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New Amebacides. V.[1] The Preparation of Some N-Alkoxyalkyl-N-benzyldichloroacetamides

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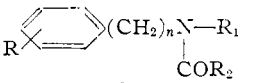
A series of N-(2-alkoxyethyl)-N-benzyldichloroacetamides and N-(3-alkoxypropyl)-N-benzyldichloroacetamides were prepared by dichloroacylation of the appropriate aminoethers. The latter were prepared by alkylation of the alkoxyalkylamine with a substituted benzyl chloride or by reductive alkylation of the alkoxyalkylamine with a substituted benzaldehyde. The reaction of ethoxyethyl chloride with substituted benzylamines was employed in the preparation of the N-(2-ethoxyethyl)-benzylamines. Some of the compounds in the present work represent the most active antiamebic agents of all the compounds reported thus far which are derived from the general structure I.

The results of our previous investigations of potential amebacides derived from the general for-



I

mula I have indicated that the most effective agents were those in which $n = 1$, R = 2,4-dichloro, 4-butoxy and 4-isopropyl, and $R_2 = CHCl_2$. These observations were made in the series where R_1 is hydroxyalkyl, alkyl, acyloxyalkyl, cyanoalkyl and carbamylalkyl. It appeared, therefore, that the direction which offered the greatest possibilities for obtaining even more active antiamebic agents was in the variation of R_1. In the present communication we are reporting the syntheses of derivatives of I in which R_1 is alkoxyethyl, alkoxypropyl and aryloxyethyl.

Most of the N-(2-alkoxyethyl)- and N-(3-alkoxypropyl)-benzylamines described in Tables I and II were prepared either by the reaction of a substituted benzyl chloride (R = 2-Cl, 2,4-Cl_2, 3,4-Cl_2, 4-NO_2) with an excess of the appropriate alkoxyalkylamine[2] or by reductive alkylation of the aminoether with a substituted benzaldehyde (R = 4-OC_4H_9, 4-$CH(CH_3)_2$ or 3,4-O_2CH_2). For the preparation of the N-(2-ethoxyethyl)-benzylamines, alkylation of the benzylamine was first carried out with 2-ethoxyethyl chloride. Later, a better procedure was developed which involved alkylation of the benzylamine with the tosyl ester of 2-ethoxyethanol. Several of the crude N-alkoxyalkylbenzylamines were converted directly to the hydrochloride salts which were used as such in the acylation step.

Dichloroacetylation of the benzylaminoethers was effected by treatment with dichloroacetyl chloride in the presence of dilute sodium hydroxide solution. For the preparation of N-(2-methoxyethyl)-4-isopropylbenzylamine and the corresponding 3,4-methylenedioxybenzylamine, the hydrochloride salt of the benzylaminoether was heated with dichloroacetyl chloride in benzene until the reaction mixture became homogeneous. In the 2-alkoxyethyl series all the dichloroacetamides were obtained as crystalline solids with the exception of N-(2-methoxyethyl)-N-(3,4-methylenedioxybenzyl)-dichloroacetamide. On the other hand, in the 3-alkoxyalkyl series most of the dichloroacetamides were obtained as high boiling viscous oils.

All of the compounds listed in Tables III and IV were screened in hamsters for amebacidal activity according to the method of Dennis, Berberian and Hansen.[3] In many respects the results obtained in the present series parallel those found for the N-benzyl-N-hydroxyalkyldichloroacetamides.[4]

The unsubstituted benzyl derivatives showed relatively lower therapeutic activity. The alkoxyethyl series was considerably more effective than the alkoxypropyl series. The most active compounds again were those in which R is 2,4-dichloro and 4-isopropyl. The peak in activity with variations in R_1 appeared to be associated with the ethoxyethyl group. Replacement of the alkoxy group by a phenoxy group resulted in a marked decrease in amebacidal activity. Of all the compounds reported thus far, N-(2-ethoxyethyl)-N-(4-isopropylbenzyl)-dichloroacetamide, with an approximate ED_{50} value of 1 mg./kg., appears to be the most potent antiamebic agent.

Acknowledgment.—The authors are indebted to Mr. M. E. Auerbach and Mr. K. D. Fleischer and staffs for the analytical data and corrected melting points and to Dr. D. A. Berberian and Mr. R. G. Slighter for the screening data.

Experimental[5]

Preparation of N-(3-Alkoxypropyl)-benzylamines (Table I).—Procedure A was employed in the preparation of the N-(3-alkoxypropyl)-chlorobenzylamines and N-(3-methoxypropyl)-4-nitrobenzylamine. Procedure B was employed in the preparation of the 4-butoxybenzylamines.

(A) 3,4-Dichlorobenzyl chloride (19.5 g.) was added dropwise with stirring to 30.9 g. of 3-ethoxypropylamine without any external cooling. The temperature rose to about 95° during the addition. Stirring was continued for 2 hr. and the mixture was allowed to stand overnight at room temperature. The solution was made strongly basic with 35% sodium hydroxide and the organic layer was taken up in ethylene dichloride. After drying with anhydrous potassium carbonate the solvent was removed by distillation under reduced pressure and the residue was fractionally distilled. In several cases the residue was dissolved in isopropyl alcohol and the calculated amount of alcoholic hydrogen chloride was added. The hydrochloride salt was filtered off and recrystallized from ethyl alcohol.

(B) A mixture of 4-butoxybenzaldehyde (17.9 g.) and 13.2 g. of 3-butoxypropylamine was heated *in vacuo* on a steam-bath for a few minutes, dissolved in 150 ml. of absolute ethyl alcohol and then reduced catalytically with palladium-on-charcoal at a hydrogen pressure of about two at-

(1) Paper IV, A. R. Surrey and George Y. Lesher, THIS JOURNAL, **78**, 2573 (1956).

(2) W. P. Utermohlen, *ibid.*, **67**, 1506 (1945); W. R. Boon, *J. Chem. Soc.*, 307 (1947).

(3) E. W. Dennis, D. A. Berberian and S. Hansen, *Am. J. Trop. Med.*, **29**, 683 (1949).

(4) A. R. Surrey, THIS JOURNAL, **76**, 2214 (1954).

(5) All melting points are corrected unless otherwise indicated.

TABLE I

N-(3-ALKOXYPROPYL)-BENZYLAMINES R-C$_6$H$_4$-CH$_2$NHCH$_2$CH$_2$CH$_2$OR$_3$

R	R$_3$	B.p., °C.	Mm.	n^{25}D	Yield, %	Formula	Nitrogen, % Calcd.	Found	M.p., °C.	Hydrochlorides, analyses, % Calcd. C	H	Cl$^-$	Found C	H	Cl$^-$
2,4-Cl$_2$	CH$_3$	132–134	0.5	1.5312	86	C$_{11}$H$_{15}$Cl$_2$NO	5.64	5.62	128.5–130.5	46.40	5.66	12.45	46.61	5.99	12.57
2,4-Cl$_2$	CH$_2$CH$_3$	132–134	.5	1.5203	77	C$_{12}$H$_{17}$Cl$_2$NO	5.34	5.32	127.8–133.8	48.26	6.07	11.89	48.60	6.18	11.91
2,4-Cl$_2$	CH(CH$_3$)$_2$	140–142	.3	1.5170	89	C$_{13}$H$_{19}$Cl$_2$NO	5.07	5.12	141.6–142.2	49.92	6.45	11.34	50.05	6.41	11.42
2,4-Cl$_2$	(CH$_2$)$_3$CH$_3$	146–148	.3	1.5100	76	C$_{14}$H$_{21}$Cl$_2$NO	4.83	4.98	115.2–117.6	51.47	6.79	10.85	51.71	6.67	10.83
3,4-Cl$_2$	CH$_3$					C$_{11}$H$_{15}$Cl$_2$NO			214.1–215.7	46.40	5.66	12.45	46.65	5.83	12.50
3,4-Cl$_2$	CH$_2$CH$_3$					C$_{12}$H$_{17}$Cl$_2$NO			217.1–219.2	48.26	6.07	11.89	48.22	6.07	12.13
3,4-Cl$_2$	CH(CH$_3$)$_2$	134–137	.2	1.5178	67	C$_{13}$H$_{19}$Cl$_2$NO	5.07	5.11	208.0–209.2	49.92	6.45	11.34	49.72	6.64	11.30
3,4-Cl$_2$	(CH$_2$)$_3$CH$_3$	162–165	.7	1.5152	76	C$_{14}$H$_{21}$Cl$_2$NO	4.83	4.84	184.4–185.8	51.47	6.79	10.85	51.36	6.79	10.83
4-OC$_4$H$_9$	CH$_3$					C$_{15}$H$_{25}$NO$_2$			164–165[a]	62.58	9.11	12.32	62.17	8.98	12.32
4-OC$_4$H$_9$	(CH$_2$)$_3$CH$_3$					C$_{18}$H$_{21}$NO$_2$			125–126[a]	65.53	9.78	9.78	65.11	9.74	10.82
4-NO$_2$	CH$_3$					C$_{11}$H$_{16}$N$_2$O$_3$			188–190[a]			13.60			13.49

[a] Uncorrected melting point.

TABLE II

N-(2-ALKOXYETHYL)-BENZYLAMINES R-C$_6$H$_4$-CH$_2$NHCH$_2$CH$_2$OR$_3$

R	R$_3$	B.p., °C.	Mm.	n^{25}D	Yield, %	Formula	Nitrogen, % Calcd.	Found	M.p., °C.	Hydrochlorides, analyses, % Calcd. C	H	Cl$^-$	Found C	H	Cl$^-$
H	CH$_2$CH$_3$	75	0.4	1.4985	15	C$_{11}$H$_{17}$NO	7.81	7.78							
4-CH(CH$_3$)$_2$	CH$_3$	142–144	11	1.4995	54	C$_{13}$H$_{21}$NO	6.75	6.67							
4-CH(CH$_3$)$_2$	CH$_2$CH$_3$	95–100	0.3	1.4914	47	C$_{14}$H$_{23}$NO	6.33	5.98							
4-CH(CH$_3$)$_2$	(CH$_2$)$_3$CH$_3$	170–174	7.0	1.4898	58	C$_{16}$H$_{27}$NO	5.62	5.58							
2-Cl	CH$_2$CH$_3$	106–111	1.3	1.5089	58	C$_{11}$H$_{16}$ClNO	6.56	5.98							
2,4-Cl$_2$	CH$_3$	100–105	0.4	1.5302	64	C$_{10}$H$_{13}$Cl$_2$NO	5.98	5.61							
2,4-Cl$_2$	CH$_2$CH$_3$	100–104	.5	1.5209	52	C$_{11}$H$_{15}$Cl$_2$NO	5.64	5.33	131–134[a]	46.42	5.66	12.46	46.61	5.95	12.06
2,4-Cl$_2$	(CH$_2$)$_3$CH$_3$	135–140	.4	1.5147	50	C$_{13}$H$_{19}$Cl$_2$NO	5.07	4.82							
3,4-Cl$_2$	CH$_2$CH$_3$	119–125	.5	1.5230	54	C$_{11}$H$_{15}$Cl$_2$NO	5.64	5.43	183.5–186.1	46.42	5.66	12.46	46.77	5.15	12.28
3,4-Cl$_2$	(CH$_2$)$_3$CH$_3$	144–148	.4	1.5150	40	C$_{13}$H$_{19}$Cl$_2$NO	5.07	4.89	158.6–160.1	49.94	6.45	11.34	50.32	6.63	11.23
3,4-Cl$_2$	C$_6$H$_5$	150–156	.02	1.5755	64	C$_{15}$H$_{15}$Cl$_2$NO	4.73	4.61	201–205.2	54.31	4.86	10.68	54.20	4.90	10.59
4-OC$_4$H$_9$	CH$_3$	134–137	.6	1.5005	67	C$_{14}$H$_{23}$NO$_2$	5.89	5.61							
4-OC$_4$H$_9$	CH$_2$CH$_3$	118–122	.02	1.5015	56	C$_{15}$H$_{25}$NO$_2$	5.57	4.92	160–160.8	62.59	9.11	12.32	62.45	8.89	12.10

[a] Uncorrected melting point.

TABLE III

N-(3-ALKOXYPROPYL)-N-BENZYLDICHLOROACETAMIDES R-C$_6$H$_4$-CH$_2$NCH$_2$CH$_2$CH$_2$OR$_3$ (COCHCl$_2$)

R	R$_3$	B.p., °C.	Mm.	Yield, %	Formula	Chlorine,[a] % Calcd.	Found	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
2,4-Cl$_2$	CH$_3$	159–162	0.01	63	C$_{13}$H$_{15}$Cl$_4$NO$_2$	19.75	19.79	43.48	43.55	4.21	4.70
2,4-Cl$_2$	CH$_2$CH$_3$	162–164	.01	75	C$_{14}$H$_{17}$Cl$_4$NO$_2$	19.01	18.78	45.07	44.92	4.59	4.78
2,4-Cl$_2$	CH(CH$_3$)$_2$	170–172	.02	84	C$_{15}$H$_{19}$Cl$_4$NO$_2$	18.32	18.14	46.53	47.11	4.95	5.26
2,4-Cl$_2$	(CH$_2$)$_3$CH$_3$	174–176	.05	41	C$_{16}$H$_{21}$Cl$_4$NO$_2$	17.68	17.81	47.91	48.29	5.28	5.71
3,4-Cl$_2$	CH$_3$	98.0–103.0[b]		86	C$_{13}$H$_{15}$Cl$_4$NO$_2$	19.75	19.67	43.48	43.26	4.59	4.39
3,4-Cl$_2$	CH$_2$CH$_3$	60.1–61.8[b]		63	C$_{14}$H$_{17}$Cl$_4$NO$_2$	19.01	18.81	45.07	45.53	4.59	5.01
3,4-Cl$_2$	CH(CH$_3$)$_2$	178–180	0.03	57	C$_{15}$H$_{19}$Cl$_4$NO$_2$	18.32	18.75	46.53	46.22	4.95	5.04
3,4-Cl$_2$	(CH$_2$)$_3$CH$_3$	185–188	.01	59	C$_{16}$H$_{21}$Cl$_4$NO$_2$	17.68	17.57	47.91	48.09	5.28	5.46
4-OC$_4$H$_9$	CH$_3$	188–189	.04	63	C$_{17}$H$_{25}$Cl$_2$NO$_3$	19.56	19.18	56.35	56.31	6.96	7.23
4-OC$_4$H$_9$	(CH$_2$)$_3$CH$_3$	188–189	.01	69	C$_{20}$H$_{31}$Cl$_2$NO$_3$	17.54	17.45	59.40	59.12	7.73	7.51
4-NO$_2$	CH$_3$	93.2–95.1[b]		73	C$_{13}$H$_{16}$Cl$_2$N$_2$O$_4$	21.16[c]	21.00	[d]			

[a] Determination of readily hydrolyzable chlorine. [b] Corrected melting point. [c] Total chlorine. [d] Calcd. N (NO$_2$): 4.18. Found N (NO$_2$): 4.15.

nospheres. The catalyst was removed by filtration, the solvent distilled, and the residue was dissolved in ethyl acetate and treated with an equivalent amount of alcoholic hydrogen chloride. The product was recrystallized from ethyl alcohol–ether.

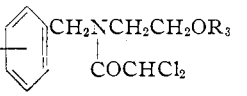
Preparation of N-(2-Alkoxyethyl)-benzylamines (Table II).—The following examples illustrate the procedures employed in the preparation of the N-(2-ethoxyethyl)-benzylamines. The remaining N-(2-alkoxyethyl)-benzylamines were prepared according to methods A and B described above.

(C) A mixture of 57 g. of 2,4-dichlorobenzylamine and 17.6 g. of 2-chloroethyl ethyl ether was heated with stirring for 7 hr. at 140–150°. Ether was added to completely precipitate the 2,4-dichlorobenzylamine hydrochloride which was removed by filtration. The filtrate was freed of ether by distillation and the residue distilled to give unreacted 2,4-dichlorobenzylamine and N-(2-ethoxyethyl)-2,4-dichlorobenzylamine. Alternatively, after removing unreacted materials, the residue was dissolved in absolute ether and the solution was saturated with dry hydrogen chloride. The crystalline hydrochloride was collected, washed with a little dry ether and dried at 50°. Recrystallization from dry acetone gave an analytically pure product.

(D)[6] A mixture of 14.2 g. of 2-chlorobenzylamine, 26.8

(6) The initial work on this method was carried out by Dr. J. R. Mayer in this Laboratory.

TABLE IV

N-(2-ALKOXYETHYL)-N-BENZYLDICHLOROACETAMIDES 

R	R_3	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine,[a] % Calcd.	Chlorine,[a] % Found
H	CH_2CH_3	69.7–73.0	56	$C_{13}H_{17}Cl_2NO_2$	53.80	54.13	5.91	6.02	24.43	24.20[b]
4-$CH(CH_3)_2$	CH_3	73.7–78.5	61	$C_{15}H_{21}Cl_2NO_2$	56.61	56.44	6.15	6.36	22.28	22.00[b]
4-$CH(CH_3)_2$	CH_2CH_3	74.0–76.0	95	$C_{16}H_{23}Cl_2NO_2$	57.85	57.44	6.97	6.62	21.34	21.14
4-$CH(CH_3)_2$	$(CH_2)_3CH_3$	68.4–70.0	100	$C_{18}H_{27}Cl_2NO_2$	59.99	59.97	7.56	7.58	19.67	19.73
2-Cl	CH_2CH_3	70.0–72.8	50	$C_{13}H_{16}Cl_3NO_2$	48.22	48.26	4.97	5.36	32.77	32.60[b]
2,4-Cl_2	CH_3	82.6–85.6	22	$C_{12}H_{13}Cl_4NO_2$	41.77	41.95	3.80	3.87	41.11	41.30[b]
2,4-Cl_2	CH_2CH_3	72.6–74.0	18	$C_{13}H_{15}Cl_4NO_2$	43.49	43.21	4.21	4.16	19.79	19.74
3,4-Cl_2	CH_2CH_3	50.3–52.9	33	$C_{13}H_{15}Cl_4NO_2$	43.49	43.55	4.21	3.97	39.58	38.95[b]
3,4-Cl_2	$(CH_2)_3CH_3$	48.0–49.6	66	$C_{15}H_{19}Cl_4NO_2$	46.53	46.92	4.95	5.18	36.64	36.00[b]
3,4-Cl_2	C_6H_5	129.7–132.2	34	$C_{17}H_{15}Cl_4NO_2$	50.16	50.53	3.71	3.89	17.42	17.11
4-OC_4H_9	CH_2CH_3	70.3–71.8	32	$C_{17}H_{25}Cl_2NO_3$	56.35	55.87	6.95	6.88	19.57	19.54
4-OC_4H_9	C_6H_5	79.8–84.4	44	$C_{21}H_{25}Cl_2NO_3$	61.47	61.27	6.14	6.48	17.28	17.84
3,4-O_2CH_2	CH_3	[c]	16	$C_{13}H_{15}Cl_2NO_4$	48.77	48.97	4.72	4.53	22.14	22.10[b]

[a] Determination of readily hydrolyzable chlorine. [b] Total chlorine. [c] Obtained as an oil, b.p. 197–200° (0.04 mm.).

g. of the tosyl ester of 2-ethoxyethanol and 12.1 g. of triethylamine was heated with stirring for 24 hr. on a steam-bath. After cooling, the reaction mixture was taken up in ethylene dichloride and the solution was washed several times with water. The solvent was removed by distillation and the product was fractionated under reduced pressure; yield 58%.

Preparation of N-(Alkoxyalkyl)-N-benzyldichloroacetamides (Tables III and IV).—The two general methods employed for the preparation of these compounds are illustrated by the following examples.

(E) Dichloroacetyl chloride (10 g.) was added dropwise with stirring at a temperature of about 0–5° to 16 g. of N-(2-ethoxyethyl)-2,4-dichlorobenzylamine in 150 ml. of ethylene dichloride and 70 ml. of 1 *N* sodium hydroxide. After the addition had been completed, the mixture was allowed to warm up to room temperature and stirred for another 3 hr. The ethylene dichloride layer was separated and washed successively with 1 *N* hydrochloric acid, 10% sodium carbonate solution and water. The ethylene dichloride was removed by distillation *in vacuo* and the residue was distilled under reduced pressure. On standing, the fraction which distilled at 134–137° (0.01 mm.), solidified. It was recrystallized from Skellysolve B to give an analytically pure sample of N-(2-ethoxyethyl)-N-(2,4-dichlorobenzyl)-dichloroacetamide.

Where the starting material was an N-(alkoxyalkyl)-benzylamine hydrochloride an additional mole of 1 *N* sodium hydroxide was used.

(F) A mixture of 27 g. of N-(2-methoxyethyl)-4-isopropylbenzylamine hydrochloride and 22 g. of dichloroacetyl chloride in 200 ml. of benzene was refluxed with stirring for 3 hr. The reaction was considered complete when no further evolution of hydrogen chloride was evident and the reaction mixture was homogeneous. A small amount of methanol was added and the benzene was removed *in vacuo*. The residue, which solidified, was recrystallized from isopropyl alcohol to give an analytically pure sample of N-(2-methoxyethyl)-N-(4-isopropylbenzyl)-dichloroacetamide.

N-(2,4-Dichlorobenzyl)-N-(3-methoxypropyl)-trichloroacetamide.—This compound was prepared by procedure (E) using trichloroacetyl chloride. The yield was 71%, m.p. 47.8–49.4°.

Anal. Calcd. for $C_{15}H_{14}Cl_5NO_2$: C, 39.68; H, 3.59. Found: C, 39.81; H, 3.55.

N-(2,4-Dichlorobenzyl)-N-(3-isopropoxypropyl)-chloroacetamide.—This compound was prepared by procedure (E) using chloroacetyl chloride. The yield was 62%, b.p. 160–161° (0.02 mm.).

Anal. Calcd. for $C_{15}H_{20}Cl_3NO_2$: C, 51.07; H, 5.72. Found: C, 50.72; H, 5.80.

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