37

A STUDY OF THE ACTION
OF
POTASSIUM HYPOBROMITE AND SODIUM HYPOCHLORITE
ON
ADIPAMIDE

(Hoffman Reaction of adipamide)

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OF
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ON
ADIPAMIDE

A thesis presented to the Department of Chemistry of Union College in partial fulfillment of the requirements for the degree of Bachelor of Science in Chemistry.

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Approved by H E Sheffer

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TABLE OF CONTENTS

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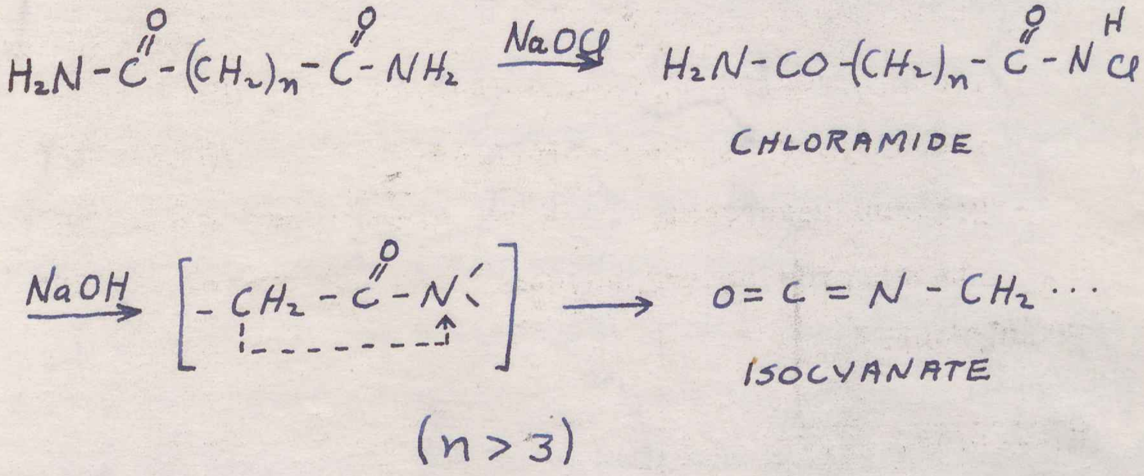
Introduction

The Hofmann reaction of an amide with a hypohalite to give a primary amine in excellent yields is the basis of many syntheses in organic chemistry. This project is concerned with the study of the action of sodium hypobromite and sodium hypochloride on adipamide. Isolation of reaction products, if possible, identification of the products, and determination of the yield of the reaction were desired. It was hoped that a diamine, putrescine, would result from this reaction, and therefore the steps in isolation of the products were carried out with this in view.

Historical Data

In 1881, Hofmann[1] first prepared primary amines by means of a reaction which bears his name. This process, the reaction of an amide with a hypohalite, affords primary amines in good yields and free from secondary or other amines. The reaction results in an amine with one less carbon atom than the original amide.

Not much work has been done on the action of a hypohalite on a diamide to give a diamine with two less carbon atoms. The reaction proceeds as follows:

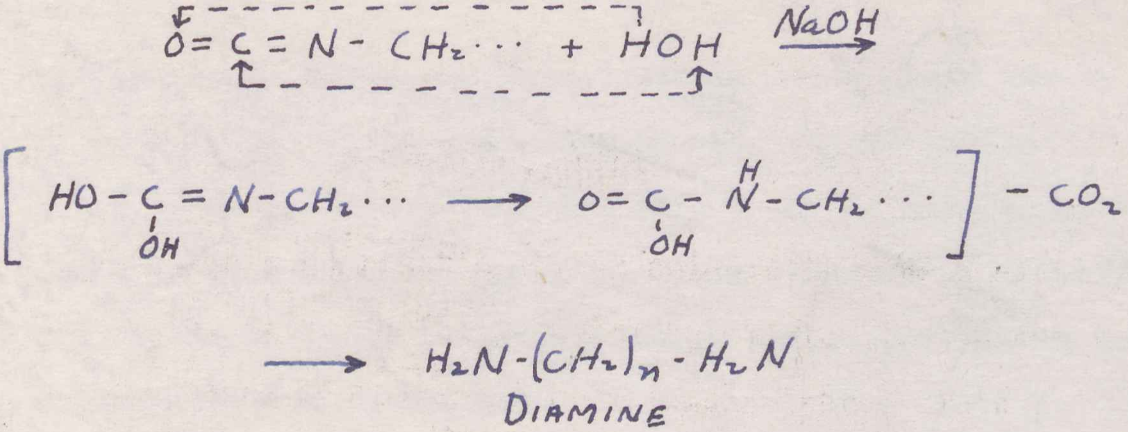


$$H_2N-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-NH_2 \xrightarrow{NaOCl} H_2N-CO-(CH_2)_n-\overset{O}{\overset{\|}{C}}-N\genfrac{}{}{0pt}{}{H}{Cl}$$

$$\xrightarrow{NaOH}\left[-CH_2-\overset{O}{\overset{\|}{C}}-N\right] \longrightarrow O=C=N-CH_2\cdots$$

$(n > 3)$

This repeats on the other end of the molecule and the isocyanates are easily hydrolyzed in the presence of a base to the diamine by the process of decarboxylation.



$$O=C=N-CH_2\cdots + HOH \xrightarrow{NaOH}$$

$$\left[HO-\underset{OH}{C}=N-CH_2\cdots \longrightarrow O=\underset{OH}{C}-\overset{H}{N}-CH_2\cdots \right] - CO_2$$

$$\longrightarrow H_2N-(CH_2)_n-H_2N$$

DIAMINE

In 1895, V. Solonina[2] reported the preparation of the higher diamines, hexa-, hepta-, and octomethylene diamine, from the respective diamides using NaOBr. However, no results were mentioned as to yield of the diamine. It is doubtful whether a large amount of the amine was formed, because of the instability of the NaOBr at the temperature the reaction was run, 35° C. In 1896, the preparation of the 1,4-diamino-3-methylbutane from the diamide of γ methyl adipic acid using NaOBr was reported in Berichte[3], but again no data as to yields were reported.

The reaction of succinamide with a hypohalite was discussed in "Organic Reactions,"[4] and two products were evidently forthcoming. The first and foremost was dihydrouracil, and at a higher temperature, in the presence of an excess of alkali, β alanine was obtained. Rosekrans[5] investigated this reaction and obtained dihydrouracil in small amounts. No β alanine was found. Therefore the results of this reaction have been checked and were found in part to agree with the existing literature. Evidently after one end of the molecule rearranges, ring closure takes place due to the stability of the six membered ring formed giving dihydrouracil. It is doubtful that a stable ring compound would be formed in the reaction using adipamide. Therefore the reaction should proceed smoothly under the correct conditions to give putrescine.

It was desired to repeat Rosekrans'[5] conditions used in the succinamide reaction because of their general agreement with the available literature.[2,3] In 1937, Hauser and Renfrow[6] reported that the rate of rearrangement in a Hofmann reaction was proportional to the amount of alkali present, the temperature of the reaction and the ease of escape of the halogen in the halamide stage. If the rate of the reaction could be increased in this way, giving less time for possible hydrolysis of the amide to the acid, the yield of the final product should be increased. NaOCl should therefore be more efficient than NaOBr for two reasons: (1) chlorine being more negative than bromine should therefore be bound less strongly, and (2) because of the higher stability of the NaOCl the temperature of the reaction could be increased, thereby increasing the rate of rearrangement. This was born out by Graebe and Rostoyyeff[7] in 1902.

Therefore it was decided to investigate the results of replacing KOBr with NaOCl. The results seem to justify the conclusions reached above as the yield of the diamine was increased over 20% by the use of the hypochlorite.

There should be no reason why the change of the cation from K to Na should have an appreciable effect on the reaction, and so NaOCl was used in place of KOCl because of its ready availability as "Chlorox."

EXPERIMENTAL

Preparation of Adipamide.

Adipamide was prepared from adipic acid through the acid chloride. Adipyl chloride was first prepared and then slowly dropped into a concentrated ammonia solution (28% NH_3). The amide was collected on a buchner funnel and washed with water and dried. A very pure product was obtained.

The acid chloride was prepared in two ways, one using thionyl chloride[8] and the other using PCl_3[9]. The first was more efficient and gave a better yield than the second.

TABLE I

Preparation of Adipyl Chloride

	Weight	Moles
Adipic Acid	50 g	.34
Thionyl Chloride	250 g	2.12
NH_3	750 g	45

The adipic acid and thionyl chloride were refluxed for three hours on a water bath at 50° - 60° C. The crude acid chloride was added directly to three liters of concentrated ammonia (28%). The yield was 19.6 grams, melting at 218° - 220° C, corresponding to the value given in the Handbook of Physics and Chemistry, 220° C, 39% of the theorectical yield.

A mixed melting point determination gave a melting point of 218° - 219° C. The adipamide used for this determination was obtained from the Eastman Kodak Company.

TABLE II

Preparation of Adipyl Chloride

	Weight	Moles
Adipic acid	60 g	.41
PCl_3	37.3 g	.27
*		
NH_3	750 g	45

Adipic acid and PCl_3 were refluxed for three hours on a water bath at 50° - 60° C. One reaction product, phosphorous acid, H_3PO_3, collected in the bottom of the flask. The adipyl chloride was decanted from the H_3PO_3 and dropped into three liters of ammonia (28%). The adipamide was collected as above. The yield here was only 12 grams, 20% of the theorectical amount, melting point 218° - 220° C.

The loss in these reactions probably resulted from the readiness of the acid chloride to hydrolyze to the acid even in the presence of a large excess of ammonia. Concerning the reaction using PCl_3, Whitmore[9] stated that much of the PCl_3 was hydrolyzed to HCl, and the formation of adipyl chloride was not quantitative in any sense.

In any case, neither of the above preparations were very satisfactory. However, only small amounts of adipamide were required for the reactions studied.

<u>Hofmann Reactions</u>:

TABLE III

Hofmann Reaction

Run A	Weight	Molecular Weight	Moles	Mole Ratios
Br_2	11 g	159.8	.069	2
KOH	8.7 g	56.1	.154	4.5
H_2O	24.8 g	18	1.37	40
Adipamide	5 g	146	.035	1
KOH	6.8 g	56.1	.121	3.5
H_2O	18.7 g	18	1.04	30
Run B				
NaOCl	4.6 g	74	.064	2
KOH	8.1 g	56.1	.154	4.5
H_2O	104 g	18	5.8	165
Adipamide	5 g	146	.035	1
KOH	6.8 g	56.1	.121	3.5
H_2O	18.7 g	18	1.04	30

TABLE III
(continued)

Run C	Weight	Molecular Weight	Moles	Mole Ratios
Br_2	11 g	159.8	.060	2
KOH	8.7 g	56.1	.154	4.5
H_2O	95 g	18	5.3	151
Adipamide	5 g	146	.035	1
KOH	6.8 g	56.1	.121	3.5
H_2O	18.7	18	1.04	30

There were four runs made, two using KOBr and two with NaOCl. The method followed for a typical run is given below.

<u>For runs A and C:</u>

The alkali and water were placed in a 500 cc three necked flask, fitted with a mechanical stirrer. Crushed ice was added and the whole flask placed in a brine and ice bath. The bromine was added slowly, with stirring, by means of a dropping funnel, to the alkali water solution. Making sure the temperature was at -5° C or below, the adipamide was added slowly, and the mixture allowed to react at -5° C for forty minutes. At the end of that time the remainder of the alkali was added and the solution allowed to rise to room temperature. The reaction was completed by heating in a water bath to 80° - 85° C for approximately 10 minutes.

This procedure was the same as that followed by Rosekrans,[5] and the same phenomena were noted: namely, the orange color and the percipitation of the KOBr and the clearing of the solution upon heating. An animal-like ammoniacal odor was noted in the reaction mixture after heating.

For run B: (Two runs performed)

For this run the procedure was essentially the same, except that the source of the NaOCl was ordinary commercial "Chlorox", 5.25% NaOCl. The adipamide was added directly to the 106 cc of Chlorox with stirring. At the second stage of the reaction, before heating, the solution was clear with a faint yellowish tinge. Upon heating the color changed to brown. The odor was very penetrating, and resembled that of piperadine, characteristic of putrescine or cadaverine.

The temperature of these runs was not as carefully controlled because of the greater stability of the NaOCl as stated earlier. However, it was not allowed to rise above 5° C.

Preparation of the Derivative:

It was desired to isolate the pure diamine from the reaction mixture, but difficulties presented themselves due to the affinity of putrescine for water. Extraction with ether was attempted with no visible results. One reason for failure here was probably that the amine was present in comparatively small amounts, not over 4% by volume.

An alternate method was tried, described by V. Solonina,[2] but no results were forthcoming. It was finally decided to remove the putrescine from the reaction mixture by forming a derivative and thereby try to obtain information concerning the yield of the product. It was decided to prepare the dibenzoyl derivative of putrescine directly from the reaction mixture, by the addition of benzoyl chloride.

The reaction mixtures from all four runs were treated similarly. The mixture was filtered from any foreign matter and warmed slightly. While still warm, benzoyl chloride was added in small amounts with vigorous shaking, and a small heat effect was noted. A white percipitate came down at once. The process was continued until about 7 grams of benzoyl chloride had been added. The mixture was tested with litmus from time to time to make sure it remained alkaline.

The mixture was filtered and the percipitate washed with dilute alkali and then with water to remove any benzoyl chloride. It was dried and weighed. From run "A" three grams of white powder were obtained, melting at 165° - 170° C. Upon recrystallization from alcohol and water, white needles were obtained which melted at 175° - 177° C. The value of the melting point of the N, N' dibenzoyl derivative of putrescine in Heilbron: <u>Dictionary of Organic Compounds</u> was given as 177°C.

After standing a day, the original reaction mixture was again heated, and about two grams of additional benzoyl chloride were added. A small amount of the derivative was obtained, 1 gram, making a total yield of 4 grams of 39% of the theorectical amount. After separatipn of this last batch, nc more ammoniacal odor was noted on standing. It was assumed that all the putrescine had been removed.

The results of the remaining runs are tabulated in Table IV.

TABLE IV

Reaction Results

Run	Hypohalite	Theorectical yield of putrescine	Theorectical yield of derivative	Actual yield	% of derivative
A	KOBr	3.1 g	10.1 g	4 g	39.6%
B_1	NaOCl	3.1 g	10.1 g	9.1 g	90%
B_2	NaOCl	3.1 g	10.1 g	9.5 g	94%
C	KOBr	3.1 g	10.1 g	7.3 g	72.2%

Since further identification of the derivative was desired, a nitrogen determination was run using the Hengar semimicro process. The results established the identity of the compountd as the N, N' derivative of putrescine.

TABLE V

Nitrogen Determination

Sample	Determined % of Nitrogen	Actual % by weight
1	9.55	9.45
2	9.45	9.45

Experimental Results:

1. Adipamide was prepared from adipic acid, using thionyl chloride and ammonia. A yield of 39% was obtained. As an alternate reaction PCl_3 was used in place of the thionyl chloride, and the yield was only 20%.

2. Putrescine, or tetramethylene diamine, was prepared by the Hofmann reaction of KOBr with adipamide. The yield of the dibenzoyl derivative from run "A" was 39.6%. Increasing the amount of water in run"C", gave a yield of 72.2%, nearly double that of run "A". The increase in yield was attributed to the faster and more complete solution of the adipamide and hence the shortening of the reaction time.

3. 3. Putrescine was also prepared by the action of NaOCl on adipamide. Two runs,"B_1"and"B_2"were made as checks. The yields obtained were 90% and 94% respectively. This increase in yield over runs"A"and"C" was in agreement with the findings of Graebe and Rostovyeff,[7] who stated that

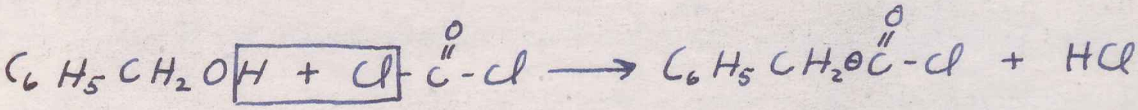
NaOCl was more valuable than NaOBr in the Hofmann reaction because of its greater stability, and the greater ease of rearrangement of the chloramide over the bromamide.

4. The N, N' dibenzoyl derivative of putrescine was prepared by adding benzoyl chloride directly to the reaction mixture. This material was identified by its melting point and an analysis for nitrogen.

In reviewing the work done on the reaction of a diamide with a hypohalite to give a diamine, it is discovered that only a few of the diamides have been investigated and that there has been no good method developed for isolating the pure diamine, if formed.

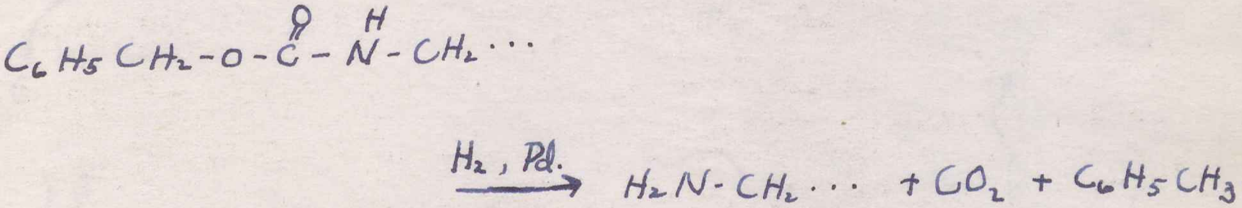
It was found in 1926[3], and checked by Rosekrans[5], that the reaction of succinamide and NaOBr did not give ethylene diamine, but rather dihydrouracil or β alanine, depending on reaction conditions. Solonina[2] found that the Hofmann reaction with sebacamide, etc., gave diamines, but no data are availlable concerning the Hofmann reaction with glutaramide. It would be interesting to see what the products of this reaction would be.

As to the isolation of the diamine, one suggestion has been to prepare the carbobenzoxy derivative rather than the benzoyl chloride derivative, using carbobengoxychloride, and then reducing the derivative with hydrogen over a palladium catalyst. The carbobenzoxychloride could be prepared by the condensation of benzyl alcohol and phosgene. The products of the reduction of the derivative would be CO_2, toluene, and the amine.



$$C_6H_5CH_2O\boxed{H + Cl}-\overset{O}{\overset{\|}{C}}-Cl \longrightarrow C_6H_5CH_2O\overset{O}{\overset{\|}{C}}-Cl + HCl$$

CARBOBENZOXY CHLORIDE



$$C_6H_5CH_2-O-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-CH_2\cdots \xrightarrow{H_2,\ Pd.} H_2N-CH_2\cdots + CO_2 + C_6H_5CH_3$$

It appears that the Hofmann reaction applied to diamides is a general reaction except for succinamide. It remains for glutaramide to be investigated. The Hofmann reaction with glutaramide should give 1,3-diaminopropane.

SUMMARY:

1. Putrescine was prepared by the Hofmann degradation of adipamide with KOBr and NaOCl. NaOCl gave a greater yield of the diamine.

2. The N, N' dibenzoyl derivative of putrescine was prepared directly from the reaction mixture by the addition of benzoyl chloride. The compound was identified by means of the melting point and a nitrogen analysis.

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