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A study in local anesthesia diethanolaminoethylester of para-aminobenzoic acid.

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UNIVERSITY OF LOUISVILLE

A STUDY IN LOCAL ANESTHESIA
DIETHANOLAMINOETHYLESTER OF PARA-AMINOBENZOIC ACID

A Dissertation

Submitted to the Faculty
Of the Graduate School of the University of Louisville
In Partial Fulfillment of the
Requirements for the Degree
Of Master of Science

Department of Chemistry

By

Wilbur P. Crouch

(1931)

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INTRODUCTION

The story of anesthetics is as old as the world itself. As soon as man had developed to the extent that he was able to think, he has attempted to ease pain, especially where abnormal conditions of the body had to be relieved. Some of the earliest attempts at general anesthesia were with erode fat and with mixtures of the stone of Memphis. Some of the earlier attempts at local anesthesia were by cutting of some of the main arteries, and by application of pressure upon some of the main arteries or nerves of the limbs, thereby causing that part to fall asleep. This method is described in the friezes on the tombs of the Egyptians as early as 2500 B.C.(1). Freezing of a portion of the body with a mixture of salt and ice in the early ages and later ether and ethyl chloride have been used. Ethyl chloride is still used in this fashion.

For many centuries the natives of Peru and Bolivia knew that the leaves of the coca plant were an agent for lessening pain. One of the crude early methods was the chewing of the leaves and allowing the saliva to drip into the wound. In 1860 Neiman isolated levo-cocaine from the leaves of the erythroxylen coca by grinding the leaves into a powder and extracting with sulfuric acid. This compound was found to possess local anesthetic properties, and in 1884 Dr. Keller demonstrated at Vienna the

importance of cocaine in surgery. It was found by experimentation that the best solution to use was a 2 % solution of the hydrochloride salt. At first cocaine was used principally in the eyes, but it was later found to be a very good local anesthetic for external work, especially for tumors, and ear, nose and throat surgery(2).

After the isolation of cocaine, a great deal of work was done in the determination of the structure of the cocaine molecule. Lossen(3) found it to be $C_{17}H_{21}O_4N$, which is the one-methylester of two-benzoylcecgina. Next, it was necessary to find out what part of the molecule governed the power of anesthesia, whether it was one group or several groups acting in unison to produce this action, or whether the position of the group, or groups, in the molecule had anything to do with the anesthetic action and the toxicity. It was discovered that in practically all cases, the compound that showed anesthetic action had at least one amine group and one hydroxyl group, although there were found exceptions to this, for example, benzyl alcohol. It was found also that in order for a compound to show anesthetic action the hydroxyl group must be esterified.

The properties of a good anesthetic are as follows, according to Fournneau(4):

1. Easily soluble in water.
2. Should be capable of undergoing sterilization by heat in water solution.
3. Almost tasteless.
4. Possess no pronounced toxic properties.
5. Cause no smarting sensation when introduced under the eye-lids or injected under the skin.
6. Have a strong anesthetic action, intense and continuous, but not violent.
7. Have no permanent effect on the nerve fibers, and should pass away completely.
8. Should show vasoconstrictive activity and render the tissues and surfaces with which it comes in contact bloodless.
9. Not too costly.
10. Not form precipitates with the heavy metals, for example, Mercury.

According to this, cocaine had several drawbacks as a local anesthetic. It was too toxic. Also its solutions decomposed rapidly, becoming moldy with age. Thus it became advisable to make new compounds synthetically or by the alteration of the cocaine molecule.

Simplifying the cocaine molecule seemed to be the general trend in research in making new local anesthetics. In 1897 Merling(5) developed the Eucaines, which were made in the following manner: three molecules of acetone were allowed to react with ammonia, giving triacetoneamine, which upon treatment by various steps gave N-methylbenzoyltriacetonealkaminecarboxylic acid methyl ester or alpha-eucaine. This was found to be too toxic and was soon displaced by the hydrochloride salt of benzoylvinyl-acetonealkamine or beta-eucaine, which was found to be much more active than cocaine as a local anesthetic, and only one-fifth as toxic. In 1917 von Braun(6) discovered an entirely new local anesthetic which was simpler in structure than the preceding ones and was called Escaine, a derivative of ecgonidine.

Up to now the only ones considered have been the anesthetics with the complicated structures. The esters of the amino-benzoic acids and the amine-hydroxybenzoic acids are examples of another type of local anesthetics. Some are insoluble in water, so cannot be used hypodermically, but are used as dusting powders for open wounds. One of the most important of

this class is the methyl ester of amino-hydroxybenzoic acid. Being acid, they are thus irritant, but form derivatives that are soluble and neutral to litmus. The most important derivative is the hydrochloride salt of diethylglyccoll or Nirvanine(7).

A great deal of research has been done upon the derivatives of aminobenzoic acid, and many good local anesthetics have been synthesized. The first in order is the ethylester of para-aminobenzoic acid, known as Anaesthesin, introduced by Bing and Kobert(8). Further work on compounds of this type has shown that only where an amine group was present, was the anesthetic action anywhere similar to that of Anaesthesin.

The next in order of this series is Novocaine or Procaine, introduced in 1905 by Einhorn and Uhlfelder(9). It is the diethylamino-ethylester of para-aminobenzoic acid, a derivative of Anaesthesin. This compound, when injected as the hydrochloride salt and with adrenalin, is a very important local anesthetic, and is gradually replacing cocaine as such. It is non-irritant, powerful, and is one-seventh as toxic as cocaine. Unlike solutions of cocaine, which

deteriorate upon standing, solutions of novocaine can be boiled without decomposition and can stand for a considerable length of time without deteriorating.

After the discovery of novocaine, extensive work was done, especially by Heckel and Rogers(10), on several local anesthetics of the novocaine type, by the modification of the amino alcohol which forms the ester of benzoic acid up to the hexyl alcohol. It was found that the trans form of the dimethylaminohexyl para-aminobenzoate hydrochloride has about twice the anesthetic power as the corresponding cis form. One of this type is Butyn(11), which is the dibutylaminopropyl-ester of para-aminobenzoic acid. It is used as the hydrogensulfate salt and is much more toxic than novocaine, so must be used with caution. Butyn can be sterilized by boiling. Still another of this type is Tutocaine(12), introduced in 1924 from Germany. It is the dimethylaminomethylbutyl-ester of para-aminobenzoic acid. Tutocaine has no vasoconstrictive activity and must therefore be administered with adrenalin. Solutions of adrenalin and tutocaine can be administered without fear of decomposition, but upon standing

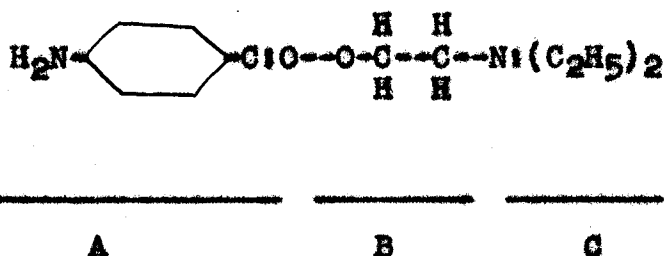
deteriorate rapidly. A local anesthesia of twenty-four hours duration can be obtained by using the liquid that contains 0.2 to 0.5 % tuteocaine and 0.1 % adrenalin. The liquid can be sterilized, is not toxic, does not cause inflammation at the site of injection, and the main point in its favor is that the liquid itself is an anesthetic.

The latest investigation into this type deals with the pyrrole series of local anesthetics,, introduced by Blicke and Blake in 1930(13). Various compounds were tried but none came up to the local properties of cocaine.

The difference between aromatic compounds and the corresponding aliphatic compounds is largely of degree and not of kind. Upon studying the esters of the carboxylic acids, it was found that the diethylaminoethylester of a carboxylic acid where the carboxylic group was attached to an unsaturated carbon atom, there was local anesthetic action(14).

According to A. J. Hill there are fourteen different types of compounds that show local anesthetic action. Several of these types have been mentioned already(15).

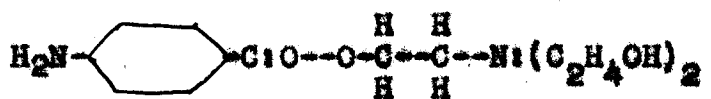
As has been shown, variation of the novocaine molecule has been the object of many research projects. For theoretical considerations, the novocaine molecule may be divided up into three parts(16):



In Butyn, there is a change of part B to propyl, and of part C to dibutyl amine. Tuteccaine has the variation of part B to methybutyl, and of part C to dimethylamine. Cow has found(17), upon studying the effect of the substitution of hydroxyl groups in part B, that the increase in the number of hydroxyl groups reduced the toxicity:

The primary object of our investigation was to vary part C of the novocaine molecule, using in one case diethanol amine instead of diethyl amine, and in the other, one ethanol radical is substituted for an ethyl radical, as is shown in the following formulae:

I.

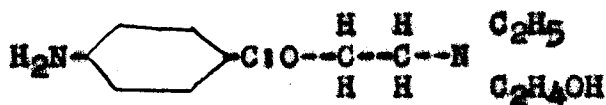


A

B

C

II.



A

B

C

It was hoped that these changes would increase solubility, and lower toxicity without too great a change in the physiological action.

EXPERIMENTAL

PRELIMINARY EXPERIMENTAL

The preliminary experimental has been a study of the properties of the ethanol amines, because of the importance of these compounds in the proposed synthesis.

PREPARATION OF TRIETHANOLAMINEHYDROCHLORIDE(18)

25 c.c., 0.19 moles, of triethanol amine was allowed to react with 100 c.c. of N/10 hydrochloric acid. A reaction took place immediately and upon cooling a precipitate of white crystals was obtained with a melting point of 166° C.. The product was then recrystallized twice from hot alcohol, and the melting point raised to 176° C.. The product was soluble in water, hot alcohol, insoluble in ether. The yield was 24 grams, 95 % of the theoretical, based upon the hydrochloric acid used.

PREPARATION OF TRIETHANOLAMINEHYDROBROMIDE

25 c.c., 0.19 moles, of triethanolamine was allowed to react with 75 c.c. of a 40 % solution of hydrobromic acid. A reaction took place immediately and upon cooling a white precipitate was formed with a melting point of 180° C.. The product was recrystallized twice from

hot alcohol, and the melting point was raised to 186° C.. The yield was 21 grams, 71 % of the theoretical, based upon the triethanolamine used. The product was soluble in water, hot alcohol, and insoluble in ether.

PREPARATION OF DIETHANOLETHYLAMINE-
HYDROBROMIDE(19).

14 grams, 0.13 moles, of diethanolamine was allowed to react with 14 grams, 0.128 moles, of ethyl bromide. A reaction took place immediately and upon cooling to room temperature a white crystalline precipitate was obtained which melted at 131° C.. The product was recrystallized from hot alcohol, and the melting point was raised to 137° C.. The product was soluble in water, hot alcohol, and insoluble in ether. The yield was 20 grams, 71 % of the theoretical, based upon the diethanolamine used.

This method of preparation of this salt has not been used in this fashion according to the literature.

PREPARATION OF THE SODIUM SALT OF
DIETHANOLAMINE.

Sodium was allowed to react with 5 grams, 0.047 moles, of diethanolamine until no further

reaction took place. A white solid was obtained which was soluble in water and alcohol, but no anhydrous solvent was found that would dissolve the reaction product. Melting point above 360° C..

PREPARATION OF THE SODIUM SALT OF
TRIETHANOLAMINE.

Sodium was allowed to react with 5 grams, 0.034 moles, of triethanolamine until no further reaction took place. A white solid was obtained, soluble in water and alcohol, but as in the preceding experiment no anhydrous solvent was found. Melting point above 360° C.. Solvents tried were as follows: Toluene, benzene, xylene, chloroform, carbontetrachloride, ethylenedibromide, carbondisulfide, ligroin, gasoline, kerosene, ether, ethylacetate, absolute alcohol, ethylenetetra bromide, and pyridine. Pyridine was the only one that in any way had any action upon the material and that only slightly when heated.

SUBSTITUTION OF THE HYDROXYL GROUP OF
TRIETHANOLAMINE WITH A BROMINE GROUP.

1 gram, 0.004 moles, of triethanolamine hydrobromine was treated with an excess of a

saturated solution of hydrobromic acid, and was then sealed in a Carius tube. The Carius furnace was then heated for six and a half hours, the temperature being kept around 200-225° C.. After allowing the tube to cool overnight, it was opened and the contents crystallized from hot alcohol. The melting point of the product was 175° C.. The product was then recrystallized twice from hot alcohol and the melting point was raised to 185° C.. A mixed melting point was then taken with a sample of pure triethanolamine hydrobromide and the melting point was 183° C., thereby proving that there had not been any replacement of the hydroxyl groups by bromine atoms.

REACTION OF ACETIC ANHYDRIDE WITH
TRIETHANOLAMINE .

10 grams, 0.07 moles, of triethanolamine was mixed with 10 grams, 0.089 moles, of acetic anhydride and warmed on a water bath for 4 hours. The reaction product was then treated with dry hydrogen chloride and a white precipitate was formed, melting point 165° C..

A mixed melting point with a sample of pure triethanolaminhydrochloride gave a melting point of 169° C., showing that there had not been a reaction between the alcoholic groups of the triethanolamine molecule and the acetic anhydride.

FINAL EXPERIMENTAL

PREPARATION OF THE BETA-CHLOROETHYLESTER
OF PARA-NITROBENZOIC ACID.

90 grams, 0.49 moles, of para-nitrobenzoyl chloride and 50 grams, 0.6 moles, of ethylene chlorohydrin (125 c.c. of the 40 % solution) were heated in a round bottom flask connected to a reflux condenser on an oil bath at a temperature of 100-110° C. for 2½ hours. The reaction product was cooled, filtered, washed with water and dried on a porous plate. The melting point of this product was 55° C., literature 56° C. (20). It was soluble in hot alcohol, and insoluble in water and ether. The yield was 91 grams, corresponding to 82 % of the theoretical. There was obtained 10 grams of para-nitrobenzoic acid, 11 % of the theoretical, which was probably formed by hydrolysis. The hydrogen chloride gas that was given off during the reaction was neutralized by absorbing in a solution of dilute ammonium hydroxide.

It was found in the first run that the yield of para-nitrobenzoic acid was entirely too high. There were only two factors to take into consideration in this procedure, first the temperature, and the second was the time. Several

runs were made using only 10 grams, 0.054 moles, of para-nitrobenzoyl chloride and 4.34 grams, 0.058 moles, of ethylene chlorohydrin (11 c.c. of the 40 % solution). Time was the only factor varied. It was found that the highest yield, 89 % of the theoretical, of the desired product was obtained in the run that was heated for only twenty minutes, and the yield of para-nitrobenzoic acid was reduced to 0.44 grams, or 5 % of the theoretical.

REDUCTION OF THE BETA-CHLOROETHYLESTER
OF PARA-NITROBENZOIC ACID.

10 grams, 0.043 moles, of the ester was dissolved in alcohol and reduced with tin and dilute hydrochloric acid. The temperature was not allowed to rise above 40° C. and was kept for the most part between 35-40° C.. After the reaction was complete, the flask was allowed to cool to room temperature, and a white crystalline precipitate was formed. This compound was recrystallized from alcohol and the melting point was found to be 165° C.. According to the literature, upon reduction of the beta-chloro-ethylester of para-nitrobenzoic acid the product crystallizes out having a melting point of 87° C..

A chlorine determination of the compound was run by the Volhard method and the percentage of free chlorine was found to be 10.66 %, while the chlorine percentage in the hydrochloride salt of the beta-chloroethyl ester of para-aminobenzoic acid theoretically is 10.8 %. The yield was only 5 grams of the reaction product, 49 % of the theoretical, based upon the amount of the ester used. This compound was needlelike in structure and white in color. It was soluble in water and alcohol, and insoluble in ether.

In a second run 10 grams, 0.043 moles, of the ester was dissolved in alcohol and reduced with stannous chloride and dilute hydrochloric acid. The temperature control was the same as in the first run. After the reaction was complete, the flask was allowed to cool to room temperature and a white crystalline solid precipitated. This compound was recrystallized from alcohol and the melting point was found to be 164° C., the same as in the first run. A mixed melting point was then run on the two samples and the melting point did not change. The yield was 3.6 grams of the reaction product, or 35.3 % of the theoretical.

In a third run 10 grams, 0.043 moles, of the ester was dissolved in alcohol and reduced with iron and dilute hydrochloric acid, under the same conditions as in the first two runs, and upon cooling to room temperature a white precipitate was formed. This product could not be purified by recrystallization from alcohol because of the iron chloride present in the sample. The compound was washed with ether six times and the melting point was found to be 161° C., A mixed melting point with a sample from run one was taken, and was found to be 159° C., showing these two to be identical. Although the best yield was obtained in this run, 6.7 grams or 65.6 % of the theoretical, the excess iron chloride could not be eliminated, and therefore this method of reduction could not be used in the preparation of the amine desired.

In a fourth run 10 grams, 0.043 moles, of the ester was dissolved in a mixture of alcohol and acetone and reduced under the same conditions as in the first run. Upon cooling to room temperature, no precipitate was formed. The solution was then treated with hydrogen sulfide to precipitate out the excess stannous and stannic chlorides, filtered and the filtrate evaporated to about one half its volume and allowed to cool.

A white crystalline solid was obtained that melted at 164° C.. The yield was 3.1 grams, 32 % of the theoretical, of the reduced ester. 5.2 grams of para-aminobenzoic acid hydrochloride, or 68.5 % of the theoretical, was also obtained.

In a fifth run 10 grams, 0.043 moles, of the ester was dissolved in a mixture of alcohol and acetone and reduced as in run two under identical conditions. The stannous and stannic chlorides were precipitated out with hydrogen sulfide, and the excess acid was neutralized with a saturated solution of sodium carbonate. The solution was then evaporated to about half its volume. When cooled, a white crystalline precipitate formed, melting point 164° C.. The yield was 3.6 grams, corresponding to 37.2 % of the theoretical. There was also obtained 4.8 grams of para-aminobenzoic acid hydrochloride, corresponding to 63.3 % of the theoretical, based upon the acid formed.

In a sixth run 10 grams, 0.043 moles, of the ester was dissolved in acetone and reduced as in the preceding experiment under the same conditions. When the reaction product was cooled no precipitate appeared, so the solution was

evaporated to about half its volume on a water bath and then cooled. Only 1.3 grams of the reduced ester was formed or 12 % of the theoretical. On further evaporation of the filtrate, 6.4 grams, 85 % of the theoretical, of para-aminobenzoic acid hydrochloride was formed.

It was evident from these experiments that the best agents to use for reduction were tin and dilute hydrochloric acid in alcoholic solution.

REACTION OF DIETHANOLAMINE AND THE BETA-
CHLOROETHYLESTER OF PARA-NITROBENZOIC ACID.

In this run 10 grams, 0.098 moles, of diethanolamine and 20 grams, 0.087 moles, of beta-chloroethylester of para-nitrobenzoic acid were placed in a flask connected to a reflux condenser and warmed on a water bath for 45 minutes. The product was allowed to cool to room temperature, and was then extracted with chloroform. Yellow needlelike crystals were obtained on evaporation of the chloroform extract, melting at 115° C.. When recrystallized from chloroform, the melting point was 130° C.. This material was soluble in water and alcohol, yield was 12 grams.

This reaction product was then analyzed for free chlorine by the Volhard method(22), and

only 1.059 % free chlorine was found. The theoretical percentage of free chlorine in the hydrochloride salt of diethanolamine-ethyl ester of para-nitrobenzoic acid is 10.6 %.

A water solution of this product was tested on the tip of the tongue for anesthetic properties and a slight numbness occurred.

REACTION OF BETA-CHLOROETHYLESTER OF PARA-AMINOBENZOIC ACID HYDROCHLORIDE AND DIETHANOLAMINE.

In the first run 5 grams, 0.0212 moles, of beta-chloroethyl ester of para-aminobenzoic acid hydrochloride and 3 grams, 0.028 moles, of diethanolamine were placed in a flask connected to a reflux condenser and heated on a water bath for three hours. On cooling to room temperature there were two substances in the reaction chamber, a liquid and a solid. The liquid was extracted with chloroform, and when the chloroform extract was evaporated, a white crystalline solid was obtained, melting at 172° C.. Since this melting point was so near the melting point of triethanolamine hydrochloride, a mixed melting point was taken with a sample of pure triethanolamine hydrochloride. There

was a change of 1 degree in the melting point, showing the two to be identical. The yield was 2.8 grams or 74.3 % of the theoretical. The formation of the triethanolamine hydrochloride indicated that there had been an addition of the diethanolamine to the chlorine atom on the end of the ethyl chain, and a subsequent splitting of the ester.

Although hydrolysis of the ester had taken place in the reaction described above, analysis of the solid was next taken into consideration. The reaction product was found to be only slightly soluble in water and cold alcohol, soluble in mineral acids, and insoluble in ether and chloroform. Upon dissolving this product in hot alcohol, decomposition took place giving a pale yellow crystalline solid. Upon analysis of this product it was found to be para-amine benzoic acid. This indicated that this product was some complex compound of para-aminobenzoic acid. The melting point was not sharp, softening at 90° C., and finally melting at 101° C..

Analysis for free chlorine by the Volhard method gave 10.88 % free chlorine. The theoretical per cent of free chlorine in the hydrochloride salt of diethanolaminoethylester of para-aminobenzoic acid hydrochloride was calculated to be 10.41 % for one atom of chlorine or 20.82 % for two atoms of chlorine. The yield was 0.5 grams.

In a second run, 5 grams or 0.0212 moles of the ester and 3 grams, 0.028 moles, of diethanolamine were dissolved in alcohol and were refluxed for 2 hours on a water bath. As before, there were two products formed. The liquid was extracted with chloroform as before, and was found to be triethanolamine hydrochloride. The yield was 2.2 grams or 56.5 % of the theoretical, or a decrease of 17.8 % from that obtained in the first run. The free chlorine in the solid product was titrated by the Volhard method and calculated to be 10.95 % or only a variation of 0.07 % from that obtained in the first run. Before testing for chlorine the compound was washed with water and cold alcohol to be sure that all of the triethanolamine hydrochloride was eliminated. The yield was 1.6 grams.

In a third run, the same mole fractions were used as in the first two runs. The mixture was placed in a flask connected to a reflux condenser and was then dissolved in alcohol. Due to the fact that there had been hydrolysis taking place in both of the former runs, it was the object of this run to determine whether temperature had anything to do with this. The reaction was kept at a temperature not greater than 40° C. and for the most part it was kept between $38-40^{\circ}$ C.. This reaction was allowed to run for two hours at this temperature, after which it was allowed to cool to room temperature. As in the preceding runs there were two reaction products. Upon analysis of these products, they were found to be identical to those that had occurred in the two previous runs. The yield of triethanolamine hydrochloride was 1.9 grams or 50.3 % of the theoretical. This was a decrease of 6.5 %, when compared to the second run, apparently caused by a variation in temperature of 38.4° C.. The yield of the solid material was 1.8 grams.

It was found that in the three runs tried that there had been hydrolysis in every case, also the higher the temperature, the higher the percent of hydrolysis taking place.

In a fourth run the same mole percentages of the ester and diethanolamine were used as in the three previous runs. This experiment was conducted as in the previous runs with the exception that after completion of the heating of the material, the product was placed in an evaporating dish with a watch glass cover and allowed to stand for a week. This was *done* for the purpose of determining whether or not the triethanolamine hydrochloride would crystallize out upon standing. It was found that on the third day a few crystals appeared and at the end of the week the liquid portion of the reaction product had become solid. These crystals were dissolved in hot alcohol and recrystallized. The yield was 2.5 grams or 66.7 % yield of the theoretical.

PREPARATION OF BETA-CHLOROETHYLESTER OF
PARA-AMINO BENZOIC ACID.

Due to the fact that strong alkali appeared to break the ester formation, it was necessary to try various concentrations to see what one was the best for the splitting out of the hydrogen chloride molecule from the amine molecule.

It was found that the ester linkage was broken whenever a solution of greater strength than 10 % sodium hydroxide was used. Also that the linkage was broken whenever a high concentration of sodium carbonate was used. A five percent solution of sodium carbonate was found to give the highest yield.

5 grams, 0.0212 moles, of beta-chloroethyl ester of para-aminobenzoic acid hydrochloride was treated with a 5 % solution of sodium carbonate in a slight excess. A white precipitate was formed at this point, and the reaction product was filtered, washed with water and the precipitate dried on a porous plate. The melting point was 84-85° C., literature 86-87° C.(21). The yield was 1.3 grams or 34 % of the theoretical.

REACTION OF BETA-CHLOROETHYLESTER OF PARA-AMINO BENZOIC ACID AND DIETHANOL AMINE.

5 grams, 0.025 moles, of the ester was placed in a flask with 2.5 grams, 0.023 moles, of diethanol amine and heated on a water bath for 2 hours. The reaction was then allowed to cool to room temperature, ether extracted and the ether extract evaporated, which gave no residue. The solution was then vacuum distilled,

at a temperature of 67° C., and a pressure of 10 mm.. The product decomposed at this stage and a large percentage of diethanol amine was obtained. A small sample of para-aminobenzoic acid was obtained, but not in sufficient quantities other than to obtain a melting point and a mixed melting point with a pure sample in order to prove that it was the product named. Triethanol amine hydrochloride was formed in this experiment, either by hydrolysis or because of decomposition by temperature. This was not determined. The yield of diethanol amine was 1.3 grams, and of triethanolamine hydrochloride, 1.1 grams.

In a second run, the same mole percentages were used as in the first run. The mixture of materials was placed in a pressure flask and heated at a temperature between $110-120^{\circ}$ C. for 3 hours. The flask was then allowed to cool to room temperature and the products analyzed. The product was extracted with alcohol and the alcoholic solution evaporated. It was found upon analysis of the residue from this evaporation that the product was triethanolamine hydrochloride. This was proven by a mixed melting point with a sample of pure triethanolamine hydrochloride, which

melted at 174° C.. The yield was 1.4 grams or 32 % of the theoretical.

In a third run, the same mole percentages were used as in the preceding runs and the mixture was dissolved in alcohol. The flask was then attached to a reflux condenser and warmed on a water bath for 2 hours. After allowing the flask to cool to room temperature, 10 c.c. of a 10 % solution of sodium hydroxide was added and then ether extracted. No product appeared upon evaporation of the ether extract, so the residue from the ether extraction was then vacuum distilled at the same conditions as in the first run. The reaction products were the same as those in run one. The yield of diethanol amine was 1.4 grams, and of triethanolamine hydrochloride, 1.04 grams.

It was evident from this series of runs on this reaction that there had been a slight addition of the diethanolamine molecule to that of the beta-chlore atom of the ester but that hydrolysis had taken place in every run. Approximate yields were obtained in every case.

PREPERATION OF ETHYLAMINOETHANOL

To 30 c.c. of the 33 % solution of ethylamine having a specific gravity of 1.2 25/4, 0.46 moles. 40 c.c. of the 40 % solution of ethylenechlorohydrin was added and warmed on a water bath at 60° C. for 1 hour. The hydrochloride salt of ethylaminoethanol was then treated with a 20 % solution of sodium hydroxide until the solution was neutralized, a total of 52 c.c. of sodium hydroxide being used in all. The solution was then distilled up to 110° C. where the sodium chloride crystallized out, and was then cooled and filtered. The filtrate was placed in a Claisen flask and fractionated. All distillate up to 165° C. was thrown away, keeping all between 165-170° C.(19) This fraction was then distilled in the same apparatus as before, keeping only the fraction that came off at 167-169° C.. The yield was 26.2 grams or 78.1 % of the theoretical. The properties of this product corresponded to those given in the literature(19). The product was soluble in water and alcohol, and was insoluble in ether.

REACTION OF ETHYLAMINOETHANOL AND BETA-
CHLOROETHYLESTER OF PARA-AMINO BENZOIC ACID.

5 grams, 0.025 moles, of the ester was placed in a flask and 2.2 grams, 0.026 moles, of ethylaminoethanol added. The flask was heated on a water bath for 2 hours. There were two substances in the reaction chamber upon cooling which upon analysis were found to be the same as what had been added, thus proving that there had not been a reaction at this temperature.

In a second run the same mole percentages were used as on the first run. The mixture was dissolved in alcohol and heated on a water bath at the boiling point of alcohol for 2 hours. After being allowed to cool somewhat the solution was placed in an evaporating dish and the alcohol driven off by evaporation. The remaining solution was then vacuum distilled at a temperature of 65° C. and 8 mm. pressure. The product decomposed at this temperature and only a small sample of liquid was obtained which upon analysis was proved to be ethylaminoethanol, boiling point 168° C. at 757mm..

CONCLUSIONS

CONCLUSIONS

It is evident from these experiments that in the preparation of diethanolaminoethyl ester of para-aminobenzoic acid by the action of diethanolamine on the beta-chloroethyl ester of para-aminobenzoic acid, hydrolysis takes place before a final product can be isolated. However in the reaction of diethanolamine on the beta-chloroethyl ester of para-nitrobenzoic acid there is a reaction from which a final product can be isolated. This substance produces a slight numbness on the tip of the tongue when a dilute solution of this product is applied. However it does not contain the amount of free chlorine indicated for the hydrochloride salt of diethanolaminoethyl ester of para-nitrobenzoic acid.

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