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Howland, Louis Harold 1902-1964, "Preparation of acridyl ethyl amine." (1926). *Electronic Theses and Dissertations*. Paper 644.

<https://doi.org/10.18297/etd/644>

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University of Louisville
Preparation of Acridyl Ethyl Amine

A Dissertation
Submitted to the Faculty
of the
Graduate School of Liberal Arts
in Partial Fulfilment
of the
Requirements
for the Degree
of
Master of Science

Department of Chemistry

By

Louis Harold Howland

1926

PREPARATION OF ACRIDYL ETHYL AMINE

Part I

Theoretical

Acridine is a compound that has a ring system similar to anthracene except that one of the CH_2 groups is replaced by a $-\text{N}-$ group.

Anthracene

Acridine

It is possible for this compound to have desmotropic forms as those that follow:

When an amino group is present in the 3 or 6 position, there is possible another desmotropic form that probably causes a deepening in the color of the compound.

The numbering of the ring system is as follows:

Acridine and its derivatives are obtained by the destructive distillation of coal. It occurs in the crude anthracene obtained from the coal tar. Many of its derivatives are used as dyes and may be readily synthesized.

The first acridine dye was obtained from the mother liquors from the manufacture of magenta by Nicholson in 1863. The constitution of this compound was discovered by Fisher and Koerner who prepared it by the condensation of o-nitro-benzaldehyde with aniline and then reducing the nitro group.

Other acridine dyes are acridine yellow, benzo-flavine, flaveosine, acridine orange, and acridine orange R extra.

Acridine Yellow

Benzoflavine

Flaveosine

Acridine Orange

Acridine Orange R Extra

In recent years it has been found that certain

acridine derivatives have a value in medicine as antiseptics. Such compounds as 3, 6 diamino acridine, proflavin, acid tryptaflavine, flavizid, 6, 9 diamino acridine, and rivanol are used medicinally

Proflavin

Acid Tryptaflavine

3, 6 Diamino Acridine

Flavizid

6, 9 Diamino Acridine

Rivanol

There are certain compounds that are alkaloids and not related to acridine that have as their physiological property the raising of the blood pressure. The group or rather the chain present that seems to give them this property is the =C-C-N= group.

This class of compounds includes such compounds as tyramine, histamine, adrenaline, arterenal, homorenol, epinine, hordinine, furyl ethyl amine, tetra-furyl

ethyl amine, phenyl ethyl amine, and naphthyl ethyl amine.

Tyramine

Histamine

Adrenaline

Arterenol

Homorenol

Epinephrine

Hordenine

Furfuryl Ethyl Amine

Tetra-furfuryl Ethyl Amine

Phenyl Ethyl Amine

Naphthyl Ethyl Amine

Since it has been noticed that the acridine ring system in various forms as in combination with the amino groups and also that the ethyl amine derivatives with a ring system in the beta position have special physiological effects, it has been thought that an interesting physiological effect could be

produced by the combination of the two systems into one compound. This compound is acridyl ethyl amine. Now since the compound was not hitherto known it was necessary to devise a method of synthesis. There are probably many ways of synthesis for this compound but the object of this work has not been to find all these but only such of them as would enable the obtaining of the amine in large enough quantities to test it for its properties.

It is known that a methyl group in such a linking as is present in methyl acridine is very reactive and

readily forms the aldol condensation with aldehydes. Some examples of compounds with such a linking and having similar properties are alpha methyl pyridine and alpha and gamma methyl quinoline.

Alpha Methyl Pyridine

Alpha and Gamma Methyl
Quinoline

In the manufacture of acridyl ethyl amine the question arises as to what aldehyde or aldehyde derivative to condense with this methyl group in order to get the amine. It is known that by Curtius

decomposition that an amine can be prepared from an acid. The question is how to get the acid. If chloral is condensed with methyl acridine you get a compound of the following formula.

This on hydrolysis gives acridyl acrylic acid which on reduction gives acridyl propionic acid. Curtius decomposition is used here and the reaction is as follows.

Part II

Practical or Experimental

Preparation of Acridyl Propionic¹ Acid by Way of Methyl Acridine.

Preparation of Methyl Acridine

50 gms. of diphenylamine and 30 gms. of glacial acetic acid are heated from 10 to 14 hours at 220°C with 85 gms. of zinc chloride. The mixture is put in a 500 cc. Erlenmeyer flask which is fitted up with a tall air condenser. This is then heated on an oil bath. The temperature is allowed to rise very slowly until the above mentioned temperature is reached. When the heating is ceased before the heating is complete, a calcium chloride tube must be put on the condenser to keep out moisture.

(Best results were obtained by heating ten hours at 220°C.)

This melt obtained is then dissolved in fairly concentrated sulphuric acid (3 parts sulphuric acid to 1 part water) at 100°C. About 150 or 200 cc. are used. This solution of the melt is poured into several volumes of cold water. This is then filtered. The residue on the filter and in the flask is then extracted many times with 10% hydrochloric acid at the boiling point (about 500 cc. each time) until no more methyl acridine is in the filtrate or the 10% hydrochloric acid extract.

The extracting is done by heating slowly on water-bath for some time then bringing to boiling on free flame.

The extracts are allowed to cool then both they and the mother liquid are treated with excess ammonia until distinctly alkaline. Methyl acridine is precipitated.

All these solutions containing precipitated methyl acridine are filtered together. The filtrates are discarded. The residue of methyl acridine is washed well with cold water until free from ammonia and inorganic salts.

The residue is dissolved in about 3 or 4 liters of boiling water and hydrochloric acid (10 cc. to 90 cc. of water), is filtered while hot and then allowed to cool. It is best or, rather seems to be best, to dissolve it first in 500 cc. of the hydrochloric acid solution, filter while hot, cool, and then put it into several liters of water. It is then purified by fractional precipitation. Ammonia is added until the first precipitate forms. This is allowed to stand over night and then is filtered. The precipitate which contains some methyl acridine and many impurities may be extracted over again with the next melt.

The material (methyl acridine) which is precipitated by adding excess ammonia to the filtrate is fairly pure.

The precipitation process can be used for further purification.

You can purify it more by crystallizing several

times from a saturated alcoholic solution. This is filtered, washed, dried, and weighed if the amount is wanted.

The melting point is taken to determine the purity of the compound.

Methyl acridine is yielded in larger quantities when small batches are made at a time.

Condensation with Chloral

9.2 gms. of methyl acridine and 11 gms. of chloral are refluxed for 4 hours in 100 gms. of pure benzene. All of the apparatus that is used here must be absolutely dry.

The chloral used is generally prepared just before use by shaking chloral hydrate in a separatory funnel with concentrated sulphuric acid. When the liquid separates into layers, the chloral is separated and put in an air tight bottle. It is purified by distilling over dry calcium carbonate in dry apparatus.

The condensation product that is formed after the above mentioned 4 hours refluxing is filtered off, washed with pure benzene, dried, and weighed.

The yield is approximately 18 grams.

Saponification

23 gms. of the condensation product are powdered

very finely. This product is added to a cool alcoholic potash solution made up as follows:

45-50 gms. of sodium hydroxide are dissolved in 150 cc. of water, then cooled and added to 100 cc. of alcohol. This is let stand until thoroughly mixed.

The mixture is put on a cold water-bath, then is heated up slowly until the powder goes into solution. The alcohol which dissolves the powder separates in a layer on top. When this alcohol layer starts to boil, the temperature must be reduced and kept just below the boiling point of the upper layer. Heat for $\frac{1}{2}$ hour, then pour it into 8 to 10 volumes of cold water while the solution is still hot. At this point it is best to let it stand over night. Next filter and wash good with cold water. Dissolve the residue in about 300 cc. of hot water. Only the sodium salt of acridyl acrylic acid goes into solution.

Filter while hot. Again extract the residue with 300 cc. of boiling water and filter while still hot. Allow the combined filtrates to cool and then treat them with acetic acid, until slightly acid. It is necessary to be slightly acid, for if it is only neutral the precipitate will be too fine to filter. Allow to stand over night and filter off the solution from the acridyl acrylic acid. Wash, dry, and weigh.

lized with hydrochloric acid and then acetic acid. If present, acridyl acrylic acid will be precipitated out.

Also make the filtrates strongly alkaline with sodium hydroxide. If the acid is present the sodium salt will be precipitated. The wash water from the purification should also be treated thus.

The methyl acridine which occurs as an impurity is saved to use in another condensation.

Reduction of Acridyl Acrylic Acid

Put in a beaker 10 gms. of acridyl acrylic acid and 70 cc. of water. Add dilute caustic soda until the acid goes into solution. Be careful not to precipitate the sodium salt.

Treat gradually in an ice cold solution with 200 gms. of 2% sodium amalgam. Then let it stand at atmospheric temperature for a while and then as soon as the sodium amalgam has become liquid heat the solution on the water-bath for a short time.

Decant off the solution from the mercury and neutralize it with hydrochloric acid. Acridyl propionic acid is precipitated.

The acridyl acrylic acid that is unchanged is saved to be reduced with the next batch.

The yield of acridyl propionic acid from the above method is very poor.

Preparation of Acridyl Propionic Acid by Direct Condensation

Put 50 gms. of diphenyl amine and 15 gms. of succinic acid in a flask with 50 grams of zinc chloride. Attach to the flask an upright air condenser. Put it on an oil bath and let the temperature rise gradually to between 180° and 200° and keep it there for 7 hours.

Extract this melt with 250 cc. of 10% sodium hydroxide solution by heating it on a water-bath for several hours and then bringing it to boiling on a free flame. Next, filter while hot, cool and precipitate the acridyl propionic acid by neutralization with acetic acid.

The extraction must be repeated until no more precipitate is obtained upon neutralization.

The acridyl propionic acid is filtered, after having been completely precipitated, washed and dried. It may be somewhat purified by resolution in 5% sodium hydroxide solution and reprecipitation by acetic acid.

The yield by this method is about 10%, while by the first method mentioned it was a good deal below 5%.

Making the Amine from the Acid

Preparation of the Ester

Reflux for 4 hours absolutely dry acridyl propionic acid with absolutely dry 5% hydrochloric acid in methyl alcohol in dry apparatus.

The amount of materials used is 5 gms. of acridyl

propionic acid with 50 cc. of 5% hydrochloric acid in methyl alcohol. This is made by passing dry hydrochloric acid gas into absolute methyl alcohol.

After the refluxing, the solution is evaporated to $\frac{1}{4}$ of its volume.

Dilute with water and precipitate with sodium carbonate.

Shake out with ether 3 or 4 times and dry the combined ether extracts with anhydrous sodium sulphate over night.

Filter to get rid of the sodium sulphate. Wash with dry ether several times.

Evaporate the ether.

Extract the residue with dry petroleum ether. When about 10 gms. of ester are present extract with 100 cc. of the petroleum ether by refluxing for $1\frac{1}{2}$ hours. Do this several times using old liquid over until you get no crystallization on cooling.

The hot extract is poured in a flask and allowed to cool.

The ester crystallizes out.

Pour off the liquid from the crystals and extract again with the liquid. Put the next hot extracts with the crystals from the first crystallization.

After the first extraction is complete, the ether may be saved for subsequent extractions.

The crystals of the ester, after the ether has been poured off, are dried.

The melting point of the ester is 95°C.

Hydrazide

Heat the ester with hydrazine hydrate under an air condenser for 10 hours on water-bath. Do not let any moisture get in the flask.

Heat for one hour without a condenser on the water-bath.

Dissolve the contents of the flask in absolute alcohol and heat again for one hour to get rid of the hydrazine.

The hydrazide is obtained by crystallization from the alcohol. It can be purified by several recrystallizations from alcohol.

The azide can be made by treatment with nitrous acid.

The melting point of the hydrazide is 205°-206°C.

The hydrochloric salt of the hydrazide decomposes at 207°C.

Analysis: Obtained: C, 72.64%; H, 5.872%

Theoretical: C, 72.453%; H, 5.66%

Urethane

The materials used are 1 gm. of the hydrazide, 0.6 gm. of amyl nitrite, and 0.35 gm. of hydrochloric acid.

Dissolve the hydrazide in absolute alcohol. Next add the amyl nitrite and the hydrochloric acid, the latter being dissolved in ethyl alcohol.

Let this solution stand for several hours in the cold and then boil under a reflux condenser.

A violent evolution of nitrogen takes place.

After boiling for 8 hours the solution is evaporated to dryness on a water-bath.

The residue contains the urethane. In order to get the urethane dissolve the residue in water and precipitate with ammonia. Filter and dry.

To purify, recrystallize the urethane from petroleum ether that contains a little absolute alcohol.

It crystallizes as fine needles that melt at 144°C .

The melting point of the hydrochloric salt is $217^{\circ}\text{--}218^{\circ}\text{C}$.

The picrate decomposes at 195°C .

Analysis:

Urethane: Obtained: C, 73.300%; H, 6.870%

Theoretical: C, 73.469%; H, 6.122%

Hydrochloric salt: Obtained: Cl, 10.674%

Theoretical: Cl, 10.710%

Picrate: Obtained: C, 55.066%; H, 4.523%

Theoretical: C, 55.570%; H, 4.015%

Acridyl Ethyl Amine

Boil 1 gm. of the urethane with 20 cc. of concentrated hydrochloric acid for 7 hours under a reflux condenser. On cooling, part of the hydrochloric salt of the amine separates out in long needles. To get the free base dissolve the salt in water and precipitate with ammonia.

The free base decomposes in the air or reacts with carbon dioxide to form the carbonate.

The amine melts at 145°C .

The Picrate

The hydrochloride of the amine dissolved in alcohol is treated with a saturated solution of picric acid in alcohol.

It decomposes at 225°C .

The Hydrochloric Salt

It decomposes at $225^{\circ}\text{--}230^{\circ}\text{C}$.

The Benzoyl Derivative

The benzoyl derivative is made by putting the hydrochloric salt of the amine in 10% sodium hydroxide and treating with benzoyl chloride.

This is purified from alcohol.

The benzoyl derivative melts at 213°C .

Analysis: Obtained: C, 81.331%; H, 6.185%

Theoretical: C, 80.990%; H, 5.521%

Conclusions

The yield of acridyl propionic acid made by the condensation of chloral and methyl acridine and its subsequent saponification and reduction was found to be low. The best yields of the acridyl propionic acid were obtained by the direct formation of the acid by the condensation of diphenylamine and succinic acid in the presence of zinc chloride at a temperature of 200°C.

In making the ester the most ordinary methods of formation either did not give good results or failed entirely. It was found, however, that by using dry HCl gas dissolved in absolute alcohol and refluxing on the water-bath a good yield was obtained. When the purified ester was heated on a water-bath with freshly prepared hydrazine hydrate, the hydrazide was given in good quantities.

In making the urethane it was not necessary to stop at the azide state since the compound so easily lost nitrogen and rearranged to the urethane. This was all carried out in a single operation.

The amine was prepared from the urethane by boiling with concentrated hydrochloric acid. The hydrochloric salt was stable but the free amine could not be kept easily in a free state. The free amine partially decomposed and partially combined with the carbonic acid of the air.

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Berlin

Verlag von Julius Springer

1923