

mmol) in H₂O (10 ml). Acidification gave thiol 7, which showed no change by ir or tlc.

Mercury (II)Bis(2-carboxy-1-cyclohexyl Mercaptide) (14).—Thiol 7 (20 mg, 0.12 mmol) in 2 ml of EtOH was treated with an excess of 10% Hg(CN)₂ solution in EtOH. The mercaptide **14** precipitated on cooling, and recrystallization from EtOH-H₂O gave colorless plates (13.6 mg, 42%); mp 160–161°; ir (KBr) 3300–2400, 1690, 1440, 1400, 1240, and 1200 cm⁻¹, tlc on Brinkmann MN Polygram (polyamide) developed in MeOH at ca. 25° showed only a single spot under uv light (*R_f* 0.24). *Anal.* (C₁₄H₂₂HgO₄S₂) C, H, S.

2-(2'-Protoaminoethylthio)-1-cyclohexanecarboxylate (8).—Thiol 7 (1.02 g, 6.4 mmol) in 6 ml of EtOH was added during 10 min to a stirred solution of **4** (1.64 g, 6.4 mmol) in 4 ml of 1:7 EtOH-H₂O. After 4 hr at ca. 25°, a cold solution of KOH (0.71 g, 12.7 mmol) in 5 ml of H₂O was added, and the mixture was stirred at 0° for 0.3 hr. In order to initiate precipitation, Et₂O (1 ml) was added. After 2 hr at 0° a white solid separated. Disulfide **8** was collected and washed with H₂O and with EtOH. A white powder resulted (0.86 g, 57%); mp 217–219° dec. Recrystallization from H₂O (100°) gave **8** as colorless plates with mp 230° dec. Tlc of **8** on Eastman Chromagram Type K301R (silica gel) developed with EtOH-H₂O-NH₄OH (25:3:4)¹⁴ at ca. 25° showed only a single spot (*R_f* 0.55); ir (KBr) 3200–2200, 1610, 1510, 1400, and 1275 cm⁻¹. *Anal.* (C₈H₁₇NO₂S₂) C, H, N, S.

trans-2-Aminoethyl 2-Chlorocyclohexyl Disulfide·HCl (10).—The thiol **9** (1.51 g, 10 mmol) and **4** (2.57 g, 10 mmol) were stirred in 20 ml of 2:1 EtOH-H₂O for 0.5 hr at ca. 25°. Evaporation below 30° gave a white residue, which was dissolved in 25 ml of H₂O and was extracted with 50 ml of Et₂O to remove unchanged **9**. The aqueous layer then was shaken with 50 ml of Et₂O while 10 ml of an iced aqueous solution of KOH (1.7 g, 30 mmol) was added. The H₂O layer was extracted twice more with Et₂O. Each organic layer was backwashed with H₂O and immediately shaken with the same portion of 1.0 ml of 12 N HCl in 10 ml of H₂O cooled in an ice bath. The HCl solution then was treated with 5 ml more of 12 N HCl. Precipitation of **10** occurred immediately. The crude **10** was isolated by filtration, washed with hexane (20 ml), and carefully dried in a desiccator (CaCl₂). Disulfide **10** was washed with Me₂CO and dried under reduced pressure; 0.53 g (20%), mp 148–150°.

Tlc of **10** on Eastman Chromagram (Type K301R) developed with 95% EtOH at ca. 25° showed only a single spot (*R_f* 0.42); ir (KBr) 3200–2300, 1575, 1500, 1440, and 725 cm⁻¹. *Anal.* (C₈H₁₇ClNS₂) C, H, Cl, S.

α-(2-Protoaminoethylthio)cinnamate (12).—Thiol **11** (23.00 g, 0.13 mol) in 200 ml of EtOH was added with stirring to **4** (33.00 g, 0.13 mol) in 120 ml of 1:1 EtOH-H₂O. The mixture was stirred for 4 hr at ca. 25°. Evaporation below 30° gave a paste, which was dissolved in 100 ml of H₂O. A cold solution of KOH (14.1 g, 0.25 mol) in 100 ml of H₂O was added slowly. A red oil separated. The mixed oil and H₂O were washed with 100 ml of Et₂O. The aqueous layer was decanted from the oil, which then solidified. Recrystallization from H₂O (100°) gave **12** as a red-orange powder having mp 135–138° dec; 9.27 g (28%); ir (KBr) 3100–2200, 1600, 1540, 1450, 1340, 850, 780, 750, and 680 cm⁻¹. An identical sample (by ir) was recrystallized repeatedly from H₂O to give **12** having constant mp 136–138° dec. *Anal.* (C₁₁H₁₃NO₂S₂) C, H, N, S.

(14) D. Braun and H. Geenen, *J. Chromatog.*, **7**, 56 (1962).

Effect of Organic Compounds on Reproductive Processes. VIII. Methanesulfonyloxyacetyl Derivatives of Diamines

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For some time we have been interested in the effects of various alkylating agents on the reproductive processes of houseflies and mice. Certain *N,N*-bis(aziri-

dineacetyl)- α,ω -diamine derivatives were effective as chemosterilants for houseflies¹ and some acted as sterilants for male mice.² These amides seemed to be less toxic than the corresponding urea derivatives³ and we were anxious to replace the aziridine alkylating function with another one, namely, the methanesulfonyl group. A series of these derivatives was synthesized from the corresponding hydroxyacetyl derivatives and evaluated for its effects on the reproduction of houseflies and mice. Tables I and II summarize the chemical data on the carbomethoxyacetyl and hydroxyacetyl intermediates and Table III summarizes the data on the final methanesulfonates.

TABLE I
BIS(CARBOMETHOXYACETYL)DIAMINES,
CH₃OCOCH₂CONH(CH₂)_nNHCOCH₂OCOCH₃

n	Yield, %		Mp, °C	Recrystn solvent	Formula ^a
6	37	187.5–188.5		H ₂ O	C ₁₄ H ₂₄ N ₂ O ₆
7	44	159–160		H ₂ O	C ₁₅ H ₂₆ N ₂ O ₆
8	47	147.5–148.5		Dioxane + H ₂ O	C ₁₆ H ₂₈ N ₂ O ₆
9	47	116–118		Dioxane + H ₂ O	C ₁₇ H ₃₀ N ₂ O ₆
10	49	117.5–119		EtOH + H ₂ O	C ₁₈ H ₃₂ N ₂ O ₆
11	60	95.5–97		EtOH + H ₂ O	C ₁₉ H ₃₄ N ₂ O ₆ ^b
12	37	122.5–124.5		Dioxane + H ₂ O	C ₂₀ H ₃₆ N ₂ O ₆
<i>p</i> -CH ₃ C ₆ H ₄ CH ₂		214–216.5		Dioxane + H ₂ O	C ₁₆ H ₂₆ N ₂ O ₆ ^c
<i>m</i> -CH ₃ C ₆ H ₄ CH ₂	36	142.5–143.5		MeOH - Et ₂ O	C ₁₈ H ₃₀ N ₂ O ₆

^a All compounds were analyzed for C, H, N. ^b C: calcd, 59.0; found, 58.5. ^c C: calcd, 57.2; found, 57.7.

TABLE II
BIS(HYDROXYACETYL)DIAMINES,
HOCH₂CONH(CH₂)_nNHCOCH₂OH

n	Yield, %		Mp, °C ^a	Formula ^d
6	25	126–129		C ₁₀ H ₂₀ N ₂ O ₄
7	78	115–116		C ₁₁ H ₂₂ N ₂ O ₄
8	75	116–117.5		C ₁₂ H ₂₄ N ₂ O ₄
9	82	126–127		C ₁₃ H ₂₆ N ₂ O ₄
10	83	122.5–123.5		C ₁₄ H ₂₈ N ₂ O ₄
11	93	122–123		C ₁₅ H ₃₀ N ₂ O ₄
12	74	129.5–131 ^b		C ₁₆ H ₃₂ N ₂ O ₄
<i>p</i> -CH ₃ C ₆ H ₄ CH ₂	95	225–227 ^c		C ₁₂ H ₁₆ N ₂ O ₄

^a All recrystallizations were from H₂O except for those noted. ^b Recrystallized from EtOH-H₂O. ^c Recrystallized from dioxane-H₂O. ^d See Table I, footnote a.

TABLE III
BIS(METHANESULFONYLOXYACETYL)DIAMINES,
H₃CSO₂OCH₂CONH(CH₂)_nNHCOCH₂OO₂SCH₃

Compd	n	Yield, %	Mp, °C ^a	Formula ^b
1	7	31	103.5–106	C ₁₃ H ₂₆ N ₂ O ₈ S ₂
2	8	39	127–129	C ₁₄ H ₂₈ N ₂ O ₈ S ₂
3	9	33	109–113	C ₁₅ H ₃₀ N ₂ O ₈ S ₂
4	10	33	120–124	C ₁₆ H ₃₂ N ₂ O ₈ S ₂
5	11	57	115–118	C ₁₇ H ₃₄ N ₂ O ₈ S ₂
6	12	75	127–130	C ₁₈ H ₃₆ N ₂ O ₈ S ₂

^a Recrystallized from Me₂CO-Et₂O. ^b See Table I, footnote a.

Experimental Section

***N,N'*-Bis(carbomethoxyacetyl)- α,ω -alkylenediamines.**—A solution of carbomethoxyacetyl chloride (0.04 mol) in 100 ml of C₆H₆ was added slowly to the diamine (0.02 mol) dissolved in 100 ml of C₆H₆, and 5 g of anhydrous K₂CO₃ was suspended in the same solvent. The reaction mixture was stirred at room tem-

(1) W. A. Skinner, H. C. Tong, T. E. Shellenberger, and G. W. Newell, *J. Med. Chem.*, **8**, 647 (1965).

(2) W. A. Skinner and H. C. Tong, *Experientia*, **24**, 924 (1968).

(3) W. A. Skinner, M. Cory, and J. I. DeGraw, *J. Med. Chem.*, **10**, 1186 (1967).

TABLE IV

EFFECT OF CANDIDATE CHEMOSTERILANTS IN THE FOOD OF ADULT HOUSEFLIES IN SCREENING TESTS (BOTH SEXES MAINTAINED ON TREATED DIET FROM EMERGENCE TO OVIPOSITION)

Compd	Type of food	Treated Diet				Untreated diet	
		Concn. %	Mortality, parent generation, %	Egg hatch, %	Pupae, no.	Egg hatch, %	Pupae, no.
1	Sugar	1.0	0	84	84	86	86
	Fly food	1.0	0	87	87	88	88
2	Sugar	1.0	0	56	56	86	86
	Fly food	1.0	0	70	70	88	88
3	Sugar	1.0	0	91	91	86	86
	Fly food	1.0	0	87	87	88	88
4	Sugar	1.0	0	79	79	86	86
	Fly food	1.0	0	90	90	88	88
5	Sugar	1.0	0	79	79	86	86
	Fly food	1.0	0	71	71	88	88

Discussion

Table IV summarizes the results of the chemosterilant test in houseflies. None of these compounds were significantly active in contrast to the corresponding aziridine analogs previously studied.¹

Table V summarizes the results of the evaluation of these compounds in the male mouse. None of the methanesulfonate derivatives had activity comparable to that of the corresponding aziridine analogs. However, the C₁₀ derivative, **4**, does seem to have a delayed effect as evidenced by reduction of litter sizes in weeks 9-14. This effect is similar to that observed by Jackson in the case of busulfan and isopropyl methanesulfonate which affected sterility only after several weeks.²

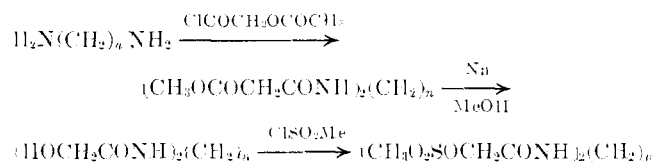
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TABLE V

EFFECT ON REPRODUCTION IN THE MALE SWISS-WEBSTER MOUSE

Compd	Dose, oral, mg/kg	Weeks														No. of mice
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
2	5 × 40	10	10	0	10	11	13	5	7	2	7	11	3	14	4	2
3	5 × 40	5	6	4	12	12	7	9	5	5	8	0	5	9	7	2
4	5 × 40	10	12	12	10	11	0	5	12	4	0	0	0	3	4	2
Control	Saline	1	2	7	2	9	10	9	7	3	8	4	4	10	8	3

SCHEME I



perature for 2 hr, and then at reflux for another 2 hr. The solvent was evaporated *in vacuo* and the residue was washed with water giving the crude product. Recrystallization from the solvents indicated (Table I) gave analytical samples.

***N,N'*-Bis(hydroxyacetyl)- α,ω -alkylenediamine.**—The *N,N'*-bis(carbomethoxyacetyl)- α,ω -alkylenediamine (5 mmol) was dissolved in 60 ml of MeOH in which an analytical amount of Na has been dissolved. The reaction mixture was stirred at room temperature for 2 hr. Evaporation of the solvent *in vacuo* left a white crystalline product. Recrystallization (Table II) gave analytical samples.

***N,N'*-Bis(methanesulfonyloxyacetyl)- α,ω -alkylenediamine.**—MeSO₂Cl (4 mmol) in 2 ml of Et₂O was added slowly with cooling to the *N,N'*-bis(hydroxyacetyl)- α,ω -alkylenediamine (2 mmol) dissolved in a mixture of 2 ml of pyridine and 4 ml of Et₂O. After stirring for 2 hr at room temperature, Et₂O was evaporated and ice-water was added to the residue. The white precipitate was filtered, dried, and recrystallized (AcMe-Et₂O) to give the compounds (Table III).

Biological Methods

Housefly Chemosterilant Assay.—These studies were conducted by the U. S. Department of Agriculture at its Insects Affecting Man and Animals Research Laboratory, Gainesville, Fla. The method used was essentially that previously reported.⁴

Mice Chemosterilant Assay.—These studies were conducted by H. C. Tong, Stanford Research Institute, by the method previously reported.²

ment Program. We wish to thank Mr. Tong for the mice studies and Dr. Weidhaas and J. Roos for the housefly studies.

(5) H. Jackson, "Antifertility Compounds in the Male and Female," C. C. Thomas, Springfield, Ill., 1966, pp 50, 72.

Cassaine Analogs. VI.¹ Resolution of (\pm)-7-Deoxy-16,17,18,20-tetranorcassaic Acid and Biological Activity of Derived Esters

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Recently we described a series of simplified analogs of the *Erythrophleum* alkaloid cassaine (**1**)² which were prepared in an effort to find a synthetically feasible and medicinally acceptable analog of cassaine, a cardiotoxic agent. These simplified structures, exemplified by formula **2**, proved to be only 0.1 (or less) as active as the natural product. It was of immediate concern whether at least half of the loss of activity could be attributed to the racemic nature of the synthetic compounds. Cassaine is a single (levorotatory) enantiomer.

Many efforts at resolving various racemates at several stages in the synthetic sequences reported ear-

(1) Paper V, S. J. Daum and R. L. Clarke, *J. Med. Chem.*, **11**, 1069 (1968).

(2) (a) R. L. Clarke, S. J. Daum, P. E. Shaw, T. G. Brown, Jr., G. L. Groblewski, and W. V. O'Connor, *ibid.*, **10**, 582 (1967); (b) *ibid.*, **10**, 593 (1967).

(4) G. C. LeBlanc, *J. Econ. Entomol.*, **54**, 684 (1961).