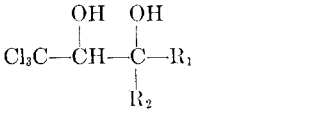
0.1 ml/10 g of body weight. The ED_{50}'s were derived from "eye-fit" linear plots on probit paper. The results of these tests are listed in Table I.

TABLE I
PHARMACOLOGICAL SCREENING RESULTS[a]



Test compounds	R_1	R_2	Isomer	ED_{50}, mg/kg Ip	ED_{50}, mg/kg Po	LD_{50}, mg/kg Ip	LD_{50}, mg/kg Po
Chloral hydrate				317	510	1050	1500
1	CH_3	H	Threo	280	310	>640	1180
2	CH_3	H	Erythro	250	480	>640	1400
3	CH_3	CH_3		480		>640	
4	C_3H_7	H		450		>640	

[a] One of the more significant findings was that the *threo*-1,1,1-trichlorobutane-2,3-diol (**1**) was as potent orally as ip.

Experimental Section

Melting points, obtained on a Thomas-Hoover capillary melting point apparatus, are uncorrected. Ir spectra were recorded on a Perkin-Elmer 137 ir spectrometer. The dipole moments were determined in PhH using a Sargent oscillometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

***threo*- and *erythro*-1,1,1-Trichlorobutane-2,3-diols (1 and 2).**—To a suspension of LAH (43.5 g, 1.14 moles) in Et_2O (2.5 l) was added a soln of 1,1,1-trichloro-3-acetoxybutan-2-one (296.85 g, 1.27 moles) in Et_2O (500 ml). After the completed addition the reaction mixt was stirred at reflux temp for 24 hr. Usual work-up yielded 232.0 g of dark oil. Vpc analysis indicated the presence of 2 major components, present to the extent of 61.2% and 28.7%. These components were separated by fractional distn using a 12.5-cm column filled with glass helices followed by fractional crystns. In this way the threo isomer **1** was isolated from $CHCl_3$ in 99.8% purity [bp 72.5° (1.45 mm), mp 62–63°] and the erythro isomer **2** in 98.2% purity [bp 76° (1.2 mm), mp 85.5–87°] measured by vpc analysis: threo isomer **1**, *anal.* ($C_4H_7Cl_3O_2$) C, H, Cl; erythro isomer **2**, *anal.* ($C_4H_7Cl_3O_2$) C, H, Cl.

1,1,1-Trichloro-3-methylbutane-2,3-diol (3).—To a suspension of LAH (slight excess) in Et_2O (400 ml) was added a soln of 1,1,1-trichloro-3-acetoxy-3-methylbutan-2-one[1] (90 g, 0.037 mole) in Et_2O (100 ml), and the reaction mixt was stirred at room temp for 40 hr. The oil obtained from the work-up was purified first by distn, bp 68–72° (0.1 mm), then by recrystn of the solidified distillate from CCl_4–heptane (1:1). The diol **3** melted at 57–58° and weighed 5.2 g (68% yield). *Anal.* ($C_5H_9Cl_3O_2$) C, H, Cl.

1,1,1-Trichlorohexane-2,3-diol (4).—To a suspension of LAH (slight excess) in Et_2O (400 ml) was added a soln of 1,1,1-trichloro-3-acetoxyhexan-2-one [prepd from hex-1-yn-3-ol by the same method as reported by Bowman and coworkers, bp 48.5° (0.035 mm)] (15.0 g, 0.0575 mole) in Et_2O (100 ml). After the completed addition (20 min), the reaction mixt was stirred at room temp for an additional 30 min and acidified with HCl, the org layer was sepd, dried ($MgSO_4$), concd, distd, and, when the distillate solidified, crystd from CCl_4 giving 1.2 g of **4**, bp 94–105° (0.5–0.6 mm), mp 75–77.5°. *Anal.* ($C_6H_{11}Cl_3O_2$) C, H, Cl.

Acknowledgments.—The author wishes to thank Dr. K. Doebel for many helpful discussions, Dr. P. Nicolson and associates of the Analytical Research Department for the microanalytical and spectral results, and Dr. J. Saelens of the Pharmacology Department for the pharmacological results. The author is also indebted to Mr. H. Tomaselli and Mrs. V. Bedenko for their technical assistance.

Synthesis and Antimicrobial Evaluation of Some 5-(5-Nitrofurylidene)rhodanines, 5-(5-Nitrofurylidene)thiazolidine-2,4-diones, and Their Vinylogs[1]

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This paper describes the synthesis and antimicrobial evaluation of 5-(5-nitrofurylidene)rhodanines and 5-(5-nitrofurylidene)thiazolidine-2,4-diones substituted in the 3 position with the object of modifying the solubility, physical properties, and microbial reduction pattern in the series. Some vinylogs of these compounds were also prepared. The antibacterial, antiprotozoal, and antifungal activities of these compounds were compared with those of some commercially available drugs and correlations of structure with the activity in this series of compounds are discussed.

The synthesis of 5-(5-nitrofurylidene)rhodanine (**1**) was reported by Sasaki[2] in 1954. Owing to its poor water solubility **1** appeared to lack promise as an antibacterial agent. Later, however, Koschucharoff[3] found it to be the most active of a series of 5-nitrofurylidene derivatives tested against a variety of fungi, including *Candida albicans*, *Trichophyton*, *Epidermophyton*, and *Microspora*. Antibacterial activity of **1** against *Escherichia coli* and *Staphylococcus aureus* with dilutions of 1:4000 to 1:8000 was also observed. This paper describes the synthesis and microbiological evaluation of 5-(5-nitro-2-furylidene)rhodanines substituted in the 3 position with the object of modifying the solubility, physical properties, and microbial reduction of the NO_2 group of **1**.[4] Further modification in the sta-

(1) Abstracted in part from the Ph.D. Thesis of S. K. Mallick, Chelsea College of Science, University of London, London, England, 1966.

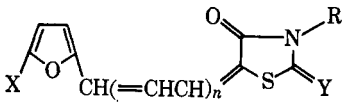
(2) T. Sasaki, *Chem. Pharm. Bull.*, **2**, 104 (1954).

(3) (a) P. Koschucharoff, *Pharmazie*, **15**, 492 (1960); (b) P. Koschucharoff and T. Harisanova, *ibid.*, **17**, 134 (1962).

(4) Subsequent to the completion of this work, E. Jeney and T. Z. Solnai, *Arch. Exp. Veterinaermed.*, **21**, 259 (1967), reported **2**, **3**, **7**, **8**, and **12** (Table I) to possess no appreciable activity against *Staph. aureus*, *Strep. pyogenes*, *Staph. albus*, *Sh. dysenteriae*, *Sal. typhosa*, *E. coli*, *A. aerogenes*, and *P. vulgaris*. The yields of these compounds were low and some of the melting points did not agree to those made in our laboratory. The comparative data are presented in footnote *b*, Table I.

TABLE I

5-(5-NITRO-2-FURYLIDENE)- AND 5-(5-NITROFURYLACRYLIDENE)RHODANINES AND -THIAZOLIDINE-2,4-DIONES



No.	X	Y	n	R	Mp, °C	% yield	Formula	Anal.
1	NO_2	S	O	H	201–202[a]	90–98		
2	NO_2	S	O	CH_3	192–193[b]	90	$C_9H_6N_2O_4S_2$	C, H, S
3	NO_2	S	O	C_2H_5	151[b]	55–66	$C_{10}H_8N_2O_4S_2$	C, H, S
4	NO_2	S	O	$CH(CH_3)_2$	167–168	81	$C_{11}H_{10}N_2O_4S_2$	C, H, N
5	NO_2	S	O	$CH_2CH{=}CH_2$	145–146	86	$C_{11}H_8N_2O_4S_2$	C, H, N
6	NO_2	S	O	C_6H_5	197–198	73	$C_{14}H_8N_2O_4S_2$	C, H, N
7	NO_2	S	O	$C_6H_5CH_2$	193–194[b]	52	$C_{15}H_{10}N_2O_4S_2$	C, H, N
8	NO_2	S	O	p-$ClC_6H_4CH_2$	223–224[b]	89	$C_{15}H_9ClN_2O_4S_2$	C, H, N
9	NO_2	S	O	C_2H_4OH	165	77–93	$C_{10}H_8N_2O_5S_2$	C, H, N
10	NO_2	S	O	$C_2H_4OCH_3$	135	87	$C_{11}H_{10}N_2O_5S_2$	C, H, N
11	NO_2	S	O	$C_6H_5CH_2CH_2$	212–213	85	$C_{16}H_{12}N_2O_4S_2$	C, H, N
12	NO_2	S	O		241–242	91	$C_{14}H_{14}N_2O_4S_2$	C, H, N
13	NO_2	S	O	$N(CH_3)_2$	219–220	67	$C_{10}H_9N_3O_4S_2$	C, H, N, S
14	NO_2	S	O	$C_2H_4N(C_2H_5)_2$[c]	210 dec	76	$C_{14}H_{18}BrN_3O_4S_2$	C,[d] H, N
15	NO_2	S	O	CO_2CH_3	205–206	87	$C_{10}H_6N_2O_6S_2$	
16	NO_2	S	1	H	210 dec	64	$C_{10}H_6N_2O_4S_2$	C, H, N
17	NO_2	S	1	CH_3	230 dec	52	$C_{11}H_8N_2O_4S_2$	C, H, N
18	NO_2	O	O	H	225–226[e]	80		
19	NO_2	O	O	CH_3	210	52	$C_9H_6N_2O_5S$	C, H, N, S
20	NO_2	O	O	p-$ClC_6H_4CH_2$	200–201	45	$C_{15}H_9ClN_2O_5S$	C, H, N
21	NO_2	O	1	H	212–215 dec	55	$C_{10}H_6N_2O_5S$	C, H, N
22	NO_2	O	1	CH_3	230	68	$C_{11}H_8N_2O_5S$	C, H, N
23	NO_2	O	1	$CH_2CO_2C_2H_5$	151	57	$C_{14}H_{12}N_2O_7S$	C, H, N
24	NO_2	O	1	$C_6H_5CH_2$	187–188	32	$C_{17}H_{12}N_2O_5S$	C, H, N
25	NO_2	O	1	p-$ClC_6H_4CH_2$	203	36	$C_{17}H_{11}ClN_2O_5S$	C, H, N, S
26	H	S	O	H	232[f]	84		
27	H	S	O	CH_3	142–143	95	$C_9H_7NO_2S_2$	C, H
28	H	O	O	H	233[g]			
29	H	O	O	CH_3	144–145	58	$C_9H_7NO_3S$	C, H, N
30	H	S	1	H	248–249[h]	68		
31	H	O	1	H	217–218	71	$C_{10}H_7NO_3S$	C, H, N
32	H	O	1	CH_3	145–146	77	$C_{11}N_9NO_3S$	C, H

[a] F. C. Brown, C. K. Bradsher, S. M. Bond, and M. Potter, *J. Amer. Chem. Soc.*, **73**, 2357 (1951), reported mp 201–201.5°. [b] E. Jeney and T. Z. Solnai, *Arch. Exp. Veterinaermed.*, **21**, 259 (1967), reported **2**, mp 190°, yield 20%, **3**, mp 154°, yield 18%, **7**, mp 145°, yield 17%, **8**, mp 208°, yield 36%, **12**, mp 242°, yield 32%. [c] HBr salt. [d] C, calcd 37.8; found 37.0. [e] G. Sanchez and J. Fernadez-Bolanas, *An. Real. Soc. Espan. Fis. Quim.*, **496**, 51 (1953), reported mp 225–226°. [f] Julian and Sturgis, *J. Amer. Chem. Soc.*, **57**, 1126 (1935), reported mp 229–231°. [g] M. I. Ganitkevitch, *Trudy L'vov. Med. Inst.*, **12**, 64 (1957), reported mp 232°. [h] Brown, *et al.*,[a] mp 251°.

bility of microbial reduction product was sought by increasing the extent of conjugation in the system by the introduction of a vinyl group in the molecule. The corresponding 2-oxocompounds, the 5-(5-nitro-2-furylidene)thiazolidine-2,4-diones, and their vinylogs were prepared for comparative purposes.

Reports of antifungal properties of some simple rhodanines[5] and thiazolidene-2,4-diones[6] and their corresponding alkylidene derivatives[7] caused doubt about the need of the 5-nitro group to confer antifungal activity. The activities of furan analogs of some of the most active 5-nitrofuran derivatives were therefore compared.

(5) (a) G. Kerk, *Meded. Landbouwhogesch. Opzoekingssta Staat Gent*, **18**, 402 (1953); (b) F. C. Brown, C. K. Bradsher, E. C. Morgan, M. Tetenbaum, and P. Wilder, *J. Amer. Chem. Soc.*, **78**, 384 (1956); (c) W. Weiniawaski, J. Swiderski, and P. Kubikowski, *Rocz. Chem.*, **32**, 545 (1958).

(6) N. K. Sundholm and J. B. Skaptason, U. S. Patent 2,510,725 (1950).

(7) (a) F. C. Brown, C. K. Bradsher, S. M. Bond, and M. Potter, *J. Amer. Chem. Soc.*, **73**, 2357 (1951); (b) G. Hagelloch and K. Liebermeister, *Z. Naturforsch. B*, **6**, 147 (1951); (c) E. Schraufstratter, *ibid.*, **56**, 190 (1950); (d) H. Taniyama, *Yakugaku Zasshi*, **77**, 1236 (1957); (e) N. M. Turkevitch and E. V. Vladzimirskaya, *Zh. Obsch. Khim.*, **27**, 2566 (1957); (f) C. Lapiere, *J. Pharm. Belg.*, **11**, 3 (1956); (g) L. Musial and J. Staniec, *Rocz. Chem.*, **38**, 1105 (1964); *ibid.*, **39**, 839 (1965).

Rhodanine and thiazolidine-2,4-dione both possess active CH_2 groups and will thus condense with aldehydes, especially in the presence of basic catalysts. In the present study, a basic catalyst, piperidine, could be employed to promote condensations with furfural, but had to be avoided with 5-nitrofurfural because of the instability of this compound to alkaline conditions. The substituted rhodanines and thiazolidine-2,4-diones were prepared by procedures reported in the literature and condensed with 5-nitrofurfural or 5-nitrofurylideneacrolein by two principal routes: (a) some of the simpler rhodanine derivatives condensed in good yield with 5-nitrofurfural when heated together in EtOH under reflux for 1 to several hr; and (b) the 2 compounds to be condensed were dissolved in AcOH, anhyd NaOAc was then added, and the mixt was refluxed from 1 to several hr. The analogs prepared are listed in Table I.

Antimicrobial Screening.—The compounds prepared in this study were tested for antibacterial, antiprotozoal, and antifungal activity *in vitro*, using the serial dilution and agar diffusion techniques. The results are shown in Tables II and III. With selected

TABLE II
In Vitro ANTIBACTERIAL ACTIVITY OF 5-(5-NITRO-2-FURYLIDENE)- AND 5-(5-NITRO-2-FURYLACRYLIDENE)RHODANINES AND -THIAZOLIDINE-2,4-DIONES

	Minimal inhibitory concentration, μg/ml				
No.	*Staphylococcus aureus*	*Streptococcus pyogenes*	*Escherichia coli*	*Salmonella typhi*	*Pseudomonas aeruginosa*
1	0.1	1.5	6.3	3.1	>100
2	0.8	3.1	>100	>100	>100
3	1.5	6.3	100	100	100
4	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]
5	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]
6	0.4	0.1	>100	<100	>100
7	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]
8	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]
9	25	>100	>100	50	>100
15	>100	>100	>100	>100	>100
16	0.4	1.5	6.3	6.3	25
17	25	25	>100	>100	>100
18	0.15	0.15	1.25		
19	1.5	1.5	3.0	3.0	100
21	1.5	3.1	3.1	6.3	>100
22	50	100	100	100	
26	>100	>100	>100	>100	>100
27	>100	>100	>100	>100	>100
28	>100	>100	>100	>100	>100
29	>100	>100	>100	>100	>100
30	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]
31	>100	>100	>100	>100	>100
32	>100	>100	>100	>100	>100

[a] The minimal inhibitory concn is greater than a satd soln.

TABLE III
In Vitro ANTIPROTOZOAL AND ANTIFUNGAL ACTIVITY OF 5-(5-NITRO-2-FURYLIDENE)- AND 5-(5-NITRO-2-FURYLACRYLIDENE)RHODANINES AND -THIAZOLIDINE-2,4-DIONES

	Minimal inhibitory concentration, μg/ml		
No.	*Trichomonas vaginalis*	*C. albicans*	*Trichophyton mentagrophytes*
1	1.5	3.9	50
2	1.5	0.8	>100
3	>0.6	12.5	>100
4		1.5	
5		1.5	
6		0.8	
7	100	100	
10	Inactive[a]	0.8	
16	0.6	3.1	
17	5.0	>100	
18		15[b]	44[b]
19	1.5	0.7	50
20	>100	0.15	Inactive[a]
21		3.1	
22	25	>100	
23	0.3	Inactive[a]	Inactive[a]
25	100	>100	
26	>100	>100	>100
27	>100	>100	>100
28	>100	>200	>100
29	>100	>100	>100
30	Inactive[a]	Inactive[a]	Inactive[a]
31	>100	>100	>100
32	>100	>100	>100
Metronidazole	>0.6		
Amphotericin B		1.5	
Nystatin		12.5	

[a] The minimal inhibitory concn is greater than a satd soln. [b] Agar diffusion technique.

compounds, activities in the presence and absence of up to 20% serum and 10% whole blood, were compared. Urinary excretion tests in rats were also performed with some of the more *in vitro* active compounds. The urine, collected overnight after an oral dose of 100 mg/kg, was sterilized by filtration through a No. 5 porocity sintered glass plate for activity against *Candida albicans* and *Trichomonas vaginalis*. Some of the compounds were subjected to urinary excretion tests in mice and compared with chloramphenicol and benzylpenicillin. The urine, pooled 5 hr following oral administration of 500 mg/kg to mice, was tested against 8 organisms by the agar diffusion technique. Selected compounds were evaluated for *in vivo* activity in mice infected with *C. albicans* and *T. foetus*.

As can be seen from Tables II and III, the parent rhodanine derivative **1** was one of the more active compounds tested, exhibiting good antibacterial antifungal, and antiprotozoal activity. N-Alkylation appeared to decrease antibacterial activity progressively in the rhodanine series as the size of the alkyl group was increased, *viz.*, **2**, **3**, **4**, and **5**. Introduction of hydrophilic groups in the *N*-alkyl substituent, *i.e.*, **9**, **13**, **14**, and **15** also resulted in greatly decreased activity, suggesting that solubility and aq–lipid partitioning are not the only factors responsible for reduction of activity resulting from N-substitution. This view is further supported by the high bacteriostatic activity observed for the *N*-phenyl derivative **6**. Thiol tautomerism, quite likely in **1** but impossible in **6**, is also excluded as an important factor. The role of N-substitution in determining antifungal activity in the rhodanine series failed to demonstrate a clear relationship. The relatively nonpolar derivatives **2**, **4**, **5**, and **6**, as well as the more polar compounds **9** and **13** exhibited very high activity against *C. albicans*. The vinylogs **16** and **17** also exhibited significant antibacterial and antifungal activities, with N-methylation decreasing activity against the bacteria and fungi tested.

The replacement of the thiocarbonyl group of the

rhodanine by the CO of the thiazolidine-2,4-diones also gave rise to significantly active antibacterial and antifungal compounds *in vitro*. The parent compound **18** exhibited broad spectrum antibacterial activity, being more active than benzylpenicillin against *Staph. aureus*, *Strep. pyogenes*, and *E. coli* and having the same order of activity as chloramphenicol against *Staph. aureus*, *E. coli*, *and Ps. aeruginosa*. Its activity against *C. albicans* was much less than that of amphotericin B. However, the *N*-methyl and the *N*-*p*-chlorobenzyl derivatives, **19** and **20**, respectively, are significantly more active against *C. albicans* than amphotericin B. It is interesting to note that the *N*-*p*-chlorophenyl analogs in the rhodanine series, **8**, were not sufficiently soluble for MICs against bacteria to be obtained, illustrating the increased water solubility achieved by replacing S with O. The vinylogs **21** and **22** were somewhat less active than the parent compounds **19** and **20**. High *in vitro* antitrichomonal activity was observed in both series, **3**, **16**, and **23** being comparable to metronidazole in activity.

In the light of reported antimicrobial activity of substituted rhodanines, it was decided to prepare and test some corresponding 5-(2-furylidene)rhodanines (**20**, **29**) and -thiazolidine-2,4-diones (**28**, **29**) to determine the contribution of the NO_2 substituent. As expected the 5-(2-furylidene) derivatives were inactive.

Minimum effective concentrations of some selected compounds were determined *in vitro* in the presence of serum and whole blood. The activity of **1** against *S. aureus* was not markedly reduced by 10% whole blood. However, the anti-*Candida* activity of **2** was reduced by a factor of **2** in the presence of 20% serum and by a factor of 10 in the presence of whole blood. The results for **21**, listed in Table IV, show a marked decrease in potency in the presence of either serum or whole blood.

TABLE IV

In Vitro ANTIBACTERIAL ACTIVITY OF 5-(5-NITRO-2-FURYL-ACRYLIDENE)THIAZOLIDINE-2,4-DIONE IN THE PRESENCE OF 20% SERUM AND 10% WHOLE BLOOD

	Minimum inhibitory concentration, μg/ml			
	Staph. aureus	*Strep. pyogenes*	*E. coli*	*S. typhi*
21	1.5	3.1	3.1	6.3
21 + 20%	3	12.5	7100	100
21 + 10% whole blood	12.5	12.5	7100	100

In vitro tests on the pooled urine of mice each given a single oral dose of 500 mg/kg of **18** gave an inhibition zone of 13 mm for *Staph. aureus* compared to 21 mm for benzylpenicillin and 28 mm for chloramphenicol measured by the agar diffusion method. No inhibition against *E. coli*, *Ps. aeruginosa*, *Klebsiella pneumoniae*, *P. vulgaris*, *C. albicans*, or *T. mentagrophytes* was observed. Compound **2** was active against *T. foetus* (14 mm), but inactive against *Staph. aureus*, *E. coli*, *Ps. aeruginosa*, *K. pneumoniae*, and *P. vulgaris*. Pooled urine from 3 rats, each given oral doses of 100 mg/kg of selected compounds, collected overnight and sterilized by filtration, was diluted and tested for activity against *C. albicans* and *T. vaginalis*. Compound **2** was active at 1:10 dilution against *T. vaginalis*. The same dilution was inactive against *C. albicans*. Compound **16** was active at 1:10 dilution against both *T. vaginalis* and *C. albicans*. Compound **6** was inactive against both organisms at 1:10 dilution. For comparison, the pooled urine obtains from 3 rats given 10 mg/kg of metronidazole orally was active against *Trichomonas vaginalis* at 1:80 dilution.

Compounds **1**, **2**, **3**, **6**, **16**, and **17** were examined for *in vivo* activity in rats infected with *C. albicans*. Administration of 0.04% (*ca.* 100 mg/kg) of **2** by weight in the diet gave significant protection in 3 tests. Two tests indicated marginal activity for **6**. The other compounds were inactive when administered in daily doses of 50 mg/kg sc for 3 days to rats infected with *C. albicans*. Amphotericin B (0.7 mg/kg) and nystatin (25 mg/kg) injected sc gave considerable extension of survival time. Sc administration of daily doses up to 50 mg/kg of **20** to mice infected with *T. foetus* failed to demonstrate activity. For comparison, metronidazole was active at 12.5 mg/kg.

Experimental Section

3-Substituted Rhodanines.—The 3-substituted rhodanines used were prepared by heating the amines, in excess or in the presence of NH_3, with CS_2 in EtOH to form the dithiocarbamates, which were then treated with $ClCH_2CO_2H$, its Na salt or Et ester, to form the *S*-carboxymethyldithiocarbamate. The latter was poured into 6 *N* HCl and heated at 90–95° for 30–60 min.

3-(2-Diethylaminoethyl)rhodanine.—To a soln of 10 g (0.1 mole) of 2-diethylaminoethylamine in 20 ml of EtOH cooled to 0–5° was added dropwise 7.6 g (0.1 mole) of CS_2 in 25 ml of Et_2O. After the addition was complete, stirring was continued for 1 hr. The pptd diethylaminoethyl dithiocarbamate (16.1 g, mp 139–140°) was collected, air-dried, and immediately used in the next step. It (3.1 g, 0.01 mole) was dissolved in 20 ml (30 g, 0.2 mole) of ethyl bromoacetate and the mixt was heated at 80° for 1 hr. On cooling, 3-(2-diethylaminoethyl)rhodanine·HBr was obtained as short yellow needles, mp 147–148° from EtOH–Et_2O *Anal.* C, H, N, S.

3-Substituted Thiazolidine-2,4-diones.—The 3-benzyl-, 3-*p*-chlorobenzyl-, and 3-ethoxycarbonylmethylthiazolidine-2,4-diones were prepared by alkylation of potassium thiazolidine-2,4-dione with the appropriate alkyl halide.[8]

3-Methylthiazolidine-2,4-dione was prepared by treatment of thiazolidine-2,4-dione with CH_2N_2 according to the procedure of Klein and Prijs.[9]

3-Methyl-5-(5-nitro-2-furylidene)rhodanine (2).—A mixt of 5.0 g (0.03 mole) of 3-methylrhodanine and 5.0 g (0.03 mole) of 5-nitro-2-furaldehyde was refluxed in 100 ml of 95% EtOH for 2 hr. The mixt was allowed to cool and the solid which sepd was collected and recrystd from EtOH and dioxane to give 1.5 g (55%) of **2** as red needles, mp 192–193°.

The 3-substituted 5-(5-nitro-2-furylidene)rhodanines **1**, **3**, **9**, and **14** (Table I) were also prepared by this general procedure.

3-Methyl-5-(5-nitro-2-furylidene)thiazolidene-2,4-dione (19).—A mixt of 2.6 g (0.02 mole) of 3-methylthiazolidine-2,4-dione, 2.8 g of 5-nitro-2-furaldehyde (0.02 mole), and 1.4 g of anhyd NaOAc was refluxed in 40 ml of gl AcOH for 2 hr. The mixt was poured onto crushed ice and allowed to stand overnight. The pptd solid was collected and recrystd from EtOH and dioxane to give 2.0 g (52%) of **19** as short greenish yellow needles, mp 210°.

The 3-substituted 5-(5-nitro-2-furylidene)rhodanines **1**, **3-13**, and **15** and the 3-substituted 5-(5-nitro-2-furylidene)thiazolidine-2,4-diones **18-20** (Table I) were also prepared by this general procedure.

5-(5-Nitro-2-furylacrylidene)rhodanine (16).—A soln of 1.3 g (0.01 mole) of rhodanine, 1.7 g (0.01 mole) of 5-nitro-2-furylacrolein (prepd by the procedure of Ryuzo Ueno),[10] and 0.8 g of NaOAc in 20 ml of AcOH was refluxed for 2 hr. The solid which pptd on cooling the soln was collected, dried, and crystd

(8) Chien-pen-lo and E. Y. Shropshire, *J. Amer. Chem. Soc.*, **76**, 4853 (1953).

(9) G. Klein and B. Prijs, *Helv. Chim. Acta*, **37**, 2057 (1954).

(10) Ryuzo Ueno, Japanese Patent 15,635 (1962).

from EtOH and dioxane to give 1.8 g (64%) of **16** as reddish gray needles, mp 210° dec.

The 3-Me analog **17** and the 5-(5-nitro-2-furylacrylidene-thiazolidene-2,4-diones **21–25** were prepd similarly.

5-(2-Furylidene)-2-methylrhodanine (27).—A soln of 3.0 g (0.02 mole) of 3-methylrhodanine, 2.0 g (0.02 mole) of furfural, and 0.5 ml of piperidine was heated under reflux in 30 ml of 95% EtOH for 30 min. The cryst which formed on cooling were collected, dried, and recrystd from 95% EtOH to give 4.25 g (95%) of **27** as long golden yellow needles, mp 142–143°.

5-(2-Furylidene)rhodanine (**26**) and the thiazolidine-2,4-diones **28** and **29** were prepd similarly.

5-(2-Furylacrylidene)thiazolidene-2,4-dione (31).—A mixt of 1.2 g (0.01 mole) of thiazolidine-2,4-dione, 1.2 g (0.01 mole) of 2-furylacrolein, and 0.5 ml of piperidine in 30 ml of 95% EtOH was refluxed for 1 hr. The mixt was allowed to cool overnight causing the pptn of a yellow solid which was collected, dried, and recrystd from EtOH and dioxane to give 1.5 g (71%) **30** as reddish brown needles, mp 217–218°.

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Antimalarials. "Distal" Hydrazine Derivatives of 7-Chloroquinoline

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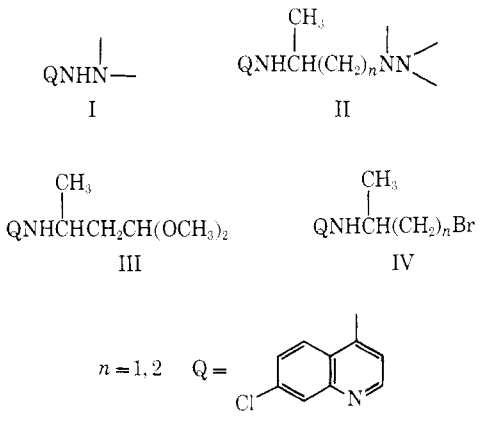
Twenty-six derivatives of 7-chloroquinoline have been prepared which incorporate a hydrazine feature in the side chain attached at position 4. They were tested for their antimalarial activity against *Plasmodium berghei* in mice. They ranged in activity from extremely toxic to highly curative.

In a previous publication[1] we reported quinoline derivatives with a "proximal" hydrazine feature as shown in the generic structure I. We are now reporting some derivatives with a "distal" hydrazine feature as represented by the generic structure II. Compounds



21–26 (Table I) contain both the proximal and the distal hydrazine moieties. Compounds **12–14** and **16** incorporate a hydrazinium bromide feature. These compounds, although found active or curative, were also quite toxic.

Chemistry.—The intermediate III was prepared by the reaction of 4,7-dichloroquinoline and β-aminobutyraldehyde dimethyl acetal. It was hydrolyzed *in situ* to the aldehyde and reacted with the appropriate hydrazine for the preparation of hydrazones **1–4**. These hydrazones were intended for reduction to the corresponding hydrazine derivatives. But our efforts to reduce them catalytically or chemically did not prove successful. Fragmentation of the molecule generally took place accompanied, sometimes, by the reduction of the quinoline ring or removal of the ring Cl. The Br intermediate IV, $n = 2$, the preparation of which was reported by us before,[2] proved to be very useful and gave rise to **5**, and **7–14**. Similarly the Br intermediate IV, $n = 1$, was made and used for the preparation of **15** and **16**. For **17–20** and **21–26**, piperazine and 1,4-diaminopiperazine were used to react with 4,7-dichloroquinoline. The intermediates, thus formed, led to final compounds through 1 or 2 steps without much difficulty.

Biological Tests.—All compounds except **20** were tested for their antimalarial activity against *Plasmodium berghei* in mice by Dr. L. Rane according to the procedure already published.[3] The results are given in Table II.

In general, the hydrazones **1–4** were extremely toxic. Test results of hydrazine derivatives with an unsubstituted end NH_2 were mixed, showing activity as well as toxicity except for **15** which showed excellent curative activity without being toxic. Toxicity seemed to disappear with substitution on the end NH_2. Compd **22** appears to be the best, in which the end NH_2 is substituted by a second molecule of 7-chloroquinoline. It showed curative activity with as low a dose as 40 mg/kg, and no toxicity even up to the maximum dose of 640 mg/kg.

Experimental Section

7-Chloro-4-(2-dimethylacetal-1-methylethylamino)quinoline (III).—A mixt of 4,7-dichloroquinoline (50.0 g, 0.25 mole), β-aminobutyraldehyde dimethyl acetal (67.0 g, 0.5 mole), KI (0.2 g), and 200 ml of ethoxyethanol was heated under reflux for 24 hr. Ethoxyethanol was then removed under reduced pressure, the residue was basified with 30% NaOH and extd with Et_2O, and the ext was dried (K_2CO_3), filtered, and concd. The residue was distd at 125–135° (5×10^{-4} mm) to give 34.0 g (46.2%) of the product which was crystd twice from Et_2O, mp 138–141°. *Anal.* ($C_{15}H_{19}ClN_2O_2$) C, H, N.

General Preparation of 1–4.—A soln of III (0.02 mole) in 100 ml of EtOH was added to an ice-cold soln of the required hydrazine

(1) T. Singh, R. G. Stein, and J. H. Biel, *J. Med. Chem.*, **12**, 801 (1969).

(2) T. Singh, R. G. Stein, J. F. Hoops, J. H. Biel, W. K. Hoya, and D. R. Cruz, *ibid.*, **14**, 283 (1971).

(3) T. S. Osdene, P. B. Russell, and L. Rane, *ibid.*, **10**, 431 (1967).