The Preparation of Some Amides of Dichloroacetaldehyde*

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The amides of dichloroacetaldehyde were synthesized and their physical and chemical constants were determined. None of the compounds showed any appreciable hypnotic or analgetic activity. Two of the compounds, the isovaleramide and 2-ethylbutyramide derivatives showed some anticonvulsant activity.

VARIOUS substituted amides have been reported in the literature. Jacobsen (1) prepared the chloral derivatives of acetamide, benzamide, and urea. Other chloral derivatives reported are those of formamide (2) propionamide (3), valeramide (3), caproamide (3), and caprylamide (3). Schiff and Tassinari (4) synthesized the α, α, β-trichlorobutyraldehyde derivatives of acetamide, ammonia, and benzamide.

LaRocca, *et al.* (5), synthesized 24 chloral and α, α, β-trichlorobutyraldehyde amides, 18 of these compounds being new. These compounds were made by condensing on a steam bath equimolar portions of chloral hydrate (or α, α, β-trichlorobutyraldehyde) and the appropriate aliphatic amide, the condensation requiring one to eight hours. The condensed solids were washed with water to remove any unreacted starting materials and recrystallized repeatedly from dilute alcohol until melting points were constant. The products were then dried over phosphoric anhydride *in vacuo*. All of these compounds were white crystalline solids, insoluble in water, but soluble in alcohol and acetone. Purification was tedious due to the difficulty in removing traces of unreacted amide from the final product. In general, the α, α, β-trichlorobutyraldehyde amides melted somewhat higher than the chloral derivatives.

Work with these various amide derivatives has shown their potentialities as sedative-hypnotics. Byrum and LaRocca (6), investigated the chloral and α, α, β-trichlorobutyraldehyde amides for sedative-hypnotic action, determining the HD_{50} and LD_{50} for 19 different compounds. They found chloral butyramide, chloral isovaleramide, chloral 2-ethylcaproamide, and chloral 2-ethylbutyramide to be the most active. These compounds compared favorably with chloral hydrate as to milligram potency, therapeutic ratio, and duration of action.

Substituted amides have also shown potentialities as fungicides. Leonard and Blackford (7) made a study of the α-bromoacetamides and reported remarkable levels of fungus inhibition. LaRocca, Leonard, and Weaver (5) tested some chloral and α, α, β-trichlorobutyraldehyde amides for fungicidal activity, but their preliminary assays indicated these compounds have little activity as fungicides.

In view of the favorable results obtained in the studies of amide derivatives, it was decided that the synthesis of some dichloroacetaldehyde amides should be attempted in order that further studies on substituted amides could be made.

EXPERIMENTAL

Materials.—Many of the intermediates used in this investigation were purchased through ordinary commercial sources. The aliphatic acids used in preparing the acid chlorides were purchased from Eastman Kodak Company. Westvaco Chemical Company supplied the dichloroacetaldehyde.

Synthesis of Intermediates.—The acid chlorides used in the preparation of the various amides were made by reacting the corresponding fatty acid with PCl_3, using a ratio of three moles of fatty acid to one mole of PCl_3. The reacting mixture for each acid chloride preparation was placed in a beaker and heated on a water bath for approximately one minute, or until cloudiness occurred. Upon placing the mixture in an ice bath, phosphorus acid in the form of a viscous liquid settled to the bottom of the beaker. The acid chloride was then removed by decanting.

Various of the amides used were prepared by adding the appropriate acid chloride, drop by drop, from a separatory funnel into a concentrated ammonium hydroxide solution cooled by a dry ice and acetone bath. The precipitate of amide was filtered off with suction and purified by dissolving in hot benzene and filtering again while hot. The hot filtrate contained the amide which crystallized out immediately upon cooling. This method of preparation was not practical for some of the amides due to the violent reaction of certain of the acid chlorides with ammonium hydroxide solution and the difficulty in keeping the reacting temperature low enough for sizable yields to be obtained. In these instances the ammonium salt method of preparation was used, or else the amide was purchased through ordinary commercial sources.

* Received August 8, 1953, from the Pharmaceutical Research Laboratories of the University of Georgia School of Pharmacy, Athens.

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‡ The authors wish to acknowledge the generous financial assistance of the American Foundation for Pharmaceutical Education and Eli Lilly and Company.

TABLE I.—DICHLOROACETALDEHYDE AMIDES[a]

RCONHCH(OH)CHCl$_2$

Amide	Yield, %	M. P., °C.[b]	Nitrogen		Chlorine	
			Calcd.	Found[c]	Calcd.	Found[c]
Acetamide	18	113	8.14	7.98	41.3	39.8
Propionamide	25	116	7.53	7.33	38.1	37.9
Butyramide	17	55	7.00	6.85	35.5	34.1
Isobutyramide	11	93	7.00	6.99	35.5	33.7
Valeramide	10	72	6.54	6.14	33.1	32.7
Isovaleramide	13	94	6.54	6.47	33.1	32.6
Caproamide	21	72	6.14	5.88	31.1	30.9
2-Ethylbutyramide	53	117	6.14	6.05	31.1	31.0
Benzamide	47	115	5.98	5.85	29.9	29.7
Phenylacetamide	32	92	5.64	5.63	28.6	28.3

[a] The *Chemical Abstracts* name for these compounds, N-(2,-2-dichloro-l-hydroxyethyl) amides was not used in this paper because it is unwieldy.
[b] All melting points on calibrated Fisher-Johns apparatus.
[c] Average of two determinations.

Depolymerization of Dichloroacetaldehyde.—Due to the tendency of dichloroacetaldehyde to polymerize and solidify, it was necessary to depolymerize much of it immediately before use. A modification of Fieser's method for depolymerizing paraldehyde (8) was employed.

Thirty grams of the polymerized dichloroacetaldehyde (solid) was placed in a 500-cc. round-bottomed flask fitted with a Claisen head, to which was attached a ground glass adapter and cooled condenser. Cotton was fitted into the space between the adapter and the receiver, a 250-cc. Erlenmeyer flask. A mixture of 1 cc. each of sulfuric acid and water was poured into the flask with the aldehyde, then heat applied. The dichloroacetaldehyde distilled at 85–88°. To avoid charring of the mixture, distillation was discontinued after about two-thirds of the material had been converted into the dichloroacetaldehyde monomer.

Synthesis of Dichloroacetaldehyde Amides.—One-tenth mole of the appropriate amide was allowed to react with 0.16 mole of dichloroacetaldehyde at room temperature (approximately 27°) until solidification occurred. The time required for this condensation varied from one to seven days. The paraffin-like solid was dissolved in boiling chloroform and this hot solution then filtered using a Büchner funnel with a high-grade filter paper. The filtrate was placed under a stream of compressed air until crystallization began. After twenty-four hours in the refrigerator the product was filtered, using a fritted glass crucible and suction. Recrystallization was repeated until the melting point was constant. The product was dried over calcium chloride *in vacuo*. The condensation of phenylacetamide with dichloroacetaldehyde was carried out in a refrigerator.

Analytical Methods.—Each compound was first tested qualitatively for nitrogen and chlorine by application of the sodium fusion process. Then quantitative determinations were made using the peroxide bomb fusion method for chlorine and a modification of the Kjeldahl method for nitrogen. The analytical data for ten new compounds are given in Table I.

Pharmacological Data.—These compounds were screened by Eli Lilly and Company for possible anticonvulsant, hypnotic, and analgetic activity.

Only two compounds showed any anticonvulsant activity. Dichloroacetaldehyde isovaleramide in oral doses of 400 mg./Kg. in rats gave 80% protection as determined by the Metrazol test method and 40% protection as determined by the electroshock method. The 2-ethylbutyramide derivative at the same dosage level gave 60% protection by the Metrazol test and zero protection by the electroshock method.

None of the compounds showed significant hypnotic or analgetic activity.

SUMMARY

The synthesis and physical properties of ten dichloroacetaldehyde amides have been described. All ten are new compounds.

The pharmacological screening of these compounds has shown the absence of significant hypnotic or analgetic activity. Two of the compounds, the isovaleramide and 2-ethylbutyramide derivatives show some anticonvulsant activity.

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