

(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.* (C₈H₁₁N₃O₄S) 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 H₂O and isolation with EtOAc furnished the acid 4 (3.2 g), mp 162–163° [from EtOAc-petroleum ether (bp 60–80°)]. *Anal.* (C₆H₇N₃O₄S) C, H, N.

2-[*N*-(2-Cyanoethyl)acetamido]-5-nitrothiazole (5). **Method A.** A mixture of nitrile 1 (5.0 g), Ac₂O (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 H₂O, 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 H₂O. The aqueous layer was decanted from the oil, which was then washed with H₂O 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 H₂O. Solid was collected, washed thoroughly with H₂O, 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 COCl₂ 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 COCl₂ was removed with a stream of N₂, and the reaction mixture was left overnight at room temperature. The cooled (0°) vigorously stirred mixture was then saturated with NH₃ and evaporated *in vacuo*. The residue was stirred with H₂O (*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), Ac₂O (40 ml), and AcOH (40 ml) was heated 2 hr at 100° and then poured into ice-H₂O to give the *N*-acetyl derivative 59 of acid 4 (59%), mp 171–173° (from EtOAc). *Anal.* (C₈H₉N₃O₅S) 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 NEt₃ (5.5 ml) in CHCl₃ (300 ml) at 0°, and the mixture was stirred 0.5 hr at 0°. Redistilled NHET₃ (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 H₂O (5 × 100 ml), dried (MgSO₄), and evaporated to provide the *N,N*-diethyl analog 60 of primary amide 24 (33%). mp 122–124° (from *i*-PrOH). *Anal.* (C₁₂H₁₈N₄O₄S) 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.* (C₁₃H₂₁N₅O₄S) C, H, N.

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Antiparasitic 5-Nitrothiazoles and 5-Nitro-4-thiazolines. 3¹

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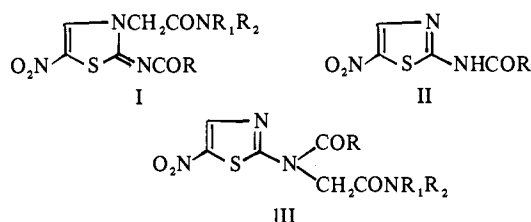
Alkylation of the sodium salt of 2-formamido-5-nitrothiazole in *N,N*-dimethylformamide with a variety of alkylating agents is shown to give exclusively exocyclic *N*-alkylated products IV. Removal of the *N*-formyl group was readily achieved with hydrazine hydrate or 1 equiv of sodium hydroxide, and 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 re-

cently.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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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 ₂ CONH ₂	25	203 dec	EtOH	42	C ₆ H ₆ N ₄ O ₄ S
2	CH ₂ CONHMe	25	214–215	AcOH	81	C ₇ H ₈ N ₄ O ₄ S
3	CH ₂ CONMe ₂	25	178.5–179.5	EtOH	61	C ₈ H ₁₀ N ₄ O ₄ S
4	CH ₂ CONEt ₂	25	140–141	EtOH	21	C ₁₀ H ₁₄ N ₄ O ₄ S
5	CH ₂ CONPr ₂	25	111–112	EtOH	51	C ₁₂ H ₁₈ N ₄ O ₄ S
6	CH ₂ CONBu ₂	25	106–107	EtOH	40	C ₁₄ H ₂₂ N ₄ O ₄ S
7	CH ₂ CONHCH ₂ Ph	25	185–186	EtOH	39	C ₁₃ H ₁₂ N ₄ O ₄ S
8	CH ₂ CONHCH ₂ CH ₂ CN	25	176–177	EtOH	39	C ₉ H ₉ N ₅ O ₄ S
9	CH ₂ CO ₂ Et	25	119–120	EtOH	77	C ₈ H ₉ N ₃ O ₅ S ^c
10	CH ₂ CONHCO ₂ Me	25	199–200	EtOAc	16	C ₈ H ₉ N ₄ O ₅ S
11	CH ₂ CONHCO ₂ Et	50	174–176	EtOH	36	C ₉ H ₁₀ N ₄ O ₅ S
12	CH ₂ CON(Me)CO ₂ Et	60	170–172	EtOH	33	C ₁₀ H ₁₂ N ₄ O ₅ S
13	CH ₂ CON(CH ₂ Ph)CO ₂ Et	60	131–132	EtOH	12	C ₁₆ H ₁₆ N ₄ O ₅ S
14	CH ₂ CONHCO ₂ Bu	25	154–155	EtOH	62	C ₁₁ H ₁₄ N ₄ O ₅ S
15	CH ₂ CONHCOMe	25	189–193	EtOH	22	C ₈ H ₈ N ₄ O ₅ S
16	CH ₂ CONHCONH ₂	25	220–222	AcOH ^b	42	C ₇ H ₇ N ₅ O ₅ S
17		65	209–212	DMF	25	C ₁₄ H ₁₀ N ₄ O ₅ S
18	CH ₂ CH ₂ N(Me)CHO	80	175–177	EtOH	20	C ₈ H ₁₀ N ₄ O ₄ S
19	CH ₂ CH ₂ CH ₂ CN	60	105–107	EtOH	66	C ₈ H ₈ N ₄ O ₄ S
20		65	210–212	DMF	79	C ₁₅ H ₁₂ N ₄ O ₅ S
21	CH ₂ C(Me)=CCl ₂	40	92–94	Aqueous MeOH	27	C ₈ H ₇ Cl ₂ N ₃ O ₅ S
22	CH ₂ CONHNHCO ₂ Et	25	181–182	EtOH	6	C ₉ H ₁₁ N ₅ O ₆ S
23		60 ^a	241–243 dec	AcOH	9	C ₁₂ H ₁₀ N ₆ O ₆ S ₂

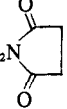
^aMole ratio of the sodio salt of 2-formamido-5-nitrothiazole:1,4-dichloro-2-butene was 2:1. ^bFollowed by hot H₂O wash. ^cC: calcd, 37.1; found, 37.6.

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 ₂ CO ₂ H	9	A	2, 100	190–191	H ₂ O	54	C ₅ H ₅ N ₃ O ₄ S
25	CH ₂ CONHMe	2	B	0.25, 25	239–240	EtOH	47	C ₆ H ₈ N ₄ O ₄ S ^b
26	CH ₂ CONEt ₂	4	B	0.25, 25	192–194	EtOAc	47	C ₉ H ₁₄ N ₄ O ₄ S
27	CH ₂ CH ₂ CH ₂ CONH ₂	19	C	1.5, 25	198–200	<i>i</i> -PrOH	67	C ₇ H ₁₀ N ₄ O ₃ S ^c
28	CH ₂ CH ₂ NHMe	18	A ^a	1, 100	173–174 dec	EtOH	52	C ₆ H ₁₀ N ₄ O ₂ S · HCl
29	CH ₂ CONHCO ₂ Me	10	D	0.5, reflux	204–205	MeOH	32	C ₇ H ₈ N ₄ O ₅ S
30	CH ₂ CONHCO ₂ Et	11	E	0.25, reflux	190–191	EtOH	91	C ₈ H ₁₀ N ₄ O ₅ S
31	CH ₂ CONHCO ₂ Bu	14	E	0.1, reflux	155–156	EtOH	38	C ₁₀ H ₁₄ N ₄ O ₅ S ^d
32	CH ₂ CONHNHCO ₂ Et	22	E	0.25, reflux	225–227 dec	EtOH	52	C ₈ H ₁₁ N ₅ O ₅ S

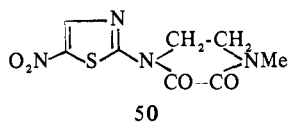
^aReaction mixture evaporated *in vacuo* and residue recrystallized. ^bN: calcd, 25.9; found, 25.4. ^cC: calcd, 36.5; found, 37.2. ^dN: calcd, 18.5; found, 18.0.

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

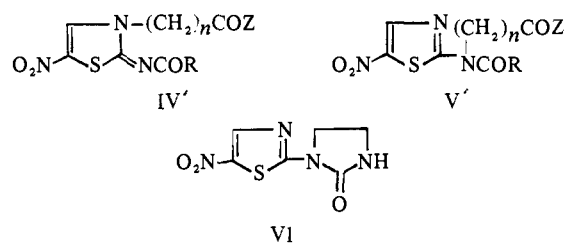
Compd	R	Z	Starting material	Method	Reaction time, hr; temp, °C	Mp, °C	Recrystn solvent ^a	% yield	Formula
33	Me	CH ₂ CONHMe	25	F	1, 100	229-230	A	62	C ₈ H ₁₀ N ₄ O ₄ S
34	Me	CH ₂ CONEt ₂	26	F	0.5, 120	141-142	B	68	C ₁₁ H ₁₆ N ₄ O ₄ S
35	Me	CH ₂ CONHCO ₂ Me	29	F	1, 100	219-220	C	52	C ₉ H ₁₀ N ₄ O ₆ S
36	<i>c</i> -C ₃ H ₅ ^d	CH ₂ CONHCO ₂ Me	29	G	2, 25	198.5-199.5	C	27	C ₁₁ H ₁₂ N ₄ O ₆ S
37	Me	CH ₂ CONHCO ₂ Et	30	F	0.5, 100	177	A	29	C ₁₀ H ₁₂ N ₄ O ₆ S
38	Et	CH ₂ CONHCO ₂ Et	30	F	1, 100	145-146	D	24	C ₁₁ H ₁₄ N ₄ O ₆ S
39	<i>c</i> -C ₃ H ₅	CH ₂ CONHCO ₂ Et	30	G	2, 25	170-171	A	50	C ₁₂ H ₁₄ N ₄ O ₆ S
40	CH ₂ CH ₂ CO ₂ Et	CH ₂ CONHCO ₂ Et	30	H	3, reflux	200-201	A	41	C ₁₄ H ₁₈ N ₄ O ₆ S
41	CH=CHCO ₂ Et	CH ₂ CONHCO ₂ Et	30	H	6, reflux	180-182 ^b	E	33	C ₁₄ H ₁₆ N ₄ O ₆ S
42		CH ₂ CONHCO ₂ Et	30	G	1, 25	243-244	F	39	C ₁₄ H ₁₅ N ₅ O ₈ S
43	Ph	CH ₂ CONHCO ₂ Et	30	G	2, 25	146-147	A	33	C ₁₅ H ₁₄ N ₄ O ₆ S
44	2-Furyl	CH ₂ CONHCO ₂ Et	30	G	2, 25	195-196	A	65	C ₁₃ H ₁₂ N ₄ O ₈ S
45	2-Thienyl	CH ₂ CONHCO ₂ Et	30	G	2, 25	181-182	A	50	C ₁₃ H ₁₂ N ₄ O ₆ S ₂
46	NHEt	CH ₂ CONHCO ₂ Et	30	I	2.5, reflux	177	G	27	C ₁₁ H ₁₅ N ₃ O ₆ S
47	NHCOCH ₂ Cl	CH ₂ CONHCO ₂ Et	30	J	1, 25	178-179	A	19	C ₁₁ H ₁₂ ClN ₅ O ₇ S
48	NHCH ₂ CH=CH ₂	CH ₂ CONHCO ₂ Et	30	I	2, reflux	135-136	A	31	C ₁₂ H ₁₅ N ₃ O ₆ S
49	Me	CH ₂ CONHNHCO ₂ Et	32	F	0.25, reflux	197-199	A	29	C ₁₀ H ₁₃ N ₂ O ₆ S ^c

^aA, EtOH; B, EtOAc; C, MeOH; D, C₆H₆-EtOAc; E, C₆H₆; F, AcOH; G, *i*-PrOH. ^bHalf melts ca. 130° and then resolidifies. ^cN: calcd, 21.1; found, 20.6. ^d*c*-C₃H₅ 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 surprisingly⁴ 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.



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 earlier² 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 NR₁R₂) of the parent acids. In



contrast, maximal activity against *S. mansoni* occurs for propionamides V' in which *n* is 2 and *Z* is NR₁R₂. Nitrothiazoles V' where *n* is 1 and *Z* is alkoxy or NR₁R₂ are either inactive or only slightly active in the mouse primary screen [although V', in which *n* is 1 and *Z* is N(R₁)CO₂R₂ 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)hydantoin which are known^{5,6} to be effective antischistosomal agents].

In those compounds IV' and V' in which R is NHR₁, 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		Live schistosomes ^c	
	Route × days ^b	mg/kg per day	% mice positive	% 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

^aSee ref 3. ^bD represents drug-diet; G represents gavage. ^cGroups of six and eight animals, respectively, were used in the diet and gavage studies. The worm burden of the controls averaged 15 per mouse.

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

Table V. *In Vitro* Antibacterial^{a,b} and Trichomonocidal^c Activity of Nitrothiazoles 1-50

Compd	Minimum inhibitory concn, $\mu\text{g/ml}$					
	<i>Staphylococcus aureus</i> UC-76	<i>Streptococcus pyogenes</i> C203	<i>Salmonella typhimurium</i> V-31	<i>Shigella sonnei</i> C-10	<i>Escherichia coli</i> Vogel	<i>Trichomonas vaginalis</i>
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

^aSee ref 10. ^bSee ref 11. ^cSee 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 ED₅₀ 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 H₂ 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-H₂O. The separated solid was washed well with H₂O 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 H₂O 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 H₂O. Neutralization (NaHCO₃) 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). N₂H₄·H₂O (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 H₂O 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 Ac₂O (6 ml); then the cooled solution was poured into ice-H₂O 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 Me₂CO (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 Me₂CO). *Anal.* (C₈H₈N₄O₅) 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-H₂O. Isolation with Et₂O furnished 51 (3.3 g), mp 33.5-34.5° (from Et₂O). *Anal.* (C₁₂H₁₄ClNO₂) C, H, N.

Ethyl (Bromoacetyl)carbamate (52). Bromoacetyl chloride (16.5 ml) in EtOAc (10 ml) was added dropwise to ethyl carbamate (20.8 g) and NEt₃ (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 H₂O and then EtOAc-petroleum ether (bp 60-80°). *Anal.* (C₈H₉BrNO₂) 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 $\pm 0.4\%$ of the theoretical values.

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Notes

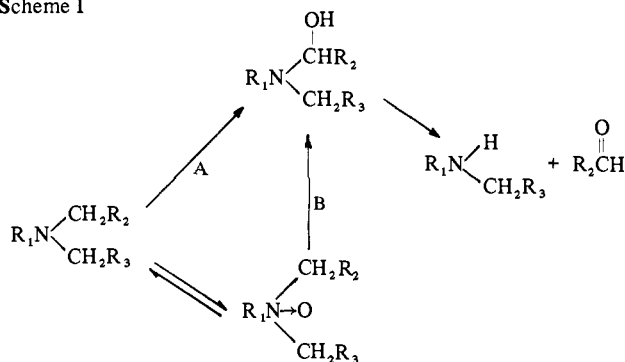
Molecular Orbital Calculations on Suspected Intermediates in Oxidative Amine Metabolism[†]Sidney D. Nelson,*[‡] Peter A. Kollman, William F. Trager,[‡]*School of Pharmacy, Department of Pharmaceutical Chemistry, University of California, San Francisco, California 94122*

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Many biologically important amines such as nicotine,¹ morphine,² and others³ 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 Bickel⁷ 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

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oxygen atoms to a neighboring carbon atom since the product aldehyde contains ¹⁸O when the initial source of oxygen is ¹⁸O₂.⁸ 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 calculations¹⁰ 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 C₃H₉NO 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 Liu¹⁴; 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 populations¹⁵ 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 ≡ ζ(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, ΔH[‡] 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