R. S. Nelson

Preparation of Diethylaminoethyl Esters of Pyromucic and Picolinic Acids

PREPARATION OF DIETHYLAMINOETHYL ESTERS OF PYROMUCIC AND PICOLINIC ACIDS

BY

RUDOLPH STOKES NELSON

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THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

Rudolph Stokes Nelson

ENTITLED Preparation of Diethylaminoethyl Esters of Pyromucic and Picolinic Acids.

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE DEGREE OF Bachelor of Science in Chemistry

Roger Adams
Instructor in Charge

APPROVED: W. A. Noyes

HEAD OF DEPARTMENT OF Chemistry

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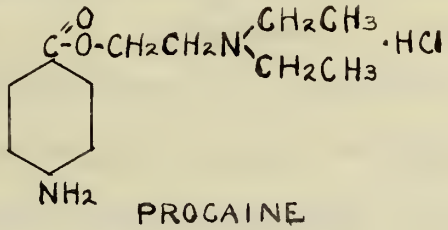
Introductory.

Since 1890, when the structure of cocaine first became known through the work of Merk [1], Liebermann [2], and Einhorn, [3] a great deal of work has been done in attempting to determine to what group or groups its valuable physiological properties are due. Numerous compounds have been prepared whose structures have been based to more or less extent upon some portion of the cocaine molecule. Among these, one of the most important and most widely used is the hydrochloride of the diethylaminoethyl ester of p-aminobenzoic acid patented in Germany in 1905 under the name of novocaine by Lucius and Brunning, [4] and known in this country as procaine.

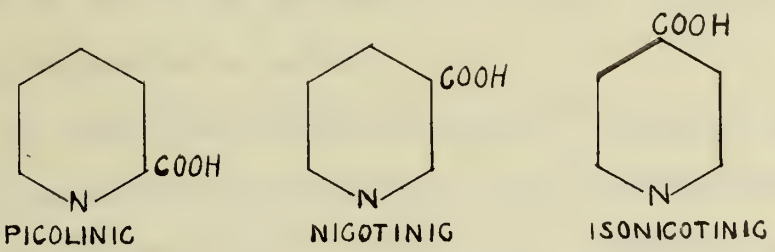


PROCAINE

It is equally as powerful an anesthetic as cocaine while it is but one seventh as toxic, and it is superior to other drugs of a similar nature in that it is soluble in water, is non-irritating, increases the vasoconstrictor action of adrenaline, and is less destructive generally on the tissues.

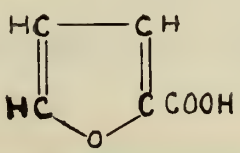
The purpose of the present work was to prepare some esters similar in structure to procaine and test their physiological action. A large number of compounds of this nature have already been made in which the p-aminobenzoic acid was retained and different alkylamino alcohols substituted. [5] In many cases they possessed

anesthetic properties to a marked degree, but none were found suitable for use because of their irritant action and relatively high toxicity. Not much work seemed to have been done, however, in preparing compounds in which the diethylaminoethyl alconol group of procaine was retained and the effect of substituting different acids determined. One of these which seemed most likely to give the best results was one containing a pyridincarboxylic acid, which exists in three isomeric forms, having the carboxyl group in either the alpha, beta, or gamma position, which are known as picolinic, nicotinic, and isonicotinic acids respectively.



As may be observed from their structural formulae, the basicity of these acids would probably be similar to that of the p-aminobenzoic acid which is in procaine. The amino group in the phenyl in procaine is necessary to give a monohydrochloride which has a neutral reaction; the hydrochloride of the unsubstituted phenyl derivative is acid. Accordingly it may be expected that the hydrochloride of the picolinic ester will give a neutral salt.

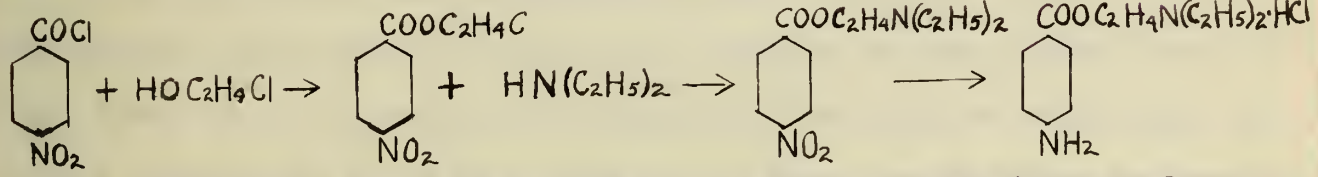
It was considered worthwhile also to prepare the ester of a heterocyclic acid, choosing in this case a furan carboxylic acid, namely, pyromucic acid, whose formula is given here, and to test out its physiological properties even though it may have an acid reaction.

PYROMUCIC  ACID

Theoretical.

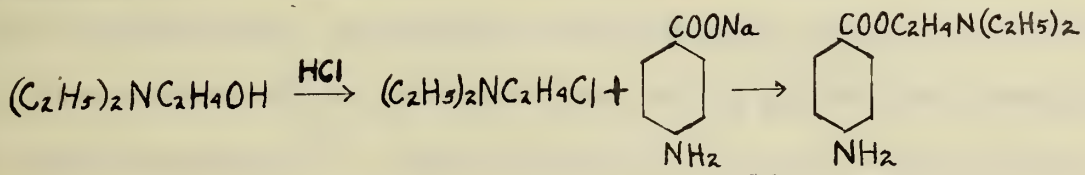
The methods of preparation of procaine are as follows:

1. P-nitrobenzoyl chloride[6] is treated with ethylene chlorhydrin to give the corresponding ester, which is then heated in a sealed tube with diethylamine. On reduction of the nitro group procaine is obtained.

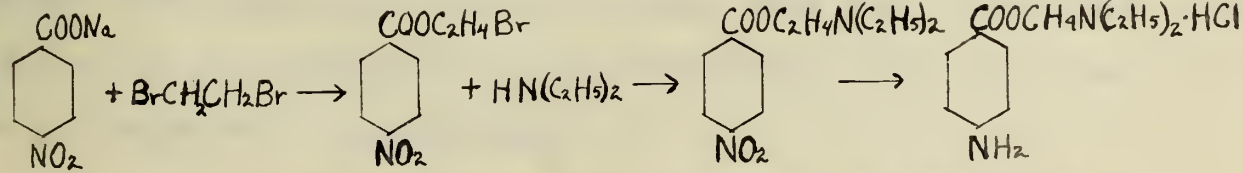


2. P-aminobenzoic acid is esterified with ethylene chlorhydrin by the action of sulfuric acid, and the ester obtained is treated with diethylamine as above.

3. Diethylaminoethyl chloride[8] is first prepared by the action of concentrated hydrochloric acid on diethylaminoethyl alcohol. This is then allowed to react with carefully dried p-amino sodium benzoate.[9]



4. B-bromethyl p-nitrobenzoate[10] is prepared from p-amino sodium benzoate and ethylene dibromide, preferably with an amine or copper as a catalyst. This ester is then treated with diethylamine.



These methods may be generalized as follows:

1. The esterification is made directly with the amino alcohol, or

2. The b-bromethyl ester is prepared from either the free acid or its sodium salt and this then condensed with diethylamine.

The former of these seemed the best to use since acid chlorides are in most cases very easily prepared and the diethylaminoethyl alcohol can be made to react directly, thus requiring fewer steps in the process. It is, as a rule, more difficult to form esters with amino alcohols, it being necessary in some cases to resort to the preparation of an ester containing a halogen in the alcohol and to then treat with the amine. The objection to this is that under ordinary pressures, it is not possible to heat the reacting substances sufficiently since diethylamine boils at 55° C., and, if the reaction is carried out in a sealed tube, a side reaction takes place, resulting in the decomposition of the ester with the subsequent formation of the acid amide. With this in mind, it was decided to prepare the amino ester if possible by means of the acid chloride. Pyromucyl chloride is easily prepared by the action of thionyl chloride.

It was necessary to prepare the picolinic acid by the oxidation of the corresponding methylpyridin using potassium permanganate as the oxidizing agent.[11] From the acid, the acid chloride has also been prepared by the action of thionyl chloride.[12]

In this case, however, the acid chloride was not obtained, and direct esterification with diethylaminoethyl alcohol was next tried. When this also failed, the next step was to carry out a reaction for the preparation of the chlorethyl ester which was then to be condensed with diethylamine.

Experimental

1. Preparation of Diethylaminoethyl Ester of Pyromucic Acid.

(a) Pyromucic Acid.

The acid which was available was in an impure state. 90 grams of this crude acid were dissolved in 400 ccs. water and heated to boiling. Considerable decomposition took place on this heating. When it had dissolved, the solution was set aside to permit the crystals to form on cooling. 63 grams crystals were obtained.

(b) Pyromucyl Chloride.

63 grams of pure acid were placed in a 500 cc. roundbottomed flask fitted with a condenser, 300 grams of thionyl chloride were added and the mixture refluxed over a flame for 2 hours. If the refluxing is not carried out under the hood, it is advisable to fit to the top of the condenser a stopper with a tube attached, to carry away the hydrochloric acid and sulfur dioxide fumes that come off.

The contents were then transferred to a distilling bulb and the excess thionyl chloride distilled off up to a temperature of 150°C. The fraction from 150°-180°C was then redistilled and the fraction coming over between 170°-173°C. was taken. 33 grams were obtained. If this distillation is not carried out under the hood, the receiver should be a filter flask with a tube leading from the side connection to a trap, since both thionyl chloride, and the pyromucyl chloride are very disagreeable; the latter, especially, attacks the eyes.

(c) Preparation of the Diethylaminoethyl Ester.

This is carried out best in benzene as a solvent. 12 grams diethylaminoethyl alcohol and 13 grams pyromucyl chloride were

each dissolved in 100 ccs. benzene. These solutions were then carefully mixed. The ester hydrochloride separated out immediately. To insure completeness of the reaction, the solution was transferred to a 300 cc. flask fitted with a condenser, and refluxed for 2 hours. The hydrochloride settled on the bottom.

Since these amines are usually very hydroscopic, a small portion of the benzene in which the ester hydrochloride was suspended was diluted with ether , and filtered by suction. The solid on the filter paper took up water almost instantly in which it dissolved and passed through the filter.

The suspension in benzene was extracted successively with three 50 cc. portions of dilute hydrochloric acid. (The benzene was treated to recover the excess amino alcohol.) This extract was then neutralized with 30% sodium hydroxide solution, and the free ester separated out as an oily liquid. It was quickly taken up in ether and dried over potassium sulfate. The solution was transferred to a Claissen distilling bulb, the ether evaporated off, and the ester distilled over under reduced pressure. At 4 mm. it distills at 129°C. (uncorr.)

The product first obtained was accidentally lost, and a second run was made of the following amounts: 17-1/2 grams amino-alcohol, 19 grams pyromucyl chloride. 10 grams product were obtained with the same boiling point.

It darkens and decomposes on standing, giving off ammonia. Its nitrogen was determined by Kjeldahl's method with the following result:

	Calc.	Found.
$C_{11}H_{17}NO_3$	6.64%	6.20%

Preparation of Diethylaminoethyl Ester of Picolinic Acid.

(a) Picolinic Acid Hydrochloride

To 180 grams of potassium permanganate in 5 liters of boiling in a 12 liter flask fitted with a large condenser were added 50 grams of a-picolin. The solution was refluxed until the color of the permanganate disappeared. When the oxidation has once commenced, the solution must be kept boiling continually unless a stirrer is used. Once the manganese dioxide settles, it is impossible to prevent the solution from bumping violently. The odor of the picolin was so strong after the reaction was complete that about one liter of liquid was distilled over to recover what was believed to be unoxidized a-picolin. The manganese dioxide was filtered off by suction. One half the solution was lost here when the filter flask broke. The remainder was neutralized with hydrochloric acid and concentrated to 200-250 ccs. on the steam cone , and the picolinic acid precipated as the copper salt by the addition of a concentrated copper sulfate solution. This, after filtering off by suction, was boiled up with 400 cc. water to which a little hydrochloric acid had been added, hydrogen sulfide then passed in, and the precipitate of copper sulfide filtered off. About 4 hours is required to completely precipitate the copper. The filtrate yielded 10 grams of the acid hydrochloride on evaporation.

On another similar oxidation, 20 grams more of the hydrochloride were obtained.

(b) Potassium Picolinate.

The oxidation was carried out as above but the precipitation of the copper picolinate was omitted, the solution being evaporated

to dryness after the neutralization. 25-30 grams were obtained which contained a little potassium chloride as an impurity.

(c) Picolinic Acid.

In the above described operations, the yields were so small that variations in the procedure were tried in an attempt to increase them. It was thought that the ring might be broken during the process of oxidation, and if such was the case, the addition of the oxidizing agent in smaller portions would result in the oxidation of only the methyl group. Accordingly, a wide tube provided with a stopper was inserted in the stopper beside the condenser, and through it solid potassium permanganate was added to the boiling solution of a-picolin from time to time.

The copper picolinate was obtained as before, but this time no acid was added on decomposition with hydrogen sulfide. The copper sulfide carries down copper picolinate with it and a thin film of copper sulfide forms on the particles of copper picolinate, thus preventing their going into solution. It was found necessary to heat the solution to boiling and subject it repeatedly to the action of hydrogen sulfide to get complete decomposition. Two or three days' actual time was required for this treatment. The copper sulfide was filtered off and treated to recover any picolinate it might contain. The filtrate was evaporated in vacuum since the acid decomposes very easily, giving off carbon dioxide. About 6 grams were obtained. The theory yield is 65 grams. This acid melted at 128°C. while literature gives it at 132°C.

It was thought that the poor yields might be due to decomposition on account of the alkalinity of the oxidizing solution. Accordingly, 65 grams of magnesium sulfate was added to the oxidizing

solution.

It had the effect of precipitating the manganese dioxide which settled on the bottom causing the flask to bump violently. On going through the same procedure as before no better yields of the acid were obtained.

Finally the "a-picolin" used was distilled. Pure a-picolin distills at 132°C. From 50 grams of material only 20 grams passed over at 128° to 135°C. Enough was then distilled so that 50 grams, which distilled over between these temperatures was obtained. This was then oxidized as at first - added to the boiling permanganate solution. The copper precipitate was decomposed as before by repeated saturation with hydrogen sulfide, and a little aluminium hydroxide added to bring down the copper sulfide. After very careful work, although the copper picolinate precipitate was larger than ever before, only 10 grams acid were obtained. The acid must decompose in the boiling solution when hydrogen sulfide is passed in, since every precaution was taken, the filtrate being evaporated under reduced pressure as before.

(d) Picolinyl Chloride.

10 grams picolinic acid hydrochloride were placed in a flask fitted with a condenser with 50 grams thionyl chloride and refluxed for 2 hours as in the preparation of the pyromucyl chloride. The excess thionyl chloride was distilled off leaving only a black gummy mass.

It was thought that perhaps the acid chloride might be prepared directly from the potassium picolinate, the yield of which was comparatively large, without going through the preparation of the free acid or the hydrochloride, with its small yields. The potassium

picolinate was treated in the same way as the hydrochloride, but with no better results. No more attempts were made to prepare the acid chloride.

(e) Esterification with Diethylamino Ethyl Alcohol.

According to the method for the preparation of the ethyl ester of quinolinic acid,[13] 10 grams picolinic acid hydrochloride and an excess of amino alcohol, each dissolved in a small amount of sulfuric acid, were carefully mixed and gently warmed. Charring took place to quite an extent, and upon neutralization it was impossible to recover anything.

(f) Esterification with Ethylene Chlorhydrin.

7 grams copper picolinate were placed in a flask with 15 grams ethylenechlorhydrin and dry hydrochloric acid gas passed in. When the solution had become saturated, a condenser was affixed to the flask, and the contents refluxed on the steam cone for a short time. The excess chlorhydrin was distilled off under reduced pressure, leaving a gummy residue from which it was impossible to extract the ester hydrochloride which would be soluble in water.

In the meanwhile 8 grams of picolinic acid had been prepared. This was placed in a flask with an excess of ethylene chlorhydrin and dry hydrochloric acid gas again passed in. The solution heated up showing that a reaction was taking place. A white crystalline precipitate came down, which did not resemble the hydrochloride of picolinic acid in the least. After refluxing on the steam cone for 2 hours, this light, flocculent precipitate, which was presumably the hydrochloride of the ester, was filtered off. It was very soluble in water, insoluble in ether, and melted at 210 °C. The filtrate was vacuum distilled but no more of this substance was ob-

tained. After an amount was taken for the condensation with diethylamine, there was not enough of the material left for analysis.

10 grams picolinic acid were again subjected to dry hydrochloric acid gas in an excess of ethylene chlorhydrin. The evolution of heat as well as the separation of a precipitate as before, indicated that the reaction was taking place, but this time, after refluxing, it was impossible to filter immediately. The flask was stoppered and allowed to remain for 12 hours. It was found that during this time the acid hydrochloride had formed and separated out. This was filtered off, dried in vacuum on the steam cone, and again treated with the gas in ethylene chlorhydrin. After refluxing for 8 hours, the precipitate was filtered off by suction and washed with ether. A light, white, powdery substance was obtained, insoluble in ether and soluble in water. It did not melt or decompose up to a temperature of 295°C. The melting point of the acid hydrochloride could not be found in literature. It was allowed to stand over solid sodium hydroxide, and at the time of writing it was being analyzed for its chlorine content.

(g) Condensation of Chlorethyl Ester with Diethylamine.

To about 2-1/2 grams chlorethyl picolinate in a small flask with a condenser, about 5 grams of diethylamine were added, and the mixture heated on a water bath for 1-1/2 hours. A light yellow precipitate was filtered off, the diethylamine evaporated off, and the residue taken up in water, neutralized with sodium carbonate and extracted with ether. After drying, this was evaporated, and a minute amount of a brownish, oily liquid was left. It was impossible to determine if this was the compound sought.

Conclusions.

The diethylaminoethyl ester of pyromucic acid was prepared, but the yield was poor. Its physiological action has not yet been tried out.

The preparation of the diethylaminoethyl ester of picolinic acid by means of the acid chloride could not be carried out, since it was impossible to prepare any of the picolinyl chloride. The acid decomposed badly on treatment with thionyl chloride.

The failure of the attempts to esterify with diethylaminoethyl alconol by means of sulfuric acid may be ascribed to both the instability of the acid, and the difficulty of esterification by the amino alcohol.

It is probable that the substance obtained when hydrochloric acid gas was passed into the picolinic acid and ethylene chlorhydrin was the chlorethyl ester. If the analysis proves that such is the case, it should be possible to obtain the compound desired on treatment of this with diethylamine.

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