Effect of Organic Compounds on Reproductive Processes. V. Alkylating Agents Derived from Aryl-, Aralkyl-, and Cyclohexylmethylenediamines

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Studies in these laboratories of the effect of organic compounds on reproductive processes have resulted in the discovery of interesting structural requirements for this type of activity as regards chemosterilization of the housefly (*Musca domestica* L.). Previously,[1] several bis(aziridineacetyldiamine) derivatives were found to cause sterility in the housefly. The degree of their activity was shown to be dependent upon the distance between the two alkylating groups. In addition, an apparent structural requirement in this series for activity as housefly chemosterilants was the presence of an N-unsubstituted amide function. In order to further explore the influence of the carrier moiety on the chemosterilant activity of bis(aziridineacetyldiamines), a series derived from aryl-, aralkyl-, and cyclohexylmethylenediamines, was prepared and evaluated in houseflies.

These compounds were synthesized from the N,N′-bis(bromoacetyl)-α,ω-diamines by reaction with aziridine in the presence of anhydrous potassium carbonate. The chemical properties of these alkylating agents are summarized in Tables I and II.

Experimental Section

The various N,N′-bis(bromoacetyl)-α,ω-diamines and N,N′-bis(aziridineacetyl)-α,ω-diamines were prepared as previously described.[2]

Biological Methods and Results.—The compounds listed in Tables I and II were evaluated as inhibitors of reproduction in our colony of houseflies (*Musca domestica* L.). The method used was that previously reported.[2] At 1% concentration in the feed only those compounds listed in Table III were active. All compounds were mixed dry in the diet.

The oral LD_{50} of **15** in mice was determined to be 70 mg/kg, while the oral LD_{50} in mice of the active housefly chemosterilant, N,N′-bisaziridineacetyl-1,8-octamethylenediamine, was 1070 mg/kg.

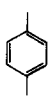
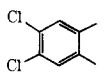
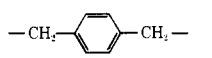
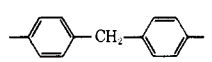
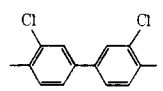
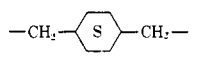
Discussion

Again as in the series of alkylating agents previously investigated[1,2] only the bisaziridineacetyl derivatives were effective as housefly chemosterilants. As the data in Table III indicate, the influence of the carrier moiety on the chemosterilant activity is considerable. Those compounds derived from aromatic diamines are less active than those derived from the nonaromatic amines. The two most active compounds (**12** and **15**) have very similar carrier groups as regards spacial considerations but should be metabolized quite differently and **12** has been found to be more toxic to mice. Compound **12** appears to be somewhat more active as a housefly chemosterilant and is being studied further in other animal species. The isomeric *m*-xylylenediamine derivative

TABLE I

N,N′-BIS(BROMOACETYL)-α,ω-DIAMINES

$BrCH_2CONHRNHCOCH_2Br$

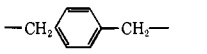
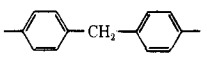
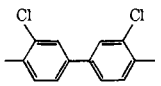
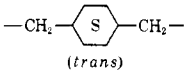
Compd	R	Cryst solvent	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1		DMF	>300	26	34.3	2.88	8.00	34.4	2.98	7.98
2		Ethanol	199–201	21	34.3	2.88	8.00	34.7	2.99	8.01
3		Ethanol	190.5–192.5	38	34.3	2.88	8.00	34.3	3.04	8.38
4		Ethyl acetate	170–172	55	28.7	1.92	6.68	29.0	2.01	6.97
5		2-Methoxyethanol	220–221.5	16	38.1	3.73	7.41	38.4	3.75	7.47
6		2-Methoxyethanol	234–236	26	46.4	3.66	6.37	46.8	3.92	6.52
7		Ethanol	247.5–249	51	38.8	2.44	5.66	39.0	2.60	6.00
8		DMF	228–230	62	37.5	5.25	7.30	37.8	5.36	7.50

(1) W. A. Skinner, M. Cory, T. E. Shellenberger, and J. I. DeGraw, *J. Med. Chem.*, **9**, 520 (1966).

(2) W. A. Skinner, H. C. Tong, T. E. Shellenberger, and G. W. Newell *ibid.*, **8**, 647 (1965).

TABLE II

N,N′-BIS(AZIRIDINEACETYL)-α,ω-DIAMINES

Compd	R	Crystn solvent	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
9		Benzene	188–190	19[a]	61.3	6.61	20.4	61.2	6.60	20.4
10		Benzene	124–125	18	61.3	6.61	20.4	61.1	6.82	20.6
11		Benzene–cyclohexane	128–129	20	49.0	4.70	16.3	48.8	4.41	16.4
12		Benzene–cyclohexane	148–149.5	30	63.6	7.30	18.5	63.3	7.30	18.3
13		Benzene–cyclohexane	115.5–118	15[a]	69.2	6.64	15.4	69.5	6.78	15.6
14		Benzene	224–226	25[a]	57.3	4.81	13.6	57.3	4.75	13.5
15	 (*trans*)	Benzene–cyclohexane	146–148	56[a]	62.3	9.15	18.2	62.2	9.03	18.2

[a] Tetrahydrofuran was used as the solvent for the reaction.

TABLE III

EFFECTS OF COMPOUNDS ON THE REPRODUCTION OF HOUSEFLIES

Compd	Wt % in feed	No. of flies	% egg hatch[a,b] Days of oviposition 1	2	3	4	5	6	7
Control	...	400	94	94	92	96	94	83	—
	...	250	92	97	90	98	88	91	87
9	1	300	3	13	4	31	26	67	23
	1	200	2	2	6	5	6	3	19
10	1	300	1	35	44	32	35	54	39
11	1	300	52	67	57	67	—	—	—
	0.1	300	88	66	35	83	—	—	—
	0.01	300	92	89	85	95	—	—	—
12	1	300	0	5	0	3	/	15	/
	1	200	/	/	/	/	/	/	/
	0.1	200	3	1	/	/	/	/	/
	0.01	200	21	15	17	20	75	17	28
13	1	300	56	33	48	52	70	83	38
14	1	300	91	98	85	—	—	58	88
15	1	300	1	5	/	/	/	/	/
	0.1	300	0	—	/	35	30	36	40
	0.01	300	73	82	88	87	89	71	79

[a] Slant lines indicate no eggs laid. [b] Horizontal lines indicate no eggs set.

had previously been found to possess only minimal activity as a housefly chemosterilant.[1] A comparison between the activities of **9**, **13**, and **14** would indicate that the distance between the alkylating groups of **13** and **14** is too large for maximal activity.

In Japanese quail (*Coturnix coturnix* japonica), **15** at dietary levels not adversely affecting egg production has been found to have a marked effect on reproduction as evidenced by low egg fertility and hatchability. Details of these studies are being reported elsewhere.

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Structure and Anticoagulant Activity of Bridge-Substituted Dicoumarols[1]

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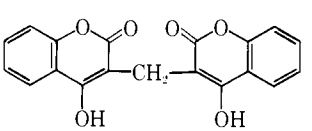
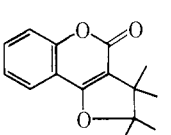
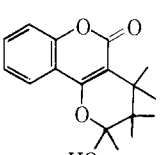
Studies by Overman, *et al.*,[3] and Mentzer, *et al.*,[4] on the anticoagulant activity of coumarin derivatives showed that the minimum structural requirement was a 4-hydroxycoumarin unit with a substituent in position 3 bearing a suitably placed carbonyl group. For maximal activity a bis arrangement as in dicoumarol (I) was considered to be necessary.



I



II



III

(1) Some of the results presented in this paper are taken from the theses of S. D. S. S. (All India Institute of Medical Sciences) and B. R. S. (Delhi University).

(2) All India Institute of Medical Sciences.

(3) R. S. Overman, M. A. Stahman, C. F. Huebner, W. R. Sullivan, L. Spero, D. G. Doherty, M. Ikawa, L. Graf, S. Roseman, and K. P. Link, *J. Biol. Chem.*, **153**, 5 (1944).

(4) C. Mentzer, P. Meunier, J. Lacocq, O. Billet, and D. Xuong, *Bull. Soc. Chim. France*, **12**, 430 (1945).