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New Amoebacides—VI.[1] The Preparation of some *N,N'*-Disubstituted-*N,N'*-bis(haloacyl)-1,4-xylylenediamines

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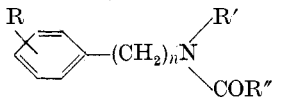
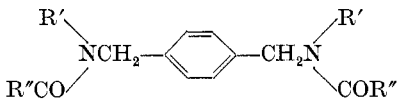
In our previous studies of potential amoebacidal agents derived from the general formula



(I)

our attention has been focused mainly on variations in R'. For the most part, R has been halogen, alkyl, and alkoxy, and R" has been varied to include CH_2Cl, $CHCl_2$ and CCl_3. In practically all cases, the presence of a dichloroacetyl group was found to be essential for optimal activity. The variations in R were not as critical. One of the more active members of this new class of antiamoebic agents, *N*-(2,4-dichlorobenzyl)-*N*-(2-hydroxyethyl)-dichloroacetamide,* was found to have an ED_{50} of 12 mg/kg against *Endamoeba criceti* in hamsters and to be an effective agent in man.

The present communication is concerned mainly with the preparation of symmetrical compounds in which R = $(CH_2)_nN(R')$-COR" and where $n = 1$. These are represented by the structural formula II.



(II)

Several of the symmetrical products in this group have been found to possess unusually high antiamoebic activity.[2] They are the most potent agents that have been examined in these Laboratories

* Mantomide ®

and appear to be more active than other synthetic amoebacidal agents described in the literature. The most effective compounds in clearing hamsters of spontaneous infection with *Endamoeba criceti* have an oral ED_{50} of 1 mg/kg and also exhibit *in vitro* activity (*E. histolytica*) in the range 1:1,000,000 to 1:17,000,000. A clinical evaluation of representative compounds from this new series indicates that they are also very effective amoebacidal agents in man.

During histopathologic studies in rats, one of the more effective amoebacidal compounds was discovered also to exert an antispermatogenic effect.* This new activity, which is unaccompanied by any obvious side effects, has been investigated and confirmed in every species tested.† Subsequent studies indicated that this activity is very sensitive to structural alterations.

The compound of choice in the present series which showed this activity is *N*,*N*′-diethyl-*N*,*N*′-bis(dichloroacetyl)-1,4-xylylenediamine (Win 13,099). It has an oral ED_{50} in hamsters (*Endamoeba criceti*) of $1 \cdot 9 \pm 0 \cdot 26$ mg/kg, an *in vitro* amoebacidal titre (*E. histolytica*) of 1:17,000,000, and an oral toxicity in mice $> 16{,}000$ mg/kg. It is interesting that the corresponding dibromoacetyl compound (II; $R' = C_2H_5$, $R'' = CHBr_2$) has an oral ED_{50} (in hamsters) $= 0 \cdot 85 \pm 0 \cdot 20$ mg/kg and is inactive as an antispermatogenic agent. The *N*,*N*′-dimethyl homologue (II; $R' = CH_3$, $R'' = CHCl_2$) was capable of blocking spermatogenesis whereas the higher homologue (II; $R' = C_3H_7$, $R'' = CHCl_2$) showed only slight activity. The isomeric isopropyl compound (II; $R' = i\text{-}C_3H_7$, $R_2 = CHCl_2$) was ineffective in this test. Other variations in R′, as well as in R″, gave compounds (Table II) which showed only amoebacidal properties. Nuclear substitution of a chlorine atom only enhanced the amoebacidal action. The ED_{50} of 2-chloro-*N*,*N*′-diethyl-*N*,*N*′-bis-(dichloroacetyl)-1,4-xylylenediamine in hamsters was found to be $0 \cdot 47 \pm 0 \cdot 14$ mg/kg. A comparison of Win 13,099 with the *meta*-isomer, *N*,*N*′-diethyl-*N*,*N*′-bis(dichloroacetyl)-1,3-xylylenediamine, showed the latter to be less

* A detailed account of these observations will be reported by Dr. F. Coulston and Dr. H. P. Drobeck.

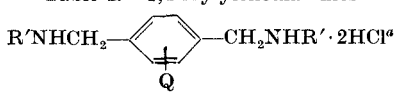
† The antispermatogenic activity of all of the compounds was investigated by Dr. A. L. Beyler and Dr. G. O. Potts. These data, as well as their endocrinologic studies, will be published elsewhere.

active as an antiamoebic agent and inactive in blocking spermatogenesis.

The question as to whether the antispermatogenic activity is related to the high *in vitro* and/or *in vivo* amoebacidal properties of the xylylene derivatives or whether the two phenomena are independent of each other has not been resolved in the present series. The compounds which showed the antispermatogenic effect are also potent antiamoebic agents. This relationship has also been found to be true for practically all of the other compounds investigated.

Most of the bis-amides listed in Table I were prepared from terephthaldehyde by reductive alkylation of the appropriate primary amine followed by bis-acylation of the resulting secondary amines. The yields were quite satisfactory in both steps.

Table I. 1,4-Xylylenediamines



R'	Q	Yield, %	Formula (base)	Chlorine,[b] %	
				Calcd.	Found
H	2,5-$(CH_3)_2$	24	$C_{10}H_{16}N_2$	N_k, 13·67	11·41
CH_3	H	79	$C_{10}H_{18}N_2$	29·91	29·40
C_2H_5	H	72	$C_{12}H_{20}N_2$	26·74	26·50
C_2H_5	2-Cl	23	$C_{12}H_{19}ClN$	23·62	23·23
C_3H_7	H	92	$C_{14}H_{24}N_2$	24·20	24·03
i-C_3H_7	H	46	$C_{14}H_{24}N_2$	24·18	23·93
CH_2CH_2OH[c]	H	50	$C_{12}H_{20}N_2O_2$	N_{AP}, 12·47	11·95
$CH_2CH_2OC_2H_5$	H	37	$C_{16}N_{28}N_2O_2$	20·07	19·93

[a] The dihydrochloride salts melted above 250°. [b] Ionic chlorine. [c] Isolated as base, m.p. 127–129° (uncorr.).

Initially, terephthaldehyde was prepared by hydrolysis of α,α,α′,α′-tetrabromo-*p*-xylene with concentrated sulphuric acid.[3] However, this method proved unsatisfactory for the preparation of large quantities of the bis-aldehyde. A better method was found in applying the Hass and Bender procedure[4] to α,α′-dibromo-*p*-xylene. The use of this reaction has apparently not been reported for the preparation of bis-aldehydes. We have found that

the reaction of 2-nitropropane with α,α′-dibromo-*p*-xylene in alcohol with potassium hydroxide as the base, gives yields of terephthaldehyde up to 80 per cent. The isomeric isophthaldehyde was also obtained in similar yields by this procedure.

Attempts to employ α,α′-dichloro-*p*-xylene in place of the dibromo analogue for the preparation of the bis-aldehyde by the above procedure were unsuccessful. The synthesis of α,α′-dichloro-*p*-xylene was carried out starting with *p*-xylene and sulphuryl chloride in the presence of benzoyl peroxide. On a 0·1 molar scale using 150 mg of catalyst, the reaction is very rapid, giving yields around 65 per cent. Less catalyst failed to give a satisfactory reaction even over a longer period of time. Experiments involving diluents ($CHCl_3$ or CCl_4) similarly failed to give comparable yields. When the reaction was scaled up several times, it was necessary to increase the quantities of benzoyl peroxide in order to obtain reasonable yields of the bis-chloro compound.

The bis-secondary amines listed in Table I were prepared by condensation of terephthaldehyde with two moles of the primary amine in alcohol solution followed by catalytic hydrogenation of the resulting bis-anil in the presence of palladium–charcoal. In no instance was the intermediate bis-anil isolated.

In some cases, large scale production of the substituted 1,4-xylylenediamines was carried out by direct alkylation of the primary amine with α,α′-dichloro-*p*-xylene. For example, with a twenty-fold excess of 70 per cent aqueous ethylamine, an 85 per cent yield of *N*,*N*′-diethyl-1,4-xylylenediamine dihydrochloride could be obtained. The corresponding 2-chloro compound was also prepared by this method.

N,*N*′-Bis(2-ethoxyethyl)-1,4-xylylenediamine was obtained by the reductive alkylation of 2-ethoxyethylamine with terephthalaldehyde using palladium–charcoal as the catalyst. The 2-ethoxyethylamine was prepared in poor yield by the reaction of the sodium salt of ethanolamine with ethyl iodide. A more satisfactory procedure for the synthesis of the amine involves three steps: (1) preparation of ethoxymethyl chloride from ethanol, hydrochloric acid and formaldehyde, (2) conversion of the chloride to the nitrile with cuprous cyanide, and (3) catalytic hydrogenation of the nitrile in the presence of ammonia in methyl

alcohol. After removing the excess of ammonia, the solution of the ethoxyethylamine could be used directly in the reaction with terephthaldehyde.

The general procedure for the preparation of the bis-amides listed in Table II involved acylation of the diamines in an ethylene dichloride–water mixture with a haloacetyl chloride in the presence of sodium hydroxide. Only in the case of the *N*,*N*′-dimethyl and *N*,*N*′-bis(2-hydroxyethyl)-1,4-xylylenediamines was it possible to effect dichloroacylation using methyl dichloroacetate. This parallels our observations with the corresponding benzylamine derivatives.

Experimental*

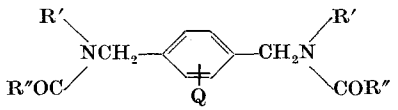
α,α′-Dichloro-p-xylene. A mixture of *p*-xylene (27 ml, 0·1 mole), sulphuryl chloride (37 ml, 0·27 mole) and benzoyl peroxide (400 mg) was refluxed on a steam bath for 70 min. An equal volume of pentane was added to the reaction mixture at room temperature and the resulting solution was cooled in ice. The crude product (22·5 g) which separated was filtered off and recrystallized from hexane, m.p. 90–95°[5] (uncorr.).

Terephthaldehyde – Modified Hass and Bender Procedure. A 3-necked flask, equipped with a stirrer, reflux condenser, and thermometer, was charged with an alcoholic solution of potassium hydroxide prepared by heating potassium hydroxide pellets (11·2 g, 0·20 mole) and commercial absolute alcohol (200 ml). To this was then added 19·6 g (0·22 mole) of 2-nitropropane in one portion. After the temperature was adjusted to 45°, α,α′-dibromo-*p*-xylene (26·4 g, 0·10 mole) was added all at once. The reaction temperature increased to reflux within about 5 min and then subsided slowly. After a total reaction time of 4 h, the mixture was filtered and the filtrate concentrated to give a solid residue. To this was added about 50 ml of water and enough 5 per cent sodium hydroxide to make the mixture alkaline. Filtration gave the crude bis-aldehyde which was recrystallized from 180 ml of 45 per cent ethanol, yield 10·4 g (78 per cent) m.p. 104–106° (uncorr.).

Ethoxyethylamine – from ethanolamine. Sodium wire (9·2 g, 0·4 mole) was added gradually with stirring to ethanolamine

* All melting points are corrected unless otherwise indicated.

Table II. *N,N'*-Bis(haloacyl)-1,4-xylylenediamines



R'	R"	Q	m.p., °C	Yield, %	Formula	Analyses, %			
						Calcd.	Found	Calcd.	Found
H	Cl_2CH	H	201·2–204·4	29	$C_{12}H_{12}Cl_4N_2O_2$	N_k, 7·83	7·71	Cl,[a] 39·59	39·30
H	Cl_2CH	2,5-$(CH_3)_2$	270·4–271·2	11	$C_{14}H_{16}Cl_4N_2O_2$	7·25	7·38	Cl,[b] 36·75	36·80
CH_3	Cl_2CH	H	105·2–107·7	50	$C_{14}H_{16}Cl_4N_2O_2$	C, 43·54	43·98	Cl,[c] 36·75	36·39
						H, 4·18	3·96		
C_2H_5	$ClCH_2$	H	100·4–103·2	65	$C_{16}H_{22}Cl_2N_2O_2$	C, 55·66	55·68	20·54	20·75
						H, 6·42	5·95		
C_2H_5	Br_2CH	H	134·8–136·4	77	$C_{16}H_{20}Br_4N_2O_2$	N_k, 4·74	4·65	Br,[b] 54·00	53·94
C_2H_5	Br_2CH	2-Cl	115·2–122·4	26	$C_{16}H_{19}Br_4ClN_2O_2$	C, 30·70	30·78	N_k, 4·47	4·45
						H, 3·06	3·40		
C_2H_5	Cl_2CH	H	98·0–102·2	63	$C_{16}H_{20}Cl_4N_2O_2$	46·40	46·06	Cl,[c] 34·23	34·13
						4·87	4·66		
C_2H_5	Cl_2CH	2-Cl	90·2–92·6	83	$C_{16}H_{19}Cl_5N_2O_2$	N_k, 6·24	6·12	Cl,[b] 39·52	39·30
C_2H_5	Cl_2CH	2,5-$(CH_3)_2$	177·0–180·0	63	$C_{18}H_{24}Cl_4N_2O_2$	6·34	6·33	32·08	32·05
C_2H_5	Cl_2CH	$(CH_3)_4$	190·6–194·6	67	$C_{20}H_{28}Cl_4N_2O_2$	5·95	5·84	30·14	30·54
C_2H_5	Cl_2FC	H	95·4–100·4	96	$C_{16}H_{18}Cl_4F_2N_2O_2$	C, 42·75	42·51	N_k, 6·22	6·18
						H, 4·04	4·19		
C_2H_5	F_2CH	H	97·2–100·2	17	$C_{16}H_{20}F_4N_2O_2$	N_k, 8·04	7·92	O, 9·20	9·20
C_2H_5	Cl_3C	H	125·8–127·4	88	$C_{16}H_{18}Cl_6N_2O_2$	C, 39·78	39·55	Cl,[c] 44·05	44·05
						H, 3·75	3·50		
C_3H_7	Cl_2CH	H	81·2–84·0	77	$C_{18}H_{24}Cl_4N_2O_2$	N_k, 6·33	6·30	Cl,[a] 32·08	31·60
i-C_3H_7	$ClCH_2$	H	126·1–128·2	42	$C_{18}H_{26}Cl_2N_2O_2$	C, 57·92	57·86	Cl,[c] 19·00	18·99
						H, 7·02	7·03		
i-C_3H_7	Cl_2CH	H	175·9–180·0	48	$C_{18}H_{24}Cl_4N_2O_2$	48·89	48·60	32·07	31·86
						5·47	5·36		
$HOCH_2CH_2$	Cl_2CH	H	162·9–164·8	55	$C_{16}H_{20}Cl_4N_2O_4$	43·08	42·84	Cl,[a] 31·79	31·90
						4·51	4·90		
$OHCOCH_2CH_2$	Cl_2CH	H	133·5–137·1	62	$C_{18}H_{20}Cl_4N_2O_6$	43·05	42·99	Cl,[c] 28·24	28·02
						4·01	3·90		
$CH_3COOCH_2CH_2$	Cl_2CH	H	152·2–154·4	96	$C_{20}H_{24}Cl_4N_2O_6$	45·33	45·26	Cl,[a] 26·76	26·84
						4·57	4·60		
$C_2H_5OCH_2CH_2$	Cl_2CH	H	137·6–143·9	77	$C_{20}H_{28}Cl_4N_2O_4$	47·82	47·77	Cl,[c] 28·23	28·19
						5·62	5·68		

(88 g, 1·44 mole) at room temperature. The temperature was kept at about 70° by controlling the rate of addition of sodium, and later by external heating. After about 2·5 h almost all the sodium had dissolved and the remaining pieces were removed. The resulting solution was cooled to room temperature and ethyl iodide (56 g, 0·36 mole) was added dropwise over a period of 0·5 h, the temperature being held below 35° by a cooling bath. Stirring was then continued for an additional 0·5 h at room temperature. The product in the semi-solid reaction mixture was extracted by repeated trituration with pentane. After the pentane solution was carefully concentrated (the ethoxyethylamine tends to co-distil with pentane), the higher boiling material was collected up to 140°. This gave 8·0 g of a colourless, liquid, $n_D^{25} = 1 \cdot 410$.[6] The crude product (28 per cent yield) was used directly in the next step.

Ethoxyethylamine – from ethoxyacetonitrile. A mixture containing ethoxyacetonitrile (22 g, 0·26 mole) (prepared from ethoxymethyl chloride according to the procedure of Rigler and Henzel[7]), 16 per cent methanolic ammonia (200 ml) and Raney nickel was reduced at room temperature at a pressure of hydrogen of 1900 lb/in². After 3 h, the uptake of hydrogen was 62 per cent of theory. The catalyst was filtered off and the filtrate refluxed with nitrogen gas bubbling through it until the major portion of ammonia was removed.

Titration of an aliquot indicated a yield of 81 per cent based on the uptake of hydrogen. The solution was treated directly with half an equivalent of terephthaldehyde and refluxed for 1 h. The bis-anil was hydrogenated at 45° and 400 lb of pressure of hydrogen using 300 mg of $PdCl_2$ and 3·0 g of charcoal. The catalyst was filtered and the filtrate was concentrated *in vacuo*. After the addition of alcoholic hydrogen chloride and ether, there was obtained 16·0 g of 1,4-bis(ethoxyethylaminomethyl)benzene dihydrochloride which melted above 300°. This represents a 46 per cent yield based on terephthaldehyde.

The following example illustrates the general procedure used for the preparation of the secondary amines listed in Table I.

N,N′-*Diethyl-1,3-xylylenediamine dihydrochloride.* A mixture containing isophthalaldehyde (11 g, 0·082 mole), 70 per cent aqueous ethylamine (65 g), 95 per cent ethanol, (25 ml) palladium

chloride (300 mg), and activated charcoal (3 g) was subjected to hydrogenation at 30–40 lb pressure at room temperature. After 2 h the uptake of hydrogen was 90 per cent of theory. The reaction mixture was filtered and the filtrate evaporated to an oil and acidified with alcoholic HCl. Benzene was added and the mixture azeotroped to dryness. The resulting solid was recrystallized from 2-propanol to give 14 g of pale-grey solid (65 per cent), m.p. 212–213°.

Anal. Calcd. for $C_{12}H_{20}N_2 \cdot 2HCl$: Cl^-, 26·74. Found: Cl^-, 26·72.

The following example illustrates the general procedure for the preparation of the bis(haloacetyl)compounds listed in Table II.

N,N′-*Diethyl*-N,N′-*bis*(*dichloroacetyl*)-*1,3-xylylenediamine.* A mixture containing *N,N′*-diethyl-1,3-xylylenediamine dihydrochloride (13·5 g, 0·051 mole), water (50 ml), ethylene dichloride (100 ml), and sodium hydroxide (8·5 g, 0·21 mole) was stirred in an ice-salt bath. To this was added dichloroacetyl chloride (16·6 g, 0·112 mole) dissolved in ethylene dichloride (50 ml) while maintaining a temperature of 0–5°. After stirring for an additional 15 min in the cooling bath, the layers were separated and the organic layer was washed successively with dilute aqueous acid, water, dilute aqueous acid, water, dilute aqueous base, and water. Evaporation gave an oil (18·2 g, 87 per cent) which was dried at 0·2 mm for several hours.

Anal. Calcd. for $C_{16}H_{20}Cl_4N_2O_2$: Cl_{OX}, 34·23; N_k, 6·77. Found: Cl_{OX}, 34·72; N_k, 6·44.

Summary. The preparation of a series of *N,N′*-substituted *N,N′*-bis-(haloacyl)-1,4-xylylenediamine derivatives is presented. Many of these symmetrical compounds were found to be very potent antiamoebic agents both *in vitro* and *in vivo*. A limited number of the more active amoebacidal agents in the present work were found to have antispermatogenic activity.

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