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

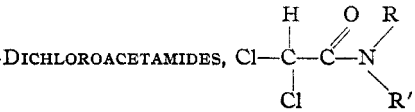
Organic Fungicides. III. The Preparation of Some α,α-Dichloroacetamides

BY ALBERT D. SWENSEN[1] AND WARREN E. WEAVER

The previous papers of this series described the preparation of α-bromoacetyl and α-bromopropionyl derivatives of a number of aliphatic amines.[2] In order to investigate systematically the fungicidal activity of the α-halo amides, the synthesis of similar α,α-dichloroacetamides was undertaken.

The lower members of the series possess a camphoraceous odor and exhibited no lachrymatory or other irritating properties. The N-methyl and N-ethyl compounds were recrystallized from water; the other solids from water and ethanol. All the compounds were white when pure.

TABLE I

α,α-DICHLOROACETAMIDES, 

These substances were all prepared by Method I except the first three members of the Series, which were prepared by Method II.

R	R′	Yield, %	B. p.,[a] °C.	Mm.	M. p.,[a] °C.	$n^{25}D$	d^{25}_4	*MR* Calcd.	*MR* Obs.	Formula	Nitrogen % [e] Calcd.	Found	
CH_3–	H–	72	98	8	79[b]					$C_3H_5NOCl_2$	9.87	10.26	9.95
CH_3–	CH_3–	76	97	9	Liq.	1.4931	1.3256	34.16	34.21	$C_4H_7NOCl_2$	8.98	9.11	9.17
C_2H_5–	H–	77	104	8	59[c]					$C_4H_7NOCl_2$	8.98	8.72	8.99
C_2H_5–	C_2H_5–	85	100	4	Liq.[d]	1.4813	1.2074	43.40	43.40	$C_6H_{11}NOCl_2$	7.61	7.69	7.40
n-C_3H_7–	H–	89	111	7	50					$C_5H_9NOCl_2$	8.24	8.35	8.39
n-C_3H_7–	*n*-C_3H_7–	81	87	0.3	Liq.	1.4779	1.1337	52.64	52.95	$C_8H_{15}NOCl_2$	6.60	6.85	6.64
iso-C_3H_7–	H–	45			127					$C_5H_9NOCl_2$	8.24	8.57	8.18
iso-C_3H_7–	iso-C_3H_7–	62	75	.6	81–82					$C_8H_{15}NOCl_2$	6.60	6.40	6.24
CH_2=CH—CH_2–	H–	87	93	.8	Liq.	1.4968	1.2801	38.31	38.39	$C_5H_7NOCl_2$	8.34	8.28	8.52
n-C_4H_9–	H–	74	88	.3	43					$C_6H_{11}NOCl_2$	7.61	7.45	7.58
n-C_4H_9–	*n*-C_4H_9–	78	109	1	Liq.	1.4746	1.0893	61.88	62.02	$C_{10}H_{19}NOCl_2$	5.83	5.96	5.79
iso-C_4H_9–	H–	71	87	0.2	83					$C_6H_{11}NOCl_2$	7.61	7.79	7.64
iso-C_4H_9–	iso-C_4H_9–	58	92	.1	103–104					$C_{10}H_{19}NOCl_2$	5.83	6.14	5.99
$CH_3CH_2CH(CH_3)$–	H–	59	91	.3	87					$C_6H_{11}NOCl_2$	7.61	7.68	7.67
$CH_3CH_2CH(CH_3)$–	$CH_3CH_2CH(CH_3)$–	57	101	.3	Liq.	1.4788	1.1146	61.88	61.08	$C_{10}H_{19}NOCl_2$	5.83	6.08	6.10
n-C_5H_{11}–	H–	77	95	.3	Liq.	1.4751	1.1501	48.02	48.50	$C_7H_{13}NOCl_2$	7.07	7.08	7.02
n-C_5H_{11}–	*n*-C_5H_{11}–	78	121	.3	Liq.	1.4736	1.0613	71.12	70.91	$C_{12}H_{23}NOCl_2$	5.22	5.24	5.46
$CH_3CH_2CH_2CH(CH_3)$–	H–	75	98	1	72–73					$C_7H_{13}NOCl_2$	7.07	6.99	7.01
n-C_6H_{13}–	H–	74	116	1	31–32					$C_8H_{15}NOCl_2$	6.60	6.57	6.87
$CH_3CH_2CH(C_2H_5)CH_2$–	H–	77	93	0.2	58					$C_8H_{15}NOCl_2$	6.60	6.95	6.70
n-C_7H_{15}–	H–	85	115	.3	Liq.	1.4733	1.0943	57.26	57.97	$C_9H_{17}NOCl_2$	6.19	6.51	6.13
n-C_8H_{17}–	H–	88	124	.3	31–32					$C_{10}H_{19}NOCl_2$	5.83	5.94	6.02
$CH_3(CH_2)_3CH(C_2H_5)CH_2$–	H–	89	123	.5	Liq.	1.4749	1.0820	61.88	62.44	$C_{10}H_{19}NOCl_2$	5.83	5.88	6.09
n-$C_{10}H_{21}$–	H–	80	140	.2	40					$C_{12}H_{23}NOCl_2$	5.22	4.97	5.39

[a] All temperatures are uncorrected. [b] McKie[3] reported m. p. 79°. [c] McKie[3] reported m. p. 67.8°; Wallach and Kamenski[4] reported m. p. 59° and b. p. 225°. [d] Miller and Johnson[4] reported b. p. 124–126° (19 mm.). [e] Microanalyses by Oakwold Laboratories, Alexandria, Va.

Only a few α,α-dichloroacetamides have been synthesized previously and described in the literature. N,N-Dimethyl-α,α-dichloroacetamide,[3] N-ethyl-α,α-dichloroacetamide[3,4] and N,N-diethyl-α,α-dichloroacetamide[5] have been prepared by the reaction of the amine or its hydrochloride with the acid chloride. Physical constants and analyses for all the compounds prepared in this Laboratory are given in Table I. Unlike the previously described bromo amides, some of the disubstituted amides were solids. Furthermore, the molecular refractivities of the N-amyl and N-heptyl derivatives showed significant exaltation.

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(2) Weaver and Whaley, THIS JOURNAL, **69**, 515 (1947); Weaver and Whaley, *ibid.*, **69**, 1144 (1947).

(3) McKie, *J. Chem. Soc.*, 2213 (1923).

(4) Wallach and Kamenski, *Ann.*, **214**, 221 (1884).

(5) Miller and Johnson, *J. Org. Chem.*, **1**, 135 (1936).

Experimental

Reagents.—The α,α-dichloroacetyl chloride, dimethylamine, ethylamine, diethylamine, allylamine, di-*n*-butylamine and the amine hydrochlorides were obtained from Eastman Kodak Company (White Label), the isopropylamine from Commercial Solvents Corporation, and the ethylene dichloride from Carbide and Carbon Chemicals Corporation. The other amines used were provided by Sharples Chemicals, Inc. None of the reagents were purified before use.

Methods.—The methods used have been described in detail previously.[2]

I. A solution of the amine in ethylene dichloride maintained at −10 to −20°, was treated with the acid chloride. After filtering off the precipitated amine hydrochloride, the filtrate was washed with dilute hydrochloric acid and water, dried over anhydrous magnesium sulfate and distilled. With the higher molecular weight amines, it was found advantageous in certain cases to use very dilute sulfuric acid instead of hydrochloric acid. The amine hydrochlorides seemed to be more soluble in ethylene dichloride than the amine hydrobromides. The N-isopropyl compound was obtained by removing the solvent and recrystallizing the residue from dilute ethanol.

II. When amine hydrochlorides were used, the reaction was carried out in the presence of 40% sodium hydroxide.

The mycological findings will be described elsewhere.

Summary

Twenty-four α,α-dichloroacetamides have been prepared preliminary to their evaluation as fungicidal agents. Twenty-one of these are new compounds.

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[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, SCHOOL OF SCIENCE, OREGON STATE COLLEGE]

Quinazolines. VII. The Synthesis of Methyl 2,4-Dimethyl-8-quinazolyl Ketone[1]

BY ROBERT W. ISENSEE AND BERT E. CHRISTENSEN

The problem of synthesizing amino alcohols from quinazoline compounds is best approached through the preparation of the acetyl or carboxy intermediate which by means of the Mannich or diazomethane reaction can usually be converted to the amino ketone and finally to the alcohol.

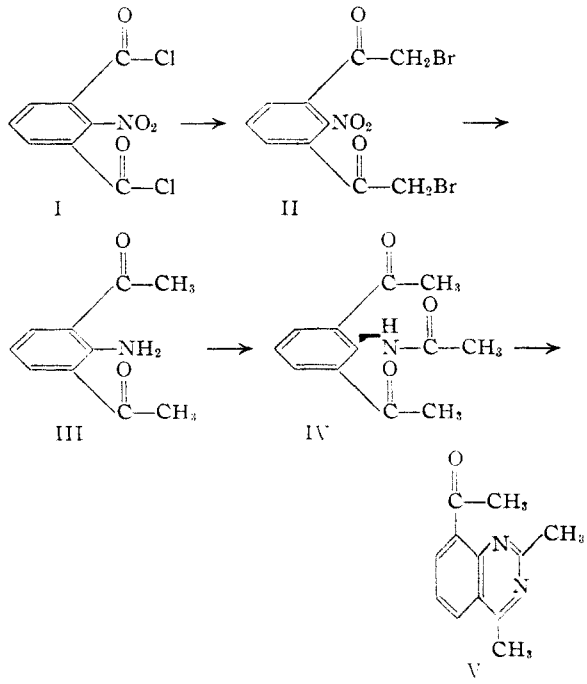
For example, in a recent study, *p*-toluic acid was used to synthesize acetamino-1,4-diacetylbenzene which on cyclization gave the 7-acetyl-2,4-dimethylquinazoline.[2] In the current work, *m*-toluic acid was nitrated[3] and then oxidized[4] to 2-nitroisophthalic acid which served as the initial intermediate for the continuation of these studies.

Fusion of 2-aminoisophthalic acid according to the directions of Niementowski[5] yielded 4-hydroxy-8-quinazolinecarboxylic acid, which was readily converted to the bromomethyl ketone by the usual procedures. Although there was evidence that the bromomethyl ketone would couple with various secondary amines, it was not possible to isolate any product because of the apparent instability of the amino ketone.

In the earlier work the intermediate 1,4-diacetylbenzene was obtained by the condensation of sodio acetoacetic ester and terephthalyl chloride followed by an acid and a basic hydrolysis, as described by Ruggli and Gassenmeier.[6] This method for the preparation of diacetylbenzene proved however to be a laborious process productive of low yields. For this reason 2-nitroisophthalyl chloride (I) (see Fig. 1) was converted to 1,3-dibromoacetyl-2-nitrobenzene (II), by means of the diazomethane reaction. The product subsequently was reduced with stannous chloride to the 2-amino-1,3-diacetylbenzene (III). This procedure proved to be so superior to the acetoacetic ester condensation that it was later used for the preparation of *p*-diacetylbenzene. The acetylation of the 2-amino-1,3-diacetylbenzene, as one might predict, proved to be quite difficult, while the acetamino derivative (IV) gave poor yields on cyclization in contrast to other similar reactions.

The methyl 2,4-dimethyl-8-quinazolyl ketone (8-acetyl-2,4-dimethylquinazoline) (V) gave a Mannich product with cold aqueous formaldehyde and dimethylamine hydrochloride. Although the acetyl substituent appears to be the one most likely involved in this reaction the active methyl group in certain cases[7] are also reactive. Considering the fact that these condensations proceed at room temperature[2] together with the activity of certain groups at the 4-position[8] it is possible that the reaction may have involved an active methyl rather than the acetyl substituent.

Fig. 1



This appears to be quite probable in view of the fact that similar experiments with 2,4-dimethylquinazoline yields a Mannich product; further-

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(2) Christensen, Graham and Griffith, THIS JOURNAL, **67**, 2001 (1945).

(3) Muller, *Ber.*, **42**, 430 (1909).

(4) Vohl, *Ber.*, **43**, 3480 (1910).

(5) Niementowski, *J. prakt. Chem.*, [2] **51**, 564 (1895).

(6) Ruggli and Gassenmeier, *Helv. Chim. Acta*, **22**, 496 (1939).

(7) Heou-Feo, *Compt. rend.*, **192**, 1242 (1931).

(8) Tomisek and Christensen, THIS JOURNAL, **67**, 2112 (1945).