[CONTRIBUTION FROM THE CHEMISTRY DIVISION OF THE NAVAL RESEARCH LABORATORY]

THE PREPARATION AND FUNGICIDAL ACTIVITY OF SOME AMIDES OF CHLORAL AND α,α,β-TRICHLOROBUTYRALDEHYDE[1]

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Previous work in this laboratory has shown the potentialities of substituted amides as fungicides. A recent study of the α-bromoacetamides revealed remarkable levels of fungus inhibition (1). Therefore, chloral hydrate and α,α,β-trichlorobutyraldehyde, both known to be toxic to fungi, were condensed with some simple amides and fungus-inhibitive properties of the products were assayed preliminary to the preparation of condensation products of the halogenated amides.

Various chloral amides have been reported in the literature. Jacobsen (2) reported the preparation of the chloral derivatives of acetamide, benzamide, and urea. Among the other derivatives which have been prepared are those of formamide (3), propionamide (4), valeramide (4), caproamide (4), and caprylamide (4). Less is known of the α,α,β-trichlorobutyraldehyde amides. Schiff and Tassinari (5) reported the synthesis of the derivatives of acetamide, ammonia, and benzamide.

Physical constants, analytical data, and assay data for the chloral and α,α,β-trichlorobutyraldehyde amides prepared in this laboratory are given in Tables I and II. The fungus inhibitions of these compounds, especially those of Table II, are generally low at the molar concentrations employed. Inhibition observations in this laboratory on certain halogenated paraffins have indicated little activity from halogenation alone. The influence of certain functional groups along with halogens is less understood, although in the case of the α-chloroacetanilides (1), more chlorine atoms resulted in less toxic compounds. Since the chloral addition products are alkylsubstituted rather than acylsubstituted, this comparison does not suffice. The greater ease of hydrolysis, by acids and bases, of the chloral derivatives as compared to ordinary N-alkyl amides may demonstrate this point.

In the case of the present study a few generalizations may be made. The chloral derivatives of Table I show increasing activity as the carbon chain lengthens, with a rough maximum at 8 to 9 carbon atoms. Compounds with less than five carbon atoms in the amide chain show least activity. Branching of the amide chain shows inconclusive results with respect to the straight-chain isomers.

The α,α,β-trichlorobutyraldehyde derivatives are generally somewhat less toxic than the corresponding chloral compounds. Introduction of an *alpha* chlorine atom in the amido portion definitely augments activity, as shown by the greater effectiveness of the α-chloroacetamide derivative compared to the acet-

[1] This paper is No. IV of a series on organic fungicides. For paper No. III, see Swensen and Weaver, *J. Am. Chem. Soc.*, **70**, 4060 (1948).

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amide analog. The greater activity of the isovaleramide and 2-ethylbutyramide products with respect to the normal isomers would indicate enhancement of

TABLE I

CHLORAL AMIDES[a] RCONHCH(OH)CCl$_3$

AMIDE	YIELD, %	M.P., °C.[b]	N[c]		INHIBITION, %	
			Calc'd	Found	10^{-2} mole/l	10^{-3} mole/l
Acetamide	80	170[d]			16	2
Propionamide	76	177[e]			29	−4
Butyramide	79	139			37	0
Valeramide	78	139[f]	5.6	5.8	78	14
Isovaleramide	41	134	5.6	5.6	63	12
Caproamide	69	137[g]	5.3	5.2	71	24
2-Ethylbutyramide	78	113	5.3	5.5	65	24
Oenanthamide	81	133	5.1	5.4	47	27
Caprylamide	100	126[h]	4.8	4.7	71	43
2-Ethylcaproamide	88	91	4.8	5.0	82	49
Pelargonamide	76	121	4.6	4.7	78	43
Capramide	59	119	4.4	4.4	67	35

[a] The *Chem. Abstr.* name for these compounds, N-(2-trichloro-1-hydroxyethyl)amides, was not used in this paper because it was unwieldy. [b] All melting points on calibrated Fisher-Johns apparatus. [c] Micro-analyses by Oakwold Labs., Alexandria, Virginia. [d] M.p. 158° (2). [e] M.p. 166–167° (4). [f] M.p. 142° (4). [g] M.p. 139° (4). [h] M.p. 125–126° (4).

TABLE II

α,α,β-TRICHLOROBUTYRALDEHYDE AMIDES[a] RCONHCH(OH)CCl$_2$CHClCH$_3$

AMIDE	YIELD, %	M.P., °C.[b]	N[c]		INHIBITION, %	
			Calc'd	Found	10^{-2} mole/l	10^{-3} mole/l
Acetamide	70	188[d]	5.9	5.9	8	0
α-Chloroacetamide	43	139	5.2	5.3	100	27
Propionamide	65	155	5.6	5.5	16	4
Butyramide	66	140	5.3	5.5	22	0
Valeramide	69	136	5.1	5.2	22	4
Isovaleramide	14	134	5.1	5.2	69	53
Caproamide	62	137	4.8	4.8	37	0
2-Ethylbutyramide	42	116	4.8	4.9	100	—
Oenanthamide	72	136	4.6	4.7	31	2
Caprylamide	66	131	4.4	4.2	34	4
Pelargonamide	57	131	4.2	4.4	34	27
Capramide	43	120	4.0	3.7	41	51

[a] The *Chem. Abstr.* name for these compounds, N-(2,2,3-trichloro-1-hydroxybutyl)-amides, was not used in this paper because it was unwieldy. [b] All melting points on calibrated Fisher-Johns apparatus. [c] Micro-analyses by Oakwold Labs., Alexandria, Virginia. [d] M.p. 158° (5).

activity with branching in the amide chain. These compounds are the only exception to the general rule of less activity anticipated from the α,α,β-tri-

chlorobutyraldehyde amides. It is somewhat more difficult to discover a peak in activity, but the data seem to indicate that the activity is perhaps still on the ascendent curve at 9 and 10 carbon atoms.

At this stage, it would be premature to predict the ultimate utility of these compounds as fungicides. Thus far they have been assayed against only one organism and even though additional assays prove promising, pharmacological studies and practical tests of end-use must precede final judgment.

EXPERIMENTAL

Materials. α,α,β-Trichlorobutyraldehyde was furnished by the Westvaco Chlorine Products Corporation and the fraction distilling at 163–165° was used in this work.

Synthesis. Equi-molar portions of chloral hydrate (or α,α,β-trichlorobutyraldehyde) and the appropriate amide were heated on a steam-bath until the reaction mixture solidified (1 to 8 hours). The solid was washed with water to remove any unreacted starting materials and recrystallized repeatedly from dilute alcohol until the melting point was constant. The product was dried over phosphoric anhydride *in vacuo*.

All the compounds are white crystalline solids, insoluble in water but soluble in alcohol and acetone. Purification of the compounds 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. It is also interesting to note that the melting points of both acetamide derivatives are appreciably higher than the values reported in the early German literature.

Fungicidal assay. The fungus-inhibitive properties were determined by the procedure described by Leonard and Blackford (1) and may be summarized as follows. Nutrient agars are prepared containing the toxic agents in the appropriate concentrations. After the media has solidified in the Petri plates, the center of each dish is inoculated with an aqueous suspension of the test organism, *Trichoderma viride* USDA T-1. During subsequent incubation at 30°, the diameters of the respective mycelia are measured periodically, usually twice daily. The values are then plotted against time and the growth rate determined as the slope of the best line through the points. Inhibition is then calculated as follows:

$$I = \frac{C - T}{C} \times 100\%$$

where I = percentage inhibition
C = growth rate of control, mm./hour
T = growth rate of toxic, mm./hour

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SUMMARY

The synthesis and physical properties of twenty-four chloral and α,α,β-trichlorobutyraldehyde amides have been described. Of these, eighteen are new compounds.

Though fungicidal assays indicate the compounds to be of relatively low potencies, more exhaustive tests are required.

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