TABLE I

Compd	Bp (mm) or mp, °C[a]	Cryst solvent	Yield, %	Formula	Analyses[b]
1a	162–163.5	EtOAc	63.0	$C_{16}H_{18}ClN_3$	C, H, N
b	159–160	EtOAc	31.0	$C_{17}H_{20}ClN_3$	C, H, N
c	152–153	EtOAc	56.0	$C_{18}H_{22}ClN_3$	C, H, N
2a	87–89	CH_2Cl_2–Et_2O	89.0	$C_8H_{10}N_2O$	C, H, N
b	85–86.5	EtOAc	76.0	$C_9H_{12}N_2O$	C, H, N
3a	159–161		74.0	$C_9H_{13}IN_2O$	C, H, N
b	148–150	EtOH	82.0	$C_{16}H_{15}IN_2O$	C, H, N
c	Liquid		83.0	$C_{11}H_{17}IN_2O$	
4a	115–120 (0.7)		60.0	$C_9H_{16}N_2O$	
Oxalate	125–126.5	*i*-PrOH		$C_{11}H_{18}N_2O_5$	C, H, N
b	125–130 (0.03)		83.0	$C_{16}H_{18}N_2O$	
Oxalate	150–151	*i*-PrOH		$C_{22}H_{26}N_2O_8$	C, H, N
c	110–115 (0.3)		43.0	$C_{11}H_{20}N_2O$	N
5a	88–90 (17)		61.0	$C_7H_{14}N_2$	N
Phenylurea deriv	128–129	EtOAc		$C_{14}H_{19}N_3O$	C, H, N
b	93 (15)		50.0	$C_8H_{16}N_2$	
Phenylurea deriv	138–139	EtOAc		$C_{15}H_{21}N_3O$	C, H, N
c	98 (8)		36.0	$C_9H_{18}N_2$	
Phenylurea deriv	122–123	EtOAc		$C_{16}H_{23}N_3O$	C, H, N

[a] All melting points are uncorrected. [b] All analyses were within ±0.4% of the theoretical values except for **2a** (C: calcd, 63.98; found, 64.55).

TABLE II

Compd	Activity[a] D	C	TD	Increase in MST
1a	20	0	0	4.2
	40	0	0	4.6
	80	0	0	5.8
	160	0	0	9.2 (active)
	320	0	0	10.2 (active)
	640	2	1	... (curative, toxic)
1b	20	0	0	8.1 (active)
	40	0	0	8.7 (active)
	80	0	0	11.9 (active)
	160	0	0	18.7 (active)
	320	1	0	... (curative)
	640	4	0	... (curative)
1c	20	0	0	4.9
	40	0	0	6.5 (active)
	80	0	0	9.5 (active)
	160	0	0	14.1 (active)
	320	1	0	... (curative)
	640	3	0	... (curative)

[a] D, dose in mg/kg of body weight; C, cures; MST, mean survival time in days of the treated mice; TD, toxic death when the mice die within 2–5 days after infection which is attributed to drug toxicity. A compound is active if the increase in MST of the treated mice exceeds 6.3 days (MST of the control group) and curative if one or more mice live for 60 days or more post-infection.

4-Acetylaminopyridinium Alkyliodides (3).—A solution of 1 equiv of the acetylaminoalkylpyridine and 1 equiv of RI in Me_2CO was stirred at room temperature for 6–8 hr. A precipitate of the quaternary salt usually appeared which was removed by filtration. **3a** was pure enough at this stage to give satisfactory elemental analyses, **3b** was crystallized from EtOH, and **3c** was used as such for reduction.

1-Alkyl-4-acetylaminoalkyl-1,2,3,6-tetrahydropyridines (4).—A solution of 1 equiv of the 4-acetylaminoalkylpyridinium alkyliodide in MeOH was treated with 4 equiv of $NaBH_4$ with stirring. After 2 hr of additional stirring the solvent was evaporated under reduced pressure, the residual solid dissolved in a minimum amount of H_2O, strongly basified with NaOH, extracted with CH_2Cl_2, dried ($MgSO_4$), and solvent was removed under reduced pressure. The product was purified by distillation. **4a** and **4b** were converted to oxalates for identification.

1-Alkyl-4-aminoalkyl-1,2,3,6-tetrahydropyridines (5).—The Ac derivatives were hydrolyzed by refluxing with excess 4 *N* NaOH for 12 hr. The amines were hygroscopic and were converted to phenylureas for identification.

4-Substituted Amino-7-chloroquinolines (1).—A mixture of 1 equiv of 4,7-dichloroquinoline, 1.1 equiv of the 1-alkyl-4-aminoalkyl-1,2,3,6-tetrahydropyridine, and sufficient PhOH to give a clear solution was heated at 140–150° for 4 hr. The reaction mixture was cooled, poured into 2 *N* NaOH, and stirred. **1c** was extracted with CH_2Cl_2, and the combined extracts were dried ($MgSO_4$) and evaporated to give solid product which was purified by recrystallization.

Acknowledgment.—This work was supported by the U. S. Army Medical Research and Development Command under Research Contract No. DA-49-193-MD-2869. This note is Contribution No. 574 from the Army Research Program on malaria.

N-Acyl- and N-Sulfonylcysteine Derivatives

TELLIS A. MARTIN

Mead Johnson Research Center, Evansville, Indiana 47721

Received May 9, 1969

Additional work on N-acylcysteines[1–4] includes the synthesis of larger N-acyl, N-sulfonyl, and N-carbamoyl analogs as well as two dicysteine derivatives listed in Table I. The mucolytic activity[4,5] of representative sulfhydryl compounds is demonstrated (Table II). The biological activities of the compounds as potential

(1) T. A. Martin and C. W. Waller, U. S. Patent 3,184,505 (1965).

(2) T. A. Martin, J. R. Corrigan, and C. W. Waller, *J. Org. Chem.*, **30**, 2839 (1965).

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

(4) T. A. Martin, D. H. Causey, and J. R. Corrigan, *ibid.*, **11**, 625 (1968).

(5) A. L. Sheffner, *Ann. N. Y. Acad. Sci.*, **106**, 298 (1963); *Pharmacotherapeutica*, **1**, 46 (1965).

amino acid antagonists in bacteria[6a] are described elsewhere.[6b] Other investigators have reported[7] the preparation of the racemic form of **5** and some related S-alkyl analogs *via* a serine intermediate, and found them to be weak antibacterial agents.

The N-sulfonyl derivatives (**4** and **7**) were readily prepared by heating the S-diphenylmethyl-N-sulfonyl analogs (**14** and **18**) with trifluoroacetic acid and phenol. Catalytic reduction of **4** afforded **5** in satisfactory yield. The dicysteine derivatives (**8**, **9**), carrying the 2-acetamido-3-mercaptopropionamido moiety in the racemic form, were prepared in three steps: (a) condensation of DL-N-acetyl-S-benzylcysteine 4-nitrophenyl ester[8] and L-S-benzylcysteine methyl ester to give **10**, (b) alkaline hydrolysis to yield **11** or ammonolysis to give **12**, followed by (c) debenzylation.

Experimental Section[9]

Examples of Preparative Methods. A. L-N,N'-Di(isovaleryl)cystine (19).—A mixture of 60 g (0.25 mole) of L-cystine, 250 ml of Et_2O, and 250 ml of 2 *N* NaOH was stirred for 0.5 hr. After adding 4.2 g of $NaHCO_3$, the following two materials were added simultaneously during 1 hr while maintaining the reaction temperature at 3–8°: 62.5 g (0.52 mole) of isovaleryl chloride and 275 ml of 2 *N* NaOH. Complete solution resulted during this time. After stirring at room temperature overnight, 50 ml of 6 *N* HCl was added slowly to precipitate 5 g of unchanged starting material. The Et_2O layer was discarded. The volume of the aqueous layer was increased to 1.5 l. and then acidified with 6 *N* HCl. The resulting solid was collected, washed with water, and air dried; yield 44 g (43%).

B. L-N-Isovalerylcysteine (1).—To a warm (40°) mixture of 48 g (0.12 mole) of **19**, 48 ml of HOAc, and 368 ml of 10% aqueous EtOH was added 8 g of Zn dust. The reaction temperature increased to 48°. Complete solution resulted while warming at 50–60° during 45 min. The temperature was maintained for an additional period of 2 hr while two 2-g portions of Zn dust were added. Finally, to ensure complete reduction 80 ml of 3 *N* HCl was added at 40–50°, followed by 3 g of Zn dust, and warming at 50–60° for **1** hr. The excess Zn was collected and the filtrate was concentrated to give 33 g (67%) of **1** in two crops.

C. L-N,N'-Di(benzoyl)cystine (22).[10]—To a mixture of 24 g (0.1 mole) of L-cystine, 100 ml of Et_2O, 310 ml of 3% EtOH, and 105 ml of 2 *N* NaOH was added simultaneously at 5–10° during 20 min 30 g (0.214 mole) of benzoyl chloride and 115 ml of 2 *N* NaOH. A precipitate formed during these additions. After stirring overnight at room temperature, the volume was increased with H_2O to 1.5 l. to dissolve the precipitate. After extracting with Et_2O, the aqueous layer was warmed to 50° and acidified with 1 *N* HCl to precipitate the product, which was collected at room temperature, washed with hot H_2O, and dried; yield 28 g (62%).

A second preparation, employing four times the quantities used above, gave 510 g of damp filter cake. After drying 10 g to constant weight, a yield of 3.2 g (91%) of product was obtained. The remainder of the damp solid was used below.

D. L-N-Benzoylcysteine Piperazinium Salt (2).—A mixture of the above damp filter cake (**22**) (500 g; dry weight, 160 g or 0.36 mole), 320 ml of HOAc, and 1200 ml of 26% EtOH was stirred at 35–40° while 32 g of Zn dust was added in batches during 0.5 hr. The resulting thick slurry became quite mobile during 2 hr at 40–50°. On adding 280 ml of 3 *N* HCl and warming at 40–50° for 1 hr, complete solution had resulted. Two additional warming periods (14 and 15 hr) at 40–45° were made, introducing 8-g portions of Zn dust at the start of each period. The mixture was concentrated at 40–45° under reduced pressure until a precipitate occurred. The solid, containing excess Zn dust, was collected on a filter and washed with EtOAc to dissolve the product. This EtOAc layer along with three 1-l. additional portions used to extract the aqueous layer were combined, washed with H_2O, and dried over anhydrous $MgSO_4$. On concentrating the EtOAc solution to 139 g (85%) of oil, crystallization to a semisolid occurred during 2 days. To a solution of this material in 250 ml of MeOH was added a solution of 58 g (0.3 mole) of piperazine hydrate and enough MeOH to make a total volume of 100 ml. After seeding and stirring overnight, the solid was collected, 52 g of crude **2**.

After concentrating the filtrate, 12 g of piperazinium acetate was obtained (discarded). The filtrate was treated with 10 g of additional piperazine hydrate to yield 35.5 g of the crude **2**, total yield 87.5 g (45%). In order to ensure removal of traces of piperazinium acetate, the crude solids was slurried with 250 ml of H_2O and acidified with 135 ml of 6 *N* HCl. The free acid was extracted with EtOAc. The EtOAc layer was washed with three 250-ml portions of H_2O, dried over anhydrous $MgSO_4$, and concentrated to a spongy, white solid, yield 56 g (35%). This solid was converted to the piperazinium salt by employing 24.3 g of piperazine hydrate as described above; yield 34 g (18%).

E. L-N-Benzoylcysteine (3).[11]—A total of 32.4 g (0.06 mole) of **2** was slurried with 285 ml of EtOAc and 41 ml of 3 *N* HCl. The EtOAc layer was washed with 15% aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated to give 17.7 g (66%) of **3**.

F. L-S-Diphenylmethyl-N-(4-nitrobenzenesulfonyl)cysteine (14).—A solution of 6.2 g (0.028) mole of freshly recrystallized 4-$NO_2C_6H_4SO_2Cl$ in dry Et_2O was added slowly at 0–10° to a mixture of 7.5 g (0.026 mole) of L-$(C_6H_5)_2CHSCH_2CH(NH_2)CO_2H$[12] and 56 ml of 1 *N* NaOH. The reaction mixture was stirred at room temperature for 1 day, heated under reflux for 4 hr, and acidified with 1 *N* HCl. On adding 300 ml of Et_2O, 3 g of starting cysteine was recovered. The ethereal layer was concentrated to give 7.5 g (61%) of **14**.

G. L-N-Sulfanilylcysteine (5).—A mixture of 1.7 g (0.0055 mole) of **4**, 60 ml of anhydrous EtOH, and 0.5 g of 10% Pd–C was subjected to low pressure H_2 for 18 hr. After replacing fresh catalyst, the reaction was complete during 26 hr with the uptake of a total of 400 ml of H_2. The catalyst was collected, and the filtrate was diluted with Skellysolve B to give on cooling 0.9 g (59%) of solid.

H. L-3,3'-Dithiobis(2-ureidopropionamide) (26).—A mixture of 6.2 g (0.02 mole) of L-3,3'-dithiobis(2-aminopropionamide) hydrochloride,[3] 3.2 g (0.04 mole) of KCNO, and 60 ml of H_2O was heated at 60–65° for 1 hr. The reaction mixture was concentrated to a small volume. The resulting solid was collected and washed with H_2O; yield 4.5 g (70%).

I. L-3-Mercapto-2-ureidopropionamide (6).—A mixture of 10 g (0.031 mole) of **26**, 100 ml of 7% aqueous HOAc, and 5 g of Zn dust was warmed at 50–55° for 2 hr. A total of 2 ml of concentrated H_2SO_4 was added slowly. After 2 hr, the excess Zn was collected and the filtrate was concentrated to a semisolid. On slurrying with EtOAc–H_2O, the solid was collected and washed with H_2O and EtOAc; yield 7.6 g (75%).

J. L-S-Diphenylmethyl-N-methanesulfonylcysteine Methyl Ester (15).—A total of 25 g (0.22 mole) of $MeSO_2Cl$ was slowly added to a chilled (5–8°) mixture of 68 g (0.2 mole) of L-S-diphenylmethylcysteine methyl ester hydrochloride[12] and 300 ml of pyridine. After stirring for 15 hr, the reaction mixture was cooled at 15–20° while acidified with 520 ml of 7.4 *N* HCl. The resulting sticky solid was extracted with EtOAc. After concentrating, the oil was dissolved in 2-PrOH to crystallize 61 g (80%) of product in two crops.

K. L-3-(Diphenylmethylthio)-2-(methanesulfonamido)propionic Acid Piperazinium Salt (16).—After a yellow solution of 19 g (0.05 mole) of **15**, 150 ml of dioxane, and 55 ml of 2 *N* NaOH was allowed to stand for 4 hr, an additional 25 ml of 2 *N* NaOH was added. After 1 hr, the solution was concentrated to a small volume and then acidified with 54 ml of 3 *N* HCl. The crude acid was isolated by extraction with EtOAc and concentration. It was dissolved in MeOH and converted to the salt by adding a solution of 5.3 g (0.025 mole) of piperazine hydrate in MeOH; yield 11.5 g (56%).

(6) (a) W. A. Zygmunt and T. A. Martin, *J. Med. Chem.*, **11**, 623 (1968); (b) W. A. Zygmunt and T. A. Martin, *ibid.*, **12**, 953 (1969).

(7) Y. Chen-e and M. N. Shchukina, *Zh. Obshch. Khim.*, **26**, 2872 (1956).

(8) W. D. Cash, *J. Org. Chem.*, **27**, 3329 (1962).

(9) The ir spectra (Beckman IR-9) of all the described compounds are consistent with the assigned structures. The melting points are corrected (Thomas–Hoover capillary apparatus). In general, all preparative operations involving sulfhydryl compounds were carried out in an atmosphere of nitrogen, using deionized water.

(10) E. M. Fry, *J. Org. Chem.*, **15**, 438 (1950).

(11) H. Zahn and K. Traumann, *Z. Naturforsch.*, **9b**, 518 (1954).

(12) L. Zervas and I. Photaki, *J. Am. Chem. Soc.*, **84**, 3887 (1962).

TABLE I

L-$R_1SCH_2CHCOR_3$
|
NHR_2

No.	R_1	R_2	R_3 (salt)[a]	Prepn method (variation)[b]	Yield, %	Mp, °C	Recrystn solvent[c]	Formula[d]	$[\alpha]^{25}D$, deg (solvent)[e]
1	H	$COCH_2CH(CH_3)_2$	OH	B	67	112–114	A	$C_8H_{15}NO_3S$	−31.6 (1)
2	H	COC_6H_5	OH (1)	D	18	173.5–175 dec		$(C_{10}H_{11}NO_3S)_2 \cdot C_4H_{10}N_2$	+21.4 (2)
3	H	COC_6H_5	OH	E	66	85.5–87		$C_{10}H_{11}NO_3S$	−42.4 (1)
4	H	$SO_2C_6H_4NO_2$-*p*	OH	Ref 12	81	162–163.5	B	$C_9H_{10}N_2O_6S_2$[f]	
5	H	$SO_2C_6H_4NH_2$-*p*	OH	G	59	157.5–159.5	C	$C_9H_{12}N_2O_4S_2$	
6	H	$CONH_2$	NH_2	I	75	175–176	D	$C_4H_9N_3O_2S$	+13.9 (3)
7	H	SO_2CH_3	NH_2	Ref 12	54	125–127	D	$C_4H_{10}N_2O_3S_2$	−2.0 (2)
8	H	$COCH_3$	CH_2SH | $NHCHCO_2R$	(1)	75	170.5–171 dec	E	$C_8H_{14}N_2O_4S_2$	−50.8 (1)
9	H	$COCH_3$	CH_2SH | $NHCHCONH_2$	(1)	60	214–215 dec	F	$C_8H_{15}N_3O_3S_2$	−28.25 (4)
10	$C_6H_5CH_2$	$COCH_3$	$CH_2SCH_2C_6H_5$ | $NHCHCO_2CH_3$	(1, 2)	23	136.5–137.5	B	$C_{23}H_{28}N_2O_4S_2$	−61.26 (3)
11	$C_6H_5CH_2$	$COCH_3$	$CH_2SCH_2C_6H_5$ | $NHCHCO_2H$	(1)	90	149–150	G	$C_{22}H_{26}N_2O_4S_2$	−53.5 (4)
12	$C_6H_5CH_2$	$COCH_3$	$CH_2SCH_2C_6H_5$ | $NHCHCONH_2$	(1)	67	196–197	H	$C_{23}H_{27}N_3O_3S_2$	−46.43 (3)
13	$(C_6H_5)_2CH$	$COCH_2Cl$	OCH_3	(3)	57	94–95	I	$C_{19}H_{20}ClNO_3S$	−47.2 (5)
14	$(C_6H_5)_2CH$	$SO_2C_6H_4NO_2$-*p*	OH	F	61	134–137	I	$C_{22}H_{20}N_2O_6S_2$[g]	
15	$(C_6H_5)_2CH$	SO_2CH_3	OCH_3	J	80	76.5–77.5	J	$C_{18}H_{21}NO_4S_2$	−3.2 (5)
16	$(C_6H_5)_2CH$	SO_2CH_3	OH (1)	K	56	196–198 dec	C	$(C_{17}H_{19}NO_4S_2)_2 \cdot C_4H_{10}N_2$	−2.5 (4)
17	$(C_6H_5)_2CH$	SO_2CH_3	OH	L, M	69, 68	126–128	I	$C_{17}H_{19}NO_4S_2$	0.0 (5)
18	$(C_6H_5)_2CH$	SO_2CH_3	NH_2	N	64	195–196	K	$C_{17}H_{20}N_2O_3S_2$	−3.2 (4)
19	HO_2CCHCH_2S | $NHCOCH_2CH(CH_3)_2$	$COCH_2CH(CH_3)_2$	OH	A	43	169.5–171.5	L	$C_{16}H_{28}N_2O_6S_2$	−168.4 (1)
20	$CH_3O_2CCHCH_2S$ | $NHCOCH_2CH(CH_3)_2$	$COCH_2CH(CH_3)_2$	OCH_3	(3)	56	129–130	G	$C_{15}H_{32}N_2O_6S_2$	−148.2 (6)
21	$CH_3O_2CCHCH_2S$ | $NHCOCH_2NHCO_2CH_2C_6H_5$	$COCH_2NHCO_2CH_2C_6H_5$	OCH_3	(4)	65	105–106	I	$C_{28}H_{34}N_4O_{10}S_2$[h]	−36.7 (5)
22	HO_2CCHCH_2S | $NHCOC_6H_5$	COC_6H_5	OH	C	62	194.5–195.5 dec	E	$C_{20}H_{20}N_2O_6S_2$	−209 (6)

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	$C_{14}H_{23}N_3O_8S_2$	−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.

Acknowledgment.—The author is grateful to Dr. A. L. Sheffner and Mr. L. W. Jacobs for the mucolytic data, to Mr. J. P. Catlett and Mr. W. F. Kavanaugh for technical assistance, to Dr. J. R. Corrigan and Dr. W. T. Comer for their interest and advice in this work, and to Mr. C. M. Combs, Mr. C. I. Kennedy, and Mr. J. G. Schmidt for analytical and spectral data.

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

WALTER A. ZYGMUNT AND TELLIS A. MARTIN

Mead Johnson Research Center, Evansville, Indiana 47721

Received May 9, 1969

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).