[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

New Amebacides. I. The Preparation of Some N-Benzyl-N-hydroxyalkyldichloroacetamides

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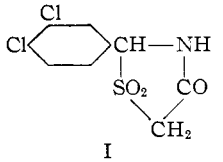
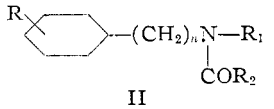
The dichloroacetylation of some N-benzylhydroxyalkylamines with dichloroacetyl chloride or ethyl or methyl dichloroacetate to give N-benzyl-N-hydroxyalkyldichloroacetamides is described. Several of the products have been found to be potent amebacidal agents.

In our search for potent amebacides it was found that several 2-(halophenyl)-4-thiazolidone-1-dioxides[1] showed significant amebacidal activity when tested in hamsters. The most active compound in this series is the 2-(3,4-dichlorophenyl)-4-thiazolidone-1-dioxide (I). Following this lead, we have investigated several series of compounds which



I

theoretically may be derived from the thiazolidone structure I. One of the possible structures, which results from the removal of the $-SO_2-$ group, is a benzylacetamide. Inasmuch as this compound showed appreciable amebacidal activity, we carried out an extensive study of compounds having the general formula II. The present paper deals with



II

the preparation of one of the series of compounds, namely, N-hydroxyalkyl-N-(substituted-benzyl)-dihaloacetamides (II, n = 1; R = alkyl, alkoxy, chloro, dichloro, NO_2; R_1 = CH_2CH_2OH, $CH_2CHOHCH_3$, $CH_2CH_2CH_2OH$; and R_2 = $CHCl_2$, $CHBr_2$) which contain some of the most potent amebacidal agents tested in these laboratories.

The N-benzylethanolamines, intermediates for the present work which are described in Table I, were prepared by either of two methods depending upon the availability or ease of formation of the appropriate benzyl chloride or benzaldehyde. In the first method the benzyl chloride was added to a large excess of ethanolamine and the product was obtained by pouring the reaction mixture into a large volume of water and extracting with chloroform. This procedure was especially useful with the chlorobenzyl chlorides. The N-(dichlorobenzyl)-2-hydroxypropyl- and 3-hydroxypropylamines were also prepared by this method using 2-hydroxy- and 3-hydroxypropylamines. The second method involved the reductive alkylation of ethanolamine with the appropriate benzaldehyde. Yields of products from both methods were good, ranging from 55 to 90%. Most of the N-benzylethanolamines are low melting solids. In a few cases oils were obtained which were characterized by their hydrochloride salts.

(1) A. R. Surrey and R. A. Cutler, THIS JOURNAL, **76**, 578 (1954).

Initially, the dichloroacetylations of the N-benzylethanolamines were carried out with dichloroacetyl chloride using two moles of amine or one mole of the amine in the presence of dilute sodium hydroxide solution. The yields of dichloroacetamides by this method were 30 to 64%. Later, it was found that acylation could be readily performed using ethyl or methyl dichloroacetate or ethyl dibromoacetate under very mild conditions. For example, when a mixture of N-(2,4-dichlorobenzyl)-ethanolamine and methyl dichloroacetate in ethylene dichloride was stirred at room temperature, a clear solution was obtained after one hour. In about five hours a 45% yield of N-(2,4-dichlorobenzyl)-N-(2-hydroxyethyl)-dichloroacetamide had separated from the reaction mixture. After stirring for 24 hours the yield was increased to 65%. The product was a colorless crystalline solid which was analytically pure. A similar yield was obtained by heating a mixture of the reactants at 60° for four hours. The procedure using the ester is simpler and usually gave better yields than the acid chloride method. Acylation of the homologous N-benzylpropanolamines was also carried out with methyl dichloroacetate to give the N-benzyl-N-(3-hydroxypropyl)-dichloroacetamides.

Ordinarily, acylation of secondary amines by means of esters, even esters derived from strong acids, requires rather strenuous conditions. The fact that the present acylations involving N-(2- and 3-hydroxyalkyl)-benzylamines can be carried out at moderate temperatures and is not successful with N-alkylbenzylamines,[2] clearly indicates participation of the hydroxyl group. The reaction may initially involve O-acylation followed by an O → N acyl migration *via* the cyclic intermediate proposed for this type of shift.[3,4]

The most active anti-amebic agents in this series are N-(2,4-dichlorobenzyl)-N-(2-hydroxyethyl)-dichloroacetamide (Win 5047), the corresponding dibromoacetamide (Win 7609) and N-(4-butoxybenzyl)-N-(2-hydroxyethyl)-dichloroacetamide (Win 5128). Replacing the 2-hydroxyethyl group by either 2-hydroxypropyl or 3-hydroxypropyl decreased the activity. Of the above-mentioned compounds, Win 5047 was selected for an intensive investigation. The results show that it is very effective both *in vitro* and *in vivo*. In intestinal amebiasis in hamsters its amebacidal activity is greater than that of chlorotetracycline or oxytetracycline.

(2) Work to be published.

(3) See, for example, E. van Tamelen, THIS JOURNAL, **73**, 5775 (1951).

(4) Examples of acyl migrations with 3-amino-alcohols have been reported recently by G. Fodor and K. Nádor, *J. Chem. Soc.*, 721 (1953), in the tropane alkaloids.

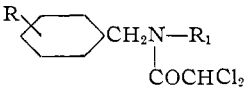
TABLE I

N-BENZYLETHANOLAMINES 

R	M.p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Hydrochlorides M.p., °C.	Hydrochlorides Analyses, % Calcd. C	Calcd. H	Calcd. Cl⁻	Found C	Found H	Found Cl⁻
2-Cl	122–124 (0.8 mm.)[a]	$C_9H_{12}ClNO$					135.2–136.9	48.68	5.90	15.97	48.56	6.07	15.76
4-Cl	126–131 (0.7 mm.)[a]	$C_9H_{12}ClNO$					172.7–173.8	N, 6.30		31.93	N, 6.23		31.96
2,4-Cl_2	62–62.8	$C_9H_{11}Cl_2NO$	Cl, 32.22		Cl, 32.43		184.7–186.7	42.12	4.70	13.80	42.30	4.66	13.78
2,6-Cl_2	57–59	$C_9H_{11}Cl_2NO$	N, 6.36		N, 6.25								
3,4-Cl_2	[b]	$C_9H_{11}Cl_2NO$					145.9–148.1	42.13	4.71	13.82	42.26	4.54	13.93
4-C_3H_7-*i*	80.9–83.3	$C_{12}H_{19}NO$	74.55	10.12	74.53	10.16	129.4–132.2	62.74	8.77	15.44	63.00	8.99	15.62
4-OCH_3	38–39	$C_{10}H_{15}NO_2$	66.52	8.28	66.66	8.74	112.2–113.6	55.15	7.41	16.29	55.45	7.61	16.10
4-OC_2H_5	63–63.6	$C_{11}H_{17}NO_2$	67.67	8.78	67.90	9.09	103–104.6	57.01	7.83	15.30	57.00	7.81	15.07
4-OC_3H_7	67–68.2	$C_{12}H_{19}NO_2$	68.86	9.15	68.75	9.10	134.2–138.2	58.65	8.21	14.43	58.67	8.31	14.40
4-OC_3H_7-*i*	75–76.6	$C_{12}H_{19}NO_2$	68.86	9.15	69.84	9.27	134.9–135.4	58.65	8.21	14.43	58.60	7.95	14.35
4-OC_4H_9	62.8–63.8	$C_{13}H_{21}NO_2$	69.92	9.48	70.23	9.23	146.6–147.5	60.11	8.47	13.65	60.28	8.38	13.62
4-OC_5H_{11}	51.9–55	$C_{14}H_{23}NO_2$	70.86	9.77	71.66	10.20	144–145.5	61.40	8.83	12.95	61.43	8.71	12.70
3,4-O_2CH_2	62.6–64.4	$C_{10}H_{13}NO_3$	61.53	6.72	61.60	7.03	152–152.6	51.83	6.09	N$_K$, 15.30	51.60	6.08	N$_K$, 15.13

[a] B.p., °C. The product was characterized as the hydrochloride salt. [b] The crude product was obtained as an oil which was converted directly to the hydrochloride salt.

TABLE II

N-BENZYL-N-HYDROXYALKYL-α,α-DICHLOROACETAMIDES 

R	R_1	Yield, %	M.p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. Cl	Found C	Found H	Found Cl
H	CH_2CH_2OH	53[a,b]	64.2–64.8	$C_{11}H_{13}Cl_2NO_2$	50.60	5.02	27.16	50.50	4.94	27.10
2-Cl	CH_2CH_2OH	59[a,b]	76.6–79.3	$C_{11}H_{12}Cl_3NO_2$	44.54	4.07	23.93[c]	44.41	4.32	23.96[c]
4-Cl	CH_2CH_2OH	60[a,d]	94.4–97.2	$C_{11}H_{12}Cl_3NO_2$	44.54	4.07	35.87	44.63	4.30	35.82
2,4-Cl_2	CH_2CH_2OH	65[e,b]	112.4–113.4	$C_{11}H_{11}Cl_4NO_2$	39.89	3.35	42.84	40.20	3.70	42.95
2,6-Cl_2	CH_2CH_2OH	55[e,f]	171.1–173.7	$C_{11}H_{11}Cl_4NO_2$	39.89	3.35	21.42[c]	39.64	3.02	21.54[c]
3,4-Cl_2	CH_2CH_2OH	61[a,b]	99.4–101.5	$C_{11}H_{11}Cl_4NO_2$	39.89	3.35	42.84	39.70	3.65	42.68
4-C_3H_7-*i*	CH_2CH_2OH	47[a,d]	84.5–85.5	$C_{14}H_{19}Cl_2NO_2$	55.27	6.30	23.31	55.17	6.49	23.07
4-OC_2H_5	CH_2CH_2OH	81[e,d]	76.9–79.1	$C_{13}H_{17}Cl_2NO_3$	50.99	5.60	23.16	51.26	5.66	23.18
4-OC_4H_9	CH_2CH_2OH	48[a,d]	88.0–88.9	$C_{15}H_{21}Cl_2NO_3$	53.90	6.33	21.22	53.57	6.44	21.47
3,4-O_2CH_2	CH_2CH_2OH	30[a,g]	101.9–103.4	$C_{12}H_{13}Cl_2NO_4$	47.08	4.28	23.17	47.09	4.39	22.89
3,4-$(OCH_3)_2$	CH_2CH_2OH	25[e,h]	116.6–117.7	$C_{13}H_{17}Cl_2NO_4$	48.45	5.32	22.01	48.54	5.16	22.14
4-NO_2	CH_2CH_2OH	64[a,f]	132.2–133.6	$C_{11}H_{12}Cl_2N_2O_4$	43.02	3.91	23.09	43.22	4.15	23.01
2,4-Cl_2	$CH_2CH_2CH_2OH$	58[a,h]	83.7–86.7	$C_{12}H_{13}Cl_4NO_2$	41.77	3.80	41.10	41.60	3.88	41.23
3,4-Cl_2	$CH_2CH_2CH_2OH$	70[e,h]	91.9–97.5	$C_{12}H_{13}Cl_4NO_2$	41.77	3.80	41.10	41.70	3.89	41.44
2,4-Cl_2	$CH_2CHOHCH_3$	69[e,h]	135.1–138	$C_{12}H_{13}Cl_4NO_2$	41.77	3.80	41.10	41.56	3.97	40.66
3,4-Cl_2	$CH_2CHOHCH_3$	31[e,h]	120.0–121.8	$C_{12}H_{13}Cl_4NO_2$	41.77	3.80	20.55[c]	42.00	3.86	20.52[c]

[a] Prepared by method A. [b] Recrystallized from benzene–Skellysolve A. [c] Determination of readily hydrolyzable chlorine. [d] Recrystallized from ether–Skellysolve A. [e] Prepared by method B. [f] Recrystallized from ethanol. [g] Ethylene dichloride–Skellysolve A. [h] Ethylene dichloride.

In addition, the compound is well tolerated in several species of laboratory animals. The effectiveness of Win 5047 in human amebiasis also has been demonstrated in preliminary clinical investigations.

Acknowledgment.—The author wishes to thank Miss Marcia K. Rukwid for her valuable technical assistance and Mr. M. E. Auerbach and Mr. K. D. Fleischer and staffs for the analytical data and corrected melting points recorded. The author is also grateful to the Biology Division of this Institute and especially to Dr. D. A. Berberian for the screening data.

Experimental[5]

Preparation of N-Benzylethanolamines.—The following examples illustrate the two procedures employed for the preparation of the benzylethanolamines.

2,4-Dichlorobenzyl chloride (78.2 g.) was added dropwise with stirring to 80 g. of ethanolamine without any external cooling. After the addition was completed stirring was continued for about two hours. The reaction mixture was allowed to stand at room temperature overnight and then poured with stirring into a large volume of water. The solid product was extracted with chloroform and this solution was dried over anhydrous potassium carbonate. After removal of the chloroform by distillation and recrystallization of the residue from Skellysolve C 56 g. of N-(2,4-dichlorobenzyl)-ethanolamine melting at 62–62.8° was obtained.

With the 2-chloro-, 4-chloro- and 3,4-dichlorobenzyl chlorides the products were obtained as oils. The first two were distilled under reduced pressure and all were characterized as hydrochloride salts.

A mixture of 44.3 g. of 4-isopropylbenzaldehyde and 18.3 g. of ethanolamine was heated *in vacuo* on a steam-bath for one hour, dissolved in 125 ml. of hot ethanol and then reduced catalytically with palladium-on-charcoal at a hydrogen pressure of about two atmospheres. The hydrogenation of the hot mixture was usually very rapid. After filtering off the catalyst and removing the solvent by distillation the residue was recrystallized from Skellysolve C to give 43 g. of N-(4-isopropylbenzyl)-ethanolamine.

With 4-methoxybenzaldehyde, the product, after removal

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

of the ethanol, was distilled (b.p. 139° at 6 mm., $n^{25}D$ 1.5431) and the distillate was treated with alcoholic hydrogen chloride to form the hydrochloride salt of N-(4-methoxybenzyl)-ethanolamine. The latter was converted back to base which was then obtained as a solid. After recrystallization from Skellysolve B it melted at 38-39°.

The bases, described in Table I, were recrystallized from ether or a Skellysolve fraction or a mixture of the two. The hydrochlorides were recrystallized from acetone or isopropyl alcohol.

Preparation of N-Benzylpropanolamines.—The following compounds were prepared from the appropriate dichlorobenzyl chloride and propanolamine.

N-(2,4-Dichlorobenzyl)-2-hydroxypropylamine, m.p. 73.8–75.0° (Skellysolve B). *Anal.* Calcd. for $C_{10}H_{14}Cl_2NO$: N, 5.99. Found: N, 5.95.

N-(3,4-Dichlorobenzyl)-2-hydroxypropylamine, m.p. 54.4–56.4° (Skellysolve B). *Anal.* Found: N, 6.17.

N-(2,4-Dichlorobenzyl)-3-hydroxypropylamine, b.p. 150–155° (0.5 mm.), $n^{25}D$, 1.5600. *Anal.* Found: N, 6.00.

N-(3,4-Dichlorobenzyl)-3-hydroxypropylamine, b.p. 155–160° (0.8 mm.), $n^{25}D$, 1.5539. *Anal.* Found: N, 6.11.

Preparation of N-Benzyl-N-(hydroxyalkyl)-dichloroacetamides.—The following example illustrates the general procedure employing dichloroacetyl chloride as the acetylating agent.

Method A. A solution of 4.63 g. of dichloroacetyl chloride in 20 ml. of ethylene dichloride was added dropwise with stirring and cooling (0–5°) to a solution of 14 g. of N-(4-butoxybenzyl)-ethanolamine in 100 ml. of ethylene dichloride. After the addition was completed the reaction mixture was allowed to stand overnight at room temperature and ether was added to precipitate N-(4-butoxybenzyl)-ethanolamine hydrochloride (8 g.). The solid was filtered off and the filtrate was washed with 1 *N* hydrochloric acid and then water. After drying over Drierite, the solvents were removed by distillation. The residue was dissolved in ether, filtered with charcoal and Skellysolve A added to incipient turbidity; yield 5 g., m.p. 81–85° (uncor.). Recrystallization from ether–Skellysolve A gave a product melting at 88–88.9°.

With N-(4-nitrobenzyl)-ethanolamine the reaction was carried out at 25°.

A variation of the above method was used in the preparation of N-(2-chlorobenzyl)-N-(2-hydroxyethyl)-dichloroacetamide. Twelve grams of dichloroacetyl chloride in 30 ml. of ethylene dichloride was added with stirring over a period of one hour to a mixture of 15 g. of N-(2-chlorobenzyl)-ethanolamine in 100 ml. of ethylene dichloride and 80 ml. of 1 *N* sodium hydroxide. The temperature was kept below 0° with external cooling. The reaction mixture was then allowed to come to room temperature with stirring and the organic layer was separated. This was washed successively with 1 *N* sodium hydroxide, water, 1 *N* hydrochloric acid, water, and dried. The residue, after removing the solvent by distillation, was recrystallized from benzene–Skellysolve A.

Method B. This method is illustrated by the preparation of **N-(2,4-dichlorobenzyl)-N-(2-hydroxyethyl)-dibromoacetamide.** A mixture of 5.5 g. of N-(2,4-dichlorobenzyl)-ethanolamine and 7 g. of ethyl dibromoacetate was heated at 60° for 3–4 hours. The mixture, which became quite viscous, was stirred in dilute hydrochloric acid and the product was extracted with chloroform. The chloroform solution was then washed with water and the solvent removed by distillation. The resulting solid residue was recrystallized from ethylene dichloride and a small amount of Skellysolve B to give 3.5 g. (33%) of product melting at 115.0–117.2°.

Anal. Calcd. for $C_{11}H_{11}Br_2Cl_2NO_2$: Br, 38.07; C, 31.46; H, 2.64. Found: Br, 37.75; C, 31.43; H, 2.85.

N-(3,4-Dichlorobenzyl)-N-(2-hydroxyethyl)-dibromoacetamide was prepared in a similar manner; yield 38%, m.p. 115.5–128.8°.

Anal. Calcd. for $C_{11}H_{11}Br_2Cl_2NO_2$: Br, 38.07; C, 31.46; H, 2.64. Found: Br, 38.39; C, 31.54; H, 2.41.

The following dichloroacetamides were also prepared according to method B starting with methyl dichloroacetate and the appropriate secondary amine:

N-(2,4-Dichlorobenzyl)-N-(2-hydroxypropyl)-dichloroacetamide, 69% yield, m.p. 135.1–138.0° (ethylene dichloride). *Anal.* Calcd. for $C_{12}H_{13}Cl_4NO_2$: C, 41.77; H, 3.80; Cl, 41.10. Found: C, 41.56; H, 3.97; Cl, 40.66.

N-(3,4-Dichlorobenzyl)-N-(2-hydroxypropyl)-dichloroacetamide, 31% yield, m.p. 120.0–121.8° (ethylene dichloride). *Anal.* Calcd. for $C_{12}H_{13}Cl_4NO_2$: C, 41.77; H, 3.80; Cl (KOH), 20.55. Found: C, 42.00; H, 3.86; Cl(KOH), 20.52.

N-(2,4-Dichlorobenzyl)-N-(3-hydroxypropyl)-dichloroacetamide, 58% yield, m.p. 83.7–86.7° (benzene–Skellysolve A). *Anal.* Calcd. for $C_{12}H_{13}Cl_4NO_2$: C, 41.77; H, 3.80; Cl, 41.10. Found: C, 4.60; H, 3.88; Cl, 41.23.

N-(3,4-Dichlorobenzyl)-N-(3-hydroxypropyl)-dichloroacetamide, 70% yield, m.p. 91.9–97.5° (benzene–Skellysolve A). *Anal.* Calcd. for $C_{12}H_{13}Cl_4NO_2$: C, 41.77; H, 3.80; Cl, 41.10. Found: C, 41.70; H, 3.89; Cl, 41.44.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Benzylation and Xanthation of Cellulose Monoalkoxide[1]

BY M. L. WOLFROM AND M. A. EL-TARABOULSI[2]

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A monobenzylcellulose was prepared by the reaction of sodium 2-cellulosate with benzyl chloride. Water, if present, causes a progressive lowering in the degree of benzylation. A topochemical, macroheterogeneous type of reaction is indicated. No glycol group was detectable in the product. Xanthation of dry sodium 2-cellulosate was not possible and required water as a catalyst; a maximum of 0.4 xanthate group per C_6-unit could be introduced. Replacement by zinc of the sodium in the cellulose alkoxide is described.

Alkali cellulose very probably consists of an addition compound in equilibrium with a true alkoxide. In the procedures established by Gaver,[3] working mainly with starch, the water in the alkali–carbohydrate reaction is removed by azeotropic distillation with a higher alcohol. A large excess of sodium

$$ROH + NaOH \rightleftharpoons ROH\cdot NaOH \rightleftharpoons RONa + HOH$$

hydroxide is employed and when the reaction is heterogeneous, the alkoxide of the carbohydrate remains on removal of other sodium compounds with ethanol.

One hydroxyl group in glycosidically bound carbohydrates forms an alkoxide much more readily than the others. Thus, in the presence of an excess of alkali, the reactions of these polyhydric units

(1) Reported in part in *Abstracts Papers Am. Chem. Soc.*, **121**, 8P (1952); presented before the XIIIth International Congress of Pure and Applied Chemistry, Stockholm, Sweden, Aug. 1, 1953.

(2) Fellow of the Egyptian Government.

(3) K. M. Gaver, Dissertation, The Ohio State University, 1945; U. S. Patents 2,397,732 (1946), 2,518,135 (1950), 2,609,368 (1952); *Abstracts Papers XIIth Intern. Congr. Pure and Appl. Chem.*, 623 (1951); K. M. Gaver, Esther P. Lasure and D. V. Tieszen, U. S. Patent 2,572,923 (1951); K. M. Gaver, Esther P. Lasure and L. M. Thomas, U. S. Patents 2,602,084 and 2,609,367 (1952).