[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

New Amebacides. III.[1] The Preparation of Some N-Benzyl-N-(2-acyloxyethyl)-dichloroacetamides

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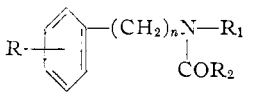
A series of N-benzyl-N-(2-acyloxyethyl)-haloacetamides has been prepared. The following acyl groups are included: formyl, acetyl, butyryl, chloroacetyl, dichloroacetyl, trichloroacetyl, 2-chloropropionyl, 3-carboxypropionyl, 4-carboxybutyryl, 2-carboxybenzoyl and 2,4-dichlorobenzoyl. Many of these compounds were found to have high amebacidal activity when tested in hamsters.

Some of the most potent antiamebic agents tested in these laboratories were obtained from a series of N-(2-hydroxyethyl)-N-(substituted-benzyl)-dichloroacetamides reported previously.[2] It seemed of interest to determine whether a free hydroxyl group in these compounds is essential for high amebacidal activity. In the present communication we are reporting the preparation of a series of compounds derived from the formula I in which n = 1, R_1 = acyloxyethyl and R_2 = CH_2Cl, $CHCl_2$ and



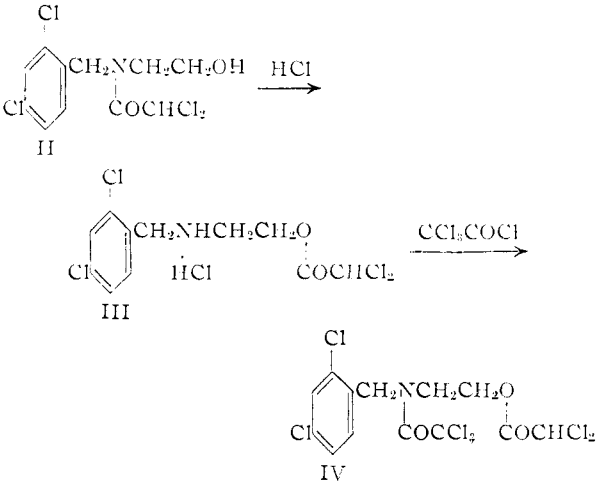
I

CCl_3. The variations in the acyl group in R_1 include formyl, acetyl, butyryl, chloroacetyl, dichloroacetyl, trichloroacetyl, 2-chloropropionyl, 3-carboxypropionyl, 4-carboxybutyryl, 2-carboxybenzoyl and 2,4-dichlorobenzoyl.

Most of the products were synthesized by acylation of the N-(2-hydroxyethyl)-N-benzyl-haloacetamides,[2] either with an acid anhydride or an acid chloride. For example, when N-(2-hydroxyethyl)-N-(2,4-dichlorobenzyl)-dichloroacetamide (II) was treated with acetic anhydride in pyridine solution the O-acetyl derivative was obtained. Treatment of the same 2-hydroxyethyl compound II with succinic anhydride in pyridine gave N-(2,4-dichlorobenzyl)-N-[2-(3-carboxypropionyloxy)-ethyl]-dichloroacetamide in 72% yield. N-[2-(2,4-Dichlorobenzoyloxy)-ethyl]-N-(2,4-dichlorobenzyl)-dichloroacetamide was prepared from II using 2,4-dichlorobenzoyl chloride as the acylating agent.

In the case of the formyl esters the N-benzyl-N-(2-hydroxyethyl)-haloacetamides were heated at steam-bath temperatures with formic acid. For the preparation of the N,O-bis-trichloroacetyl derivative of N-(2-hydroxyethyl)-2,4-dichlorobenzylamine, the latter was treated with two moles of trichloroacetyl chloride in the presence of sodium hydroxide solution. The formation of some N-(2,4-dichlorobenzyl)-2-oxazolidone[3] in this experiment was not unexpected.

Another method which was employed in this work involved an N → O acyl migration followed by acylation of the resulting amine hydrochloride. Treatment of the amide II in dioxane[4] with dry hydrogen chloride gave the O-acyl derivative III



which was heated in benzene with trichloroacetyl chloride until no further evolution of hydrogen chloride was evident. The product, N-(2,4-dichlorobenzyl)-N-(2-dichloroacetoxyethyl)-trichloroacetamide (IV) was obtained in good yield. This compound could not be obtained by the previous methods inasmuch as all attempts to prepare N-benzyl-N-(2-hydroxyethyl)-trichloroacetamides were unsuccessful.[3]

For comparative purposes, a compound in which R_1 is diethylaminoacetoxyethyl was prepared. This was obtained by allowing N-(2-chloroacetoxyethyl)-N-(2,4-dichlorobenzyl)-dichloroacetamide to react with diethylamine in refluxing benzene.

The compounds listed in Table I were screened in hamsters having the spontaneous infection *Endameba criceti*. The results have demonstrated that a free hydroxyl group in R_1 is not essential for high amebacidal activity. In fact, some of the O-acyl derivatives were more effective than the parent 2-hydroxyethyl compounds. The least active derivatives in the present work are those which contain a solubilizing group such as a free carboxylic acid or a diethylamino group. It is interesting to note that the O-dichloroacetyl derivative of N-(2-hydroxyethyl)-N-(2,4-dichlorobenzyl)-dichloroacetamide is less active than the parent compound whereas the O-chloroacetyl derivative is more active.

Acknowledgment.--The authors wish to thank Mr. M. E. Auerbach and Mr. K. D. Fleischer and staffs for the analytical data and corrected melting points recorded, and Dr. D. A. Berberian and Mr. R. C. Slighter for the screening data.

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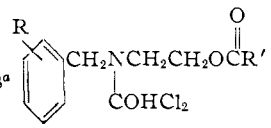
(4) A. Nickon and L. F. Fieser, *ibid.*, **74**, 5503 (1952).

TABLE I

N-ACYLOXYETHYL-N-BENZYLDICHLOROACETAMIDES[a]



R	R'	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
H	H	57.2–58.8	86	$C_{12}H_{13}Cl_2NO_3$			N, 4.83	4.84	24.44	24.00
H	CH_3	79.9–81.6	79	$C_{13}H_{15}Cl_2NO_3$			N, 4.60	4.63	23.30	23.70
4-$CH(CH_3)_2$	H	72.3–74.9	75	$C_{15}H_{19}Cl_2NO_3$	54.22	54.09	5.76	5.70	21.34	21.10
4-$CH(CH_3)_2$	$CHCl_2$	110.5–111.5	60	$C_{16}H_{19}Cl_4NO_3$	46.30	46.52	4.61	4.57	34.16	33.70
4-$CH(CH_3)_2$	$(CH_2)_2CH_3$	89.9–92.0	86	$C_{18}H_{25}Cl_2NO_3$	57.75	57.44	6.73	6.45	18.94	18.50
4-$CH(CH_3)_2$	$(CH_2)_2COOH$	96.7–100.2	62	$C_{18}H_{23}Cl_2NO_5$			N.E., 404.3	411.2	17.57	17.20
4-OC_4H_9	H	69.0–70.9	22	$C_{16}H_{21}Cl_2NO_4$	53.05	53.46	5.84	5.89	19.57	19.60
4-OC_4H_9	$CHCl_2$	76.4–77.9	72	$C_{17}H_{21}Cl_4NO_4$	45.85	45.74	4.75	4.82	31.86	32.00
4-OC_4H_9	$(CH_2)_2COOH$	138.1–139.4	90	$C_{19}H_{25}Cl_2NO_6$			N.E., 434.3	429.7	16.33	16.50
4-NO_2	CH_2Cl	117.2–118.0	98	$C_{13}H_{13}Cl_3N_2O_5$			N, 7.31	7.10	27.72	27.20
3,4-$(OC_2H_5)_2$	CH_3	72.5–74.4	62	$C_{17}H_{23}Cl_2NO_5$	52.05	51.88	5.91	5.67	18.08	17.80
2,4 Cl_2	H	88.1–90.6	66	$C_{12}H_{11}Cl_4NO_3$	40.14	40.04	3.09	3.05	19.55	19.45[b]
2,4-Cl_2	CH_3	74.0–76.0	86	$C_{13}H_{13}Cl_4NO_3$	41.85	41.66	3.51	3.99	38.02	38.28
2,4-Cl_2	CH_2Cl	72.1–75.5	83	$C_{13}H_{12}Cl_5NO_3$	38.29	38.39	2.97	2.86	26.08	25.35[b]
2,4-Cl_2	$CHCl_2$	88.4–90.0	68	$C_{13}H_{11}Cl_6NO_3$	35.32	35.22	2.51	2.76	32.09	31.70[b]
2,4-Cl_2	CCl_3	96.1–97.2	73	$C_{13}H_{10}Cl_7NO_3$	32.79	32.80	2.11	2.06	52.11	52.00
2,4-Cl_2	$(CH_2)_2Cl$	68.2–69.7	45	$C_{14}H_{14}Cl_5NO_3$	39.89	40.07	3.55	3.18	25.23	25.35[b]
2,4-Cl_2	$(CH_2)_2CH_3$	64.1–65.6	77	$C_{15}H_{17}Cl_4NO_3$	44.91	44.73	4.27	3.87	17.68	17.84[b]
2,4-Cl_2	$(CH_2)_2COOH$	95.5–96.6	72	$C_{15}H_{15}Cl_4NO_5$			N.E., 431.0	431.0	16.45	16.15[b]
2,4-Cl_2	$(CH_2)_3COOH$	103.9–106.7	56	$C_{16}H_{17}Cl_4NO_5$			N.E., 445.1	447.4	31.86	31.33
2,4-Cl_2	o-$COOHC_6H_4$	119.3–122.9	89	$C_{19}H_{15}Cl_4NO_5$			N.E., 479.0	473.0	14.80	14.54[b]
2,4-Cl_2	2,4-$Cl_2C_6H_3$	113.8–116.0	98	$C_{18}H_{13}Cl_6NO_3$	42.89	42.57	2.60	2.71	14.07	13.82[b]
2,4-Cl_2	$CH_2N(C_2H_5)_2$	61.1–63.5	46	$C_{17}H_{22}Cl_4N_2O_3$			N, 6.31	6.30	15.96	16.05[b]

[a] Some miscellaneous compounds including monochloro- and trichloroacetamide derivatives are included in the Experimental. [b] Determination of readily hydrolyzable chlorine.

Experimental

N-(2-Chloroacetoxyethyl)-N-(2,4-dichlorobenzyl)-dichloroacetamide.—The following procedure illustrates the general method of acylation employed with acid chlorides.

A slurry of 12 g. (0.16 mole) of pyridine and 17 g. (0.15 mole) of chloroacetyl chloride in 300 ml. of benzene was prepared and treated with 33 g. (0.1 mole) of N-(2,4-dichlorobenzyl) - N - (2 - hydroxyethyl) - dichloroacetamide. After stirring the mixture at room temperature for 12 hours, the resulting solution was filtered with charcoal and the solvent removed under reduced pressure. The residual oil was triturated successively with water, dilute hydrochloric acid and dilute sodium hydroxide solution to give a solid product, 34 g. (83%). After recrystallization from isopropyl alcohol followed by two recrystallizations from ethanol, the product melted at 72.1–75.5° (cor.).

N-(2-Acetoxypropyl)-N-(2,4-dichlorobenzyl)-dichloroacetamide.—This compound was prepared from N-(2,4-dichlorobenzyl)-N-(2-hydroxypropyl)-dichloroacetamide in a similar manner as above. It was obtained as a non-distillable oil that was dried at 50° (0.2 mm.) for 5 hours.

Anal. Calcd. for $C_{14}H_{15}Cl_4NO_3$: C, 43.44; H, 3.91; Cl, 36.64. Found: C, 43.69; H, 3.86; Cl, 35.80.

N-[2-(2,4-Dichlorobenzoyloxy)-ethyl]-N-(2,4-dichlorobenzyl)-dichloroacetamide.—2,4-Dichlorobenzoyl chloride (31.5 g., 0.15 mole) was added with stirring and cooling (temperature <20°) to a solution of 24 g. (0.3 mole) of pyridine in 100 ml. of dioxane. Stirring of the resulting thick slurry was continued while a solution of 33.1 g. (0.1 mole) of N-2,4-dichlorobenzyl) - N - (2 - hydroxyethyl) - dichloroacetamide in 100 ml. of dioxane was added slowly. The resulting mixture then was refluxed for 6 hours. The solution was allowed to cool and the solid that separated was broken up and filtered off. The red filtrate was poured into 2 liters of water with stirring and the stirring continued until the oil that separated solidified. The pink solid was collected on a filter and dried, 49 g. (98%). After recrystallizing twice from isopropyl alcohol the product melted at 113.8–116° (cor.).

N-[2-(3-Carboxypropionyloxy)-ethyl]-N-(2,4-dichlorobenzyl)-dichloroacetamide.—The procedure for acylation employing an anhydride is illustrated by the following example.

A mixture of 12 g. (0.16 mole) of pyridine and 15 g. (0.15 mole) of succinic anhydride was heated with 33.1 g. (0.1 mole) of N-(2,4-dichlorobenzyl)-N-(2-hydroxyethyl)-dichloroacetamide on a steam-bath for one hour and then allowed to stand at room temperature for two days. The resulting solution was taken up in ethylene dichloride and washed successively with 2 *N* hydrochloric acid, 5% sodium hydroxide solution and water. The solution was then dried over Drierite and the solvent removed under reduced pressure. An oil was obtained, 31 g. (72%), that solidified on standing. After three recrystallizations from ethanol the product melted at 95.5–96.6° (cor.).

N-Benzyl-N-(2-formyloxyethyl)-dichloroacetamide.—The following is an example of the procedure employed in the formylation reactions.

A mixture of 13.1 g. (0.05 mole) of N-benzyl-N-(2-hydroxyethyl)-dichloroacetamide and 46 g. (1 mole) of formic acid was heated on a steam-bath for two hours and then poured with vigorous stirring into a liter of water. The oily layer which separated solidified with continued stirring, 12.5 g. (86%). After recrystallization once from benzene–Skellysolve A and once from isopropyl alcohol, the product melted at 57.2–58.8° (cor.).

N-(3,4-Dichlorobenzyl)-N-(2-formyloxyethyl)-chloroacetamide.—This compound was prepared from N-(3,4-dichlorobenzyl)-N-(2-hydroxyethyl)-chloroacetamide in a manner similar to that above. The product was obtained in a 50% yield as a non-distillable oil that was dried at 50° (0.2 mm.) for 5 hr.

Anal. Calcd. for $C_{12}H_{12}Cl_3NO_3$: C, 44.40; H, 3.73; Cl, 32.77. Found: C, 44.79; H, 3.85; Cl, 33.00.

N-(2,4-Dichlorobenzyl)-N-(2-trichloroacetoxyethyl)-trichloroacetamide.—A solution of 36.5 g. (0.2 mole) of trichloroacetyl chloride in 50 ml. of ethylene dichloride was added slowly with stirring to a cold mixture (temperature <15°) of 22 g. (0.1 mole) of N-(2-hydroxyethyl)-2,4-dichlorobenzylamine, 200 ml. of ethylene dichloride and 250 ml. of 1 *N* sodium hydroxide solution. When the addition was complete the stirring was continued while the mixture was allowed to warm to room temperature. The

organic layer was separated, washed with 2 *N* hydrochloric acid and with water and filtered with charcoal. The solution was then dried over Drierite and the solvent removed under reduced pressure. The resulting oil, 21 g. (41%), was crystallized from Skellysolve C to furnish a product that melted at 100.9–103.0° (cor.).

Anal. Calcd. for $C_{13}H_9Cl_3NO_3$: C, 30.56; H, 1.78; Cl, 41.65. Found: C, 30.45; H, 1.68; Cl, 41.44.

In a previous run about 10% of 3-(2,4-dichlorobenzyl)-2-oxazolidone[3] was obtained by concentration of the Skellysolve C filtrate. About 30% of unreacted N-(2-hydroxyethyl)-2,4-dichlorobenzylamine also was recovered from the acid washings.

N-(2-Dichloroacetoxyethyl)-2,4-dichlorobenzylamine Hydrochloride.—Anhydrous hydrogen chloride was bubbled into a mixture of 16.6 g. (0.05 mole) of N-(2,4-dichlorobenzyl)-N-(2-hydroxyethyl)-dichloroacetamide and 50 ml. of anhydrous dioxane. The temperature rose to 70° and a clear solution was obtained. The solution was cooled and the solid that separated was collected on a filter and washed with ether, 16 g. (86%). When recrystallized from isopropyl alcohol the hydrochloride salt melted at 146.2–147.1° (cor.).

Anal. Calcd. for $C_{11}H_{11}Cl_4NO_2 \cdot HCl$: C, 35.94; H, 3.29; Cl^-, 9.65. Found: C, 36.35; H, 3.35; Cl^-, 9.63.

N-(2-Dichloroacetoxyethyl)-N-(2,4-dichlorobenzyl)-trichloroacetamide.—A mixture of 13 g. (0.035 mole) of N-(2-dichloroacetoxyethyl)-2,4-dichlorobenzylamine hydrochloride and 9.1 g. (0.05 mole) of trichloroacetyl chloride in 50 ml. of dry benzene was refluxed until a complete solution was obtained. This required about 1.5 hours. Ten milliliters of ethanol was added slowly and the solvent then distilled under reduced pressure. The resulting oily product solidified on treatment with isopropyl alcohol, 15 g. (87%), and after recrystallization from isopropyl alcohol melted at 72.9–76.8° (cor.).

Anal. Calcd. for $C_{13}H_{10}Cl_7NO_3$: C, 32.79; H, 2.11; Cl, 52.11. Found: C, 32.96; H, 2.08; Cl, 51.80.

N-(2,4-Dichlorobenzyl)-N-(2-diethylaminoacetoxyethyl)-dichloroacetamide.—To a refluxing solution of 13.5 g. (0.039 mole) of N-(2-chloroacetoxyethyl)-N-(2,4-dichlorobenzyl)-dichloroacetamide in 75 ml. of benzene was added dropwise 15.7 g. (0.078 mole) of diethylamine. Refluxing was continued for 5 hr. The solid diethylamine hydrochloride was filtered off and the benzene solution washed with water, dried and the solvent removed under reduced pressure. The resulting oily product solidified, 8 g. (55%), which after recrystallization from Skellysolve B melted at 61.1–63.5° (cor.).

RENSSELAER, N. Y.

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Fatty Acid Amides. VII.[2] Addition of Hydrogen Cyanide to Unsaturated Acids. Preparation of Formamido Acids, Amino Acid Sulfates and Amino Acids

BY EDWARD T. ROE AND DANIEL SWERN

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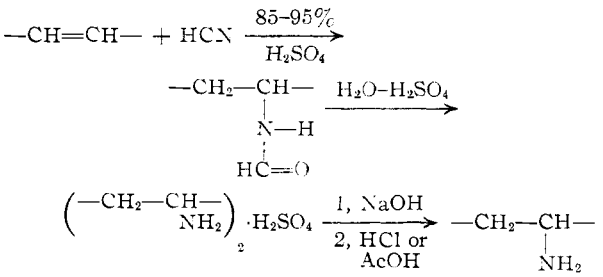
Liquid hydrogen cyanide has been added to the double bonds of oleic, 10-hendecenoic and ricinoleic acid in 85–95% sulfuric acid to give good yields of formamidostearic, formamidohendecanoic and hydroxyformamidostearic acids, respectively. The first two are rapidly hydrolyzed by refluxing with aqueous sulfuric acid to give the corresponding amino acid sulfates in high yield. These can be converted to the free amino acids by neutralization.

In our previous publication,[2] we reported the addition of various nitriles to the double bond of oleic acid in concentrated sulfuric acid to give substituted amidostearic acids. With the object of preparing more readily hydrolyzable amido acids, we have studied the similar addition of hydrogen cyanide to oleic, 10-hendecenoic and ricinoleic acids to yield formamidostearic, formamidohendecanoic and 12-hydroxyformamidostearic acids, respectively. The general equations show the reactions involved. As anticipated,[2] mixtures of isomeric products are obtained.



Hydrogen cyanide in sulfuric acid has been added to the double bonds of reactive olefins, such as diisobutylene,[3] camphene,[3] bimethallyl[4] and limonene,[4] but no work appears to have been published on such reactions with relatively unreactive double bonds.

Experimental

Starting Materials.—Pure oleic acid was obtained from olive oil fatty acids.[5] Ricinoleic acid was prepared from pure methyl ricinoleate[6] by conventional means. 10-Hendecenoic acid was obtained from the purest commercial grade.[7] Anhydrous hydrogen cyanide was prepared as needed from sodium cyanide and sulfuric acid.[8] *All reactions with hydrogen cyanide were conducted in an efficient hood.*

Formamidostearic Acids.—Simultaneously and with efficient stirring, 99 g. (0.35 mole) of oleic acid and 82 ml. (2.1 mole) of liquid hydrogen cyanide contained in a specially constructed jacketed dropping pipet (jacket filled with chopped ice) were added in one-half hour to 318 ml. (4.9 moles) of 85% sulfuric acid in a 2-l. three-neck flask. The reaction was exothermic. The temperature was maintained between 20–30° by controlling the rate of addition of the reactants and by external cooling. Stirring was continued for an additional 1.5 hours and the reaction mixture was poured with stirring onto about 3 l. of chopped ice and water. The mixture was allowed to stand for about two hours with occasional stirring, and the aqueous layer was decanted and

(1) A laboratory of the Eastern Utilization Research Branch, Agricultural Research Service, United States Department of Agriculture. Article not copyrighted.

(2) For paper VI, see THIS JOURNAL, **75**, 5479 (1953).

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