mixture was stirred at room temperature overnight and then poured into ice–HCl. The acidic solution was extracted with ether. After removal of solvent and excess phenol under reduced pressure a light tan glass was obtained: ultraviolet, λ_{max} 201 mμ (ε 79,370), 220 sh (28,040), 276 (4530), 284 sh (3900).

***cis*-3-*p*-Chlorophenyl-4-[*p*-(2-diethylaminoethoxy)phenyl]-chromane (IX).**—To a cooled solution of *cis*-3-*p*-chlorophenyl-4-*p*-hydroxyphenylchromane (0.50 g, 0.00149 mole) in 1 ml of dimethylformamide and 3 ml of toluene there was added 50% NaH in mineral oil (0.1 g, 0.02 mole). After stirring for a few minutes N-(β-chloroethyl)diethylamine (0.2 g, 0.00149 mole) was added, and the mixture was stirred overnight. After the solid was filtered off and washed with benzene, the filtrate was concentrated under reduced pressure. Water was added and the aqueous mixture was extracted with ether. The ether extract was dried ($MgSO_4$) and filtered, and the solvent was removed to yield a clear oil which was distilled. In this way 300 mg (46%) of the *cis* basic ether, bp 140–149° (1 mm), was obtained; ultraviolet, λ_{max} 222 mμ (ε 28,680), 276 (4780), 284 (4060).

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Effect of Organic Compounds on Reproductive Processes. III. Alkylating Agents Derived from Various Diamines

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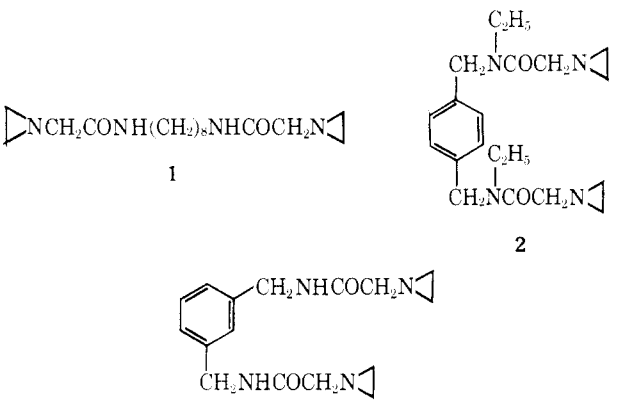
Alkylating agents derived from α,ω-alkylenediamines were synthesized and evaluated as chemosterilants in the housefly (*Musca domestica* L.). Chemosterilant activity varied with the distance between the two alkylating groups. Optimum activity was found in N,N′-bis(aziridineacetyl)-1,8-octamethylenediamine and N,N′-bis-(aziridineacetyl)-1,9-nonamethylenediamine.

As a continuation of our studies on the effect of organic compounds on reproductive processes, we have pursued the original lead[1] from compound **1**, N,N′-bis(aziridineacetyl)-1,8-octamethylenediamine, to include the synthesis and evaluation in houseflies as chemosterilants of a group of N,N′-bis(aziridineacetyl)-diamines. In the case of the xylylenediamine derivatives previously prepared[1] it was found that the N,N′-diethyl derivative (**2**) was inactive as an inhibitor of reproduction in the housefly (*Musca domestica* L.) while **3** was active. This finding led us to suspect that the amide NH was essential for activity. We have now investigated this more thoroughly by the synthesis of N,N′-dimethyl-N,N′-bis(aziridineacetyl)-1,8-octamethylenediamine (**21**) and N,N′-dimethyl-N,N′-bis(aziridineacetyl)-1,6-hexamethylenediamine (**20**). Both of these compounds were completely inactive toward inhibition of reproduction in houseflies when fed at the 1 wt % level in food. These results are in contrast to the activity of the corresponding compounds in which the amide NH was present (**1** and **13**).

In order to explore the relationship between the distance separating the two aziridinyl groups and activity as chemosterilants for houseflies the series of N,N′-bis(aziridineacetyl)-α,ω-diamines (**13**–**18**) was synthesized. These compounds were prepared from the corresponding N,N′-bis(bromoacetyl)-α,ω-diamines (**4**–**9**) by reaction with aziridine in the presence of anhydrous potassium carbonate as previously reported.[1] The properties of these alkylating agents are shown in Tables I and II along with the N,N′-dimethyl derivatives (**11**, **12**, **20**, and **21**) and the N-cyclohexyl derivatives (**10** and **19**).



1

2

3

$(CH_3)_2NCH_2CONH(CH_2)_8NHCOCH_2N(CH_3)_2$

22

$CH_3(CH_2)_7NHCOCH_2X$

23, X = Br

24, X = N

$CH_3O_2CNH(CH_2)_8NHCO_2CH_3$

25

$H_3CNH(CH_2)_8NHCH_3$

26

Two of the aziridineamides (**14** and **19**) were obtained as syrups which were converted to the crystalline chloroethylamine hydrochlorides by treatment with dry HCl in ether and characterized as such.

The activity as housefly chemosterilants of hexamethylphosphoramide and hexamethylmelamine,[2] comparable to that of the corresponding aziridine derivatives Tepa and Tretamine, led us to synthesize N,N′-

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

(2) S. C. Chang, P. H. Terry, and A. B. Borkovec, *Science*, **144**, 57 (1964).

TABLE I

N,N'-BIS(BROMOACETYL)-α,ω-ALKYLENEDIAMINES

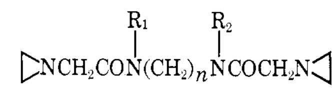
$BrCH_2CON(R_1)(CH_2)_nN(R_2)COCH_2Br$

Compd	n	R₁	R₂	Crystn solvent	Mp, °C	Yield, %	Calcd, % C	H	N	Found, % C	H	N
4	6	H	H	C_6H_6	135–138	31	33.5	5.06	44.6[a]	33.5	5.06	44.7[a]
5	7	H	H	2-Propanol	110–112	20	35.5	5.42	7.53	35.9	5.45	7.76
6	9	H	H	2-Propanol	104–106	52	39.0	6.04	7.00	39.1	6.08	7.26
7	10	H	H	C_6H_6	119–122	36	40.6	6.32	38.5[a]	40.6	6.39	38.3[a]
8	11	H	H	EtOH	109–110	48	42.1	6.59	6.54	42.2	6.62	6.62
9	12	H	H	C_6H_6	124–126	41	43.4	6.84	6.34	43.3	6.83	6.34
10	3	H	C_6H_{11}	C_6H_6	66–69	52	39.2	5.57	7.03	39.4	5.63	7.29
11	6	CH_3	CH_3	...	Oil	56	37.3	5.74	7.25	36.8	5.89	7.01
12	8	CH_3	CH_3	C_6H_6–cyclohexane	52–53	26	40.6	6.32	6.76	40.8	6.18	6.50

[a] Bromine analysis.

TABLE II

N,N'-BIS(AZIRIDINEACETYL)-α,ω-ALKYLENEDIAMINES



Compd	n	R₁	R₂	Crystn solvent	Mp, °C	Yield, %	Calcd, % C	H	N	Found, % C	H	N
13	6	H	H	C_6H_6–cyclohexane	81–83	27	59.5	9.28	19.8	59.3	9.23	19.8
14	7	H	H	*a*	Oil	69	40.7[a]	7.29	12.7	40.9	7.41	12.6
15	9	H	H	C_6H_6–cyclohexane	51–53	50	62.9	9.94	17.3	62.7	10.1	17.3
16	10	H	H	C_6H_6–cyclohexane	84–86	52	63.9	10.1	16.6	63.7	9.98	16.6
17	11	H	H	C_6H_6–cyclohexane	48–49	36	64.7	10.3	15.9	64.2	10.3	15.8
18	12	H	H	C_6H_6–cyclohexane	80–82	46	65.5	10.4	15.3	65.5	10.4	15.1
19	3	H	C_6H_{11}	*b*	Oil	78	43.6[b]	7.32	12.0	43.6	7.48	11.7
20	6	CH_3	CH_3	*c*	Oil	55	61.9	9.74	18.1	61.6	9.86	18.0
21	8	CH_3	CH_3	*d*	Oil	70	63.9	10.1	16.6	63.6	9.8	16.2

[a] Characterized as the mustard hydrochloride, $C_{15}H_{30}Cl_2N_4O_2 \cdot 2HCl$, mp 197–200°, from 2-propanol. [b] Characterized as the mustard hydrochloride, $C_{17}H_{32}Cl_2N_4O_2 \cdot 2HCl$, mp 137–140°, from 2-propanol. [c] The oil was evaporatively distilled at 180° (0.5 mm) for analysis. [d] Clear oil, single spot at R_f 0.95 as detected by iodine vapor on thin layer chromatogram (MN cellulose 300, ethanol).

bis(dimethylaminoacetyl)-1,8-octamethylenediamine (**22**) for comparison of its activity on the reproduction of houseflies.

The inactivity as a chemosterilant of the N-aziridineacetylbenzylamine previously reported[1] indicated the necessity of two aziridine groups per mole for activity. In order to confirm this, N-aziridineacetyloctylamine (**24**) was synthesized.

Experimental Section

N,N'-Bis(bromoacetyl)-α,ω-alkylenediamines and N,N'-bis(aziridineacetyl)-α,ω-alkylenediamines were synthesized as previously reported.[1]

N,N'-Bis(dimethylaminoacetyl)-1,8-octamethylenediamine (22).—To a suspension of 0.60 g (1.5 mmoles) of N,N'-bis(bromoacetyl)-1,8-octamethylenediamine in 10 ml of ethanol at 0° was added 2.6 ml (39 mmoles) of anhydrous dimethylamine. The mixture was heated at reflux for 3 hr and evaporated to dryness *in vacuo*. The solid residue was partitioned between 40 ml of 1 *N* HCl and 40 ml of chloroform. The acid layer was alkalized with 10% NaOH to pH 8–9. The basic mixture was extracted ($CHCl_3$), dried ($MgSO_4$), and evaporated to dryness *in vacuo* to yield 0.34 g of white crystals. Recrystallization from benzene–hexane mixture yielded 0.29 g (59%) of white crystals, mp 89–91°.

Anal. Calcd for $C_{16}H_{34}N_4O_2$: C, 61.1; H, 10.9; N, 17.8. Found: C, 60.9; H, 10.9; N, 17.9.

N-Bromoacetyloctylamine (23).—In a manner similar to that used for the diamines, N-bromoacetyloctylamine was prepared in 75% yield. The crystalline solid was sublimed *in vacuo* to yield white crystals, mp 25–26°.

Anal. Calcd for $C_{10}H_{20}BrNO$: C, 48.0; H, 8.06; N, 5.60. Found: C, 47.8; H, 7.95; N, 5.38.

N-Aziridineacetyloctylamine (24).—By a procedure similar to that used for the bisaziridineacetamides, N-aziridineacetyloctylamine was prepared in 66% yield. The clear gum was distilled *in vacuo*, bp 110° (0.5 mm).

Anal. Calcd for $C_{12}H_{24}N_2O$: C, 67.9; H, 11.4; N, 13.2. Found: C, 68.0; H, 11.5; N, 12.9.

Dimethyl-N,N'-octamethylene Biscarbamate (25).—To a solution of 15.0 g (0.104 mole) of 1,8-octanediamine in 250 ml of chloroform, at 0° was added 400 ml of 10% NaOH (1.12 moles). To the mixture was added 28.9 ml (0.377 mole) of methyl chloroformate. The mixture was stirred for 1 hr at 0° and acidified to pH 1–2 with 6 *N* HCl, followed by stirring for 1 hr at room temperature. The chloroform solution was washed with three 50-ml portions of water, dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The crystalline residue was recrystallized from 150 ml of ethyl acetate to yield 24.1 g (89%) of white crystals, mp 116–117.5°.

Anal. Calcd for $C_{12}H_{24}N_2O_4$: C, 55.4; H, 9.29; N, 10.8. Found: C, 55.6; H, 9.34; N, 10.9.

N,N -Dimethyl-1,8-octamethylenediamine (26).—To an ice-cold suspension of 10.5 g (0.277 mole) of $LiAlH_4$ in 400 ml of tetrahydrofuran (THF) was added a solution of 12.1 g (46.5 mmoles) of the biscarbamate in 100 ml of THF dropwise with stirring, keeping the temperature at 0–5°. The mixture was heated at reflux for 16 hr, cooled to 0–5°, and 100 ml of ethanol was added dropwise to decompose the remaining hydride. Water (15 ml) was added, and the mixture was evaporated to dryness *in vacuo*. The residue was extracted with three 100-ml portions of ether and the combined ether extracts were dried ($MgSO_4$) and chilled to 0°. Dry HCl gas was bubbled through the chilled solution. The white crystalline product was

collected by filtration and recrystallized from ethanol to yield 10.1 g (89%) of white crystals, mp 250–251°.

Anal. Calcd for $C_{10}H_{24}N_2 \cdot 2HCl$: C, 49.0; H, 10.7; N, 11.4. Found: C, 49.0; H, 10.3; N, 11.4.

Biological Section

Methods and Results.—All of the alkylating agents listed in Table I and II and compounds **22–24** were evaluated as inhibitors of reproduction in our colony of houseflies (*Musca domestica* L.). The method used was previously reported.[1] At 1 wt % concentration in the feed, only those compounds listed in Table III were active. All compounds were mixed dry in the feed.

Table III
Effects of Compounds on the Reproduction of Houseflies

Compd	n	Wt % in feed	No. of flies	% egg hatch—Days of oviposition— 1	2	3	4	5	6	7
14	7	1.0	300	39	46	42	66	50	65	49
14	7	0.1	300	76	90	77	81	80	75	82
1	8	1.0	250	..	2	1	.	0		..
1	8	0.1	250	14	10	18	18	38	23	27
1	8	0.01	250	..	77	61	72	70	62	72
15	9	1.0	300	0	0	0	0	0	0	0
15	9	0.1	300	0	..	23	42	41	22	29
16	10	1.0	300	9	16	0	0	0	17	..
16	10	0.1	300	43	73	38	57	50	80	..
17	11	1.0	150	68	44	74	53	74	38	63
Control		...	400	94	94	92	96	94	83	..
Control			250	92	97	90	98	88	91	87

Discussion.—The lack of effect on reproduction of the housefly of all of the bromoacetyl derivatives synthesized agrees with the previously reported results[1] and indicates the necessity of a more active alkylating function before interference with reproduction is achieved. With the aziridinyl derivatives, the necessity of having an NH function on the amide is emphasized by the lack of activity of **19–21**. The necessity of having a bisaziridinyl function is borne out by the lack of activity of **24**. Distance between the aziridine groups is extremely important with regard to activity of these compounds. Maximum activity was found in the C_8–C_9 compounds and dropped off at shorter and longer chain lengths. Investigations are under way in other diamines to better define the distance requirements for maximal chemosterilant activity.

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Insect Chemosterilants. III. 1-Aziridinylphosphine Oxides[1]

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Insect sterilizing activity of 40 variously substituted tri-, di-, and mono(1-aziridinyl)phosphine oxides was correlated with the degree of substitution on the aziridinyl ring and with the type of nonaziridinyl moieties attached to the phosphinylidyne group. All substitutions on the aziridinyl carbon decreased the sterilizing activity of the parent compound. Among the di- and monoaziridinyl compounds, the most effective nonaziridinyl substituents were alkylamino groups, less effective were alkoxy groups, and least effective were aryl groups. In preparing strained aziridinylphosphine oxides, 3-oxa-6-azabicyclo[3.1.0]hexane was synthesized.

Tris(1-aziridinyl)phosphine oxide (tepa) was one of the first chemicals found to effectively sterilize the males of many different insect species.[2] During the years immediately following the discovery, variously substituted aziridinylphosphine oxides were synthesized or obtained from outside sources and then screened for their insect sterilizing activity. In attempts to correlate the structure of substituted phosphine oxides with their chemosterilant activity, two approaches were investigated. One was the introduction of substituents onto one or both carbon atoms of the aziridinyl ring, and the other was the replacement of all aziridinyl moieties with various other groups. All substituted phosphine oxides described in this paper contained at least one aziridinyl group linked to the phosphinylidyne group through its ring nitrogen.

Triaziridinylphosphine Oxides.—The effects of progressive substitution of the hydrogens in tepa by methyl groups have been previously reported.[3] In a recent quantitative study,[4] tepa was found to be 13 times as active in sterilizing male house flies (*Musca domestica* L.) as its C-methyl homolog, metepa. Table I summarizes the sterilizing properties of other tepa analogs used to treat the house fly. Tepa and metepa are included for comparison. Derivation of the values used in grading the sterilizing activity of the compounds tested is discussed in the Experimental Section. Compounds designated by literature references only were synthesized in our laboratory according to published procedures.

Introducing one higher alkyl group or phenyl group into each aziridine ring drastically reduced the sterilizing activity (Table I). In this respect, the effects were comparable to those obtained by introducing two or more methyl groups into the ring.[3] The reduced physiological activity of the substituted compounds appeared to be related to their decreased susceptibility to nucleophilic reagents. Simple measurements of

(1) Presented before the Symposium on Chemosterilants of the Division of Agricultural and Food Chemistry, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 12–17, 1965. Previous paper: A. B. Bořkovec and C. W. Woods, *J. Med. Chem.*, **8**, 545 (1965).

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