The effect of interim between drug and hexobarbital administration was seen with **1**. At 1000 mg/kg (method 1) no significant activity was seen, but significant activity was seen at 400 mg/kg (method 2). Similarly, **12** did not possess significant activity with method 1, but did display an enhancement effect with method 3. In the case of **12** a part of the effect was due to increased increment of hexobarbital administered, but the increase cannot be entirely attributed to this (see **19**, methods 1 and 3). The apparent difference in activity is almost certainly due to slow absorption of the compound, slow attainment of the requisite concentration at the site of action, or biotransformation of the compound to the active form.

When administered simultaneously with the hexobarbital, the preliminary evaluations indicate that the N,N′-piperonylidenebis(acid amides) and the N,N′-arylidenebisnicotinamides are the most active in regard to their CNS depressant action.

Acknowledgments.—The authors wish to express their sincere appreciation to Mr. William R. Gibson, Head, Department of Toxicity, and Mr. Peter D. Cullen, Toxicologist, Eli Lilly and Co., Greenfield, Ind., for their valuable suggestions given during the course of this investigation.

TABLE I

EHRLICH ASCITES SCREENING DATA[a]

Compd	Dose, mg/kg	Mortality	Ascites vol, ml	T/C[b]	TPCV	T/C[b]	Bone marrow[c]
8	200.0	0	3.6	1.71			
	100.0	0	2.4	1.14			
	50.0	0	1.7	0.81			
	50.0	0	3.8	1.90			
	25.0	0	2.6	1.30			
9	30.0	0	3.0	0.70			N
	15.0	0	2.9	0.64			
10	10.0	0			1.12	2.33	N
11	20.0	0			0.02	0.04	N
	10.0	0			0.17	0.3	N
	5.0	0			0.52	1.08	
	2.5	0			0.39	0.81	
12	40.0	0			0.02	0.04	
	20.0	0			0	0	
	10.0	0			0	0	
	5.0	0			0	0	
	160.0[d]	10			...	...	
	80.0	10			...	...	
	40.0	3			0.04	0.03	↓ ↓ ↓
	20.0	1			0.04	0.03	↓ ↓
	10.0	0			0.05	0.04	↓
	5.0	0			0.05	0.04	N
	2.5	0			0.04	0.03	
	1.3	0			0.57	0.48	
	0.6	0			1.50	1.28	
	0.3	0			1.32	1.12	
13	20.0	0			0.76	1.58	N

[a] See text for a description of total packed-cell volume (TPCV) and therapeutic index (TI). [b] T/C = treated/control animals. [c] Degree of depression: ↓ ↓ ↓, strong; ↓ ↓, moderate; ↓, slight; N, negative. [d] The therapeutic index was 21. *Cancer Chemotherapy Rept.*, **17**, 56 (1962), gives LD_{10} = 1.5 mg/kg, ED_{90} = 0.096 mg/kg, and TI = 16 for $CH_3N(CH_2CH_2Cl)_2 \cdot HCl$ (HN_2).

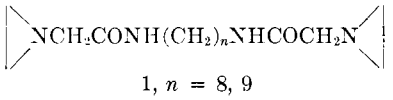
Effect of Organic Compounds on Reproductive Processes. VI. Alkylating Agents Derived from Various Diamines

W. A. SKINNER, J. LANGE, T. E. SHELLENBERGER, AND W. T. COLWELL

Stanford Research Institute, Menlo Park, California

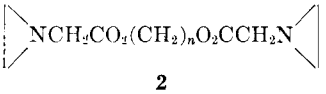
Received March 9, 1967

A program of synthesis of various alkylating agents has enabled us to define some of the chemical parameters required for chemosterilant activity in the housefly (*Musca domestica* L.).[1-3] Previous work has demonstrated activity in the series of N,N′-bis(aziridinylacetyl)-α,ω-polymethylenediamines (**1**). Optimum ac-

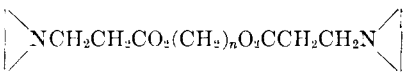


1, n = 8, 9

tivity in this series was found in compounds **1**. The series of esters (**2** and **3**) corresponding to the bisamides (**1**) did not possess chemosterilant activity.[2]



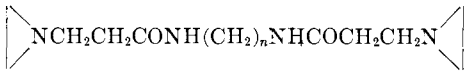
2



3

n = 6, 8, 10

We have now prepared a series of N,N′-bis(aziridinylpropionyl)-α,ω-polymethylenediamines (**4**), in which the two nitrogen functions of compounds **1** have been separated by an additional methylene group. Compounds **4** were prepared by the addition of aziridine to the corresponding bisacrylamides **5**. The bisaziridinyl-

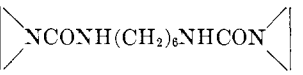


4, n = 6, 8, 10, 12

$CH_2{=}CHCONH(CH_2)_nNHCOCH{=}CH_2$

5

propionamides (**4**) and bisacrylamides (**5**) were inactive as inhibitors of reproduction in the housefly. This result appears to further define the requirement that the alkylating group must be α to the carbonyl in this series. However, several very active napthalene biscarbamoylaziridines and one aliphatic carboxamide (**6**) prepared by Borkovec[4] were active chemosterilants.



6

The rationale for testing the aziridine compounds and other alkylating agents as insect chemosterilants has been reported by Borkovec, who suggested a similarity of rapid cellular division in reproductive and cancerous systems.[5] An impetus was thus given to the investigation of a number of "carcinostatic" alkylating agents as potential insect chemosterilants. It seemed reasonable to reverse this rationale and screen the compounds prepared on this program against a tumor system. The use of the lower homologs of the bis-

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

(2) W. A. Skinner, J. Hayford, T. E. Shellenberger, and W. T. Colwell, *ibid.*, **9**, 605 (1966).

(3) W. A. Skinner, M. Cory, T. E. Shellenberger, and J. I. DeGraw, *ibid.*, **10**, 102 (1967).

(4) A. B. Borkovec and C. W. Wood, *ibid.*, **8**, 545 (1965).

(5) A. B. Borkovec, *Science*, **137**, 1034 (1962).

TABLE II

N,N′-POLYMETHYLENEBISACRYLAMIDES

$H_2C{=}CHCONH(CH_2)_nNHCOCH{=}CH_2$

Compd	n	Crystn solvent	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
7	6[a]	MeOH	145–146	51	64.2	8.99	12.5	64.1	8.93	12.3
8	8[b]	MeOH		53						
9	10	EtOH	118–122	71	68.5	10.1	9.99	68.1	9.98	10.2
10	12	MeOH	118–122	20	70.1	10.5	9.08	70.1	10.6	9.23

[a] C. Kranzlein and M. Corell [German Patent 743,466 (1952)] report mp 138–140°; British Patent 875,378 (1961) [*Chem. Abstr.* **57**, 12006*f* (1962)] reports mp 143–144°. [b] Reference 2.

TABLE III

N,N′-BIS(AZIRIDINYLACETYL)-α,ω-POLYMETHYLENEDIAMINES

$NCH_2CH_2CONH(CH_2)_nNHCOCH_2CH_2N$

Compd	n	Crystn solvent	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
11	6[a]		114–122	67						
	6[b]	EtOH–Et_2O	202–206		42.0	7.73	12.2	42.0	7.52	12.0
12	8		80–90	80						
	8[b]	EtOH	*Ca.* 165		44.7	7.92	11.6	44.6	7.92	11.7
13	10		74–90	62						
	10[b]	EtOH	180–194		47.0	8.22	10.9	47.2	8.26	11.0
14	12		85 dec	62						
	12[b]	EtOH	158–161		48.9	8.53	10.4	48.7	8.53	10.6

[a] T. Oshima, C. Saito, and T. Okagami, Japanese Patent 29,844 (1964); *Chem. Abstr.*, **62**, 11782*b* (1965). No data are given in this patent. [b] Bis HCl salts of the derived, bis-mustards (see Experimental Section).

acrylamides (n = 1–6) as antitumor agents has been claimed by several laboratories,[6] and the results of the antitumor screening of a large number of aziridine compounds have been tabulated.[7] The results obtained for some of the compounds reported in this paper are given in Table I along with data for "HN_2" obtained in a similar test system. Compound **12** (n = 8) demonstrated interesting activity in this screen, its favorable therapeutic index being coupled with a low degree of bone marrow depression.

Experimental Section

The following are general procedures for the preparation of compounds reported in Tables II and III.

N,N′-Decamethylenebisacrylamide (9).—Acrylyl chloride (11.8 ml, 13.5 g, 0.15 mole), dissolved in 150 ml of benzene, and K_2CO_3 (27.6 g, 0.20 mole) were stirred at 0° under N_2. To this solution was added 6.5 g (0.039 mole) of 1,10-decamethylenediamine dissolved in 250 ml of benzene. After addition was complete (0.5 hr), the reaction was stirred at 0° for 2 hr. Water was then added and the resulting precipitate collected by filtration. The residue was then triturated with 0.1 *N* HCl and 0.1 *N* NaOH, washed with water, filtered again, and dried *in vacuo*. This gave 8.2 g (70.7%) of white, solid acrylamide. Crystallization from methanol at −80° gave an analytical sample, mp 118–122°. Heating of these compounds led to polymerization: λ_{max}^{Nujol} 5.98 and 6.04 (C=O), 6.17 (C=C), 3.08 μ (NH).

N,N′-Decamethylenebis(β-aziridinylpropionamide) (13).—A mixture of 2.00 g (0.00712 mole) of bisacrylamide **9**, 50 ml of methanol, and 3.66 ml (3.05 g, 0.0712 mole) of aziridine was stirred at room temperature for 8 days under N_2. All of the acrylamide did not dissolve at first, but after 4 days the solution was clear. The solvent was removed *in vacuo* and the residue was dried at 1 mm for 12 hr to yield 1.04 g (61.5%) of white, spongy solid: λ_{max}^{Nujol} 6.1 (C=O), 3.04 μ (NH). An analytical sample, mp 194°, of the bis-mustard hydrochloride was prepared by reaction with gaseous HCl in ethanol.

Biological Methods and Results.—The compounds listed in Tables II and III were evaluated as inhibitors of reproduction in our colony of houseflies (*Musca domestica* L.). The method was that previously reported.[1]

Ehrlich Ascites.—The tumor was maintained routinely by weekly intraperitoneal injection of male Swiss mice (Simonsen Lab) with 1×10^6 tumor cells, in a volume of 0.2 ml of saline. For screening studies, the mice received 1×10^6 tumor cells intraperitoneally. Twenty-four hours later the mice were randomly distributed into control and experimental groups. There were ten mice per experimental group and between 30 and 40 control mice per experiment. The compounds were dissolved in H_2O or suspended by sonification in water with Tween 80, 2 drops/10 ml, and injected intraperitoneally once daily for six injections. All animals were sacrificed 24 hr after the last injection and the volume of ascites was measured. In some instances, the total packed-cell volume (TPCV) was determined. The TPCV is determined as the product of ascitocrit (per cent packed cells) and the total ascitic tumor volume (see Table I).

Where indicated and possible, the therapeutic index (TI) was determined. The TI is the ratio of the dose which kills 10% of the mice (LD_{10}) to the dose which inhibits TV 90% (ED_{90}).

In addition, sternal bone marrow samples were taken in some instances to determine degree of depression of marrow elements.

Acknowledgment.—This work was supported by U. S. Public Health Service Grant GM 11491. We wish to thank V. Tovar for assistance with the fly screening studies. The Ehrlich ascites data was obtained under the supervision of Dr. J. Scholler of these laboratories.

(6) (a) T. Oshima, C. Saito, and T. Okagami, Japanese Patent 29,844 (1964); *Chem. Abstr.*, **62**, 11782 (1965); (b) A. S. Tomcufcik, S. D. Willson, A. W. Vogel, and A. Sloboda, *Nature*, **191**, 611 (1961); British Patent 905,186 (1962).

(7) T. H. Goodridge, W. T. Huntress, and R. P. Bratzel, *Cancer Chemotherapy Rept.*, **26**, 341 (1963).

(1) S. R. Barker, C. S. Pittman, J. A. Pittman, Jr., and S. R. Hill, Jr., *Ann. N. Y. Acad. Sci.*, **86**, 545 (1960).

3-Halogenated Thyronines

PAUL BLOCK, JR.

Department of Chemistry, University of Toledo, Toledo, Ohio

Received April 4, 1967

The discovery of the thyroxine-antagonistic properties of 3,3′-diiodothyronine and 3,3′,5′-triiodothyronine[1] has led to a study in this laboratory of methods