recrystallized twice from CH_2Cl_2–EtOH to leave 7.5 g (55%) of colorless crystals with mp 245–247 °C dec: UV λ max 228 nm (ε 27 700), 258 (16 300), 309 (11 450). Anal. ($C_{18}H_{15}ClN_4O_3$) C, H, N.

8-Chloro-1-(1,2-dihydroxyethyl)-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (11b). A mixture of 4.5 g (0.012 mol) of **11a**, 200 mL of THF, 100 mL of MeOH, and 2 teaspoonfuls of Raney nickel was shaken under hydrogen at atmospheric pressure for 2 h. The catalyst was removed by filtration, the filtrate evaporated under reduced pressure, and the residue crystallized from EtOH. Recrystallization from CH_2Cl_2–EtOH yielded 3.2 g (76%) of pure colorless product with mp 211–214 °C dec: UV λ max 222 nm (ε 38 600), sh 245 (16 600), sh 290 (2900). Anal. ($C_{18}H_{15}ClN_4O_2$) C, H, N.

8-Chloro-1-(1,2-dihydroxyethyl)-6-(2-fluorophenyl)-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (11d). A mixture of 10.5 g (0.035 mol) of **1d**,[9] 3.8 g (0.042 mol) of *dl*-glyceraldehyde, and 300 mL of MeOH was boiled on a steam bath for 10 min, allowed to sit at room temperature for 16 h, and filtered. The filtrate was evaporated under reduced pressure. The residue was treated with 400 mL of 1-BuOH and 12 mL (0.073 mol) of diethyl azodicarboxylate. After refluxing for 2 h, the reaction mixture was evaporated under reduced pressure. Crystallization of the residue from CH_2Cl_2–Et_2O gave 4.5 g (35%) of product with mp 203–206 °C. Recrystallization from MeOH–Et_2O yielded colorless crystals with mp 208–210 °C: UV λ max 222 nm (ε 36 450), infl 245 (15 700), sh 280 (2800). Anal. ($C_{18}H_{14}ClFN_4O_2$) C, H, N.

8-Chloro-6-(2-fluorophenyl)-1-vinyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (12d). A solution of 5.3 g (0.017 mol) of **1d**,[9] 100 mL of CH_2Cl_2, 35 mL of MeOH, 2.5 mL of HOAc, and 3.0 mL of acrolein was stirred at room temperature for 25 min, washed with $NaHCO_3$ solution, dried, and concentrated under reduced pressure. The residue was treated with 2.5 mL (0.0155 mol) of diethyl azodicarboxylate and 125 mL of DMF and refluxed for 1.5 h. The reaction mixture was evaporated under reduced pressure. The residue was chromatographed over 150 g of silica gel using 3% (v/v) MeOH in CH_2Cl_2. Clean fractions were combined and evaporated. The product crystallized from Et_2O–petroleum ether and was recrystallized from CH_2Cl_2–petroleum ether to yield 0.5 g (8.7%) of off-white prisms with mp 176–179 °C dec: UV λ sh 211 nm (ε 45 500), sh 245 (24 000), sh 290 (2750); NMR ($CDCl_3$) δ 4.13 (d, 1) and 5.6 (d, 1) (AB system, J = 13 Hz, C_4-H), 5.6–6.8 (m, 3, CH=CH_2), 6.8–7.9 (m, 7, aromatic H). Anal. ($C_{18}H_{12}ClFN_4$) C, H, N.

8-Chloro-6-(2-chlorophenyl)-1-vinyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (12c) and 8-Chloro-6-(2-chlorophenyl)-1-[2-[1,2-bis(ethoxycarbonyl)hydrazo]-*trans*-vinyl]-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (13c). A solution of 18.0 g (0.05 mol) of **5c**, 18 mL (0.11 mol) of diethyl azodicarboxylate, and 500 mL of DMF was refluxed for 45 min and concentrated under reduced pressure. The residue was treated with Et_2O and filtered. The filtrate was evaporated, leaving a mixture according to TLC. Chromatography on 300 g of silica gel with 10% (v/v) EtOH in EtOAc did not separate the products. Two successive chromatographies over silica gel H (according to Stahl for TLC) with 5% (v/v) EtOH in CH_2Cl_2 gave 1.5 g (8%) of **12c** and 1.15 g (4%) of **13c**.

Recrystallization of **12c** from CH_2Cl_2–Et_2O yielded colorless crystals with mp 216–220 °C dec: UV λ infl 218 nm (ε 41 000), infl 254 (15 800), infl ~300 (1700); NMR ($CDCl_3$) δ 4.15 (d, 1) and 5.55 (d, 1) (AB system, J = 13 Hz, C_4-H), 5.6–6.8 (m, 3, CH=CH_2), 7–7.9 (m, 7, aromatic H). Anal. ($C_{18}H_{12}Cl_2N_4$) C, H, N.

Recrystallization of **13c** from CH_2Cl_2–hexane yielded colorless crystals with mp 199–201 °C dec: UV λ max 217 nm (ε 43 600), sh 245 (22 600), max 274 (18 450); IR (KBr) 1740 cm^{-1} (COOEt); NMR (Me_2SO) δ 1.25 (t, 6, J = 7 Hz, CH_3), 4.25 (m, 4, OCH_2), 4.25 (d, 1) and 5.25 (d, 1) (AB system, J = 13 Hz, C_4-H), 5.75 (d, 1) and 7.95 (d, 1) (AB system, J = 13.5 Hz, –CH=CH–), 7.14 (d, 1, J = 2 Hz, C_7-H), 7.3–7.9 ppm (m, 6, aromatic H). Anal. ($C_{24}H_{21}Cl_2N_6O_4$) C, H, N.

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Nitroimidazoles with Antibacterial Activity against *Neisseria gonorrhoeae*

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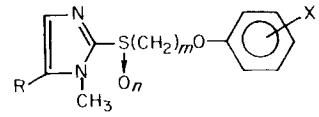
Nitroimidazoles have been prepared which show interesting activity against the bacterium, *Neisseria gonorrhoeae*, in addition to the activities usually shown by nitroimidazoles against protozoa and anaerobic bacteria. The compounds were prepared by alkylation of 1-methyl-2-mercaptoimidazole, followed by nitration. Optimum activity occurs with a 5-nitro group and a free carboxyl at the end of the group attached to the sulfur. The linkage between the sulfur atom and the carboxyl group can be alkylene or phenoxyalkylene. These compounds have only weak activity against other aerobic or facultative bacteria.

Gonorrhea is a serious public health problem in the world today.[1] Strains of the responsible organism, *Neisseria gonorrhoeae*, have arisen which are resistant to penicillin[2] and there is the possibility that resistance will also develop to alternative drugs. Thus, development of additional drugs with different structures is most desirable. An antigonococcal screening program in our laboratories uncovered interesting activity in some of the compounds reported in a previous paper.[3] A number of additional compounds were prepared to explore this activity.

Chemistry. The compounds were made by the methods described in our previous paper.[3] Yields of some of the 5-nitro compounds in Table I were low due in part to concurrent nitration of the benzene ring as seen in

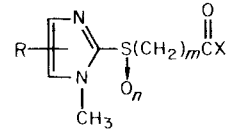
Table I



Compd	R	n	m	X	Formula	Analyses	Mp, °C	B. fragilis	C. perfringens	N. gonorrhoeae	T. vaginalis	T. foetus	P. hominis
1	H	0	2	4-Br·HBr	$C_{12}H_{13}BrN_2OS·HBr$	C, H	132–134	100 (2)[a]	>100 (2)	100 (2)	>100 (2)	>100 (2)	>100 (2)
2	NO_2	0	2	4-Br	$C_{12}H_{12}BrN_3O_3S$	C, H	104–105	100 (4)	>100 (6)	>100 (4)	10 (6)	10 (4)	10 (6)
3	H	0	2	4-NO_2·HBr	$C_{12}H_{13}N_3O_3S·HBr$	Br, N	163–166	>100 (2)	>100 (2)	100 (2)	>100 (2)	>100 (2)	>100 (2)
4	NO_2	0	2	4-NO_2	$C_{12}H_{12}N_4O_5S$	C, H, N	139.5–140.5	100 (6)	100 (4)	>100 (4)	10 (6)	100 (6)	1 (4)
5	H	0	2	4-CN·HBr	$C_{13}H_{13}N_3OS·HBr$	C, H	179.5–182	>100 (2)	>100 (4)	>100 (2)	>100 (2)	>100 (2)	>100 (2)
6	H	0	2	4-CN	$C_{13}H_{13}N_3OS$	C, H	85–85.5	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)
7	NO_2	0	2	4-CN	$C_{13}H_{12}N_4O_3S$	C, H	142.5–145		100 (2)	100 (2)	1 (2)	1 (2)	1 (2)
8	NO_2	1	2	4-CN	$C_{13}H_{12}N_4O_4S$	C, H	159.5–161	100 (2)	>100 (2)	100 (2)	10 (2)	100 (2)	100 (2)
9	H	0	2	4-CO_2H	$C_{13}H_{14}N_2O_3S$	C, H	187.5–189	>100 (2)	>100 (4)	>100 (2)	>100 (2)	>100 (2)	>100 (2)
10	NO_2	0	2	4-CO_2H	$C_{13}H_{13}N_3O_5S$	C, H	209–213	10 (2)	10 (6)	1 (4)	1 (4)	1 (4)	1 (4)
11	NO_2	1	2	4-CO_2H	$C_{13}H_{13}N_3O_6S$	C, H, N	205.5–206	100 (2)	100 (2)	100 (2)	100 (2)	100 (2)	100 (2)
12	NO_2	0	2	4-CO_2Na	$C_{13}H_{12}N_3NaO_5S$	C, H, Na		1 (2)	10 (4)	1 (8)	1 (2)	10 (2)	1 (2)
13	NO_2	0	3	4-CO_2H	$C_{14}H_{15}N_3O_5S$	C, H, N	191–193	1 (6)	10 (6)	1 (6)	1 (4)	10 (4)	1 (4)
14	H	0	4	H·HBr	$C_{14}H_{18}N_2OS·HBr$	C, H	114–115	>100 (2)	>100 (2)	100 (2)	>100 (2)	>100 (2)	>100 (2)
15	H	0	4	4-$CO_2C_2H_5$·HBr	$C_{17}H_{22}N_2O_3S·HBr$	C, H, N	134–135	>100 (4)	>100 (2)	>100 (4)	100 (4)	100 (2)	100 (2)
16	H	0	4	4-$CO_2C_2H_5$	$C_{17}H_{22}N_2O_3S$	C, H, N	36–37.5	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)
17	NO_2	0	4	4-CO_2H	$C_{15}H_{17}N_3O_5S$	C, H, N	182–187.5	10 (1)	10 (1)	100 (2)	1 (2)	1 (2)	1 (2)
18	NO_2	0	6	4-CO_2H	$C_{17}H_{21}N_3O_5S$	C, H, N	170–171	1 (2)	10 (2)	0.1 (2)	1 (2)	1 (2)	1 (2)
19	NO_2	0	6	4-$CO_2C_2H_5$,2-NO_2	$C_{19}H_{24}N_4O_7S$	C, H, N	115.5–117	10 (2)	100 (2)	>100 (2)	10 (2)	100 (2)	10 (2)
20	NO_2	0	7	2-NO_2	$C_{17}H_{22}N_4O_5S$	C, H, S	66–68	>100 (2)	>100 (2)	>100 (2)	100 (2)	100 (2)	100 (2)
21	NO_2	1	7	2-NO_2	$C_{17}H_{22}N_4O_6S$	C, H		100 (2)	>100 (2)	>100 (2)	100 (2)	100 (2)	100 (2)
22	NO_2	2	7	2-NO_2	$C_{17}H_{22}N_4O_7S·{}^1/_6C_6H_6$	C, H		>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)
23	NO_2	0	10	2-NO_2,4-$CO_2C_2H_5$	$C_{23}H_{32}N_4O_7S$	C, H, N		10 (2)	>100 (2)	>100 (2)	10 (2)	10 (2)	10 (2)
Metronidazole								1 (4)	10 (4)	>100 (4)	10 (8)	1 (8)	1 (8)

[a] See Experimental Section.

Table II



Compd	R	n	m	X	Formula	Analyses	Mp, °C	B. fragilis	C. perfringens	N. gonorrhoeae	T. vaginalis	T. foetus	P. hominis
24	5-NO_2	0	2	OH	228[a]			10 (2)[b]	10 (2)	10 (2)	10 (2)	10 (2)	10 (2)
25	5-NO_2	1	2	OH	229[a]			10 (2)	100 (2)	>100 (2)	10 (2)	10 (2)	10 (2)

26	5-NO_2	2	OH	230[a]			>100 (2)	>100 (2)	100 (2)	100 (2)	100 (2)	100 (2)	100 (2)	100 (2)	100 (2)
27	H	0	OH	231[a]			>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)
28	5-NO_2	0	OH	233[a]			1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)
29	5-NO_2	1	OH	235[a]			100 (2)	>100 (2)	100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)
30	5-NO_2	2	OH	237[a]			100 (2)	>100 (2)	100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)
31	5-NO_2	0	OH	$C_{10}H_{15}N_3O_4S$	C, H, N	125.5–126.5	100 (8)	0.1 (6)	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)
32	5-NO_2	0	OH	$C_{11}H_{17}N_3O_4S$	C, H, N	115–117.5	1 (6)	0.1 (6)	1 (6)	1 (6)	10 (4)	1 (4)	10 (4)	1 (4)	1 (4)
33	4-NO_2	0	OH	$C_{11}H_{17}N_3O_4S$	C, H, N	125–126.5	>100 (6)	>100 (4)	>100 (4)	100 (2)	100 (2)	100 (2)	100 (2)	100 (2)	100 (2)
34	5-NO_2	0	OH	$C_{12}H_{19}N_3O_4S$	C, H, N	118–119	10 (8)	0.1 (6)	0.1 (6)	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)
35	5-NO_2	0	OH	$C_{13}H_{21}N_3O_4S$	C, H, N	110–110.5	10 (8)	10 (12)	0.1 (6)	10 (6)	10 (6)	10 (4)	10 (4)	10 (4)	10 (6)
36	5-NO_2	0	OH	$C_{14}H_{23}N_3O_4S$	C, H, N	114–116	10 (10)	10 (10)	0.1 (6)	10 (4)	10 (4)	1 (4)	1 (4)	1 (4)	1 (4)
37	H	0	OH·HBr	238[a]			>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)
38	5-NO_2	0	OH	239[a]			10 (2)	10 (6)	0.1 (2)	10 (2)	10 (2)	10 (2)	10 (2)	10 (2)	10 (2)
39	5-NO_2	1	OH	$C_{15}H_{25}N_3O_5S$	C, H	119–122	>100 (4)	>100 (4)	100 (8)	100 (4)	10 (4)	100 (2)	100 (2)	100 (2)	100 (2)
40	5-NO_2	0	OCH_3	240[a]			>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)
41	5-NO_2	1	OCH_3	241[a]			>100 (2)	>100 (2)	100 (2)	>100 (2)	100 (2)	100 (2)	100 (2)	100 (2)	100 (2)
42	5-NO_2	2	OCH_3	242[a]			>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)	>100 (2)
43	5-NO_2	0	OH	$C_{16}H_{27}N_3O_4S$	C, H, N	119.5–120.5	100 (6)	>100 (8)	>100 (8)	10 (2)	10 (2)	10 (2)	10 (2)	10 (2)	10 (2)
44	5-NO_2	0	OH	$C_{20}H_{35}N_3O_4S$	C, H, N	123–123.5	>100 (6)	>100 (2)	>100 (2)	100 (2)	100 (2)	100 (2)	100 (2)	100 (2)	100 (2)

[a] Compound number in ref 3. [b] See Experimental Section.

compounds **19** and **23**. Some of the nitrations to obtain compounds such as **17** and **18** were run in CF_3COOH, followed by chromatography and ester hydrolysis in H_2SO_4. The sodium salt **12** was obtained by dissolving the acid **10** in an equivalent amount of NaOH and concentrating the solution to dryness. The NMR spectra of the compounds were consistent with the structures assigned.

Biological Results. The assays of primary interest were the in vitro tests against *N. gonorrhoeae*, the protozoa *Tritrichomonas foetus*, *Trichomonas vaginalis*, and *Pentatrichomonas hominis*, and the anaerobic bacteria, *Bacteroides fragilis* and *Clostridium perfringens*. 1-Hydroxyethyl-2-methyl-5-nitroimidazole (metronidazole, Flagyl), the agent of choice for the *T. vaginalis* infections, is highly active against these two anaerobes but not against *N. gonorrhoeae*.

The activities against the protozoa species are essentially parallel. The prime structural requirement is a 5-nitro group on the imidazole ring. Activity is usually reduced by oxidation of the sulfide to a sulfoxide and reduced further on oxidation to the sulfone. Substituents on the phenoxy ring of the compounds in Table I can be varied somewhat, with 4-cyano and carboxyl giving activity equivalent to metronidazole and 4-bromo and nitro also showing good activity. An ortho substituent seems to reduce activity.

Among the compounds of Table II lacking the aromatic ring, the 5-NO_2 group and a free carboxyl group are necessary for activity against protozoa. Peak activity is seen with chain lengths of four to seven methylenes. Conversion of the carboxyl to an ester (**40**) or oxidation of the sulfur (**29** and **30**) reduces or eliminates activity.

The presence of a 5-nitro and a carboxyl does not ensure activity since Landmark and Müller[4] report that 1-carboxymethyl-2-methyl-5-nitroimidazole is inactive vs. *T. foetus* and *T. vaginalis*.

The structural requirements for antianaerobe activity against *B. fragilis* and *C. perfringens* are narrower, with 4-carboxyl being the only acceptable substituent and with chain length restricted to m = 2–6 in the compounds of Table I. In Table II a free carboxyl is required with chain lengths of 2–10 acceptable and peak activity at m = 4–6 for *B. fragilis* and m = 7 for *C. perfringens*.

Activity against *N. gonorrhoeae* also has specific structural requirements. Besides the 5-NO_2 group on the imidazole ring, a carboxyl group on the end of the side chain is necessary to obtain activity at 10 μg/mL or less. The carboxyl cannot be esterfied and oxidation of the sulfur is deleterious.

The number of carbon atoms in the chain is important, being limited to 2–10 in Table II for good activity. Among the compounds in Table II, activity is lost when the chain length reaches 15 methylenes. Peak activity occurs with 5–10 methylenes as shown in Table II.

Some of these compounds were also screened against the bacteria, *Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus epidermidis*, *Escherichia coli*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Streptococcus faecalis*, *Propionibacterium acnes*, and *Klebsiella pneumoniae*, and the fungus, *Candida albicans*, by methods described before.[3,5] Activity was seen against some of the bacteria, but only at a concentration of 100 μg/mL. No activity was observed against *C. albicans*.

Conclusions

Addition of a carboxyl group to the side chain attached to the 2 position of a nitroimidazole ring maintains the in vitro activity reported previously[3] for similar compounds.

More importantly, a new activity against *N. gonorrhoeae* is found in these compounds.

Experimental Section

Melting points (corrected) were taken in a Thomas-Hoover capillary apparatus. Analyses indicated by symbols of the elements represent results within ±0.4% of the theoretical values. Most compounds were prepared by the methods of reference 3. Sample preparations are given for the compounds prepared by different methods.

Ethyl 4-[6-(1-Methyl-5-nitro-2-imidazolylthio)hexyloxy]benzoate (45). Ethyl 4-[6-(1-methyl-2-imidazolylthio)-hexyloxy]benzoate, 5.8 g, was dissolved in 15 mL of CF_3COOH with 2.5 mL of HNO_3 (concentrated). The solution was kept at room temperature for 18 h, heated to 90 °C for 0.5 h, and then poured into H_2O. The pH was adjusted to 6 with $NaHCO_3$ and the aqueous layer was decanted from an oil which was chromatographed on Woelm silica in a low-pressure system using 20% ethyl acetate–benzene. Fractions containing **45** (as indicated by thin-layer chromatography) were combined and evaporated to yield a solid which was triturated with ether to give 0.5 g (8%), mp 75–78 °C. Compound **19** was eluted next to yield 0.6 g (10%).

4-[6-(1-Methyl-5-nitro-2-imidazolylthio)hexyloxy]benzoic Acid (18). Compound **45**, 0.5 g, was dissolved in 4 mL of H_2SO_4 (concentrated). After 15 min the solution was diluted to 40 mL with H_2O. The solid which separated was recrystallized twice from acetone to give 0.15 g (30%) of **18**.

Sodium 4-[2-(1-Methyl-5-nitro-2-imidazolylthio)ethoxy]benzoate (12). Compound **10**, 1.8 g, was mixed with less than 1 equiv of NaOH solution and the mixture was stirred for several hours and then filtered. The filtrate was concentrated under vacuum. The residue was **12**, 0.9 g (47%).

Microbiology. Antimicrobial tests were conducted by tenfold serial dilution in suitable liquid or solid media, the highest concentration of compounds used being 100 μg/mL. Activities against the anaerobic bacteria, *C. perfringens* ATCC 13124 and *B. fragilis* ATCC 23745, were determined in Fluid Thioglycollate Broth (Bioquest, Cockeysville, Md.) while those against *N. gonorrhoeae* ATCC 19424, an aerobic bacterium, were determined on Chocolate Agar [GC Agar Base (Bioquest) supplemented with Bacto Hemoglobin and Bacto Supplement C (Difco Laboratories, Detroit, Mich.)]. Diamond medium[6] with 5% Dubos medium serum (Difco Laboratories) was used for antiprotozoal tests with *T. vaginalis* ATCC 30001, *T. foetus* 1002-96-27, and *P. hominis* ATCC 30000. The *C. perfringens* and *B. fragilis* test preparations were incubated for 24 h and the slower growing *N. gonorrhoeae* and the trichomonads were incubated for 48 h, all at 37 °C. After incubation the bacterial preparations were observed visually for the presence of growth and the trichomonad preparations were observed microscopically for the presence of motile cells. Minimal inhibitory concentrations (MIC values) are reported as the lowest concentrations of the compounds, in μg/mL, which prevented development of visible growth or resulted in the absence of motile organisms. Replicate tests were done (two to eight replicates) when the quantities of compounds available permitted, and in cases where variations in the results occurred the highest MIC values are reported.

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Chemoimmunotherapy of Cancer. 3.[1] Analytical Measurement of Chemical Half-Lives of Monofunctional Alkylators

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The objective of this study is the measurement of the rates of hydrolysis of a series of chloroethyl sulfide derivatives, under simulated physiological conditions. Interferences encountered with the conventional spectrophotometric method prompted the use of a rapid-response, chloride selective electrode. This probe was readily capable of monitoring the hydrolytic rate, which is identical with the rate of chloride ion formation. Since the desired subsecond half-lives were not achieved by any of the compounds, factors influencing the rates were investigated. The results suggest that the rate-controlling cyclization step may be inhibited, due to coordination of undissociated protonic functional groups on the aromatic portions of the structures with the lone-pair electrons on sulfur.

After three decades of clinical experience with cytotoxic alkylating agents in the treatment of cancer, myelosuppressive side effects remain a major pitfall of chemotherapy.[2] Approaches to this problem have included a number of techniques intended to permit the shunting of anticancer agents through the diseased region, while bypassing sensitive hemopoietic tissues.[3-7] The goal of developing such methods had prompted Seligman and his associates to synthesize a number of alkylators which may be rapidly deactivated by hydrolysis, following a single passage through a tumor's capillary bed. Kinetic studies of these agents showed that the desired subsecond half-lives were achieved by a number of compounds in the chloroethyl sulfide series.[8]

Our recent efforts have sought to incorporate this capability of rapid deactivation into the design of alkylators suitable for chemoimmunotherapy of cancer.[1] In this report, kinetic studies on the hydrolysis of such alkylating immunogens are presented. The structures are shown in Figure 1.

Previously, kinetic studies of alkylating agents have utilized the Epstein reagent, 4-(4′-nitrobenzyl)pyridine, to measure the unhydrolyzed mustard remaining after suitable time intervals.[8,9] Our initial studies showed this