in 75 cc. of methyl alcohol was not decolorized by 5 g. of anethole after standing for the same period of time.

Summary

1. The presence of water is unnecessary for the addition of methyl hypobromite by the reaction of bromine and methyl alcohol with ethylene derivatives. By the reaction of bromine and absolute methyl alcohol either at 25° or 65° methyl hypobromite was added to benzalacetophenone, cinnamic acid and stilbene. With cinnamic acid, esterification also takes place.

2. A solution of cinnamic acid in 50% aqueous methyl alcohol at 0° reacts with bromine with the simultaneous addition of hypobromous acid, methyl hypobromite and bromine.

3. The action of chlorine on solutions of benzalacetophenone, cinnamic acid and stilbene in methyl alcohol either at 25° or 50° results in the addition of methyl hypochlorite to the double linkage of the unsaturated compound. The product with cinnamic acid was the methyl ester of α-chloro-β-methoxy-phenylpropionic acid. The reaction with cinnamic acid was also carried out with solutions in carbon tetrachloride-methyl alcohol mixtures containing either 50 or 75% of carbon tetrachloride.

4. Attempts to add methyl hypo-iodite to cinnamic acid and anethole with the use of iodine and methyl alcohol were unsuccessful.

CLEVELAND, OHIO

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE RICE INSTITUTE]

SUBSTITUTED AMIDES. I. THE PREPARATION OF SUBSTITUTED ACETAMIDES AND THE CORRESPONDING PRIMARY AMINES[1]

BY H. O. NICHOLAS AND J. L. E. ERICKSON

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In 1879 Rudolph[2] showed that a reaction takes place between acetamide and benzyl chloride with the formation of benzylacetamide. On repeating his work for the purpose of ascertaining the general applicability of this reaction in organic synthesis, we noted that the yield of benzylacetamide was very small. Also, a large amount of ammonium chloride was formed in the reaction, a fact which he did not mention. After carefully purifying and drying the alkyl halide and the acetamide, it was found that during the course of the reaction ammonium halide was still formed, and that no halogen acid was evolved. The source of the ammonium halide was determined by passing dry hydrogen bromide through anhydrous acetamide

[1] Constructed from a thesis submitted by J. L. E. Erickson in partial fulfilment of the requirements for the degree of Master of Science at the Rice Institute.

[2] Rudolph, *Ber.*, **12**, 1297 (1879).

at 200–220°, during which process ammonium bromide was abundantly precipitated and diacetamide was formed.[3] The experimental evidence seems to show that alkyl halides react with acetamide in the following manner.

$$CH_3CONH_2 + RBr \longrightarrow CH_3CONHR + HBr$$
$$2CH_3CONH_2 + HBr \longrightarrow CH_3CONHCOCH_3 + NH_4Br$$

Substituted acetamides have been prepared by Titherley[4] by the action of alkyl halides and potassium alkyl sulfates on sodium acetamide. The yields of substituted acetamides obtained by this method were poor. Others[5] have shown that imino ethers, derived from the iminohydrin form of acetamide, when heated in the presence of alkyl halides are converted into the isomeric alkylacetamides.

Experimental Part

Benzyl- and β-Phenylethylacetamides.—A mixture of 0.4 mole of the bromide and 1.6 moles of anhydrous acetamide was placed in a Pyrex flask fitted to a condenser with a ground-glass joint, and heated on an oil-bath for three to six hours at 200–220°. A large amount of ammonium bromide precipitated. The mixture was poured into a concentrated solution of sodium carbonate and the amide was extracted with ether, dried over sodium sulfate and distilled.

Ethyl-, *n*-Propyl-, *n*-Butyl- and *iso*-Amylacetamides.—A mixture of 0.4 mole of the alkyl bromide and 1.6 moles of anhydrous acetamide was placed in a sealed Pyrex tube (65 cm. × 2.7 cm. inside diameter) and heated at 220° until the two layers had disappeared, usually for about 20–30 hours. The method of isolation and purification was the same as described above. β-Phenylethylacetamide was also prepared by this method with the same yield as obtained in the above method.

TABLE I

COMPOUNDS, PROPERTIES AND ANALYTICAL DATA

Substituted acetamide	B. p., °C.	M. p., °C.	Yield, %	Analysis		
				Calcd. for	N, %	Found, %
Benzyl-	157 (2 mm.)	61	80[a]	$C_9H_{11}ON$	9.39	9.32
β-Phenylethyl-	154 (2 mm.)	45	40	$C_{10}H_{13}ON$	8.59	8.48
Ethyl-	206	..	66	C_4H_9ON	16.09	15.96
n-Propyl-	225	..	70	$C_5H_{11}ON$	13.86	13.94
n-Butyl-	229	..	66	$C_6H_{13}ON$	12.17	12.25
iso-Amyl-	232	..	42	$C_7H_{15}ON$	10.85	10.94

[a] Benzyl chloride under the same conditions gave but a 51% yield.

On hydrolysis with concd. hydrochloric acid, the corresponding primary amines were obtained in 80–90% yields.

[3] Strecker, *Ann.*, **103**, 321 (1857). Hofmann, *Ber.*, **14**, 2732 (1881).

[4] Titherley, *J. Chem. Soc.*, **65**, 521 (1894); **79**, 391 (1901).

[5] Wheeler and Johnson, *Am. Chem. J.*, **21**, 185 (1899); *Ber.*, **35**, 164 (1902).

Summary

1. The reaction between acetamide and alkyl bromides, showing its general applicability to the synthesis of substituted acetamides and the corresponding amines, has been investigated.

2. A possible mechanism for the reaction, accounting for the production of ammonium bromide, has been suggested.

HOUSTON, TEXAS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF SASKATCHEWAN]

STUDIES IN URETHANS
I. MONO- AND DICARBETHOXY-GUANIDINES: DICARBETHOXY-ETHYL-ISO-UREA

BY S. BASTERFIELD AND L. EVELYN PAYNTER

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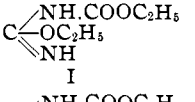
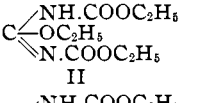
During a study of the pharmacological properties of some iso-urea derivatives, it was found by one of us[1] that carbethoxy-ethyl-iso-urea had well-marked physiological action, the chief effects being a mild central depression, a rapid and considerable fall of body temperature, and an increased muscle tonus. The muscular hypertonus suggested an action similar to that of guanidine which is known to stimulate the myo-neural receptors.[2]

It was decided for the purpose of a comparative study to prepare the mono- and dicarbethoxy-guanidines (guanidine mono- and di-formic esters) and examine their pharmacological properties. At the same time it was thought desirable to prepare the dicarbethoxy-ethyl-iso-urea, to determine the effect of introducing a second carbethoxy group into the iso-urea molecule. The compounds may be regarded as urethans, and the study of them is therefore included in a series of studies being carried on in this Laboratory on the chemistry and pharmacology of some mono- and diurethans. Formulas I and II show the structures of the iso-urea derivatives and III and IV the structures of the carbethoxy-guanidines.



I



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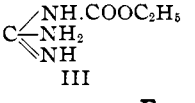
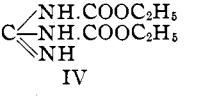


III



IV

Experimental Part

Dicarbethoxy-guanidine was first prepared by Nencki[3] by the action of ethyl chlorocarbonate on an alcohol solution of guanidine. The mono-

[1] Basterfield, *J. Pharmacol.*, **20**, 451 (1923).

[2] Camis, *J. Physiol.*, **39**, 73 (1909).

[3] Nencki, *Ber.*, **7**, 1588 (1874).