[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

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

By Alexander R. Surrey

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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-dioxides¹ 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



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



the preparation of one of the series of compounds, namely, N-hydroxyalkyl-N-(substituted-benzyl)dihaloacetamides (II, n = 1; R = alkyl, alkoxy, chloro, dichloro, NO₂; R₁ = CH₂CH₂OH, CH₂-CHOHCH₃, CH₂CH₂CH₂CH₂OH; and R₂ = CHCl₂, CHBr₂) 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-hydroxyand 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 hvdrochloride 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-(2and 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 $O \rightarrow N$ 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 oxytetracyeline.

(2) Work to be published.

(3) See, for example, E. van Tamelen, THIS JOURNAL, 73, 5773 (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.

		N-	BENZYLE	THANOL	R. AMINES	×`)CH₂NHCH	₂CH₂OH						
		Analyses, %							Hydrochlorides Analyses, %					
D	M n °C	Formula	Calco	ੀ. ਾਂ ਸ	Four	id ਸ	Mp °C	с ^с	Caled. H	C1-	c ¹	Found H	C1-	
2-C1	$122-124 (0.8 \text{ mm.})^a$	C ₉ H ₁₂ CINO	č		C		135.2-136.9	48.68	5.90	15.97	48.56	6.07	15.76	
4-Cl	$126-131 (0.7 \text{ mm})^a$	$C_9 \mathrm{H}_{12} Cl\mathrm{NO}$					172.7-173.8	N, 6.30		31.93	N, 6.23		31.96	
2,4-Cl ₂	62-62.8	C ₉ H ₁₁ Cl ₂ NO	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 ₉ H ₁₁ Cl ₂ NO	N, 6.36		N, 6.25									
3,4-Cl ₂	Ь	C ₉ H ₁₁ Cl ₂ NO					145.9-148.1	42.13	4.71	13.82	42.26	4.54	13.93	
4-C3H7-1	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	
4-0CH3	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 ₂ H 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 ₃ H 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	
4-0C3H7-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	
4-0C4H9	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	
4-0C5H11	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-O2CH2	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	NK,	51.60	6.08	Nκ,	
										15.30			15.13	

TABLE I

^a B.p., ^oC. 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

CH₂N-R₁ N-Benzyl-N-hydroxyalkyl- α , α -dichloroacetamides COCHCl₂ Analyses, % Vield, Found H Calcd H с с Cl R \mathbf{R}_1 M.p., °C. Formula CI 9% $53^{a,b}$ H CH₂CH₂OH 64.2-64.8 C₁₁H₁₃Cl₂NO₂ 50.60 5.02 27.1650.504.9427.10 $59^{a,b}$ CH_2CH_2OH 76.6-79.3 $C_{11}H_{12}Cl_3NO_2 \\$ 44.544.07 23.93° 44.41 4.32 23.96° 2-C1 $60^{a,d}$ 4-C1 CH₂CH₂OH 94.4 - 97.2 $C_{11}H_{12}Cl_3NO_2$ 44.544.0735.8744.63 4.3035.82 $65^{e,b}$ 39.89 CH₂CH₂OH 112.4-113.4 $C_{11}H_{11}Cl_4\mathrm{NO}_2$ 3.3542.8440.202,4-Cl₂ 3.7042.95 $55^{e,f}$ 2,6-Cl₂ CH₂CH₂OH 171.1-173.7 $C_{11}H_{11}Cl_4NO_2$ 39.89 3.35 21.42° 39.643.02 21.54° 61^{a,b} $C_{11}H_{11}Cl_4NO_2$ CH₂CH₂OH 99.4-101.5 39.89 3.3542.8439.70 3.65 $3, 4 - Cl_2$ 42.6847^{a,d} $C_{14}H_{19}Cl_2NO_2$ 4-C3H7-i CH₂CH₂OH 84.5-85.5 55.276.30 23.3155.176 49 23.07 $81^{e,d}$ $4-OC_2H_5$ CH₂CH₂OH 76.9-79.1 $C_{13}H_{17}Cl_2NO_3$ 50.995.6023.1651.265.6623.18 $48^{a,d}$ CH_2CH_2OH 88.0-88.9 21.224-OC₄H₉ $C_{15}H_{21}Cl_2\mathrm{NO}_3$ 53.906.3353.576.4421.473.4-O₂CH₂ CH₂CH₂OH 30^{a,g} 101.9-103.4 $C_{12}H_{13}Cl_2NO_4$ 47.084.2823.1747.094 39 22 89 $25^{e,h}$ 3,4-(OCH₃)₂ CH_2CH_2OH 116.6 - 117.7 $C_{13}H_{17}Cl_2NO_4$ 48.455.3222.0148.545.1622.14 $64^{a,f}$ CH₂CH₂OH $4-NO_2$ 132.2-133.6 $C_{11}H_{i2}Cl_2N_2O_4 = 43.02$ 3.9123.0943.224.1523.01 $58^{a,h}$ 83.7-86.7 CH₂CH₂CH₂OH $C_{12}H_{13}Cl_4NO_2$ 41.773.8041.23 $2.4-Cl_2$ 41.1041.60 3.88 $70^{e,h}$ CH₂CH₂CH₂OH 91.9-97.5 $C_{12}H_{13}Cl_4NO_2 = 41.77$ $3, 4 - Cl_2$ 3.80 41.1041.70 3.89 41.44 $69^{e,h}$ $2,4-Cl_2$ CH₂CHOHCH₃ 135.1 - 138 $C_{12}H_{13}Cl_4NO_2$ 41.77 3.80 41.10 41.563.9740.66 $31^{e,h}$ CH₂CHOHCH₃ $120.0{-}121.8 \quad C_{12}H_{13}Cl_4NO_2 \quad 41.77 \quad 3.80 \quad 20.55^\circ$ 3,4-Cl₂ 42.00 3.86 20.52

^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.

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Experimental⁵

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 $62-62.8^{\circ}$ 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 hydro-gen chloride to form the hydrochloride salt of N-(4-methoxy-benzyl)-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.

benzyl chloride and propanolamine. N-(2,4-Dichlorobenzyl)-2-hydroxypropylamine, m.p. 73.8-75.0° (Skellysolve B). Anal. Calcd. for C₁₀H₁₄Cl₂-NO: 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.), n²⁵D, 1.5600. Anal. Found: N, 6.00. N-(3,4-Dichlorobenzyl)-3-hydroxypropylamine, b.p. 155-160° (0.8 mm.), n²⁵D, 1.5539. Anal. Found: N, 6.11. Preparation of N-Benzyl-N-(hydroxyalkyl)-dichloroacet-amides.—The following example illustrates the general procedure employing dichloroacetyl chloride as the acetylat-ing agent.

ing 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 $(0-5^{\circ})$ to a solution of 14 g. of N-(4-butoxybenzyl)-ethanolamine in 100 ml. of ethylene dichlobut only being y)-ethalolaritie in 100 mill of ethylete defiber ride. After the addition was completed the reaction mix-ture 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.). Re-crystallization 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 1N 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 suc-cessively with 1 N sodium hydroxide, water, 1 N hydro-chloric 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 prepara-tion of N-(2,4-dichlorobenzyl)-N-(2-hydroxyethyl)-dibromo-acetamide. 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 $115.0-117.2^{\circ}$

Anal. Calcd. for C₁₁H₁₁Br₂Cl₂NO₂: 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. Caled. for C₁₁H₁₁Br₂Cl₂NO₂: 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

according to method B starting with methyl dichloroacetate and the appropriate secondary amine: N-(2,4-Dichlorobenzyl)-N-(2-hydroxypropyl)-dichloro-acetamide, 69% yield, m.p. 135.1-138.0° (ethylene dichlo-ride). Anal. Calcd. for Cl₂H₁₃Cl₄NO₂: 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)-dichloro-acetamide, 31% yield, m.p. 120.0-121.8° (ethylene di-chloride). Anal. Calcd. for Cl₂H₁₃Cl₄NO₂: C, 41.77; H, 3.80; Cl (KOH), 20.55. Found: C, 42.00; H, 3.86; Cl(KOH). 20.52. CI(KOH), 20.52

N-(2,4-Dichlorobenzyl)-N-(3-hydroxypropyl)-dichloroacetamide, 58% yield, m.p. 83.7-86.7° (benzene-Skelly-solve A). Anal. Calcd. for C₁₂H₁₃Cl₄NO₂: 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-Skelly-solve A). Anal. Calcd. for C₁₂H₁₃Cl₄NO₂: C, 41.77; H, 3.80; Cl, 41.10. Found: C, 41.70; H, 3.89; Cl, 41.44.

RENSSELAER, NEW YORK

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

Benzylation and Xanthation of Cellulose Monoalkoxide¹

By M. L. Wolfrom and M. A. El-Taraboulsi²

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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 indi-cated. 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 Counit 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-carbo-

(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).

hydrate reaction is removed by azeotropic distillation with a higher alcohol. A large excess of sodium

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

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