The Preparation and Biological Activity of some N,N'-Bis(haloacyl)-polymethylenediamines
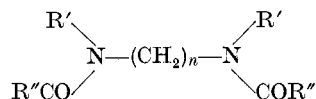
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We have reported[1] that several symmetrical N,N'-dialkyl-N,N'-bis(dichloroacetyl)-1,4-xylylenediamines were found to possess unusually high antiamoebic properties both *in vitro* and *in vivo* and that a select few also showed antispermatogenic activity in rats and other species. This most intriguing combination of activities has led to additional investigations in several directions. Primarily, we have been searching for more potent reversible antispermatogenic agents. At the same time, we wished to determine whether it was possible to separate the high amoebacidal activity from the antispermatogenic activity. Both objectives have been achieved.
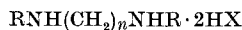
In the present communication, we are reporting our studies with some N,N'-bis(haloacyl)-polymethylenediamines (I) in which R' = H, alkyl, hydroxyalkyl, alkoxyalkyl and acyloxyalkyl; $n = 2$–12; and R" = halogenated-alkyl. Future publications will

$$
\begin{array}{c}
\text{R'} \qquad\qquad \text{R'} \\
\diagdown\qquad\qquad\diagup \\
\text{N}-(\text{CH}_2)_n-\text{N} \\
\diagup\qquad\qquad\diagdown \\
\text{R"CO} \qquad\qquad \text{COR"}
\end{array}
$$

deal with related compounds in which the aliphatic chain and R' have been varied further.

Many of the polymethylene derivatives were found to be capable of inhibiting spermatogenesis in the rat, in contrast to few in the 1,4-xylylenediamine series. As anticipated, most of these compounds were also good amoebacidal agents. However, for the first time in our current investigations, we have prepared a substance which has antispermatogenic properties and is practically devoid of amoebacidal activity in hamsters. This has been

accomplished with only one compound, N,N'-bis(dichloroacetyl)-1,8-octamethylenediamine (II). This compound has proved to be the most active one examined to date.* As an oral antispermatogenic agent, it is four to eight times as potent as N,N'-bis(dichloroacetyl)-N,N'-diethyl-1,4-xylylenediamine (Win 13,099), the most active compound in the xylylenediamine series, and approximately four hundred times less active as an amoebacidal agent. The acute oral toxicity (LD_{50}) of N,N'-bis(dichloroacetyl)-1,8-octamethylenediamine (II) in mice is greater than 16,000 mg/kg.

Table I. N,N'-Disubstituted-polymethylenediamines

$$RNH(CH_2)_nNHR \cdot 2HX$$

R	n	X	m.p. °C[a]	% Yield	Formula (base)	% Halogen Calcd.	Found
C_2H_5	4	Cl	300–302	25[b]	$C_8H_{20}N_2$	32·70	32·80
C_2H_5	5	Cl	288–290	49[b]	$C_9H_{22}N_2$	30·70	31·10
$i\cdot C_3H_7$	6	Br	229–232	72[c]	$C_{12}H_{28}N_2$	44·11	44·12
CH_2CH_2OH	6	Br	163–166	51[c]	$C_{10}H_{24}N_2O_2$	N, 7·65	N, 7·33
$CH_2CH_2OCH_3$	6	Br	194–197	54[c]	$C_{12}H_{28}N_2O_2$	40·54	40·60
C_2H_5	7	Cl	281–283	53[b]	$C_{11}H_{26}N_2$	27·40	27·40
C_2H_5	8	Cl	274–276	32[b]	$C_{12}H_{28}N_2$	26·80	27·19
C_2H_5	9	Cl	280–281	80[b]	$C_{13}H_{30}N_2$	25·40	25·20
C_2H_5	10	Br	275–276	73[c]	$C_{14}H_{32}N_2$	40·97	41·10

[a] Uncorrected. [b] Prepared by lithium aluminium hydride reduction method. [c] Prepared from ω,ω-polymethylenedibromide.

The uniqueness of this compound is especially apparent when one considers that the lower and higher homologues (I, R′ = H, R″ = $CHCl_2$, n = 5,6,7,9,10) were found to be very effective against *Endamoeba criceti* in hamsters. The same is true for the bis-tertiary amide, N,N'-bis(dichloroacetyl)-N,N'-diethyl-1,8-octamethylenediamine. These close relatives were also found to be considerably less active than II in blocking spermatogenesis.

* Details of the biological and toxicological data on this compound as well as other members of the series will be reported elsewhere.

The bis-amides listed in Table II were prepared from the corresponding diamines by a Schotten–Baumann reaction with the appropriate halogenated acyl chloride. Dichloroacylation of the primary-diamines could also be carried out with methyl dichloroacetate. The bis-acyloxy compound, N,N'-bis(acetoxyethyl)-N,N'-bis(dichloroacetyl)-1,6-hexamethylenediamine, was prepared from the bis-hydroxyethyl derivative with acetic anhydride. For the most part, the bis-amides were obtained as colourless, crystalline solids which are insoluble in water.

The intermediate N,N'-dialkyl polymethylenediamines were prepared either by lithium aluminium hydride reduction of the N,N'-dialkyl-ω,ω'-polymethylenedicarboxamides or by reaction of ω,ω'-polymethylene dibromides with an excess of the appropriate alkylamine. The hydride reduction procedure was also employed for the synthesis of N,N'-diethyl-3-methyl-1,6-hexanediamine. All of the N,N'-substituted polymethylenediamines were characterized as the dihydrochlorides or dihydrobromides.
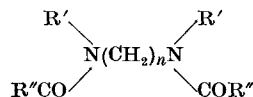
Experimental*

N,N'-*Diethyl-3-methyladipamide*. A mixture of 3-methyladipic acid (25 g, 0·156 mole) and thionyl chloride (40 g, 0·343 mole) in benzene (150 ml) was refluxed overnight and the excess thionyl chloride and solvent were removed by distillation. The crude residue was dissolved in benzene and the solution added dropwise with stirring and cooling to 250 ml of 70 per cent aqueous ethylamine. After evaporation of the unreacted ethylamine, the bis-amide was azeotroped to dryness with benzene. The crude product was crystallized with ethyl acetate; yield, 15 g (45 per cent). One recrystallization from ethyl acetate gave 11·5 g, m.p. 131–133° (uncorr.).

Anal. Calcd. for $C_{11}H_{22}N_2O_2$: N, 13·07. Found: N, 13·1.

N,N' - *Diethyl - 3 - methyl - 1,6 - hexanediamine   dihydrochloride*. Twelve grams of N,N'-diethyl-3-methyladipamide was added portionwise to a stirred suspension of lithium aluminium hydride (10 g) in a mixture of absolute ether (500 ml) and dry tetrahydrofuran (100 ml). After refluxing for 6 h, the stirred mixture was treated dropwise with 10 ml of water, 10 ml of 20 per cent sodium

* All melting points are corrected unless otherwise indicated.

Table II. N,N'-Bis(haloacyl)-polymethylenediamines

$$\begin{array}{c}
R' \qquad\qquad R' \\
\diagdown\qquad\diagup \\
N(CH_2)_nN \\
\diagup\qquad\diagdown \\
R''CO \qquad\qquad COR''
\end{array}$$

R'	R''	n	m.p., °C	Yield, %	Formula	Calcd. Cl	Calcd. N	Found Cl	Found N
H	CHCl$_2$	2	207–210	62	C$_6$H$_8$Cl$_4$N$_2$O$_2$	50·39	9·92	50·30	9·78
H	CHCl$_2$	3	135·6–137·4	32	C$_7$H$_{10}$Cl$_4$N$_2$O$_2$	47·90	9·47	49·20	9·24
C$_2$H$_5$	CHCl$_2$	3	^{a}	35	C$_{11}$H$_{18}$Cl$_4$N$_2$O$_2$	40·20	7·95	39·90	7·90
H	CHCl$_2$	4	158–160·8	73	C$_8$H$_{10}$Cl$_4$N$_2$O$_2$	45·73	9·04	45·70	8·98
C$_2$H$_5$	CHCl$_2$	4	141–142	75	C$_{12}$H$_{20}$Cl$_4$N$_2$O$_2$	38·74	7·65	38·50	7·51
H	CHCl$_2$	5	146–148	47	C$_9$H$_{14}$Cl$_4$N$_2$O$_2$	C, 33·27 H, 4·36		33·60 4·47	
C$_2$H$_5$	CHCl$_2$	5	106–107	67	C$_{13}$H$_{22}$Cl$_4$N$_2$O$_2$	37·35	7·37	37·40	7·23
H	CH$_2$Cl	6	132–133·6^b	70	C$_{10}$H$_{18}$Cl$_2$N$_2$O$_2$	26·34	10·41	26·50	10·11
H	CHBr$_2$	6	161–165	63	C$_{10}$H$_{16}$Br$_4$N$_2$O$_2$	61·97	5·43	62·30	5·50
H	CHCl$_2$	6	132·4–134·2^c	62	C$_{10}$H$_{16}$Cl$_4$N$_2$O$_2$	41·94	8·29	42·30	8·60
H	CHF$_2$	6	100·2–102·4^d	60	C$_{10}$H$_{16}$F$_4$N$_2$O$_2$	C, 44·10 H, 5·92	10·29	44·12 5·80	9·95
H	CCl$_3$	6	152·6–154·4	34	C$_{10}$H$_{14}$Cl$_6$N$_2$O$_2$	52·26	6·89	52·20	6·90
H	CCl$_2$CH$_3$	6	105·2–113·6	71	C$_{12}$H$_{20}$Cl$_4$N$_2$O$_2$	38·73	7·65	38·40	7·71
C$_2$H$_5$	CH$_2$Cl	6	^{e}	78	C$_{14}$H$_{26}$Cl$_2$N$_2$O$_2$	21·80	8·61	22·10	8·38
C$_2$H$_5$	CHBr$_2$	6	109·4–111·6	61	C$_{14}$H$_{24}$Br$_4$N$_2$O$_2$	55·90	4·90	55·75	4·79
CH$_3$	CHCl$_2$	6	122·2–123·2	61	C$_{12}$H$_{20}$Cl$_4$N$_2$O$_2$	38·74	7·65	38·60	7·59

C_2H_5	$CHCl_2$	6	72·8–74·4	64	$C_{14}H_{24}Cl_4N_2O_2$	35·97	7·11	35·41	7·07
$CH_2CH_2CH_3$	$CHCl_2$	6	56–58·2	56	$C_{16}H_{28}Cl_4N_2O_2$	33·58	6·64	33·65	6·62
$CH(CH_3)_2$	$CHCl_2$	6	105·6–110	66	$C_{16}H_{28}Cl_4N_2O_2$	33·58	6·64	34·00	6·56
$(CH_2)_3CH_3$	$CHCl_2$	6	f	70	$C_{18}H_{32}Cl_4N_2O_2$	31·50	6·22	31·60	6·12
C_2H_5	CCl_3	6	g	91	$C_{14}H_{22}Cl_6N_2O_2$	45·92	6·05	45·50	6·00
CH_2CH_2OH	$CHCl_2$	6	127·8–130·2	59	$C_{14}H_{24}Cl_4N_2O_4$	33·27	6·57	33·00	6·41
$CH_2CH_2OCOCH_3$	$CHCl_2$	6	64·2–66	62	$C_{18}H_{28}Cl_4N_2O_6$	27·77	5·49	27·50	5·51
$CH_2CH_2OCH_3$	$CHCl_2$	6	96·6–98·2	64	$C_{16}H_{28}Cl_4N_2O_4$	31·21	6·16	31·50	5·97
$CH_2CH_2OC_2H_5$	$CHCl_2$	6	92–93·6	76	$C_{18}H_{32}Cl_4N_2O_4$	29·40	5·81	29·30	5·76
C_2H_5	CH_2CH_2Cl	6	48·8–51	42	$C_{16}H_{30}Cl_2N_2O_2$	20·07	7·93	19·90	7·65
C_2H_5	CCl_2CH_3	6	f	68	$C_{16}H_{28}Cl_4N_2O_2$	33·58	6·64	33·80	6·69
H	$CHCl_2$	7	113·4–115	31	$C_{11}H_{18}Cl_4N_2O_2$	40·30	7·96	40·30	7·98
C_2H_5	$CHCl_2$	7	h	50	$C_{15}H_{26}Cl_4N_2O_2$	34·76	6·87	34·00	6·64
H	CH_2Cl	8	118·2–119·2	44	$C_{12}H_{22}Cl_2N_2O_2$	23·88	9·43	24·20	9·50
H	$CHCl_2$	8	122·4–123·6	52	$C_{12}H_{20}Cl_4N_2O_2$	38·74	7·64	38·50	7·56
C_2H_5	$CHCl_2$	8	i	66	$C_{16}H_{28}Cl_4N_2O_2$	33·28	6·57	33·70	6·34
H	CCl_3	8	123·6–126·2	43	$C_{12}H_{18}Cl_6N_2O_2$	48·80	6·44	48·50	6·36
H	$CHCl_2$	9	81·2–84	31	$C_{13}H_{22}Cl_4N_2O_2$	37·30	7·36	37·20	7·38
C_2H_5	$CHCl_2$	9	j	62	$C_{17}H_{30}Cl_4N_2O_2$	32·59	6·44	32·40	6·33
H	$CHCl_2$	10	87·8–89·8	75	$C_{14}H_{24}Cl_4N_2O_2$	35·97	7·11	36·00	7·07
C_2H_5	$CHCl_2$	10	k	62	$C_{18}H_{32}Cl_4N_2O_2$	31·49	6·22	31·31	6·14
H	$CHCl_2$	12		78	$C_{20}H_{36}Cl_4N_2O_2$	29·65	5·86	29·40	5·82

a B.p., 177–180°/0·005 mm. b Lit. m.p. 131–132° [A. P. Phillips, *J. Amer. chem. Soc.*, **77**, 2400 (1955)]. c Lit. m.p. 136° [B. J. Heywood, Brit. Pat. 712, 745 July 28, 1954]. d Disclosed but not characterized by G. W. Rigby and H. E. Schroeder, U. S. Pat.2, 409,315, Oct. 15, 1946. e n_D^{25} 1·5026. f Obtained as an oil which was dried at 40°/2·5 mm. g n_D^{25} 1·5190 h n_D^{25} 1·5100. i n_D^{25} 1·5090. j n_D^{25} 1·5069. k n_D^{25} 1·5021.

hydroxide solution, and finally with 30 ml of water. After filtration and drying over anhydrous magnesium sulphate, the solvent was removed by distillation. The residual oil was treated with alcoholic hydrogen chloride to yield 7 g of colourless dihydrochloride. Recrystallization from isopropyl alcohol–95 per cent ethanol gave 5·5 g of product, m.p. 270–271° (uncorr.).

Anal. Calcd. for $C_{11}H_{26}N_2.2HCl$: N, 10·81. Found: N, 11·06.

N,N'-Bis(dichloroacetyl)-N,N'-diethyl-3-methyl-1,6-hexanediamine. A solution of dichloroacetyl chloride (11·4 g) in ethylene dichloride (20 ml) was added dropwise with stirring to a cooled (0·5°) mixture containing *N,N'*-diethyl-3-methyl-1,6-hexanediamine dihydrochloride (9 g), sodium hydroxide (6·2 g) water (100 ml) and ethylene dichloride (100 ml). After the addition was complete, the organic layer was separated and washed successively with dilute hydrochloric acid, dilute sodium hydroxide solution, and water. The solvent was removed by distillation and the product was dried at 70° and 1 mm, n_D^{26} 1·5122.

Anal. Calcd. for $C_{15}H_{26}Cl_4N_2O_2$: Cl, 34·76; N, 6·87. Found: Cl, 35·01; N, 6·71.

1,4-Bis(ethylamino)-2-butene dihydrobromide. 1,4-Dibromo-2-butene (21·4 g, 0·1 mole) was added slowly with stirring to 70 per cent aqueous ethylamine (250 ml). After stirring for 16 h, the solvent and excess ethylamine were removed by evaporation under reduced pressure. The residue was crystallized from isopropyl alcohol to give 17 g of colourless product, m.p. 254–256° (uncorr.).

Anal. Calcd. for $C_8H_{18}N_2.2HBr$: Br, 52·56. Found: Br, 48·90.

N,N'-Bis(dichloroacetyl)-1,4-bis(ethylamino)-2-butene. The 1,4-bis(ethylamino)-2-butene dihydrobromide (17 g) was treated with dichloroacetyl chloride according to the procedure described above. A pale orange oil was obtained which was crystallized from isopropyl alcohol to give 17 g of colourless product, m.p. 110–111·2°.

Anal. Calcd. for $C_{12}H_{18}Cl_4N_2O_2$: Cl, 39·0; N, 7·70. Found: Cl, 39·3; N, 7·62.

Summary. The preparation of a series of *N,N'*-bis(haloacyl)-polymethylenediamines is reported. Several of the compounds were found to

be very effective amoebacidal agents and also capable of blocking spermato-genesis in rats.   One compound in the present series was found to be very active as an antispermatogenic agent and to have only weak antiamoebic properties.

Reference

[1] Surrey, A. R. and Mayer, J. R.   This Journal, **3**, 409 (1961).