoyl)carbanilate (XVII).—To a soln of 5 g (0.023 mole) of *o*-amino-*N*-2-thiazolylbenzamide in pyridine was added 2.8 g (0.026 mole) of ethyl chloroformate, and the mixture was heated under reflux for 4 hr. The mixture was cooled and poured into iced H_2O. The solid which formed was recrystd from MeCN to give 3.5 g (46%) of the product, mp 171–173°. *Anal.* ($C_{13}H_{13}N_3O_3S$) C, H, N.

3-(2-Thiazolyl)-2,4(1*H*,3*H*)-quinazolinedione (XVIII).—A soln of 10 g (0.046 mole) of *o*-amino-*N*-2-thiazolylbenzamide in 160 ml of Me_2CO was added dropwise at 10° to a soln of 4.6 g (0.046 mole) of $COCl_2$ in 150 ml of Me_2CO. The mixture was allowed to warm to room temp and the solid which had formed was removed by filtration and recrystd from DMF–Et_2O to give 3.2 g (28%) of the product, mp 287–289°. *Anal.* ($C_{11}H_7N_3O_2S$) C, H, N.

3-(2-Thiazolyl)-6-nitro-2,4(1*H*,3*H*)-quinazolinedione (XIX).—To 5 g (0.02 mole) of 3-(2-thiazolyl)-2,4(1*H*,3*H*)-quinazolinedione in 10.3 ml of cooled H_2SO_4 at 0° was added 1.38 ml of cooled HNO_3. The mixture was allowed to stir at 0° for an additional 2 hr and then poured into iced H_2O. The solid which formed was collected and recrystd twice from dil EtOH and then from MeCN to give 1.8 g (31%) of the product, mp 264–265°. *Anal.* ($C_{11}H_6N_4O_4S$) C, H, N.

6,8-Dinitro-3-(2-thiazolyl)-2,4(1*H*,3*H*)-quinazolinedione (XX).—To 3.5 g (0.14 mole) of 3-(2-thiazolyl)-2,4(1*H*,3*H*)-quinazolinedione in 14.4 g of cooled H_2SO_4 at −10° was added 2 g of fuming HNO_3. The mixture was maintained at 0° for 2 hr after the addition was complete, and then allowed to warm to room temp. The mixture was triturated with H_2O and neutralized with NaOH. The solid which formed was recrystd from MeCN to give 1.8 g (38%) of the product, mp 278–280°. *Anal.* ($C_{11}H_5N_5O_6S$) C, H, N.

***N'*-(*o*-Cyanophenyl)-*N*-(5-nitro-2-thiazolyl)benzamidine (XXII, R = CN).**—A soln of 5 g (0.02 mole) of *N*-(α-chlorobenzylidene)-anthranilonitrile[21] and 2.9 g (0.02 mole) of ANT in pyridine was heated at 90° for 2 hr. The solvent was removed *in vacuo*, and the residue was washed with H_2O, recrystd from MeCN, and washed thoroughly with MeCN to give 2.5 g (36%) of the product, mp 212–214°. *Anal.* ($C_{17}H_{11}N_5O_2S$) C, H, N.

***o*-[[α-[(5-Nitro-2-thiazolyl)amino]benzylidene]amino]benzamide (XXII, R = $CONH_2$).**—A soln of 1.5 g (0.005 mole) of *N'*-(*o*-

(20) 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 those elements were within ±0.4% of the theoretical values.

(21) Parke, Davis and Co., U. S. Patent 3,313,848, April 1967.

cyanophenyl)-*N*-(5-nitro-2-thiazolyl)benzamidine in THF containing a few drops of BF_3·etherate was heated under reflux for 7 hr. The solvent was removed *in vacuo*, and the residue was washed with H_2O and recrystd from DMF. Initially 0.4 g of impure material was deposited, removed by filtration, and discarded. The filtrate upon standing deposited 1 g of solid, mp 265–267°. Recrystallization from DMF–Et_2O, and then from DMF gave 0.2 g (11%) of the product, mp 265–267°. *Anal.* ($C_{17}H_{13}N_5O_5S$) C, H, N.

2-Chloroethyl 5-Nitro-2-thiazolecarbamate (XXIII).—To a soln of 87 g (0.6 mole) of ANT in 200 ml of DMF containing 52.2 g of pyridine was added dropwise a soln of 85.2 g (0.6 mole) of 2-chloroethyl chloroformate in 150 ml of Et_2O. The mixture was allowed to stir at room temp for 3 hr and filtered. The solid was washed with H_2O and collected to give 113 g of crude product. After the Et_2O was removed from the reaction mixture it was poured into H_2O to afford an additional 22 g of crude. Recrystallization from MeCN gave 103 g (68%) of the product, mp 216–218°. *Anal.* ($C_6H_6ClN_3O_4S$) C, H, N.

3-(5-Nitro-2-thiazolyl)-2-oxazolidinone (XXIV).—A soln of 2.5 g (0.01 mole) of 2-chloroethyl-5-nitro-2-thiazolecarbamate in 70% EtOH containing 0.67 g (0.012 mole) of KOH was stirred at room temp for 4 hr. The precipitate which formed was collected and recrystd from MeCN–H_2O to give 1.2 g (56%) of the product, mp 192–193°. *Anal.* ($C_6H_5N_3O_4S$) C, H, N.

2-[(5-Nitro-2-thiazolyl)amino]ethanol (XXV).—To a soln of 5 g (0.023 mole) of 3-(5-nitro-2-thiazolyl)-2-oxazolidinone in 200 ml of THF and 75 ml of H_2O was added rapidly 5.8 ml of 6 *N* NaOH (0.035 mole). The soln was swirled for 1 min and then neutralized with 4.97 ml of 11.7 *N* HCl. The soln was allowed to stand in the ice box over the weekend and was then extracted with $CHCl_3$. The extracts were dried and the solvent removed *in vacuo*. The residue was recrystd twice from THF–heptane to give 1.2 g (27.6%) of the product, mp 170–172°. *Anal.* ($C_5H_7N_3O_3S$) C, H, N.

Methyl 2-[(5-nitro-2-thiazolyl)amino]ethyl Carbonate (XXVI).—To a soln of 5 g (0.023 mole) of 3-(5-nitro-2-thiazolyl)-2-oxazolidinone in 200 ml of THF and 200 ml of MeOH was added rapidly 5.8 ml of 6 *N* NaOH (0.0462 mole). The mixture was swirled vigorously for 1 min, neutralized with 4.97 ml of 11.7 *N* HCl, dild with H_2O, and chilled overnight. The solid which formed was removed and recrystd from dil MeCN to give 2.8 g (49%) of the product, mp 124–126°. *Anal.* ($C_7H_9N_3O_5S$) C, H, N.

3-Ethyl-1-(5-nitro-2-thiazolyl)hydantoin (XXVII).—A soln of 4.6 g (0.02 mole) of ethyl *N*-(5-nitro-2-thiazolyl)glycinate and 2 g (0.028 mole) of EtNCO in DMF was warmed at about 60° for 6 hr. The mixture was cooled and poured into H_2O. The solid that formed was recrystd twice from dil EtOH to give 2.3 g of the product (45%), mp 204–206.5° (sinters from 202°). *Anal.* ($C_8H_8N_4O_4S$) C, H, N.

Similarly prepared were: 3-methyl-1-(5-nitro-2-thiazolyl)-hydantoin from MeNCO, mp 235–239° (from MeCN) in 44% yield, *Anal.* ($C_7H_6N_4O_4S$) C, H, N; and 3-(2-chloroethyl)-1-(5-nitro-2-thiazolyl)hydantoin from $ClCH_2CH_2NCO$, mp 208–210° (from MeCN) in 24% yield. *Anal.* ($C_8H_7N_4ClO_4S$) C, H, N.

Ethyl *N*-Formyl-*N*-(5-nitro-2-thiazolyl)glycinate and Ethyl *N*-(5-Nitro-2-thiazolyl)glycinate (XXVIII).—To a suspension of 72 g (1.5 moles of 50% oil dispersion) of NaH in 1.5 l. of DMF was added in portions 258 g (1.49 moles) of 2-formamido-5-nitrothiazole. Heat was evolved and the solid present dissolved. To this mixture maintained at room temp with a H_2O bath was added slowly a soln of 276 g (1.65 moles) of ethyl bromoacetate in 500 ml of DMF. The mixture was allowed to stir at room temp for 4 hr and poured into H_2O and the ppt collected by filtration. Two recrystallizations from dil EtOH followed by a recrystn from MeCN provided 180 g (52%) of XXVIII, mp 161–163°. A portion of this material, recrystd again from MeCN, had mp 163.5–165.5°. *Anal.* ($C_7H_9N_3O_4S$) C, H, N.

The first MeCN mother liquor was concd to provide 60 g (15%) of ethyl *N*-formyl-*N*-(5-nitro-2-thiazolyl)glycinate, mp 117–119°. *Anal.* ($C_8H_9N_3O_5S$) C, H, N.

It is possible that the deformylation is occurring during the EtOH recrystn. In a duplicate run of 1.39 moles the crude product obtained from pouring the reaction mixture into H_2O was recrystd directly from MeCN to give 260 g (72%) of ethyl *N*-formyl-*N*-(5-nitro-2-thiazolyl)glycinate, mp 115–118°.

Ethyl *N*-(5-Nitro-2-thiazolyl)-β-alaninate (XXX),—To a soln of 3 g (0.026 mole) of ethyl-β-aminopropionate in a mixture of EtOH and Et_2O was added 2.2 g (0.011 mole) of 2-bromo-5-nitrothiazole. The soln was heated under reflux for 1 hr and the solvents were then removed *in vacuo*. The residue was recrystd 4 times from dil EtOH to give 0.9 g (33%) of the product which still contained some impurity. This material was used directly in the next step. *Anal.* ($C_8H_{11}N_3O_4S$) H; C: calcd, 39.18; found, 39.89; N: calcd, 17.13; found, 16.66.

Ethyl *N*-(Ethylcarbamoyl)-*N*-(5-nitro-2-thiazolyl)-β-alaninate (XXXI).—A soln of 0.7 g (0.006 mole) of ethyl *N*-(5-nitro-2-thiazolyl)-β-alaninate and 0.6 g (0.0084 mole) of EtNCO in DMF was heated at 60° for 6 hr. The solvent was removed *in vacuo*, and the residue triturated with H_2O. The solid was collected and recrystd twice from *i*-PrOH to give 0.6 g (33%) of the product, mp 110–113°. *Anal.* ($C_{11}H_{16}N_4O_5S$) C, H, N.

***N*-[2-[(5-Nitro-2-thiazolyl)amino]ethyl]acetamide (XXXII).**—To a soln of 3.4 g (0.016 mole) of 2-bromo-5-nitrothiazole in 300 ml of THF was added dropwise 3.6 g (0.035 mole) of *N*-acetylethylenediamine. The mixture was stirred at room temp for an additional 0.5 hr, and the solvent was then removed *in vacuo*. The residue was recrystd from EtOH to give 1.5 g (40%) of the product, mp 174–177°. *Anal.* ($C_7H_{10}N_4O_3S$) C, H, N.

1,4-Bis(5-nitro-2-thiazolyl)-2,5-piperazinedione (XXXIII).—A soln of 3 g (0.01 mole) of *N*-(5-nitro-2-thiazolyl)glycine and 1.2 g (0.01 mole) of $SOCl_2$ in C_6H_6–THF was heated under reflux for 24 hr. A small amount of solid which was present was removed by filtration and discarded. The filtrate was concd to dryness *in vacuo* and the residue was recrystd twice from DMF–MeCN to give 0.3 g (8.1%) of the product, mp 285° dec. *Anal.* ($C_{10}H_6N_6O_6S_2$) H, N; C: calcd, 32.46; found, 32.25.

7-Methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (XXXVI) or 5-Methyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (XXXVII).—A mixture of 10 g (0.1 mole) of 2-aminothiazole and 10 g (0.078 mole) of ethyl β-aminocrotonate was heated at 180–220° for 7 hr. The reaction mixture was cooled to room temp and extracted with pet ether. The residue was digested with hot EtOH and filtered. The filtrate was concd to dryness and the residue was recrystd twice from *i*-PrOH to give 3.5 g (27%) of the product, mp 122–123°.

7(or 5)-Methyl-6-nitro-5(or 7)*H*-thiazolo[3,2-*a*]pyrimidin-5(or 7)-one (XXXVIII or XXXIX).—A suspension of 2.1 g (0.013 mole) of the above mixture in 10.5 ml of concd H_2SO_4 was treated at 0° with a mixture of 3.2 ml of HNO_3 (*d* 1.42) and 3.2 ml of concd H_2SO_4. The mixture was allowed to stir for an additional 0.5 hr and then warmed to room temp and poured into iced H_2O. The solid which formed was recrystd from MeCN to give 1.8 g (65%) of the product, mp 159–160°. *Anal.* ($C_7H_5N_3O_3S$) C, H, N.

***N*-(5-Nitro-2-thiazolyl)glycine.**—A mixture of 150 g (0.57 mole) of *N*-(5-nitro-2-thiazolyl)glycine ethyl ester in 1100 ml of concd HCl was heated at 100° for 2 hr. The solution which formed was cooled and the resulting solid was collected and recrystd from H_2O to give 48 g (42%) of the product, mp 194–195°. *Anal.* ($C_5H_5N_3O_4S$) C, H, N.

3-Chloro-*N*-2-thiazolylpropionamide.—To a soln of 9.9 g (0.1 mole) of 2-aminothiazole in DMF cooled in an ice bath were added simultaneously 7.9 g (0.1 mole) of pyridine in 60 ml of Et_2O and 12.6 g (0.1 mole) of 3-chloropropionyl chloride in 60 ml of Et_2O. The mixture was stirred for 3 hr after addition was complete. The solid was removed by filtration, washed with H_2O, and recrystd 3 times from EtOH to give 6.7 g (35%) of the product, mp 176–177°. *Anal.* ($C_6H_7ClN_2OS$) C, H, N.

5,6-Dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one·HCl (XL).—3-Chloro-*N*-2-thiazolylpropionamide (10 g, 0.0525 mole) was heated in an oil bath at 185–195° for 0.5 hr. The solid melted and then gradually resolidified. The contents of the reaction vessel were triturated with DMF and filtered to give 8 g (80%) of the product, mp 279–282°. *Anal.* ($C_6H_7ClN_2OS$) C, H, N.

2-Imino-*N*-propyl-4-thiazoline-3-propionamide·HCl (XLI).—A mixture of 5 g (0.0262 mole) of 5,6-dihydro-7*H*-thiazolo[3,2-*a*]-pyrimidin-7-one·HCl and 6 ml of *n*-$PrNH_2$ in 50 ml of DMF was heated on the stream bath for 2 hr. The solvent was removed *in vacuo* and the residue was triturated with hot CH_3CN and then recrystd from *i*-PrOH to give 3 g (46%) of the product, mp 166–168°. *Anal.* ($C_9H_{16}ClN_3OS$) C, H, N, Cl.

Ethyl 2-Imino-4-thiazoline-3-propionate·HCl (XLII).—Recrystallization of 5,6-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one·HCl from 90% EtOH gave a solid, mp 189–193°. An additional recrystn from DMF–H_2O gave mp 191–193°. *Anal.* ($C_8H_{13}ClN_2O_2S$) C, H, N.

Benzaldehyde (5-Nitro-2-thiazolyl)hydrazone.—To a soln of 1.76 g (0.03 mole) of 85% hydrazine hydrate in 100 ml of EtOH was added dropwise 3.18 g (0.03 mole) of PhCHO. This mixture

was heated to boiling and added rapidly to a solution of 6.27 g (0.03 mole) of 2-bromo-5-nitrothiazole in 150 ml of EtOH. The mixture was allowed to cool to room temp and filtered. The yellow solid was recrystd from about 300 ml of THF to give 1.4 g of the product, mp 235–240° dec. Upon standing, the filtrate of the original reaction mixture deposited additional solid which was recrystd from the THF mother liquors to provide an additional 1.9 g of product; total yield 3.3 g (44%). *Anal.* ($C_{10}H_8N_4O_3S$) C, H, N.

2-Hydrazino-5-nitrothiazole.—To a vigorously stirred soln of 8.4 g (0.04 mole) of 2-bromo-5-nitrothiazole in 500 ml of THF was added 4.7 g (0.08 mole) of 85% hydrazine hydrate. An additional 200 ml of THF was added and the suspension that formed was stirred at room temperature for 3 hr at which time tlc (Si–C_6H_6) indicated that no 2-bromo-5-nitrothiazole was present. The mixture was filtered and the solvent removed *in vacuo*. The residue was triturated with Et_2O, collected, and dried to give 4.6 g (72%) of the product as a rust-colored solid which did not have a distinct melting point.

Ethyl 3-(5-Nitro-2-thiazolyl)carbazate (XLIII).—To 12.6 g (0.06 mole) of 2-bromo-5-nitrothiazole in 225 ml of THF was added a soln of 12.5 g (0.12 mole) of ethyl carbazate in 200 ml of THF. The mixture was heated under reflux for 2.5 hr and then allowed to stir overnight at room temp. The solvent was removed *in vacuo*, and the residue was triturated with H_2O and recrystd twice from MeCN to give 7.5 g (54%) of the product, mp 194–195°. *Anal.* ($C_6H_8N_4O_4S$) C, H, N.

2-[2-(5-Nitro-2-thiazolyl)hydrazino]ethanol (XLIV).—To a hot soln of 4.18 g (0.02 mole) of 2-bromo-5-nitrothiazole in THF was added dropwise over 2 hr a soln of 3.04 g (0.04 mole) of (2-hydroxyethyl)hydrazine in MeOH. The soln was heated under reflux for 3 hr. Additional MeOH was added to bring an immiscible layer on the bottom of the flask into soln, and refluxing was continued for 3 more hr. The solvents were removed *in vacuo* and the oily residue was extracted with Et_2O. The insol residue was triturated with H_2O to give an orange solid which was recrystd twice from a mixture of EtOAc and pet ether to give 1.2 g (29%) of the product, mp 112–116°. *Anal.* ($C_6H_8N_4O_3S$) C, H, N.

2-(5-Nitro-2-thiazolyl)acethydrazide (XLVII).—A soln of 4.56 g (0.06 mole) of acethydrazide in about 600 ml of THF was added in portions to a THF soln of 6.27 g (0.03 mole) of 2-bromo-5-nitrothiazole. The mixture was heated under reflux for 1 hr, and allowed to stand at room temp overnight. It was filtered and the filtrate was evapd to dryness *in vacuo*. The residue was washed with H_2O and recrystd from THF–pet ether (bp 40–60°) to give 2.8 g (46%) of the product, mp 184–185° (prior sintering). *Anal.* ($C_5H_6N_4O_3S$) C, H, N.

2-Methyl-4-(5-nitro-2-thiazolyl)-Δ^2-1,3,4-oxadiazolin-5-one (XLVIII).—A soln of 5 g (0.023 mole) of 2-(5-nitro-2-thiazolyl)-acethydrazide in 250 ml of Me_2CO was added dropwise at 10° to a soln of 2.3 g (0.023 mole) of $COCl_2$ in 25 ml of Me_2CO. The mixture was allowed to stir at room temp overnight. Filtration gave 1.9 g of unchanged starting material. The filtrate was evapd to dryness *in vacuo*, and the residue was recrystd from *i*-PrOH to give 3.2 g (64%) of the product, mp 180–181°. *Anal.* ($C_6H_4N_4O_4S$) C, H, N.

Ethyl Acetoacetate 5-Nitro-2-thiazolylhydrazone (XLIX).—A soln of 2.1 g (0.01 mole) of 2-bromo-5-nitrothiazole in 30 ml of EtOH was heated to boiling, and a soln of 0.6 g (0.01 mole) of 85% hydrazine hydrate in 30 ml of EtOH was added dropwise over 10 min. The mixture turned deep red and a heavy yellow ppt formed. The mixture was heated an additional 5–10 min and a soln of 1.3 g (0.01 mole) of ethyl acetoacetate in 10 ml of EtOH was added dropwise. The mixture was heated under reflux for 1 hr, cooled, and filtered. The solid was recrystd from EtOH to give 0.7 g (26%) of the product, mp 158–160° dec. *Anal.* ($C_9H_{12}N_4O_4S$) C, H, N.

A better procedure was to heat a suspension of 9.6 g (0.06 mole) of 2-hydrazino-5-nitrothiazole and 12 g (0.092 mole) of ethyl acetoacetate in 900 ml of MeCN under reflux for 10 hr. The mixture was allowed to cool to room temp and filtered to remove a small amount of solid. The solvent was removed *in vacuo* and the residue was taken up in 100 ml of hot MeCN, filtered to remove insol material, and allowed to cool to room temp to provide 8.0 g (49%) of the product identical with that prepared above.

3-Methyl-1-(5-nitro-2-thiazolyl)-2-pyrazolin-5-one (L).—A suspension of 5.3 g (0.0195 mole) of the 5-nitro-2-thiazolylhydrazone of ethyl acetoacetate was suspended in 30 ml of $POCl_3$ and heated under reflux for 3 hr. All the solid gradually dissolved and after about 1.5 hr a new solid was deposited. The mixture was cooled to room temp and filtered to give 2.6 g of solid. Recrystallization from DMF afforded 0.8 g (18%) of the product, mp > 290°. *Anal.* ($C_7H_6N_4O_3S$) H, N; C: calcd, 37.16; found, 37.60.

4,5-Dichloro-2-(5-nitro-2-thiazolyl)-3(2*H*)-pyridazinone (LI).[22] —A mixture of 2.5 g (0.016 mole) of 2-hydrazino-5-nitrothiazole and 3.68 g (0.022 mole) of mucochloric acid in 68 ml of H_2O containing 6.8 ml of concd HCl was heated at 90–100° for 3 hr. The mixture was cooled to room temp and filtered. The solid was washed with Et_2O and recrystd twice from THF to give 1.5 g of the product (32%), mp 251–253°. *Anal.* ($C_7H_2Cl_2N_4O_3S$) C, H, N, Cl.

Ethyl 3-(Allylcarbamoyl)-3-(5-nitro-2-thiazolyl)carbazate (LII, R = Allyl).—A mixture of 4.64 g (0.02 mole) of ethyl-3-(5-nitro-2-thiazolyl)carbazate and 2 g (0.024 mole) of allyl isocyanate in about 150 ml of THF was heated under reflux for 6 hr. The solvent was removed *in vacuo* and the residue was recrystd from C_6H_6 to give 3.8 g (60%) of the product, mp 137–139.5°. *Anal.* ($C_{10}H_{13}N_5O_5S$) H, N; C: calcd, 38.09; found, 38.50.

Ethyl 3-[(2-Chloroethyl)carbamoyl]-3-(5-nitro-2-thiazolyl)-carbazate (LII, R = C_2H_5).—A mixture of 4.64 g (0.02 mole) of ethyl-3-(5-nitro-2-thiazolyl)carbazate and 2.5 g (0.0237 mole) of 2-chloroethyl isocyanate in 150 ml of THF was heated under reflux for 6 hr. The solvent was removed *in vacuo*, and the residue was recrystd twice from *i*-PrOH to give 2.2 g (27.6%) of the product, mp 155–159° dec. *Anal.* ($C_9H_{12}ClN_5O_5S$) H, N; C: calcd, 32.00; found, 32.44.

Ethyl 3-(Methylcarbamoyl)-3-(5-nitro-2-thiazolyl)carbazate (LII, R = CH_3).—A mixture of 7.5 g (0.0323 mole) of ethyl-3-(5-nitro-2-thiazolyl)carbazate and 2 g (0.0363 mole) of MeNCO in 50 ml of THF was heated under reflux for 6 hr. The solvent was removed *in vacuo* and the residue was recrystd twice from EtOH to give 5.5 g (59%) of the product, mp 178–181°. *Anal.* ($C_8H_{11}N_5O_5S$), C, H, N.

Ethyl 3-Carbamoyl-3-(2-thiazolyl)carbazate (LIV).—To a soln of 5 g (0.032 mole) of 1-(2-thiazolyl)semicarbazide·HCl in pyridine was added 3 g (0.032 mole) of ethyl chloroformate, and the mixture was heated on the steam bath for 1 hr. The solvent was removed *in vacuo* and the residue was triturated with H_2O and recrystd twice from EtOH to give 1.5 g of the product (20.4%), mp 221–223°. *Anal.* ($C_7H_{10}N_4O_3S$), C, H, N.

Ethyl 3-Carbamoyl-3-(5-nitro-2-thiazolyl)carbazate (LV).—Ethyl 3-carbamoyl-3-(2-thiazolyl)carbazate, 4.5 g (0.02 mole), was dissolved in 10.3 ml of concd H_2SO_4 at 0°. To the cold soln was added 1.38 ml of yellow fuming HNO_3. The mixture was stirred at 0–10° for 2 hr, allowed to warm to room temp, and poured onto ice. The solid which formed was recrystd 3 times from EtOH to give 0.5 g (9.1%) of the product, mp 224–226°. *Anal.* ($C_7H_9N_5O_5S$) C, H, N.

4-(2-Chloroethyl)-1-(5-nitro-2-thiazolyl)semicarbazide (LVI).—A soln of 8 g (0.05 mole) of 2-hydrazino-5-nitrothiazole and 5.2 g (0.05 mole) of 2-chloroethyl isocyanate in DMF was heated at 60° for 4 hr. The solvent was removed *in vacuo* and the residue was triturated with H_2O and filtered. The solid was triturated several times with a small vol of MeCN to remove dark-colored impurities, and was then recrystd from MeCN to give 1.3 g (26%) of the product, mp 164–166°. An analytical sample was prepared by one additional recrystallization from MeCN, mp 172–174°. *Anal.* ($C_6H_5ClN_5O_3S$) C, H, N.

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(22) Method of K. Dury, *Angew. Chem., Intern. Ed. Engl.*, **4**, 292 (1965).