acetone solution, when taken to dryness, yielded a solid which was analyzed by nmr, ir, and mass spectrometry.

The major constituent of the ether extract of $(NH_4)_2SO_4$-saturated urine was purified by successive chromatography on three silica gel columns, using benzene or chloroform with increasing concentrations of methanol. The fine white needles which were obtained were recrystallized from a mixture of methanol and chloroform and then analyzed by nmr, ir, and mass spectrometry. It was found to be identical with a synthetic sample of *p*-hydroxyphenylurea prepared by the method of Kalckhoff.[4]

Spectral Analyses. The nmr spectra were obtained at 100 MHz on a Varian Associates HA-100 spectrometer, using acetone-d_6 as solvent. The ir spectra were obtained on a Perkin-Elmer Model 521 infrared spectrometer, using KBr pellets. The mass spectra were obtained on an AEI-MS-902 mass spectrometer at 70 eV, using direct probe for introduction of the sample.

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Supplementary Material Available. Supplementary material consisting of the mass spectrum of authentic 5-(*p*-hydroxyanilino)-1,2,3,4-thiatriazole, mass and ir spectra of the unknown metabolite of 5-(*p*-hydroxyanilino)-1,2,3,4-thiatriazole, and the mass and ir spectra of the synthetic analog, 1-phenyltetrazoline-5-thione, will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only on microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JMED-73-1157.

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Synthesis of Antimicrobial Nitroimidazolyl 2-Sulfides, -Sulfoxides, and -Sulfones

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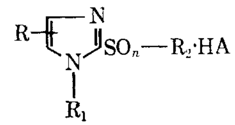
Imidazoles having a variety of alkyl and aralkyl sulfur substituents at the 2 position, and their 5- and 4-nitro analogs, were synthesized and tested for a broad spectrum of biological activities. Many of the nitroimidazoles were potent *in vitro* trichomonacides; other activities observed among the structural series prepared include antibacterial, antifungal, antinematode, and antiinflammatory.

The introduction of 1-(2-hydroxyethyl)-5-nitro-2-methylimidazole (Flagyl; metronidazole) as a highly effective agent for treatment of human trichomoniasis and of 1,2-dimethyl-5-nitroimidazole (Emtryl; dimetridazole) for turkey histomoniasis has stimulated a number of synthetic programs involving nitroimidazoles. This work has resulted in several compounds which are potential products in the human or animal fields: *e.g.*, 1-methyl-2-isopropyl-5-nitroimidazole (ipronidazole);[1] 1-(2-morpholinoethyl)-2-methyl-5-nitroimidazole (nitrimidazine);[2] 1-methyl-2-carbamoyloxymethyl-5-nitroimidazole (Ridzole; ronidazole);[3] 1-(2-hydroxyethyl)-2-(*p*-fluorophenyl)-5-nitroimidazole (flunidazole);[4] 1-methyl-2-(*p*-fluorophenyl)-5-nitroimidazole (MK-910);[5] 1-(2-ethylsulfonylethyl)-2-methyl-5-nitroimidazole (Fasigyn; tinidazole);[6] 2-amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole (CL 64885);[7] and various 2-nitroimidazole derivatives.[8] This paper describes several series of 2-(substituted mercapto)imidazoles and their nitro derivatives which were made in a search for a potent antitrichomonal agent with a broader biological activity profile than metronidazole.

Chemistry. The 1-alkyl-2-imidazolyl sulfides (Tables I, II, and VI–IX) were prepared by alkylation of the corresponding 1-alkyl-2-mercaptoimidazole with the appropriate halides in dioxane or 2-propanol.

Nitration of the sulfides was carried out by heating at 100° for 0.5–1.5 hr in aqueous nitric acid (100 parts of 70% HNO_3 to 40 parts of H_2O). This procedure was found to be preferable to H_2SO_4–HNO_3 nitrations which frequently became violent. Longer heating was inadvisable for arylmethyl sulfides owing to oxidative cleavage at the *S*-methylene bond as shown by the isolation of the corresponding benzoic acid. This oxidation could usually be detected by the appearance of solid after 45 min of heat-

Table I



	R	R_1	R_2	*n*	HA	Formula	Analyses	Mp, °C	*Trichomonas*	*T. aceti*
1	H	CH_3	CH_2CH_3	0	Citrate	$C_6H_{10}N_2S \cdot C_6H_8O_7$	C, H	86–88		>10,000
2	H	CH_3	CH_2CH_3	0	CH_3CHI	$C_8H_{15}IN_2S$	N, I	105.5–106[a]	>10,000	10,000
3	H	CH_3	CH_2CH_3	0	3,4-$Cl_2C_6H_3CH_2Cl$	$C_{13}H_{15}Cl_3N_2S$	N, Cl	140–141.5	100	1,000
4	H	CH_3	$(CH_2)_2CH_3$	0	Citrate	$C_7H_{12}N_2S \cdot C_6H_8O_7$	C, H	78–81	>10,000	>10,000
5	H	CH_3	$(CH_2)_2CH(CH_3)_2$	0	HBr	$C_9H_{16}N_2S \cdot HBr$	N, Br	130.5–133	10,000	>10,000
6	H	CH_3	$(CH_2)_3CH_3$	0	HBr	$C_7H_{12}N_2S \cdot HBr$	N, Br	98.5–100		
7	H	H	$(CH_2)_4CH_3$	0	HBr	$C_8H_{14}N_2S \cdot HBr$	N, Br	87–92[b]	100	10,000
8	H	CH_3	$(CH_2)_4CH_3$	0	HBr	$C_9H_{16}N_2S \cdot HBr$	N, Br	91–92	10,000	>10,000
9	H	CH_3	$(CH_2)_5CH_3$	0	HBr	$C_{10}H_{18}N_2S \cdot HBr$	N, S	101.5–102.5	1,000	10,000
10	H	CH_3	$(CH_2)_5CH_3$	0	CH_3CH_2I	$C_{12}H_{23}IN_2S$	N, S	55–64	1,000	
11	5-NO_2	CH_3	$(CH_2)_5CH_3$	0		$C_{10}H_{17}N_3O_2S$	N, S	Liquid	<1	
12	5-NO_2	CH_3	$(CH_2)_5CH_3$	1		$C_{10}H_{17}N_3O_3S$	C, H	41–44	10	>1,000
13	H	CH_3	$(CH_2)_7CH_3$	0	HBr	$C_{12}H_{22}N_2S \cdot HBr$	N, Br	105–107	1,000	
14	H	CH_3	$(CH_2)_7CH_3$	1		$C_{12}H_{22}N_2OS$	C, H	Liquid	1,000	
15	H	CH_3	$(CH_2)_7CH_3$	2		$C_{12}H_{22}N_2O_2S$	C, H	Liquid	1,000	
16	5-NO_2	CH_3	$(CH_2)_7CH_3$	0		$C_{12}H_{21}N_3O_2S$	C, H	Liquid	1,000	
17	5-NO_2	CH_3	$(CH_3)_7CH_3$	1		$C_{12}H_{21}N_3O_3S$	H, C[c]	Liquid	1	
18	H	CH_3	$(CH_2)_8CH_3$	0	HBr	$C_{13}H_{24}N_2S \cdot HBr$	N, Br	109–111	1,000	
19	4-CH_3	H	$(CH_2)_8CH_3$	0		$C_{13}H_{24}N_2S$	N, S	Liquid	100	1,000
20	5-NO_2	CH_3	$(CH_2)_8CH_3$	0		$C_{13}H_{23}N_3O_2S$	C, H, N	Liquid	1	>1,000
21	H	CH_3	$(CH_2)_9CH_3$	0	HBr	$C_{14}H_{26}N_2S \cdot HBr$	N, Br	110.5–112	100	100
22	5-NO_2	CH_3	$(CH_2)_9CH_3$	0		$C_{14}H_{25}N_3O_2S$	N, S	35–37	100	>1,000
23	H	CH_3	$(CH_2)_{10}CH_3$	0	HBr	$C_{15}H_{28}N_2S \cdot HBr$	N, Br	112–114	10,000	10
24	H	H	$(CH_2)_{11}CH_3$	0	HBr	$C_{15}H_{28}N_2S \cdot HBr$	N, Br	106–110	1,000	100
25	H	CH_3	$(CH_2)_{11}CH_3$	0	HBr	$C_{16}H_{30}N_2S \cdot HBr$	N, Br	112–114	1,000	10
26	H	CH_3	$(CH_2)_{11}CH_3$	0		$C_{16}H_{30}N_2S$	N, S	Liquid	100	1
27	H	CH_3	$(CH_2)_{11}CH_3$	0	CH_3CH_2I	$C_{18}H_{35}IN_2S$	N, I	67–71	10,000	100
28	H	CH_3	$(CH_2)_{11}CH_3$	0	3,4-$Cl_2C_6H_3CH_2Cl$	$C_{23}H_{35}Cl_3N_2S$	N, S	103–107.5	100	1,000
29	5-CH_2CH_3	CH_3	$(CH_2)_{11}CH_3$	0	HBr	$C_{18}H_{34}N_2S \cdot HBr$	N, Br	90–92	100	100
30	5-NO_2	CH_3	$(CH_2)_{11}CH_3$	0		$C_{16}H_{29}N_3O_2S$	C, H	42–47.5	100	
31	5-NO_2	CH_3	$(CH_2)_{11}CH_3$	1		$C_{16}H_{29}N_3O_3S$	N, S	58–60.5	1,000	
32	5-NO_2	CH_3	$(CH_2)_{11}CH_3$	0	$CH_3(CH_2)_{11}SO_3H$	$C_{16}H_{29}N_3O_2S \cdot C_{12}H_{26}O_3S$	N, S	87–88	10	100
33	H	$(CH_2)_2CH_3$	$(CH_2)_{11}CH_3$	0		$C_{19}H_{36}N_2S$	N, S[d]	Liquid	100	100
34	H	$(CH_2)_3CH_3$	$(CH_2)_{11}CH_3$	0	HBr	$C_{18}H_{34}N_2S \cdot HBr$	N, Br	74–77	100	10
35	H	CH_3	$(CH_2)_{12}CH_3$	0	HBr	$C_{17}H_{32}N_2S \cdot HBr$	N, Br	112–114	100	10
36	H	CH_3	$(CH_2)_{12}CH(CH_3)_2$	0	HCl	$C_{19}H_{36}N_2S \cdot HCl$	N, Cl	93–96	10,000	10
37	H	CH_3	$(CH_2)_{13}CH_3$	0	HBr	$C_{18}H_{34}N_2S \cdot HBr$	N, Br	115–117	10,000	10
38	H	CH_3	$(CH_2)_{13}CH_3$	1		$C_{18}H_{34}N_2OS$	N, S	55–56	100	
39	H	CH_3	$(CH_2)_{13}CH_3$	2		$C_{18}H_{34}N_2O_2S$	C, H, N	55–56	100	
40	5-NO_2	CH_3	$(CH_2)_{13}CH_3$	0		$C_{18}H_{33}N_3O_2S$	C, H	52–53[e]	>1,000	
41	5-NO_2	CH_3	$(CH_2)_{13}CH_3$	1		$C_{18}H_{33}N_3O_3S$	C, H	85–86	1,000	
42	5-NO_2	CH_3	$(CH_2)_{13}CH_3$	2		$C_{18}H_{33}N_3O_4S$	H, C[c]	95–96.5	>1,000	
43	4-NO_2	CH_3	$(CH_2)_{13}CH_3$	0		$C_{18}H_{33}N_3O_2S$	C, H	72–73	>1,000	
44	4-NO_2	CH_3	$(CH_2)_{13}CH_3$	2		$C_{18}H_{33}N_3O_4S$	N, S	109–110	>1,000	>1,000
45	H	CH_3	$(CH_2)_{14}CH_3$	0	HBr	$C_{19}H_{36}N_2S \cdot HBr$	N, Br	113–116	100	1
46	H	CH_3	$(CH_2)_{15}CH_3$	0	HBr	$C_{20}H_{38}N_2S \cdot HBr$	N, Br	114–115	1,000	10

47	H	CH_3	$(CH_2)_{15}CH_3$	1		$C_{20}H_{38}N_2OS$	C, H, N	54–55	1,000	
48	H	CH_3	$(CH_2)_{15}CH_3$	2		$C_{20}H_{38}N_2O_2S$	C, H	65.5–67	>1,000	>1,000
49	5-NO_2	CH_3	$(CH_2)_{15}CH_3$	0		$C_{20}H_{37}N_3O_2S$	N, S	58–60.5	1,000	
50	5-NO_2	CH_3	$(CH_2)_{15}CH_3$	1		$C_{20}H_{37}N_3O_3S$	C, H	89–90.5	1,000	
51	5-NO_2	CH_3	$(CH_2)_{15}CH_3$	2		$C_{20}H_{37}N_3O_4S$	C, H	94–95.5	1,000	
52	4-NO_2	CH_3	$(CH_2)_{15}CH_3$	0		$C_{20}H_{37}N_3O_2S$	C, H	74–76.5	>1,000	
53	4-NO_2	CH_3	$(CH_2)_{15}CH_3$	1		$C_{20}H_{37}N_3O_3S$	N, S	81–82.5	>1,000	
54	H	CH_3	$(CH_2)_{17}CH_3$	0	HBr	$C_{22}H_{42}N_2S\cdot HBr$	N, Br	115–117	1,000	1,000
55	H	$(CH_2)_3CH_3$	$(CH_2)_{17}CH_3$	0	HBr	$C_{24}H_{46}N_2S\cdot HBr$	N, S	88.5–89.5	10,000	1,000
56	5-NO_2	$(CH_2)_3CH_3$	$(CH_2)_{17}CH_3$	0	$CH_3(CH_2)_{17}SO_3H$	$C_{24}H_{45}N_3O_2S\cdot C_{18}H_{38}O_3S$	N, S	100–101	1,000	>1,000
57	H	CH_3	$(CH_2)_{19}CH_3$	0	HBr	$C_{24}H_{46}N_2S\cdot HBr$	N, S	116–119	>1,000	1,000

[a] J. A. Baker, *J. Chem. Soc.*, 2387 (1958), reports mp 156°. We have no explanation for the difference. The only difference in the preparation was our use of ether as solvent while Baker used acetone. Our nmr is consistent with this structure. [b] G. Weitzel, F. Schneider, H. Guglielmi, F. Seif, W.-D. Hirschman, and J. Durst, *Hoppe-Seyler's Z. Physiol. Chem.*, **348**, 1277 (1967), report the HCl salt mp 76°. [c] C: calcd, 50.15; found, 50.56. [d] S: calcd, 9.88; found, 9.43. [e] C: calcd, 55.79; found, 56.33, 56.22.

ing, at which time heating was discontinued. The benzhydryl sulfides (Table VIII) were particularly susceptible to cleavage, resulting in the preparation of only one nitro derivative in that series.

The major nitration product was a 5-nitroimidazolyl 2-sulfide. Occasionally, nitration at the 4 position occurred, yielding 4-nitro 2-sulfides which were more susceptible to nitric acid oxidation than were the isomeric 5-nitro compounds. From these reactions either the 4-nitro sulfide, the 4-nitro sulfoxide, or both could be isolated in addition to the major 5-nitro sulfide product. Thus, sulfides **43** (Table I), **108**, **122**, **125** (Table III), and **203** (Table VI) were obtained as minor products by chromatographic separation of the nitration mixture. The 4-nitro sulfide **52** and the 4-nitro sulfoxide **53** were both isolated from the reaction which gave 5-nitro sulfide **49** as the major product, while sulfoxides **137**, **140**, **142**, **146**, **152**, and **160** were the sole 4-nitration products obtained along with the corresponding 5-nitro sulfides in the respective reactions.

The structures of the isomeric products were assigned on the basis of nmr and ir spectra. The 5-H of the 4-nitro compounds appeared downfield in the nmr spectra (DMSO-d_6) relative to the 4-H of the corresponding 5-nitro isomers, the shift being in the range of 13–33 Hz. Similar downfield shifts in the spectra of 4-nitro compounds have been reported previously for isomeric 4(5)-nitroimidazole systems.[9,10] Another characteristic nmr distinction was the downfield position of the 1-methyl singlet in the 1-methyl-5-nitro compounds relative to its position in the spectra of the 4-nitro isomer. This shift was 6–14 Hz for sulfides, 10–13 Hz for sulfoxides, and 15–16 Hz for sulfones. Such a shift can be explained by the greater electron-withdrawing effect of the 5-nitro group closer to the *N*-methyl substituent.[9,11] In the ir spectra, the distinguishing feature between 5- and 4-nitro isomers is the presence of a sharp band in the 989–998-cm^{-1} region in the spectra of all of the 4-nitro compounds (either $CHCl_3$ or KBr), which was absent in the spectra of the 5 isomers.[9]

The remaining sulfoxides not obtained by *in situ* oxidation during nitration were generally best prepared by oxidation of the corresponding sulfide with 1 equiv of *m*-chloroperbenzoic acid in $CHCl_3$.[12] An exception to this procedure was compound **133** which could be obtained only upon oxidation of **107** with $NaIO_4$ in aqueous MeOH; **134** was also prepared by this method.[13]

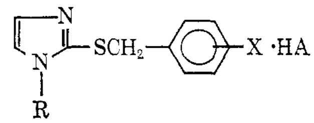
Sulfones were prepared by normal procedures from either the sulfide or sulfoxide using an excess of H_2O_2–HOAc or *m*-chloroperbenzoic acid–$CHCl_3$.

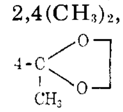
Biological Results.† The assays of primary interest in this project were the *in vitro* antiprotozoal tests against *Tritrichomonas foetus*, *Trichomonas vaginalis*, and *Tetrahymena pyriformis*. The first two gave nearly identical results, the few exceptions being within a power of ten, and were used interchangeably as indicators of activity. Activity against *T. pyriformis* was usually of a lower order of magnitude than against *T. foetus* or *T. vaginalis*.

In addition to the three protozoal assays, representative compounds were screened *in vitro* against the gram-positive bacterium *Bacillus subtilis*; the gram-negative bacteria *Escherichia coli*, *Salmonella paratyphi A*, and *Erwinia sp.*; the fungi *Trichophyton mentagrophytes*, *Candida albicans*, *Fusarium sp.*, *Verticillium albo-atrum*, and *Ceratocystis ulmi*; the alga *Chlorella vulgaris*; and the helminth *Turbatrix aceti*. These semiquantitative assays were carried out by serial dilution in the appropriate liquid media with dilution by increments of ten, with the ex-

† The conditions and media used in these tests are described more fully; see ref 14.

Table II



	R	X	HA	Formula	Analyses	Mp, °C
58	H	H	HCl	$C_{10}H_{10}N_2S\cdot HCl$	N, S	160–161.5[a]
59	CH_3	H	HCl	$C_{11}H_{12}N_2S\cdot HCl$	N, S	146–148
60	H	4-NO_2	HCl	$C_{10}H_9N_3O_2S\cdot HCl$	N, Cl	159.5–161
61	CH_3	4-NO_2	HCl	$C_{11}H_{11}N_3O_2S\cdot HCl$	N, Cl	211–212
62	CH_3	4-NO_2		$C_{11}H_{11}N_3O_2S$	N, S	72.5–78.5
63	CH_3	4-NO_2	CH_3CH_2I	$C_{13}H_{16}IN_3O_2S$	C, H, N	167–170
64	CH_2CH_2OH	4-NO_2	HCl	$C_{12}H_{13}N_3O_3S\cdot HCl$	N, S	200–202
65	CH_2CH_2OH	4-NO_2		$C_{12}H_{13}N_3O_3S$	C, H	98–98.5
66	$CH_2CH(CH_3)_2$	4-NO_2	HCl	$C_{14}H_{17}N_3O_2S\cdot HCl$	N, S	129–131
67	$(CH_2)_2CH_3$	4-NO_2	HCl	$C_{13}H_{15}N_3O_2S\cdot HCl$	N, Cl	144–146
68	CH_3	3-NO_2	HCl	$C_{11}H_{11}N_3O_2S\cdot HCl$	N, Cl	191–192
69	CH_3	2-NO_2	HCl	$C_{11}H_{11}N_3O_2S\cdot HCl$	N, S	140–142
70	CH_3	2-NO_2		$C_{11}H_{11}N_3O_2S$	C, H	81.5–84.5
71	CH_3	4-Cl, 3-NO_2	HBr	$C_{11}H_{10}ClN_3O_2S\cdot HBr$	Br, N	166–168
72	CH_3	2-Br, 4-NO_2	HBr	$C_{11}H_{10}BrN_3O_2S\cdot HBr$	C, H, Br	189–190.5
73	CH_3	4-CN	HBr	$C_{12}H_{11}N_3S\cdot HBr$	C, H	174.5–178
74	CH_3	3-CN	HBr	$C_{12}H_{11}N_3S\cdot HBr$	N, S	179.5–181.5
75	CH_3	4-$COCH_3$	HCl	$C_{13}H_{14}N_2OS\cdot HCl$	N, S	197.5–199.5
76	CH_3	3-$COCH_3$	HCl	$C_{13}H_{14}N_2OS\cdot HCl$	N, S	157.5–159
77	CH_3	2,4-$(CH_3)_2$, 5-$COCH_3$	HCl	$C_{15}H_{18}N_2OS\cdot HCl$	N, S	174–175.5
78	CH_3	2,4$(CH_3)_2$, 5-$COCH_3$		$C_{15}H_{18}N_2OS$	C, H	64–65.5
79	CH_3		HCl	$C_{15}H_{18}N_2O_2S\cdot HCl$	N, S	176–178
80	CH_3	4-$CH(CH_3)CO_2H$	HCl	$C_{14}H_{16}N_2O_2S$	N, S	128.5–133.5
81	CH_3	4-F	HCl	$C_{11}H_{11}FN_2S\cdot HCl$	N, S	145–148
82	CH_3	4-F		$C_{11}H_{11}FN_2S$	N, S	Liquid
83	CH_3	3-F	HCl	$C_{11}H_{11}FN_2S\cdot HCl$	C, H, N, Cl	151–152.5
84	CH_3	2-F	HCl	$C_{11}H_{11}FN_2S\cdot HCl$	C, H, N	133.5–134
85	CH_3	F_5		$C_{11}H_7F_5N_2S\cdot HBr$	Cl, N, S	192–195
86	CH_3	3-CF_3	HCl	$C_{12}H_{11}F_3N_2S\cdot HCl$	N, Cl	133–135
87	CH_3	3-CF_3	CH_3Br	$C_{13}H_{14}BrF_3N_2S$	N, S	155–157
88	H	4-Cl	HCl	$C_{10}H_9ClN_2S\cdot HCl$	N, S	138–140
89	CH_3	4-Cl	HCl	$C_{11}H_{11}ClN_2S\cdot HCl$	N, S	174–175.5
90	CH_3	2-Cl		$C_{11}H_{11}ClN_2S$	N, S	Liquid
91	CH_3	3,4-Cl_2	HCl	$C_{11}H_{10}Cl_2N_2S\cdot HCl$	N, Cl	159–162
92	CH_3	3,4-Cl_2	CH_3CH_2I	$C_{13}H_{15}Cl_2IN_2S$	C, H	166.5–169
93	CH_3	3,4-Cl_2		$C_{11}H_{10}Cl_2N_2S$	N, Cl	Liquid
94	CH_3	2,4-Cl_2	HCl	$C_{11}H_{10}Cl_2N_2S\cdot HCl$	N, Cl	163–166
95	CH_3	2,4-Cl_2	HNO_3	$C_{11}H_{10}Cl_2N_2S\cdot HNO_3$	N, S	135–135.5 dec
96	CH_3	2,6-Cl_2	HCl	$C_{11}H_{10}Cl_2N_2S\cdot HCl$	N, Cl	184.5–185
97	CH_3	Cl_5		$C_{11}H_7Cl_5N_2S$	C, H, Cl	155–156
98	CH_3	4-Br	HBr	$C_{11}H_{11}BrN_2S\cdot HBr$	C, H, N	158–160
99	CH_3	3-Br	HBr	$C_{11}H_{11}BrN_2S\cdot HBr$	C, H, S	142–143
100	CH_3	4-$O(CH_2)_2N(CH_2CH_3)_2$		$C_{17}H_{25}N_3OS$	N, S	Liquid
101	CH_3	3-CH_3	HCl	$C_{12}H_{14}N_2S\cdot HCl$	N, Cl	156.5–157.5
102	CH_3	4-$C(CH_3)_4$	HCl	$C_{15}H_{20}N_2S\cdot HCl$	N, Cl	190–191
103	CH_3	4-C_6H_5	HCl	$C_{17}H_{16}N_2S\cdot HCl$	C, H, N	188–189.5
104	CH_3	4-C_6H_5		$C_{17}H_{16}N_2S$	C, H, N	74.5–75
105	CH_3	2-Cl	HCl	$C_{11}H_{11}ClN_2S\cdot HCl$	N, S	158.5–160.5

[a] H. Heath, A. Lawson, and C. Rimington, *J. Chem. Soc.*, 2217 (1951), report mp 153° for the free base.

ception of the fungal tests which were done on agar. The activity level assigned is the minimum concentration at which the compound completely inhibited growth of the organism (MIC, ppm), as determined by visual examination.

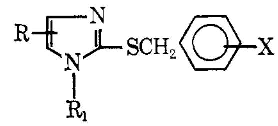
Metronidazole was screened against these organisms for comparison purposes, with the relevant results listed in Table IV.

Selected compounds were further tested for anthelmintic activity against the roundworm *Syphacia obvelata* in rats. The compound was administered to the infested rats by the intragastric route at approximately 125 mg/kg and the animals were subsequently examined for the presence of adult worms in the intestine. Only low-level activity was observed for these series of compounds in this test.

Two standard assays were used to measure antiinflammatory activity, the carrageenan-induced foot edema test and the cotton wad granuloma test. A number of compounds representing almost all the series studied showed low-level antiinflammatory activity; the most active of these were **97** and **91** (Table II).

The 5-nitro sulfides were the most active antiprotozoal compounds in each of the series produced. The 5-nitrobenzyl sulfides of Table III were of particular interest; a number were active at 1 ppm (comparable to metronidazole) and almost all at or below 100 ppm. Of the corresponding unnitrated benzyl sulfides in Table II, only **65** and **70** were inhibitory at 10 ppm, most of the remaining compounds showing minimal activity of 10^{3-4} ppm. Similarly, the most active compounds (1–10 ppm) in Table I con-

Table III



	R	R_1	X	Formula	Analyses	Mp, °C	*B. subtilis*	*Trichomonas*
106	5-NO_2	CH_3	H	$C_{11}H_{11}N_3O_2S$		100–101[a]	100	10
107	5-NO_2	CH_3	4-NO_2	$C_{11}H_{10}N_4O_4S$	N, S	139–139.5	1	<1
108	4-NO_2	CH_3	4-NO_2	$C_{11}H_{10}N_4O_4S$	N, S	145–146	100	100
109	5-CH_2CH_3	CH_3	4-NO_2	$C_{13}H_{15}N_3O_2S \cdot HCl$ 0.25$C_4H_8O_2$[b]	N, Cl	111–113	100	1
110	5-NO_2	CH_3	3-NO_2	$C_{11}H_{10}N_4O_4S$	N, S	115–116	100	1
111	5-NO_2[c]	CH_3	2-NO_2	$C_{11}H_{10}N_4O_4S$	C, H, N, S	145.4–145.6	>400	<1
112	5-NO_2	CH_3	4-Cl, 3-NO_2	$C_{11}H_9ClN_4O_4S$	C, H, N	137–140	>1,000	1
113	5-NO_2	CH_3	2-Br, 4-NO_2	$C_{11}H_9BrN_4O_4S$	C, H, S	144.5–145.5	>1,000	1
114	5-NO_2	CH_3	4-CN	$C_{12}H_{10}N_4O_2S$	S, O	185–187.5	>1,000	10
115	5-NO_2	CH_3	4-F	$C_{11}H_{10}FN_3O_2S$	N, S	141–142	>400	<1
116	5-NO_2	CH_3	3-F	$C_{11}H_{10}FN_3O_2S$	C, H, N	126.5–127.5	1,000	100
117	5-NO_2	CH_3	2-F	$C_{11}H_{10}FN_3O_2S$	C, H, S	81–82.5	1,000	10
118	5-NO_2	CH_3	4-Cl	$C_{11}H_{10}ClN_3O_2S$	N, S	114–115.5	>400	<1
119	5-NO_2	CH_3	2-Cl	$C_{11}H_{10}ClN_3O_2S$	C, H, Cl, O	103–104	>1,000	100
120	5-NO_2	CH_3	3,4-Cl_2	$C_{11}H_9Cl_2N_3O_2S$	N, S	133–134	>400	10
121	5-NO_2	CH_3	2,4-Cl_2	$C_{11}H_9Cl_2N_3O_2S$	N, S	112.5–113.5	10	10
122	4-NO_2	CH_3	2,4-Cl_2	$C_{11}H_9Cl_2N_3O_2S$	N, S	145–147	10,000	1000
123	5-NO_2	CH_3	2,5-Cl_2	$C_{11}H_9Cl_2N_3O_2S$	C, H, N	126.5–127.1	>1,000	100
124	5-NO_2	CH_3	2,6-Cl_2	$C_{11}H_9Cl_2N_3O_2S$	C, H	90–91	1,000	100
125	4-NO_2	CH_3	2,6-Cl_2	$C_{11}H_9Cl_2N_3O_2S$	C, H	126–127	>1,000	>1000
126	5-NO_2	CH_3	Cl_5	$C_{11}H_6Cl_5N_3O_2S$	Cl, C, H	168–169	>1,000	100
127	5-NO_2	CH_3	4-Br	$C_{11}H_{10}BrN_3O_2S$	C, H, Br, N, S	123–125	>1,000	1000
128	5-NO_2	CH_3	3-Br	$C_{11}H_{10}BrN_3O_2S$	Br, N	105–106	>1,000	1000
129	5-NO_2	CH_3	2-Br	$C_{11}H_{10}BrN_3O_2S$	C, H, N	101–102	1,000	100
130	5-NO_2	CH_3	3-CF_3	$C_{13}H_{15}N_3O_2S$	N, S	87–88	1,000	100
131	5-NO_2	CH_3	4-$C(CH_3)_3$	$C_{15}H_{19}N_3O_2S$	C, H, N	105.5–107.5	>1,000	1

[a] D. W. Henry, U. S. Patent 3,341,549 (Sept 12, 1967) reports mp 100–101°. [b] Solvated with 0.25 mol of dioxane. [c] Nitrated by the H_2SO_4–HNO_3 procedure.

tained a 5-nitro group. In this series, however, the length of the alkyl group seems to be an additional activity-determining factor.

The number of very active compounds decreases progressively as the 5-nitrobenzyl sulfides are oxidized to sulfoxides (Table IV) and then to sulfones (Table V). No structural correlation was observed that might account for the much wider range of activity levels in these sulfoxides and sulfones. In the alkyl series in Table I, two 5-nitroalkyl sulfoxides, **12** and **17**, were active at 10 and 1 ppm, respectively, the remainder being much less active.

The aralkyl compounds in Table VI and the benzhydryl compounds in Table VIII were generally less potent in the antiprotozoal tests than were their benzyl analogs in Table III, the highest being of the order of 100 ppm. In Table VII the most interesting compounds were the 5-nitro-2-furyl derivatives because of the expected antimicrobial activity associated with such structures.[15] Compound **213** was active against all four bacteria at 1 ppm, **207** at 10–100 ppm, and **210** at 100–1000 ppm; **207**, **210**, and **213** were also active agaist *T. foetus* at 10, 100, and 100 ppm, respectively. The activity of the carboxyalkyl compounds in Table IX depends not only on the presence of a 5-nitro group and an unoxidized sulfur but also on the nature of the carboxy function; *e.g.*, the free acid with a 10-carbon alkyl chain (**239**) was very active, whereas the corresponding methyl ester was completely inactive (**240**).

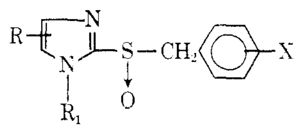
4-Nitrobenzyl sulfides are less active than the 5 isomers by a factor of 10–100 (Table III), whereas the 4-nitro sulfoxides (Table IV) are usually as active as the 5 isomers. In marked contrast to the significant activity of some of these 4-substituted compounds, the alkyl sulfides, sulfoxides, and sulfones of Table I which were nitrated at the 4 position are almost totally inactive. Similar variable activities in other 4-nitroimidazole series have been reported.[9,11,16,17]

Regarding activities in the other antimicrobial screens, the compounds in Tables I and II showed a broad spectrum of low-level activity in most of the tests used (except the 4-nitro compounds in Table I, which were devoid of activity). The 5-nitrobenzyl sulfides of Table III were very specifically active against only protozoa, whereas the corresponding benzyl sulfoxides and sulfones (Tables IV and V) were generally much more potent antibacterial and antifungal agents than even the unnitrated sulfides. In addition to the activities listed in Tables IV and V against *T. mentagrophytes*, a number of these compounds were moderately active against *Fusarium sp.*, *V. albo-atrum*, and *C. ulmi*. In Table VI, the sulfoxide **204** and the sulfone **205** have greater antifungal activities than any of the sulfides, at 1 ppm each against both *T. mentagrophytes* and *V. Albo-atrum;* **204** is also active at 10 ppm against *Fusarium sp.* There is a scattering of low-level antibacterial and antifungal activities in the remainder of the compounds, those in Table IX having more antibacterial properties than antifungal. Unfortunately, very little activity against *C. albicans* was observed in any of these compounds.

The greatest anthelmintic activity was observed in the long-chain alkyl sulfides of Table I (see activities listed). These compounds were not particularly active against *S. obvelata*, however.

Variation of the substituent at the 1 position of the imidazole ring appeared to have little influence on the antiprotozoal activity. For example, the alkyl sulfides **28**, **33**, and **34** in which the 1 substituent is CH_3, Pr, and Bu, respectively, are all active at 100 ppm against *T. foetus*. Similarly, from Table II, **61**, **64**, **66**, and **67** with the 1

Table IV



	R	R₁	X	Formula	Analyses	Mp, °C	*B. subtilis*	*Trichomonas*	*T. pyriformis*	*T. mentagrophytes*
132	H	CH_3	4-NO_2	$C_{11}H_{11}N_3O_3S$	C, H, N	164–165	1000	1000	1000	1000
133	5-NO_2	CH_3	4-NO_2	$C_{11}H_{10}N_4O_5S$	C, H, N	170.5–171.5	>400	10	<1	10
134	4-NO_2	CH_3	4-NO_2	$C_{11}H_{10}N_4O_5S$	N, S	149–151	>400	<1	>1000	>1000
135	H	CH_2CH_2OH	4-NO_2	$C_{12}H_{13}N_3O_4S$	C, H, N	145–146	1000	100	>1000	1000
136	5-NO_2	CH_3	3-NO_2	$C_{11}H_{10}N_4O_5S$	C, H, S	175–177.5	100	10	1000	10
137	4-NO_2	CH_3	3-NO_2	$C_{11}H_{10}N_4O_5S$	C, H, N	139–140	400	10		1000
138	5-NO_2	CH_3	2-NO_2	$C_{11}H_{10}N_4O_5S$	C, H, N	140.5–142	100	10	10	100
139	5-NO_2	CH_3	4-Cl, 3-NO_2	$C_{11}H_9ClN_4O_5S$	C, H, S	175.5–177	>1000	100	1000	1000
140	4-NO_2	CH_3	4-Cl, 3-NO_2	$C_{11}H_9ClN_4O_5S$	C, H, S	171.5–173	>1000	1	1000	1000
141	5-NO_2	CH_3	2-Br, 4-NO_2	$C_{11}H_9BrN_4O_5S$	C, H, S	158–160	1000	1	100	10
142	4-NO_2	CH_3	2-Br, 4-NO_2	$C_{11}H_9BrN_4O_5S$	Br, C, H	144–145	>1000	100	>1000	1000
143	H	CH_3	4-F	$C_{11}H_{11}FN_2OS$	N, S	83–84	1000	>1000	1000	>1000
144	5-NO_2	CH_3	4-F	$C_{11}H_{10}FN_3O_3S$	C, H, N	146.5–147.5	>400	10	10	10
145	5-NO_2	CH_3	3-F	$C_{11}H_{10}FN_3O_3S$	C, H, N	123–124	100	10	10	1
146	4-NO_2	CH_3	3-F	$C_{11}H_{10}FN_5O_3S$	C, H, N	155–156	1000	100	>1000	>1000
147	5-NO_2	CH_3	2-F	$C_{11}H_{10}FN_3O_3S$	C, H, N	114–115	100	10	10	10
148	5-NO_2	CH_3	F_5	$C_{11}H_6F_5N_3O_3S$	C, H, S	126–127	1000	100	10	10
149	5-NO_2	CH_3	4-Cl	$C_{11}H_{10}ClN_3O_3S$	C, H, N	163.5–165	25	100		10
150	H	CH_3	2-Cl	$C_{11}H_{11}ClN_2OS$	C, H, N	87–89	>400	>1000		1000
151	5-NO_2	CH_3	2-Cl	$C_{11}H_{10}ClN_3O_3S$	C, H, N	130.5–132	<6	100		<1
152	4-NO_2	CH_3	2-Cl	$C_{11}H_{10}ClN_3O_3S$	C, H, S	150.5–152.5	1000	100	>1000	>1000
153	5-NO_2	CH_3	3,4-Cl_2	$C_{11}H_9Cl_2N_3O_5S$	N, S	128–129	>400	100	100	<1
154	5-NO_2	CH_3	2,4-Cl_2	$C_{11}H_9Cl_2N_3O_3S$	C, H, N	125–127.5	<6	100	10	<1
155	5-NO_2	CH_3	2,5-Cl_2	$C_{11}H_9Cl_2N_3O_3S$	Cl, C, H	162.5–164.5	1000	100	1000	1
156	5-NO_2	CH_3	2,6-Cl_2	$C_{11}H_9Cl_2N_3O_3S$	C, H, S	140–141	100	10	10	1
157	5-NO_2	CH_3	Cl_5	$C_{11}H_6Cl_5N_3O_3S$	Cl, C, H	167–168	>1000	1000	>1000	
158	H	CH_3	4-Br	$C_{11}H_{11}BrN_2OS$	N, S	112–113	>1000	>1000	1000	1000
159	5-NO_2	CH_3	4-Br	$C_{11}H_{10}BrN_3O_3S$	C, H, N	171–173	<6	10		<1
160	4-NO_2	CH_3	4-Br	$C_{11}H_{10}BrN_3O_3S$	C, H	145–146		10		100
161	5-NO_2	CH_3	3-Br	$C_{11}H_{10}BrN_3O_3S$	Br, C, H	130–131.5	1000	100	100	10
162	5-NO_2	CH_3	2-Br	$C_{11}H_{10}BrN_3O_3S$	Br, C, H	134–135	100	100	100	10
163	H	CH_3	4-$C(CH_3)_3$	$C_{15}H_{20}N_2OS \cdot CHO_2$[a]	C, H, S	101–103	1000	1000	100	1000
164	5-NO_2	CH_3	4-$C(CH_3)_3$	$C_{15}H_{19}N_3O_3S$	C, H	114–114.5	1000	100	1000	10
Metronidazole							1000	1		

[a] $0.5C_2H_2O_4$ salt.

substituent being CH_3, CH_2CH_2OH, *sec*-Bu, and *n*-Pr, respectively, were active at 10–100 ppm in the same test. More variation of activities occurred in other tests but not in a discernible pattern.

Preliminary *in vivo* testing on selected compounds active against *Trichomonas* at or below 10 ppm *in vitro* was conducted as follows. Compound was administered intraperitoneally to mice infected subcutaneously with *T. foetus*, on a standard regimen of 100 mg/kg/day for 5 days. The compound was considered active if no organisms were cultured from the subcutaneous lesion site 3 days after last injection of test compound. Several compounds which showed activity were retested at 200 mg/kg; a few were also retested at 25 and 50 mg/kg. The activity level was generally lower than that of metronidazole, the most active compounds being the nitrobenzyl sulfides, sulfoxides, and sulfones.

Conclusions

Achieving potency against a range of organisms is a complex function of structural parameters and action mechanisms. Our results indicate that maximal activity in these series against a particular organism is achieved at the expense of general efficacy. This may well be due to differing mechanisms of action for the various organisms tested; it is noteworthy in this respect that metronidazole seems to be active primarily against anaerobic organisms, including *Trichomonas*.

Experimental Section‡

Starting Materials. **2-Mercapto-1-methylimidazole** was obtained from Aldrich Chemical Co.; compounds with different alkyl groups were prepared by method A of Jones, *et al.*[18]

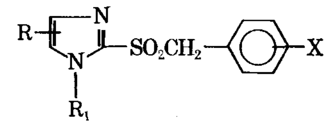
2-(α-Chloro-*p*-tolyl)-2-methyl-1,3-dioxolane was obtained by chloromethylation of the dioxolane derivative of acetophenone. After conversion to the thioimidazole derivative, the dioxolane ring was hydrolyzed by heating in aqueous solution. A mixture of 3-(4-nitrophenyl)propyl bromide and 3-(2,4-dinitrophenyl)propyl bromide was obtained by nitration of 3-phenylpropyl bromide and separated by chromatography on silica gel.

Sample Preparations. **2-(10-Carboxydecylthio)-1-methylimidazole Hydrobromide (238).** 2-Mercapto-1-methylimidazole (11.4 g, 0.1 mol), 26.5 g (0.1 mol) of 11-bromoundecanoic acid, and 50 ml of *i*-PrOH were heated 18 hr on the steam bath. Et_2O was added to the residue which was filtered to yield 36.5 g (96%) of the title compound, mp 104–105°. Alkylations with benzyl halides were usually complete in 2 hr. Generally, yields in the alkylations ran in the 70–90% range. Many of the compounds crystallized analytically pure. When recrystallization was necessary, *i*-PrOH or a mixture of MeOH–*i*-PrOH were the most satisfactory solvents.

2-Hexadecyl-1-methyl-5-nitroimidazole (49). 2-Hexadecylthio-1-methylimidazole (56.7 g, 0.17 mol) was heated with 105 ml of HNO_3 (1.7 mol) and 45 ml of H_2O. An exothermic reaction occurred and a waxy solid separated. This was dissolved in CH_2Cl_2 and an aqueous layer was discarded. The organic solution was

‡ Melting points (uncorrected) 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.

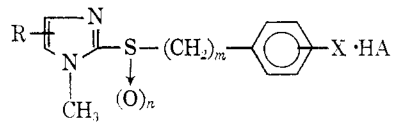
Table V



	R	R_1	X	Formula	Analyses	Mp, °C	*B. subtilis*	*Trichomonas*	*T. pyriformis*	*T. mentagrophytes*
165	H	CH_3	H	$C_{11}H_{12}N_2O_2S$	C, H, N	109.5–110	>1000	>1000	1000	>1000
166	5-NO_2	CH_3	H	$C_{11}H_{11}N_3O_4S$	C, H, N	160–161[a]	>1000	1000	1000	1
167	H	CH_3	4-NO_2	$C_{11}H_{11}N_3O_4S$	C, H, N, S	155.5–156	>1000	>1000	1	>1000
168	H	CH_2CH_2OH	4-NO_2	$C_{12}H_{13}N_3O_5S$	C, H, N	159.8–160.1	>1000	1000	>1000	>1000
169	5-NO_2	CH_3	4-NO_2	$C_{11}H_{10}N_4O_6S$	N, S	175.5–176.5	>400	100	100	100
170	H	CH_3	3-NO_2	$C_{11}H_{11}N_3O_4S$	C, H, N	134–136	>400	1000		>1000
171	5-NO_2	CH_3	3-NO_2	$C_{11}H_{10}N_4O_6S$	N, S	177–179	>400	10	1	10
172	4-NO_2	CH_3	3-NO_2	$C_{11}H_{10}N_4O_6S$	N, S	193.5–194.5	>400	10	>1000	>1000
173	5-NO_2	CH_3	2-NO_2	$C_{11}H_{10}N_4O_6S$	C, H, N	149–151	100	100		10
174	H	CH_3	4-Cl, 3-NO_2	$C_{11}H_{10}ClN_3O_4S$	C, H, N	157.8–158.6	>1000	1000	>1000	1000
175	5-NO_2	CH_3	4-Cl, 3-NO_2	$C_{11}H_9ClN_4O_6S$	C, H, S	164–165.5	>1000	1000	>1000	10
176	H	CH_3	4-F	$C_{11}H_{11}FN_2O_2S$	C, H, N	90–91	25	1000		1000
177	5-NO_2	CH_3	4-F	$C_{11}H_{10}FN_3O_4S$	N, S	130.5–131.5	100	100		<1
178	5-NO_2	CH_3	3-F	$C_{11}H_{10}FN_3O_4S$	C, H, N	123.5–124.1	1000	1000	100	1
179	5-NO_2	CH_3	2-F	$C_{11}H_{10}FN_3O_4S$	C, H, S	129–131	1000	100	10	1
180	5-NO_2	CH_3	4-Cl	$C_{11}H_{10}ClN_3O_4S$	N, S	138–139	400	100		10
181	H	CH_3	2-Cl	$C_{11}H_{11}ClN_2O_2S$	C, H, N	95.8–97	>1000	>1000	>1000	>1000
182	5-NO_2	CH_3	2-Cl	$C_{11}H_{10}ClN_3O_4S$	C, H, N	157–159	400	10	100	<1
183	H	CH_3	3,4-Cl_2	$C_{11}H_{10}Cl_2N_2O_2S$	N, S	105–106.5	>400	>1000		1000
184	5-NO_2	CH_3	3,4-Cl_2	$C_{11}H_9Cl_2N_3O_4S$	N, S	138–140	>400	1000		>1000
185	5-NO_2	CH_3	2,4-Cl_2	$C_{11}H_9Cl_2N_3O_4S$	C, H, N	147–148	>400	>1000		<1
186	5-NO_2	CH_3	2,5-Cl_2	$C_{11}H_9Cl_2N_3O_4S$	C, H, N	183–184	>1000	10	1000	1
187	5-NO_2	CH_3	2,6-Cl_2	$C_{11}H_9Cl_2N_3O_4S$	Cl, N, S	176–178	1000	100	100	1
188	4-NO_2	CH_3	2,6-Cl_2	$C_{11}H_9Cl_2N_3O_4S$	Cl, S[b]	206–207	>1000	1000	>1000	>1000
189	H	CH_3	Cl_5	$C_{11}H_7Cl_5N_2O_2S$	Cl, C, H	218–219	>1000	>1000	>1000	>1000
190	H	CH_3	4-Br	$C_{11}H_{11}BrN_2O_2S$	C, H, N	143–144.5	>1000	>1000	>1000	1000
191	5-NO_2	CH_3	4-Br	$C_{11}H_{10}BrN_3O_4S$	C, H, N	153–154.5	>400	100		<1
192	5-NO_2	CH_3	3-Br	$C_{11}H_{10}BrN_3O_4S$	Br, C, H	160.5–161.5	>1000	100	100	1
193	5-NO_2	CH_3	CF_3	$C_{12}H_{10}F_3N_3O_4S$	C, H, N	158–159	>400	100		<1
194	H	CH_3	4-$C(CH_3)_3$	$C_{15}H_{20}N_2O_2S$	C, H, N	129–131	>1000	>1000	10	>1000
195	5-NO_2	CH_3	4-$C(CH_3)_3$	$C_{15}H_{19}N_3O_4S$	C, H, N	136–137	>1000	1000	1000	>1000
196	H	CH_3	4-C_6H_5	$C_{17}H_{16}N_2O_2S$	C, H, S	153–155	>1000	>1000	>1000	>1000
197	H	CH_3	2,4-$(CH_3)_2$, 5-$COCH_3$	$C_{15}H_{18}N_2O_3S$	N, S	115.5–116.5	>400			>1000

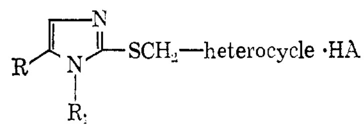
[a] W. D. Henry, U. S. Patent 3,341,549 (Sept 12, 1967) reports mp 164–165°. [b] S: calcd, 9.16; found, 9.57.

Table VI



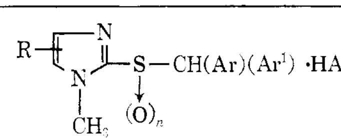
	R	m	n	X	HA	Formula	Analyses	Mp, °C
198	H	2	0	4-NO_2	HBr	$C_{12}H_{13}N_3O_2S\cdot HBr$	C, H, Br	159–161
199	H	3	0	4-NO_2	HBr	$C_{13}H_{15}N_3O_2S\cdot HBr$	C, H, S	158.5–160
200	H	3	0	2,4-$(NO_2)_2$	HBr	$C_{13}H_{14}N_4O_4S\cdot HBr$	N, S	135.5–137
201	H	3	2	2,4-$(NO_2)_2$		$C_{13}H_{14}N_4O_6S$	C, H, N	140–142.5
202	5-NO_2	3	0	H		$C_{13}H_{15}N_3O_2S$	C, H	76–76.5
203	4-NO_2	3	0	H		$C_{13}H_{15}N_3O_2S$	C, H	69–70
204	5-NO_2	3	1	H		$C_{13}H_{15}N_3O_3S$	C, H, N	76.5–78.5
205	5-NO_2	3	2	H		$C_{13}H_{15}N_3O_4S$	C, H, N	93–94

Table VII



	R	R_1	Heterocycle	HA	Formula	Analyses	Mp, °C
206	H	H	2-Furyl	HCl	$C_8H_8N_2OS\cdot HCl$	N, Cl	137.5–138
207	H	H	5-Nitro-2-furyl	HCl	$C_8H_7N_3O_3S\cdot HCl$	N, Cl	210–212 dec
208	H	$CH_2CH_2CH_3$	2-Furyl		$C_{11}H_{14}N_2OS$	N, S	Liquid
209	H	CH_3	3,5-$(Cl)_2$-2-furyl	HCl	$C_9H_8Cl_2N_2S_2\cdot HCl$	N, Cl	123–127
210	H	$CH_2CH_2CH_3$	5-Nitro-2-furyl		$C_{11}H_{13}N_3O_3S$	N, S	Liquid
211	CH_2CH_3	CH_3	2-Furyl	HCl	$C_{11}H_{14}N_2OS\cdot HCl$	N, Cl	118–120
212	H	CH_3	2-Furyl	HCl	$C_9H_{10}N_2OS\cdot HCl$	N, Cl	107–109
213	H	CH_3	5-Nitro-2-furyl	HCl	$C_9H_9N_3O_3S\cdot HCl$	N, Cl	158.5–159 dec
214	H	CH_3	2-Pyridyl	2HCl	$C_{10}H_{11}N_3S\cdot 2HCl$	N, S	217–219
215	H	CH_3	4-Pyridyl	2HCl	$C_{10}H_{11}N_3S.2HCl$	Cl, S	192–194
216	H	CH_3	2-Thienyl		$C_9H_{10}N_2S_2$	N, S	Liquid
217	H	$CH_2CH_2CH_3$	4-Pyridyl	2HCl	$C_{12}H_{15}N_3S\cdot 2HCl$	N, Cl	212.5–214 dec

Table VIII

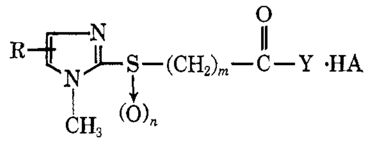


	R	n	Ar	Ar^1	HA	Formula	Analyses	Mp, °C	*Trichomonas*	*T. pyriformis*
218	H	0	C_6H_5	C_6H_5	$C_2H_2O_4$	$C_{17}H_{16}N_2S\cdot C_2H_2O_4$	C, H, N	137.5–139	>1,000	1000
219	H	0	C_6H_5	4-ClC_6H_4		$C_{17}H_{15}ClN_2S$	C, H, N	113.5–114.5	10,000	>1000
220	H	0	C_6H_5	4-ClC_6H_4	HCl	$C_{17}H_{15}ClN_2S\cdot HCl$	C, H, N	185–186	1,000	100
221	H	2	C_6H_5	4-ClC_6H_4		$C_{17}H_{15}ClN_2O_2S$	C, H, N	138–139	>1,000	>1000
222	H	0	4-BrC_6H_4	4-BrC_6H_4	HBr	$C_{17}H_{14}Br_2N_2S\cdot HBr$	Br, S	201–202	>1,000	1000
223	H	0	C_6F_5	C_6F_5		$C_{17}H_6F_{10}N_2S$	C, H, N	99.5–100	>1,000	>1000
224	5-NO_2	0	C_6F_5	C_6F_5		$C_{17}H_5F_{10}N_3O_2S$	N, S	126–128	1,000	1000
225	5-NO_2	1	C_6F_5	C_6F_5		$C_{17}H_5F_{10}N_3O_3S$	N, S	118–119	100	>1000
226	H	0	9-Fluorenyl		HBr	$C_{17}H_{14}N_2S\cdot HBr$	Br, C, H	227–228	100	10
227	H	2	9-Fluorenyl		0.5$(C_2H_2O_4)$	$C_{17}H_{14}N_2O_2S\cdot CHO_2$	C, H, N	160–163	>1,000	1000

washed with $NaHCO_3$ solution and a solid formed as a copious evolution of gas occurred. The solid was discarded and the organic layer was evaporated. The residue was triturated with MeOH. The title compound separated, 15.7 g, mp 58–60.5°. The filtrate was evaporated and the residue was dissolved in benzene and chromatographed on 2400 g of silica gel (Mallinckrodt, CC-7). From the benzene eluates an additional 3.4 g (total 30%) of the title compound was obtained. From the 2% EtOAc eluates the 4-nitro isomer, 0.8 g (1%), mp 79–80°, was obtained. Starting material was recovered from the 5% EtOAc eluates (2% recovery). From the 10% EtOAc eluates, 3.3 g (5% yield) of 2-hexadecyl sulfinyl-1-methyl-5-nitroimidazole was crystallized, mp 81–82.5°. The nitration yield in this reaction was typical. No effort was made to vary conditions and achieve maximum yields. Chromatography was often necessary to separate the 4-nitro product(s). MeOH–CH_2Cl_2 is a good solvent pair for benzylthionitroimidazoles, while hexane is useful for the alkylthio compounds.

2-Hexadecylsulfonyl-1-methyl-5-nitroimidazole (51). 2-Hexadecylthio-1-methyl-5-nitroimidazole (3.8 g, 0.01 mol) was dissolved in 15 ml of $CHCl_3$. *m*-Chloroperbenzoic acid (5.1 g, 0.02 mol of 67.5% material) was added with swirling and cooling. A solid formed which was separated and discarded. The filtrate was diluted with CH_2Cl_2, washed with Na_2CO_3 solution, dried, and evaporated. The title compound crystallized, 2.8 g (67%), mp 94–95°. Yields in the oxidation of sulfides to sulfones generally were in the 70–90% range. Many of them were purified by filtration in

Table IX



	R	n	m	Y	HA	Formula	Analyses	Mp, °C
228	5-NO_2	0	2	OH		$C_7H_9N_3O_4S$	C, H	134.5–136
229	5-NO_2	1	2	OH		$C_7H_9N_3O_5S$	C, H	130–134.5
230	5-NO_2	2	2	OH		$C_7H_9N_3O_6S$	C, H	161.5–163.5 dec
231	H	0	4	OH		$C_9H_{14}N_2O_2S$	C, H	84.5–85.5
232	H	0	4	OH	HCl	$C_9H_{14}N_2O_2S\cdot HCl$	N, S	109–109.5
233	5-NO_2	0	4	OH		$C_9H_{13}N_3O_4S$	N, S	173.5–175
234	H	1	4	OH	$C_6H_5CH_2$–S–$(NH_2)C(NH)\cdot H_2O$	$C_9H_{14}N_2O_3S\cdot H_2O\cdot C_8H_{10}N_2S$	C, H	148–149
235	5-NO_2	1	4	OH		$C_9H_{13}N_3O_5S$	N, S	Liquid
236	H	2	4	OH		$C_9H_{14}N_2O_4S$	C, H	109–111
237	5-NO_2	2	4	OH		$C_9H_{13}N_3O_6S$	N, S	141–142
238	H	0	10	OH	HBr	$C_{15}H_{26}N_2O_2S\cdot HBr$	C, H	104.5–105
239	5-NO_2	0	10	OH		$C_{15}H_{25}N_3O_4S$	C, H	113.5–114
240	5-NO_2	0	10	OCH_3		$C_{16}H_{27}N_3O_4S$	N, S	80.5–82
241	5-NO_2	1	10	OCH_3		$C_{16}H_{27}N_3O_5S$	C, H	74–76
242	5-NO_2	2	10	OCH_3		$C_{16}H_{27}N_3O_6S$	C, H	74–78
243	H	0	1	OCH_2CH_3	HBr	$C_8H_{12}N_2O_2S\cdot HBr$	N, S	128–130
244	H	0	1	NH_2	HCl	$C_6H_9N_3OS\cdot HCl$	N, S	139–140
245	H	0	1	NC_4H_8		$C_{10}H_{15}N_3OS$	C, H, N	Liquid
246	H	0	1	NHC_6H_5		$C_{12}H_{13}N_3OS$	C, H	115.5–117
247	H	0	1	NHC_6H_5	HCl	$C_{12}H_{13}N_3OS\cdot HCl$	N, S	161–162.5
248	H	1	1	NHC_6H_5		$C_{12}H_{13}N_3O_2S$	C, H	153–154.5
249	H	2	1	NHC_6H_5	$2H_2O$	$C_{12}H_{13}N_3O_3S\cdot 2H_2O$	N, S	164.5–165.5 dec
250	H	0	1	NHC_6H_4-*p*-Cl	HCl	$C_{12}H_{12}ClN_3OS\cdot HCl$	N, S	182–184
251	H	0	1	NHC_6H_4-*p*-NO_2	HCl	$C_{12}H_{12}N_4O_3S\cdot HCl$	N, S	240–241 dec
252	H	0	1	C_6H_5	HBr	$C_{12}H_{12}N_2OS\cdot HBr$	N, S	160–160.5
253	H	0	1	C_6H_4-*p*-Br	HBr	$C_{12}H_{11}BrN_2OS\cdot HBr$	C, H	182.5–184.5
254	H	0	1	C_6H_4-*o*-NO_2	HBr	$C_{12}H_{11}N_3O_3S\cdot HBr$	N, S, Br	187.5–188.5
255	H	0	1	C_6H_4-*p*-NO_2	HBr	$C_{12}H_{11}N_3O_3S\cdot HBr$	N, S	198–201 dec

a 1:1 $CHCl_3$–MeOH solution through neutral alumina. This was followed by concentration and cooling.

Sulfoxides were prepared by the same method using only 1 equiv of *m*-chloroperbenzoic acid and careful addition with adequate cooling to avoid partial oxidation to sulfone. Chromatography in benzene–EtOAc systems on silica gel (Mallinckrodt, CC-7) was often necessary to remove traces of sulfones and *m*-chlorobenzoic acid. Yields were usually in the 50–80% range.

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