(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.

Acknowledgments. The authors are indebted to Dr. R. E. Bowman for advice and encouragement, to Miss E. M. Tanner for spectroscopic measurements, to Mr. F. H. Oliver for microanalyses, to Mr. J. P. Guyett for some technical assistance, and to Drs. M. W. Fisher and P. E. Thompson and their associates of the Departments of Microbiology and Experimental Therapeutics, respectively, Parke, Davis and Co., Inc., Detroit and Ann Arbor, for the biological results.

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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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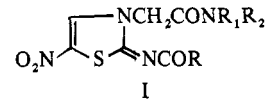

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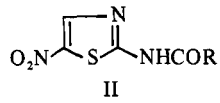

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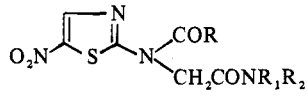


III

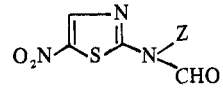
conditions afforded only thiazoles (*e.g.*, III in which R is H) and none of the ring N-alkylated thiazolines (*e.g.*, I in which R is H).

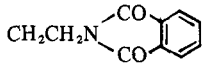
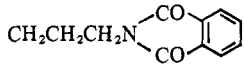
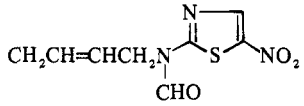
Chemistry. The preparation of the substituted 2-formamido-5-nitrothiazoles IV (Table I) is described in the Experimental Section. 2-[*N*-(5-Nitro-2-thiazolyl)formamido]-acetamides IV were found to possess characteristic uv spectra (λ_{max} *ca.* 235 and 340 nm) and were thus readily distinguished from the corresponding thiazolines I (λ_{max} *ca.* 280 and 360 nm).[2]

Removal of the *N*-formyl group to afford aminothiazoles V (Table II) was achieved by treatment of the appropriate IV with concentrated hydrochloric acid, or with 1.0 equiv of aqueous sodium hydroxide solution in ethanol at room temperature, or particularly with 1.0 mol of hydrazine hydrate in refluxing ethanol. In addition, the formyl group in methyl [*N*-formyl-*N*-(5-nitro-2-thiazolyl)glycyl]carbamate **(10)** was removed when this compound was recrystallized from boiling methanol. Substituted aminothiazoles V were treated with a variety of acylating agents and isocyanates by known methods, and the products are given in Table III.

Biology. The compounds described in the present com-

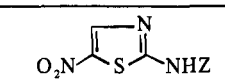
Table I. *N*-Substituted 2-Formamido-5-nitrothiazoles IV



Compd	Z	Reaction temp, °C	Mp, °C	Recrystn solvent	% yield	Formula
1	CH_2CONH_2	25	203 dec	EtOH	42	$C_6H_6N_4O_4S$
2	$CH_2CONHMe$	25	214–215	AcOH	81	$C_7H_8N_4O_4S$
3	CH_2CONMe_2	25	178.5–179.5	EtOH	61	$C_8H_{10}N_4O_4S$
4	CH_2CONEt_2	25	140–141	EtOH	21	$C_{10}H_{14}N_4O_4S$
5	CH_2CONPr_2	25	111–112	EtOH	51	$C_{12}H_{18}N_4O_4S$
6	CH_2CONBu_2	25	106–107	EtOH	40	$C_{14}H_{22}N_4O_4S$
7	$CH_2CONHCH_2Ph$	25	185–186	EtOH	39	$C_{13}H_{12}N_4O_4S$
8	$CH_2CONHCH_2CH_2CN$	25	176–177	EtOH	39	$C_9H_9N_5O_4S$
9	CH_2CO_2Et	25	119–120	EtOH	77	$C_8H_9N_3O_5S$[c]
10	$CH_2CONHCO_2Me$	25	199–200	EtOAc	16	$C_8H_8N_4O_6S$
11	$CH_2CONHCO_2Et$	50	174–176	EtOH	36	$C_9H_{10}N_4O_6S$
12	$CH_2CON(Me)CO_2Et$	60	170–172	EtOH	33	$C_{10}H_{12}N_4O_6S$
13	$CH_2CON(CH_2Ph)CO_2Et$	60	131–132	EtOH	12	$C_{16}H_{16}N_4O_6S$
14	$CH_2CONHCO_2Bu$	25	154–155	EtOH	62	$C_{11}H_{14}N_4O_6S$
15	$CH_2CONHCOMe$	25	189–193	EtOH	22	$C_8H_8N_4O_5S$
16	$CH_2CONHCONH_2$	25	220–222	AcOH[b]	42	$C_7H_7N_5O_5S$
17		65	209–212	DMF	25	$C_{14}H_{10}N_4O_5S$
18	$CH_2CH_2N(Me)CHO$	80	175–177	EtOH	20	$C_8H_{10}N_4O_4S$
19	$CH_2CH_2CH_2CN$	60	105–107	EtOH	66	$C_8H_8N_4O_3S$
20		65	210–212	DMF	79	$C_{15}H_{12}N_4O_5S$
21	$CH_2C(Me)=CCl_2$	40	92–94	Aqueous MeOH	27	$C_8H_7Cl_2N_3O_3S$
22	$CH_2CONHNHCO_2Et$	25	181–182	EtOH	6	$C_9H_{11}N_5O_6S$
23		60[a]	241–243 dec	AcOH	9	$C_{12}H_{10}N_6O_6S_2$

[a]Mole ratio of the sodio salt of 2-formamido-5-nitrothiazole:1,4-dichloro-2-butene was 2:1. [b]Followed by hot H_2O wash. [c]C: calcd, 37.1; found, 37.6.

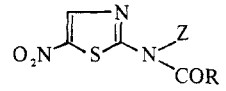
Table II. *N*-Substituted 2-Amino-5-nitrothiazoles V

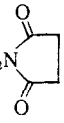


Compd	Z	Starting material	Method	Reaction time, hr; temp, °C	Mp, °C	Recrystn solvent	% yield	Formula
24	CH_2CO_2H	9	A	2, 100	190–191	H_2O	54	$C_5H_5N_3O_4S$
25	$CH_2CONHMe$	2	B	0.25, 25	239–240	EtOH	47	$C_6H_8N_4O_3S$[b]
26	CH_2CONEt_2	4	B	0.25, 25	192–194	EtOAc	47	$C_9H_{14}N_4O_3S$
27	$CH_2CH_2CH_2CONH_2$	19	C	1.5, 25	198–200	*i*-PrOH	67	$C_7H_{10}N_4O_3S$[c]
28	CH_2CH_2NHMe	18	A[a]	1, 100	173–174 dec	EtOH	52	$C_6H_{10}N_4O_2S \cdot HCl$
29	$CH_2CONHCO_2Me$	10	D	0.5, reflux	204–205	MeOH	32	$C_7H_8N_4O_5S$
30	$CH_2CONHCO_2Et$	11	E	0.25, reflux	190–191	EtOH	91	$C_8H_{10}N_4O_5S$
31	$CH_2CONHCO_2Bu$	14	E	0.1, reflux	155–156	EtOH	38	$C_{10}H_{14}N_4O_5S$[d]
32	$CH_2CONHNHCO_2Et$	22	E	0.25, reflux	225–227 dec	EtOH	52	$C_8H_{11}N_5O_5S$

[a]Reaction mixture evaporated *in vacuo* and residue recrystallized. [b]N: calcd, 25.9; found, 25.4. [c]C: calcd, 36.5; found, 37.2. [d]N: calcd, 18.5; found, 18.0.

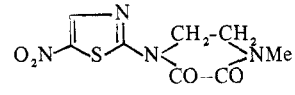
Table III. [*N*-(5-Nitro-2-thiazolyl-N-substituted]amides and -ureas VI



Compd	R	Z	Starting material	Method	Reaction time, hr; temp, °C	Mp, °C	Recrystn solvent[a]	% yield	Formula
33	Me	$CH_2CONHMe$	**25**	F	1, 100	229-230	A	62	$C_8H_{10}N_4O_4S$
34	Me	CH_2CONEt_2	**26**	F	0.5, 120	141-142	B	68	$C_{11}H_{16}N_4O_4S$
35	Me	$CH_2CONHCO_2Me$	**29**	F	1, 100	219-220	C	52	$C_9H_{10}N_4O_6S$
36	c-C_3H_5[d]	$CH_2CONHCO_2Me$	**29**	G	2, 25	198.5-199.5	C	27	$C_{11}H_{12}N_4O_6S$
37	Me	$CH_2CONHCO_2Et$	**30**	F	0.5, 100	177	A	29	$C_{10}H_{12}N_4O_6S$
38	Et	$CH_2CONHCO_2Et$	**30**	F	1, 100	145-146	D	24	$C_{11}H_{14}N_4O_6S$
39	c-C_3H_5	$CH_2CONHCO_2Et$	**30**	G	2, 25	170-171	A	50	$C_{12}H_{14}N_4O_6S$
40	$CH_2CH_2CO_2Et$	$CH_2CONHCO_2Et$	**30**	H	3, reflux	200-201	A	41	$C_{14}H_{18}N_4O_8S$
41	$CH{=}CHCO_2Et$	$CH_2CONHCO_2Et$	**30**	H	6, reflux	180-182[b]	E	33	$C_{14}H_{16}N_4O_8S$
42		$CH_2CONHCO_2Et$	**30**	G	1, 25	243-244	F	39	$C_{14}H_{15}N_5O_8S$
43	Ph	$CH_2CONHCO_2Et$	**30**	G	2, 25	146-147	A	33	$C_{15}H_{14}N_4O_6S$
44	2-Furyl	$CH_2CONHCO_2Et$	**30**	G	2, 25	195-196	A	65	$C_{13}H_{12}N_4O_7S$
45	2-Thienyl	$CH_2CONHCO_2Et$	**30**	G	2, 25	181-182	A	50	$C_{13}H_{12}N_4O_6S_2$
46	NHEt	$CH_2CONHCO_2Et$	**30**	I	2.5, reflux	177	G	27	$C_{11}H_{15}N_5O_6S$
47	$NHCOCH_2Cl$	$CH_2CONHCO_2Et$	**30**	J	1, 25	178-179	A	19	$C_{11}H_{12}ClN_5O_7S$
48	$NHCH_2CH{=}CH_2$	$CH_2CONHCO_2Et$	**30**	I	2, reflux	135-136	A	31	$C_{12}H_{15}N_5O_6S$
49	Me	$CH_2CONHNHCO_2Et$	**32**	F	0.25, reflux	197-199	A	29	$C_{10}H_{13}N_5O_6S$[c]

[a] A, EtOH; B, EtOAc; C, MeOH; D, C_6H_6-EtOAc; E, C_6H_6; F, AcOH; G, *i*-PrOH. [b] Half melts *ca.* 130° and then resolidifies. [c] N: calcd, 21.1; found, 20.6. [d] c-C_3H_5 represents cyclopropyl.

munication were tested in mice against a Puerto Rican strain of *S. mansoni*† by Dr. Paul E. Thompson and coworkers of Parke, Davis and Company, Ann Arbor, Mich. As in previous work, drugs were administered in a powdered diet for 14 days or by gavage for 5 days. Table IV lists the more active nitrothiazoles, and it can be seen that schistosomicidal activity is present in a wide variety of structural types. Thus, several of the 2-[*N*-(5-nitro-2-thiazolyl)formamido]acetamides (**5, 10, 11,** and **12**) exhibited significant antischistosome properties in mice (Table IV). Among these compounds, methyl [*N*-formyl-*N*-(5-nitro-2-thiazolyl)glycyl]-carbamate (**10**) and the *N*-methyl analog **12** showed moderate schistosomicidal activity, effecting a 47-77% reduction in the live worm burden when given at 270-302 mg/kg per day in the diet for 14 days. While the N-substituted 2-amino-5-nitrothiazoles V were all not surprisingly[4] inactive in the primary screen, acylated derivatives **34, 35, 46-48** (Table III), and **50** caused a 19-68% reduction in live schistosomes when administered in the diet at 214-391 mg/kg per day for 14 days.



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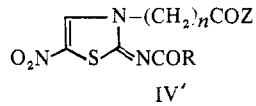
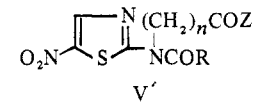
It may at this stage be relevant to make some comment on comparative structure-activity relationships existing between the 5-nitro-4-thiazolines IV′described earlier[2] and the nitrothiazoles V′discussed in this and the preceding paper.[1] It is perhaps convenient to consider first those compounds IV′and V′in which R is hydrogen or alkyl. In the nitrothiazoline series IV′, antischistosome properties are restricted to those analogs in which *n* is 1. In this particular group of 5-nitro-4-thiazoline-3-acetic acid derivatives, potent schistosomicidal activity is noticed for a wide range of *R* values (including also alkoxy and aryloxy) and for both esters (Z is alkoxy) and amides (Z is NR_1R_2) of the parent acids. In

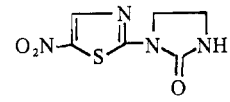
†For a description of test methods, see ref 3.



IV′



V′



VI

contrast, maximal activity against *S. mansoni* occurs for propionamides V′in which *n* is 2 and Z is NR_1R_2. Nitrothiazoles V′where *n* is 1 and Z is alkoxy or NR_1R_2 are either inactive or only slightly active in the mouse primary screen [although V′, in which *n* is 1 and Z is $N(R_1)CO_2R_2$ do possess moderate to strong schistosomicidal properties, it is possible that *in vivo* these compounds are hydrolyzed and cyclized to 1-(5-nitro-2-thiazolyl)hydantoins which are known[5,6] to be effective antischistosomal agents].

In those compounds IV′and V′in which R is NHR_1, while thiazolines IV′, *n* = 1, possess moderate to strong schisto-

Table IV. Effects of Nitrothiazoles **1-50** against *S. mansoni* in Mice[a]

Compd	Drug: Route × days[b]	Drug: mg/kg per day	Live schistosomes[c]: % mice positive	Live schistosomes[c]: % redn
5	D × 14	285	100	10
10	D × 14	302	100	47
11	D × 14	309	100	7
12	D × 14	270	100	77
34	D × 14	331	100	21
35	G × 5	200	100	26
46	D × 14	280	60	68
47	D × 14	299	100	25
48	D × 14	214	100	33
50	D × 14	391	100	19
Niridazole	D × 14	249	17	99
	G × 5	100	100	53

[a] See ref 3. [b] D represents drug-diet; G represents gavage. [c] Groups of six and eight animals, respectively, were used in the diet and gavage studies. The worm burden of the controls averaged 15 per mouse.

Table V. *In Vitro* Antibacterial[a,b] and Trichomonicidal[c] Activity of Nitrothiazoles 1-50

Compd	Minimum inhibitory concn, μg/ml					
	Staphylococcus aureus UC-76	*Streptococcus pyogenes* C203	*Salmonella typhimurium* V-31	*Shigella sonnei* C-10	*Escherichia coli* Vogel	*Trichomonas vaginalis*
10[a]	>25	>25	>25	10	10	1.56
11[a]	5	<0.08	0.63	10	1.25	6.25
14[b]	10			5	10	6.25
28[a]	20	10	>20	>20	>20	>25
29[a]	>25	>25	>25	5	5	6.25
30[b]	>25			5	<2.5	1.56
31[b]	5			5	5	6.25
47[b]	>25			5	10	6.25

[a]See ref 10. [b]See ref 11. [c]See ref 12.

somicidal activity,[7] thiazoles V′, $n = 2$, either lacked activity or were only slightly effective at high dose levels. These last results are interesting in that high activity is associated with both series IV′, $n = 1$, and V′, $n = 2$, but that this correspondence is limited to those compounds in which R is H or alkyl.

Finally, it does not appear possible to arrive at any definite conclusions with regard to structure-activity relationships existing in nitrothiazoles of general formula V′. However, in contrast with previous results,[6,8,9] it does become clear that schistosomicidal properties are in fact possessed by a wide range of nitrothiazole derivatives and that radical structural alterations may be made to niridazole VI′ without drastically diminishing antischistosome activity.

Nitrothiazoles **1-50** were also tested *in vitro* against a variety of gram-positive and gram-negative bacteria,‡ and the most active compounds are listed in Table V. Ethyl [*N*-formyl-*N*-(5-nitro-2-thiazolyl)glycyl]carbamate **(11)** appeared to be the most potent derivative, and this compound was found to have ED_{50} 14.6 (sc) and 55.7 mg/kg (po) when tested in mice infected with *Streptococcus pyogenes*.§

Many of the nitrothiazoles **1-50** also possessed some *in vitro* activity against *Trichomonas vaginalis*,# but none of the compounds were as active as metronidazole** in the *in vivo* screen.

Experimental Section††

The physical properties of thiazoles **1-49** are collected in Tables I-III, and most of the experimental details below relate to those tables.

Alkylation of 2-Formamido-5-nitrothiazole. NaH (50% suspension in oil, 0.1 mol) was added in portions to a solution of 2-formamido-5-nitrothiazole (0.1 mol) in DMF (200 ml) at 0°, and the mixture was stirred at room temperature until H_2 evolution ceased. The bromo- or chloro-alkylating agent (0.11 mol, 0.05 mol in preparation of **23**) was added, and the mixture was stirred (reaction temperature given) until it became neutral and then poured into ice-H_2O. The separated solid was washed well with H_2O and then recrystallized. The products **1-23** are listed in Table I. The alkylating agents **51** and **52** used in the preparation of thiazoles **13** and **22** are described below; other chloro or bromo compounds were prepared as described in the literature.

Method A. *N*-(5-Nitro-2-thiazolyl)glycine (24). A mixture of *N*-formyl-*N*-(5-nitro-2-thiazolyl)glycine ethyl ester **(9)** (3.0 g) and concentrated HCl (20 ml) was heated 2 hr at 100° and then cooled. Separated solid (**24** · HCl) was recrystallized from H_2O to give acid **24.**

Method B. *N*-Methyl-2-[(5-nitro-2-thiazolyl)amino]acetamide (25). A mixture of *N*-methyl-2-[*N*-(5-nitro-2-thiazolyl)formamido]-acetamide **(2)** (5.0 g), 1.0 *N* NaOH (20.5 ml), and EtOH (20 ml) was stirred 0.25 hr at 25°. Solid dissolved gradually and then the product **(25)** crystallized out.

Method C. 4-[(5-Nitro-2-thiazolyl)amino]butyramide (27). A mixture of *N*-(3-cyanopropyl)-*N*-(5-nitro-2 thiazolyl)formamide **(19)** and concentrated HCl (135 ml) was stirred 1.5 hr at room temperature and then diluted with H_2O. Neutralization ($NaHCO_3$) precipitated amide **27.**

Method D. Methyl [*N*-(5-Nitro-2-thiazolyl)glycyl]carbamate (29). Formamide **10** (10.0 g) was refluxed 0.5 hr with MeOH (200 ml), and the solution was evaporated to furnish the product **29.**

Method E. Ethyl [*N*-(5-Nitro-2-thiazolyl)glycyl]carbamate (30). $N_2H_4 \cdot H_2O$ (5.0 g, 0.1 mol) was added rapidly to the *N*-formyl compound **11** (30.2 g, 0.1 mol) in EtOH (300 ml), and the mixture was refluxed 10 min and poured into H_2O to precipitate the amino analog **30.**

Method F. *N*-Methyl-2-[*N*-(5-nitro-2-thiazolyl)acetamido]acetamide (33). Aminothiazole **25** (2.0 g) was heated (time, temperature given) with AcOH (6 ml) and Ac_2O (6 ml); then the cooled solution was poured into ice-H_2O to furnish the *N*-acetyl derivative **33.**

Method G. Methyl [*N*-(Cyclopropylcarbonyl)-*N*-(5-nitro-2-thiazolyl)glycyl]carbamate (36). Cyclopropanecarbonyl chloride (2.5 g) was added to thiazole **29** (5.2 g) in pyridine (30 ml) and Me_2CO (20 ml), and the mixture was stirred (time, temperature given) and then poured onto ice to precipitate amide **36.**

Method H. *N*-[(Carboxycarbamoyl)methyl]-*N*-(5-nitro-2-thiazolyl)-succinamic Acid Diethyl Ester (40). Thiazole **30** (2.74 g) was refluxed with ethyl 3-(chloroformyl)propionate (1.8 g) in toluene (25 ml), and the mixture was evaporated to provide amide **40.**

Method I. Ethyl [*N*-(Ethylcarbamoyl)-*N*-(5-nitro-2-thiazolyl)-glycyl]carbamate (46). Thiazole **30** (2.74 g) was refluxed with EtNCO (0.8 g) in toluene (25 ml) to afford urea **46.**

Method J. Ethyl [*N*-[(Chloroacetyl)carbamoyl]-*N*-(5-nitro-2-thiazolyl)glycyl]carbamate (47). Chloroacetyl isocyanate (1.3 g) was added dropwise to thiazole **30** (2.74 g) in THF (20 ml) at room temperature, and the mixture was stirred to precipitate urea **47.**

1-Methyl-4-(5-nitro-2-thiazolyl)-2,3-piperazinedione (50). Prepared from diamine hydrochloride **28** and $(COCl)_2$ by method G in 14% yield, piperazinedione **50** had mp 282-285° (from Me_2CO). *Anal.* ($C_8H_8N_4O_4S$) C, H, N.

Ethyl Benzyl(chloroacetyl)carbamate (51). A mixture of ethyl benzylcarbamate (8.0 g) and chloroacetyl chloride (5.7 g) was heated 2 hr at 150° and then poured into ice-H_2O. Isolation with Et_2O furnished **51** (3.3 g), mp 33.5-34.5° (from Et_2O). *Anal.* ($C_{12}H_{14}ClNO_3$) C, H, N.

Ethyl (Bromoacetyl)carbazate (52). Bromoacetyl chloride (16.5 ml) in EtOAc (10 ml) was added dropwise to ethyl carbazate (20.8 g) and NEt_3 (27.7 ml) in EtOAc (200 ml) at 0°, and the mixture was then stirred 0.5 hr at 0° and 0.5 hr at room temperature. Filtered solution was evaporated to give the product **52** (16.6 g), mp 108-110°, after recrystallization from H_2O and then EtOAc-petroleum ether (bp 60-80°). *Anal.* ($C_5H_9BrN_2O_3$) C, H, N.

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‡For a description of the test methods see ref 10 and 11.

§See ref 10.

#For a description of the test methods, see ref 12.

**Flagyl.

††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.

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Notes

Molecular Orbital Calculations on Suspected Intermediates in Oxidative Amine Metabolism†

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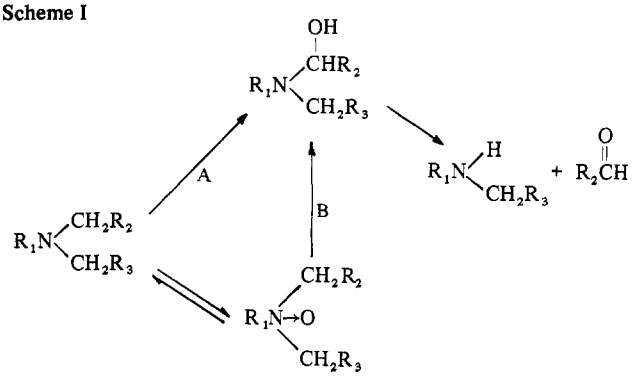
Many biologically important amines such as nicotine,[1] morphine,[2] and others[3] undergo oxidative N-dealkylation and N-oxidation reactions which often represent primary metabolic pathways for such compounds. These metabolic processes have been the subject of a tremendous amount of research in the last 10 years. (For reviews, see ref 4.) One area of continuing interest and debate is the oxidative N-dealkylation of a variety of *tert*-*N*-alkyl compounds, possibly with the exception of *tert*-butyl tertiary amines,[5] with regard to the intermediacy or nonintermediacy of *N*-oxides.[6] The postulated nondetailed mechanisms are shown in Scheme I. The major question is whether pathway A and/or B is viable *in vivo* and, if so, to what extent.

Scheme I



There is evidence supporting both mechanisms and the dispute is still unresolved although most evidence favors path A with some recent work by Bickel[7] indicating both pathways may be operative in certain cases. If the *N*-oxide is a true intermediate, the rearrangement to a carbinolamine must involve an intramolecular migration of the *N*-oxide oxygen atoms to a neighboring carbon atom since the product aldehyde contains ^{18}O when the initial source of oxygen is $^{18}O_2$.[8] *N*-Oxides have been synthesized and are fairly stable unless heated near their melting point, at which time they decompose into radicals where one of the possible recombination products is a carbinolamine.[9] Most acyclic carbinolamines spontaneously break down into an amine and an aldehyde. This surprising reactivity of carbinolamines has never been well explained. It was hoped that some insight into the process of N-dealkylation might be gained by looking into the electronic distributions and relative stabilities of postulated intermediates and products using molecular orbital methods.

We performed CNDO/2 calculations[10] on trimethylamine *N*-oxide, *N,N*-dimethylcarbinolamine, the isomeric *N*-methyl-*N*-ethylhydroxylamine, and formaldehyde plus dimethylamine (Figure 1). Hydroxylamines were included in the calculations since certain secondary and primary amines are known to be metabolized to hydroxylamines,[11] and because we wished to compare the energies of the various C_3H_9NO isomers. The conformation and bond distances for trimethylamine *N*-oxide were taken from crystal structure data;[12] for the hydroxylamines, the O-H was taken to be cis to the nitrogen lone pair, as found by Radom, *et al.*,[13] and Giguere and Liu[14]; for the carbinolamines, the completely staggered conformation, with the OH trans to the nitrogen lone pair, was found to be the lowest energy. The Mulliken atomic populations[15] calculated are relatively insensitive to conformational changes involving rotation around single bonds. As can be seen the *N*-oxide was found to be some 41 kcal/mol less stable than the corresponding carbinolamine. The *N*-oxide has a high electron density on the oxygen atom (Mulliken population on $O \equiv \zeta(O) = 8.504$) with the positive charge smeared primarily over the nitrogen and hydrogens of the rest of the molecule. Since the carbon atoms bear little of the positive charge, $\Delta H^{\ddagger}$ for the intramolecular transfer of oxygen from the nitrogen to the carbon atom would probably be significant. Thus, from a kinetic point of view, there would appear to be no *a priori* tendency for intramolecular rearrangement. However, perturbing the system could alter the situation and a mechanism whereby the oxygen with its excess negative charge would polarize one of the C-N bonds during attack on the carbon is conceivable. As the oxygen approached the carbon, the carbon would gradually transfer charge to the nitrogen, becoming more electrophilic and facilitating C-O bond formation. On the other hand, in the thermodynamically more stable carbinolamine, the carbinol carbon is very electron deficient which could render this intermediate quite reactive toward fragmentation to formaldehyde and dimethylamine, a fact

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