23	HO_2CCHCH_2S | $NHSO_2CH_3$	SO_2CH_3	OH	F	32	184.5–186 dec	M	$C_8H_{16}N_2O_8S_4$[d]	−17.8 (2)
24	$NH_2COCHCH_2S$ | $NHCO(CH_2)_2CO_2H$	$CO(CH_2)_2CO_2H$	NH_2	(5)	57	186.5–187.5 dec	D	$C_{14}H_{22}N_4O_8S_2$	−122.3 (1)
25	$NH_2COCHCH_2S$ | $NHCO(CH_2)_2Cl$	$CO(CH_2)_2Cl$	NH_2	(6)	72	185.5–186.5 dec	N	$C_{12}H_{20}Cl_2N_4O_4S_2$	−116.7 (3)
26	$NH_2COCHCH_2S$ | $NHCONH_2$	$CONH_2$	NH_2	H	70	211.5 dec	O	$C_8H_{16}N_6O_4S_2$	−54.6 (3)

[a] (1) Piperazinium. [b] See Experimental Section for the letters; (1) the optical isomerism and synthetic method are described in the text; (2) except for the use of 1 equiv of NEt_3, the procedure was similar to that given in ref 3b, method P; (3) see ref 3b, method Q; (4) prepared from L-cystine dimethyl ester dihydrochloride and carbobenzoxyglycine in the presence of NEt_3 and N,N′-dicyclohexylcarbodiimide; (5) prepared from L-3,3′-dithiobis(2-aminopropionamide) dihydrochloride and succinic anhydride in the presence of $NaHCO_3$ and aqueous THF (ref 1, 2); (6) similar to variation 5, except for the use of 3-chloropropionyl chloride and H_2O as the reaction medium. [c] A = 30% aqueous EtOH, B = EtOAc, C = 50% aqueous MeOH, D = H_2O, E = EtOH, F = DMF–H_2O, G = MeOH, H = EtOAc–MeOH, I = EtOAc–Skellysolve B, J = 2-PrOH–EtOAc–Skellysolve B, K = DMF–MeOH, L = 50% aqueous EtOH, M = 2-PrOH–H_2O, N = DMSO–MeOH, O = 5% aqueous MeOH. [d] N and S analyses. [e] c 1, in all cases; (1) 1 *N* NaOH, (2) H_2O, (3) DMSO, (4) DMF, (5) MeOH, (6) EtOH. [f] All compounds except **4**, **14**, and **23** analyzed correctly for C, H, N.

TABLE II

COMPARISON OF THE RATE AND EXTENT OF REDUCTION OF VISCOSITY OF MUCOPROTEIN SOLUTION[a]

Compd	% decrease in viscosity 3 min	30 min	60 min
L-N-Sulfanilylcysteine (**5**)	20	27	30
L-3-Mercapto-2-ureidopropionamide (**6**)	22	26	27
L-3-Mercapto-2-methanesulfonamido-propionamide (**7**)	24	30	30
2-Acetamido-N-(L-1-carboxy-2-mercapto-ethyl)-3-mercapto-DL-propionamide (**8**)	18	28	30
2-Acetamido-N-(L-1-carbamoyl-2-mercapto-ethyl)-3-mercapto-DL-propionamide (**9**)[b]	23	29	30
N-Acetyl-L-cysteine[c]	11	20	25

[a] See ref 3b, Table II. [b] Saturated solution of 0.036 *M*, instead of the usual 0.05 *M*, was used. [c] Included as reference material.

L. L-3-(Diphenylmethylthio)-2-(methanesulfonamido)propionic Acid (17).—A mixture of 6 g (0.0073 mole) of **16** was slurried with 150 ml of 33% aqueous MeOH while acidifying with 1 *N* HCl. The compound was isolated by extracting with EtOAc, concentrating, and recrystallizing from EtOAc–Skellysolve B; yield 3.7 g (69%).

M. Compound **17** may be isolated directly from the EtOAc extract of procedure K in an over-all improved yield of 68% by adding Skellysolve B and seeding.

N. L-3-(Diphenylmethylthio)-2-(methanesulfonamido)propionamide (18).—A solution of 15.2 g (0.04 mole) of **15** and 175 ml of MeOH saturated at 15° with NH_3 was allowed to stand for 2 days. The solid was collected; yield 9.3 g (64%) in three crops.

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Amides of N-Acylcysteines as Potential Amino Acid Antagonists in Bacteria

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Recently, we reported[1] on the activity of 21 cysteine or cystine analogs as potential amino acid antagonists in bacteria. Of these, N-acetyl-L-cysteine, N-propionyl-L-cysteine, L-cysteine hydantoin, and L-cystine hydantoin were the most effective inhibitors of L-cysteine utilization.

As an extension of these studies, 38 additional analogs were tested as inhibitors of cysteine or cystine utilization by *Leuconostoc mesenteroides*, a cysteine–cystine-dependent bacterium, and by *Escherichia coli*, an organism able to synthesize all its amino acid requirements. Most of these analogs[2] were amides of cysteines or cystines.

(1) W. A. Zygmunt and T. A. Martin, *J. Med. Chem.*, **11**, 623 (1968).

(2) (a) T. A. Martin, D. H. Causey, A. L. Sheffner, A. G. Wheeler, and J. R. Corrigan, *ibid.*, **10**, 1172 (1967); (b) T. A. Martin and A. L. Sheffner, U. S. Patent 3,340,147 (1967).

TABLE I
COMPARATIVE GROWTH INHIBITION OF *L. mesenteroides* BY VARIOUS CYSTEINE AND CYSTINE ANALOGS

Test compd[a]	Concn, μg/ml[b]					
	25	50	100	200	400	800
	Inhib or growth, %					
N-Acetyl-L-cysteine[3]	5	9	30	68	80	84
L-2-Acetamido-3-mercapto-propionamide[2]	7	66	92	94	100	100
L-3-Mercapto-2-ureidopropionamide	55	86	90	100	100	100
L-3-Mercapto-2-methanesulfonamido-propionamide	14	27	72	73	79	83
L-2-Acetamido-3-mercapto-N-phenylpropionamide[2]	6	29	45	88	88	88
2-Acetamido-N-(L-1-carboxy-2-mercaptoethyl)-3-mercapto-DL-propionamide	84	100	100	100	100	100
2-Acetamido-N-(L-1-carbamoyl-2-mercaptoethyl)-3-mercapto-DL-propionamide	74	100	100	100	100	100
L-2-Amino-3-benzylthiopropionamide hydrochloride[2]	7	10	20	54	65	53
L-2-Amino-3-(diphenylmethylthio)-propionamide[2]	5	12	16	18	48	69

[a] Several of the compounds listed are described elsewhere: T. A. Martin, *J. Med. Chem.*, **12**, 950 (1969). [b] Other analogs tested which required concentrations >800 μg/ml for 50% growth inhibition were: L-2-amino-3-mercaptopropionamide hydrochloride,[2] L-2-propionamido-3-mercaptopropionamide,[2] L-2-acetamido-3-mercapto-N-methylpropionamide,[2] L-3-(benzylthio)-2-formamidopropionamide,[2] L-2-acetamido-3-benzylthiopropionamide,[2] L-2-acetamido-3-benzylthio-N-methylpropionamide,[2] DL-2-acetamido-3-(benzylthio)-N-(2-hydroxyethyl)propionamide,[2] L-2-benzamido-3-(benzylthio)propionamide,[2] 2-acetamido-3-(benzylthio)-N-[L-2-(benzylthio)-1-methoxycarbonylethyl]-DL-propionamide, 2-acetamido-3-(benzylthio)-N-[L-2-(benzylthio)-1-carboxyethyl]-DL-propionamide, L-3-(diphenylmethylthio)-2-formamido-N-phenylpropionamide,[2] L-3-(diphenylmethylthio)-2-(methanesulfonamido)propionic acid, L-S-diphenylmethyl-N-methanesulfonylcysteine methyl ester, L-3-(diphenylmethylthio)-2-methanesulfonamidopropionamide, L-2-acetamido-3-acetylthiopropionamide,[2] N,N′-diacetyl-L-cystine piperazinium salt [R. Marshall, M. Winitz, S. M. Birnbaum, and J. P. Greenstein, *J. Am. Chem. Soc.*, **79**, 4538 (1957)], L-N,N′-diacetylcystine dimethyl ester [H. Heymann, T. Ginsberg, Z. R. Gulick, E. A. Konopka, and R. L. Mayer, *ibid.*, **81**, 5125 (1959)], N,N′-di(isovaleryl)-L-cystine, N,N′-di(isovaleryl)-L-cystine dimethyl ester, N,N′-dibenzoyl-L-cystine, L-N,N′-di(N-carbobenzoxyglycyl)cystine dimethyl ester, L-3,3′-dithiobis(2-aminopropionamide) dihydrochloride,[2] L-3,3′-dithiobis(2-acetamidopropionamide),[2] L-3,3′-dithiobis(2-propionamidopropionamide),[2] L-3,3′-dithiobis(2-acetamido-N-methylpropionamide),[2] L-3,3′-dithiobis[2-(3-chloropropionamido)propionamide], L-3,3′-dithiobis(2-benzamidopropionamide),[2] L-3,3′-dithiobis[2-(3-(carboxypropionamido)]propionamide], L-3,3′-dithiobis(2-ureidopropionamide).

The data in Table I list N-acetyl-L-cysteine[3] and eight of the 38 compounds tested which at a final concentration of 800 μg/ml inhibited growth of *L. mesenteroides* by at least 50%. Interestingly, the amide of N-acetyl-L-cysteine (L-2-acetamido-3-mercaptopropionamide) is about a fivefold more effective inhibitor of *L. mesenteroides* growth than is the carboxyl analog. The three additional most effective growth inhibitors were 2-acetamido-N-(L-1-carboxy-2-mercaptoethyl)-3-mercapto-DL-propionamide, 2-acetamido-N-(L-1-carbamoyl-2-mercaptoethyl)-3-mercapto-DL-propionamide, and L-3-mercapto-2-ureidopropionamide.

The nine most active compounds (Table II) were tested at equimolar concentrations in the presence of several levels of L-cysteine hydrochloride. With the exception of L-2-amino-3-(diphenylmethylthio)propionamide and L-3-mercapto-2-methanesulfonamidopropionamide, the growth inhibition observed with the remaining analogs decreased markedly with increasing levels of cysteine.

The growth inhibition found with L-3-mercapto-2-methanesulfonamidopropionamide was reversible with added L-cysteine but only at lower levels of inhibitor. Inhibition of *L. mesenteroides* growth by L-2-amino-3-(diphenylmethylthio)propionamide appears to be nonspecific and not easily reversed by cysteine even at lower levels of inhibitor.

L-2-Amino-3-mercaptopropionamide hydrochloride and L-3,3′-dithiobis(2-aminopropionamide) dihydrochloride were inactive as amino acid antagonists or as substitutes for L-cysteine or L-cystine in the growth of *L. mesenteroides*. Both compounds *per se* had only 5–10% microbiological growth replacement activity (based on an equivalent weight basis) in the absence of added cysteine or cystine. With the former compound this activity increased to 40% in the presence of 1.5 μg/ml of L-cysteine hydrochloride (a level required for about half-maximal growth). No such stimulation of the latter compound utilization, however, was noted with the further addition of L-cysteine.

L-2-Amino-3-mercaptopropionamide hydrochloride effectively inhibited growth of *E. coli* in a chemically defined medium and caused complete inhibition at 100

TABLE II
EFFECT OF VARYING CYSTEINE CONCENTRATIONS ON GROWTH INHIBITION OF *L. Mesenteroides* BY AMINO ACID ANALOGS

L-Cysteine HCl, μg/ml	Test compd, 0.003 *M*[a]								
	A	B	C	D	E	F	G	H	I
1	81	93	98	75	88	97	96	58	69
10	34	55	82	90	41	53	77	60	67
100	1	2	25	88	32	22	20	48	60
1000	3	2	3	82	37	1	1	9	61

[a] A, N-acetyl-L-cysteine; B, L-2-acetamido-3-mercaptopropionamide; C, 3-mercapto-2-ureidopropionamide; D, L-3-mercapto-2-methanesulfonamidopropionamide; E, L-2-acetamido-3-mercapto-N-phenylpropionamide; F, 2-acetamido-N-(L-1-carboxy-2-mercaptoethyl)-3-mercapto-DL-propionamide; G, 2-acetamido-N-(L-1-carbamoyl-2-mercaptoethyl)-3-mercapto-DL-propionamide; H, L-2-amino-3-benzylthiopropionamide; I, L-2-amino-3-(diphenylmethylthio)propionamide.

[3] (a) T. A. Martin, J. R. Corrigan, and C. W. Waller, *J. Org. Chem.*, **30**, 2839 (1965); (b) T. A. Martin and C. W. Waller, U. S. Patent 3,184,505 (1965).

μg/ml. Of the remaining compounds tested in *E. coli* moderate growth inhibition (80–90%) was found with L-3,3′-dithiobis(2-aminopropionamide) dihydrochloride (300 μg/ml) and L-2-amino-3-(diphenylmethylthio)-propionamide (600 μg/ml).

None of the 38 compounds tested showed any significant cysteine–cystine replacement activity for growth of *L. mesenteroides*. In summary, none of the 38 compounds tested showed significant growth inhibition of *L. mesenteroides* and *E. coli*. In most instances, this inhibition was readily reversed by the addition of cysteine.

The microbiological assay and testing procedures were similar to those previously described.[1]

Antiamebic, Antimalarial, and Anthelmintic Effects of Distal Hydrazine Analogs of Azacrine, Quinacrine, and 7-{[3-(Octylamino)propyl]amino}benz[c]acridine[1,2]

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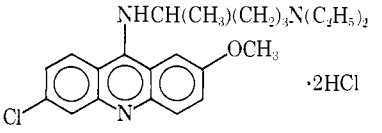
An array of basically substituted 9-aminoacridines,[3–11] 7-aminobenz[*c*]acridines,[3,4,9,10,12–14] and aminobenzonaphthyridines[4,9,15–18] exhibit noteworthy antiprotozoal, anthelmintic, antibacterial, and antitumor properties. Among them, quinacrine (I),[3–6] 3-chloro-9-{[4-(diethylamino)-1-methylbutyl]amino}acridine 10-oxide dihydrochloride (II),[7] 7-{[3-(octylamino)propyl]amino}benz[*c*]acridine dihydrochloride (III),[13] and azacrine (IV)[15] have been demonstrated to have appreciable antiprotozoal and anthelmintic activity in man. It was therefore of interest to synthesize representative {[3-(2,2-dialkylhydrazino)alkyl]amino}acridines, benz[*c*]acridines, and benzo[*b*][1,5]-naphthyridines to enable a determination of the effects of a distal hydrazine moiety on antiprotozoal and anthelmintic activity.



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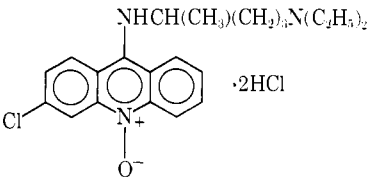

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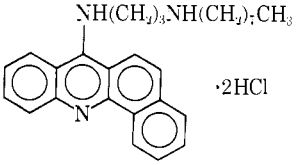

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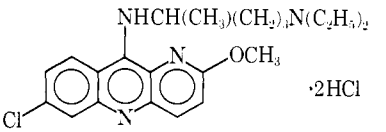
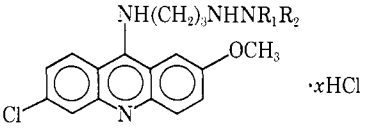


IV

The condensation of 6,9-dichloro-2-methoxyacridine with 2-(3-aminopropyl)-1,1-dimethylhydrazine,[19] 1-[(3-aminopropyl)amino]piperidine,[19] and 1-[(3-aminopropyl)amino]-4-methylpiperazine[19] in phenol afforded 6-chloro-9-{[3-(2,2-dimethylhydrazino)propyl]amino}-2-methoxyacridine dihydrochloride (Va) (55%), 6-chloro-2-methoxy-9-{[3-(piperidinoamino)-propyl]amino}acridine dihydrochloride (Vb) (38%), and 6-chloro-2-methoxy-9-({3-[(4-methyl-1-piperazinyl)amino]propyl}amino)acridine trihydrochloride (Vc) (40%), respectively (Table I, procedures I and II). 7-{[3-(Piperidinoamino)propyl]amino}benz[*c*]acridine dihydrochloride (VIa) and 7-({3-[(4-methyl-1-piperazinyl)amino]propyl}amino)benz[*c*]acridine hydrochloride (VIb) (68%) were obtained in a similar



Va, $NR_1R_2 = N(CH_3)_2$
b, $NR_1R_2 = N(CH_2)_5$
c, $NR_1R_2 = N[(CH_2)_2]_2NCH_3$

(1) This is paper X of a series on synthetic amebicides and paper XVII of a series relating to antimalarial substances. For the previous paper, see L. M. Werbel, E. F. Elslager, A. A. Phillips, D. F. Worth, P. J. Islip, and M. C. Neville, *J. Med. Chem.*, **12**, 521 (1969).

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