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Purification and properties of pyrrole

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BOSTON UNIVERSITY

GRADUATE SCHOOL

Thesis

PURIFICATION AND PROPERTIES OF PYRROLE

Submitted by

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(A.B., Boston University, 1929)

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I INTRODUCTION

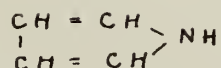
Pyrrrole is a colourless liquid which turns brown on standing and has an odor like chloroform. It boils between 130° and 131° C. There are several references in the literature on work which has been done by various investigators, but there is some doubt as to the purity of the product with which they were dealing. No quantitative data on the determination of purity are stated, the fact that it boiled at a constant temperature probably having been taken as sufficient evidence that it was pure.

In Dr. Holmes' investigations, he has reached the conclusion that such is the case, and under his supervision I shall try to obtain a product in the purest state possible and determine its chemical and physical properties by quantitative methods. Injections of pyrrrole have a toxic effect and it will be of interest to find whether or not the toxicity is raised or lowered on purification.

II HISTORICAL

Occurrence

Pyrrole is found in bone oil which is obtained from the distillation of animal bones and also from coal tar. It is a very weak base and has the structural formula,



It was first discovered in bone oil by Renge and was investigated by Andersen who took the bone oil fraction from 100° - 150° C. and washed with dilute H₂SO₄ to free from pyridine bases, and then with KOH to hydrolyze the nitriles. This then distilled and the 120° - 140° C. fraction is heated with KOH. This forms the solid potassium salt in which the H joined to the nitrogen is replaced by K. This salt is separated from the oil, washed with ether and decomposed with water, according to the equation



This is distilled and purified by fractional distillation.

Pyrrole reacts with both K and KOH to form this potassium salt and a weighing of the relative

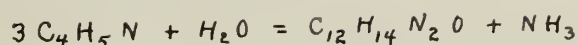
merits of each is in favor of the use of KOH which forms a softer and more workable flux upon fusion. With KOH there is obtained upon refluxing with pyrrole for some time a mixture of two layers. The KOH is in the lower layer mixed with water, while the pyrrole floats on top and can be readily separated. When K is used the final result is a hard difficultly workable mass. (1)

In another article (1a) by Weidel and Ciamician, pieces of metallic K are dropped into the warm oil, in a reflux apparatus, of the bone oil distillate (115° to 130° C. fraction). The potassium pyrrole so formed is ether washed, hydrolyzed, and steam distilled. The oily layer is separated, dried with NaOH and fractionated. The pyrrole so obtained boiled at 126.2° C. (746.5 mm.). It had an odor like chloroform at first which was later somewhat biting. It was colorless at first, but became yellow after a few days, and finally green. This boiling point conflicts greatly

(1) Ciamician and Dennstedt; Ber. 19, p.173 (1880).
(1a) Weidel and Ciamician; Ber. 13, p.65 (1880).



with that of Andersen which is 133°C. Andersen's data (2) on polymerization in the presence of acids to form pyrrole-red was confirmed and the following equation formulated for the reaction:

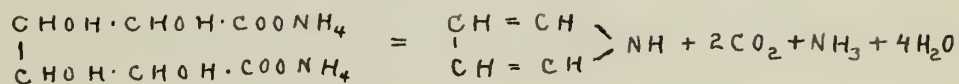


In this reaction the calculated amount of ammonia was found to be evolved. About 8% of the bone oil was found to consist of pyrrole. (3)

The occurrence of pyrrole in coal tar is due to the reaction between C₂H₂ and NH₃ to form pyrrole. This reaction takes place at about 550°C. with iron oxide as a catalyst. (4)

Syntheses

Pyrrole may be prepared by the distillation of ammonium mucate. (5) The reaction is as follows:



The average yield of pyrrole by this process is 4%

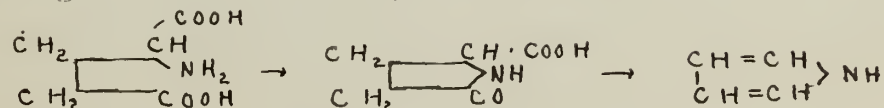
- (2) Ann. Chem. Pharm. 70, 32; 80,44; 94, 358; 100,335; 155, 270 .
- (3) Weidel and Ciamician: Ber. 13 p.65 (1880) .
- (4) Chemical Abstracts 14 p.3674 Stuer and Grop. German patent.
- (5) E. Khotinsky; Ber. 1909, 42 p.2506 .



of the mucic acid. This is increased to 13.4 % if the latter is converted into the ammonium salt and heated in a current of NH_3 up to 270°C . after having been mixed with glycerol. The current of gas is then stopped and the mixture of pyrrole and glycerol distilled at $320^\circ - 330^\circ\text{C}$. Khotinsky believes that a splitting out of ammonia precedes pyrrole formation. In dry distillation this is lost, but by the addition of glycerine some is retained and also more uniform heating is afforded. (6)

Blicke and Powers found that if ammonium mucate was mixed thoroughly with its weight of glycerine at 100°C . and heated on a sand bath until no more distillate came over, that the yield was 40 - 52 % of the theoretical. They found that if NH_3 was passed into the reacting mixture that uncontrollable foaming took place. (7)

Pyrrole is also obtained from the distillation of glutamic acid. (8)



- (6) Khotinsky; C.A. 3, p.2565; Ber. 42.p.2506-7.
 (7) Blicke and Powers; C.A. 22, p.778.
 Ind. and Eng. Chem. 19, p.1334-5 (1927).
 (8) Monatsch d. Chem. 3, 228 - Haitinger.

Another method of production is the reduction of succinimide with Zn dust and acetic acid (9):



Pyrrole can also be synthesized by passing acetylene and ammonia over bauxite, an iron catalyst, at 550° C. (4)

Metallic Salts of Pyrrole

The potassium salt has been discussed in great detail under the work of Ciancician and Dennstedt on bone oil. (1) This potassium salt may be transformed into the silicon salt by cooling with a mixture of ice and salt and adding with constant shaking SiCl_4 . This is allowed to stand over night. This salt has the formula $\text{Si}(\text{C}_4\text{H}_4\text{N})_4$ and melts at 173.4° C. (10)

A pyrrole derivative of the form $\text{R}_2\text{Hg}(\text{HgCl}_2)_4$ is obtained as a white crystalline precipitate when a solution of pyrrole in acetic acid is treated with 4 % HgCl_2 .

(9) Bell; Ber. 13, p.877 (1880)

Bernthsen; Ber. 13, p.1049 (1880).

(4) Chemical Abstracts 14, p.3674; Stuer and Grop., German patent.

(1) Ciancician and Dennstedt; Ber. 19, p.173 (1880).

(10) Reynolds, J. Chem. Soc. 95, p.505-8.



This is decomposed on treating with H_2S . Tetra substituted pyrroles do not react. Therefore, the Hg must be linked to C rather than to N. This compound melts at $143^\circ C$. with decomposition. Changing conditions of temperature and solvents produce compounds with various melting points. (11)

Reaction with Grignard Reagent

Pyrrole also reacts with the Grignard reagent $MeMgI$ in absolute ether. If it is added slowly a heavy brown oil C_4H_4NMgI (12) is formed.

Test for Pyrrole

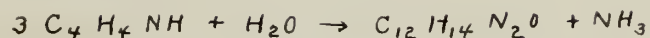
The most sensitive and most easily applied test for pyrrole is the so-called pine chip test. A pine chip moistened with HCl is colored a bright red when it is held in pyrrole vapor. This is due to a reaction between the pyrrole and the coniferin in the wood. (13)

Characteristic Reactions

In the presence of strong acids pyrrole forms a red polymer known as pyrrole-red. This reaction

- (11) C.A. 20, p.387; Fisher and Muller, Z. Physiol. Chem. 148, 55-79 (1925)
- (12) C.A. 5, p.686; Bernardo Oddo, Gazz. Chir., Ital. 39. I 649-59
- (13) C.A. 17, p.3306; Khotinsky, J. Russ. Phys. Chem. Soc. I p.149-53 (1917)

is believed by Weidel and Ciamician to take place according to the equation:



In proof of this they state that they have found that the calculated amount of ammonia is evolved. (14)

By the iodination of pyrrole in the presence of caustic potash, tetraiodopyrrole has been produced by Ciamician and Silber. (15) The same compound is also obtained by the action of iodine on potassium pyrrole. (16)

It has been found that tetraiodopyrrole is produced in quantitative yield by the action of iodine on pyrrole dissolved in ammonia. (17) The best conditions for carrying out the reaction are as follows: To an ammoniacal solution of pyrrole, which has been weighed by means of a weighing buretts, a .5 N solution of iodine is added slowly from a burette. A voluminous white precipitate is formed which turns gray on standing. As the end point is approached the solution is tested for iodine by using starch

(14) Weidel and Ciamician; Ber. 13, p.65 (1880).

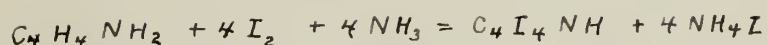
(15) Ciamician and Silber; Ber. 18, p.1766 (1885).

(16) Ciamician and Dennstedt; Ber. 15, p.2582 (1882).

(17) J.A.C.S. 33, p.451 (1917) Lal Datta and Prosad.



as an outside indicator. The end point is reached when the faintest blue possible is produced by the action of the iodine on the starch. The reaction that takes place is as follows:



It is seen from this equation that the pyrrole molecule is equivalent to eight atoms of iodine. The purity of the pyrrole is found by determining the ratio of the number of cubic centimeters of iodine which reacts with the pyrrole of given weight, to the number with which a pure sample would react. Lal Datta claims to have used pyrrole of 99% purity, but he does not state the method of purification and we have not been able to confirm his results.

Physiological Action

The physiological action of pyrrole and its derivatives is characterized by their paralyzing action on the peripheral nerves connected with the mechanism of the heart. By introduction of a side ring such as the inactive pyridine ring, the physiological effect is intensified. The action of methyl pyrrolidine resembles that

of nicotine, atropine, or cocaine, as might be anticipated from their similarity in structure. (18)

(18) Chem. Zent. 73, n.390 (1920) Tunnidiffe and Rosenheim.

III EXPERIMENTAL

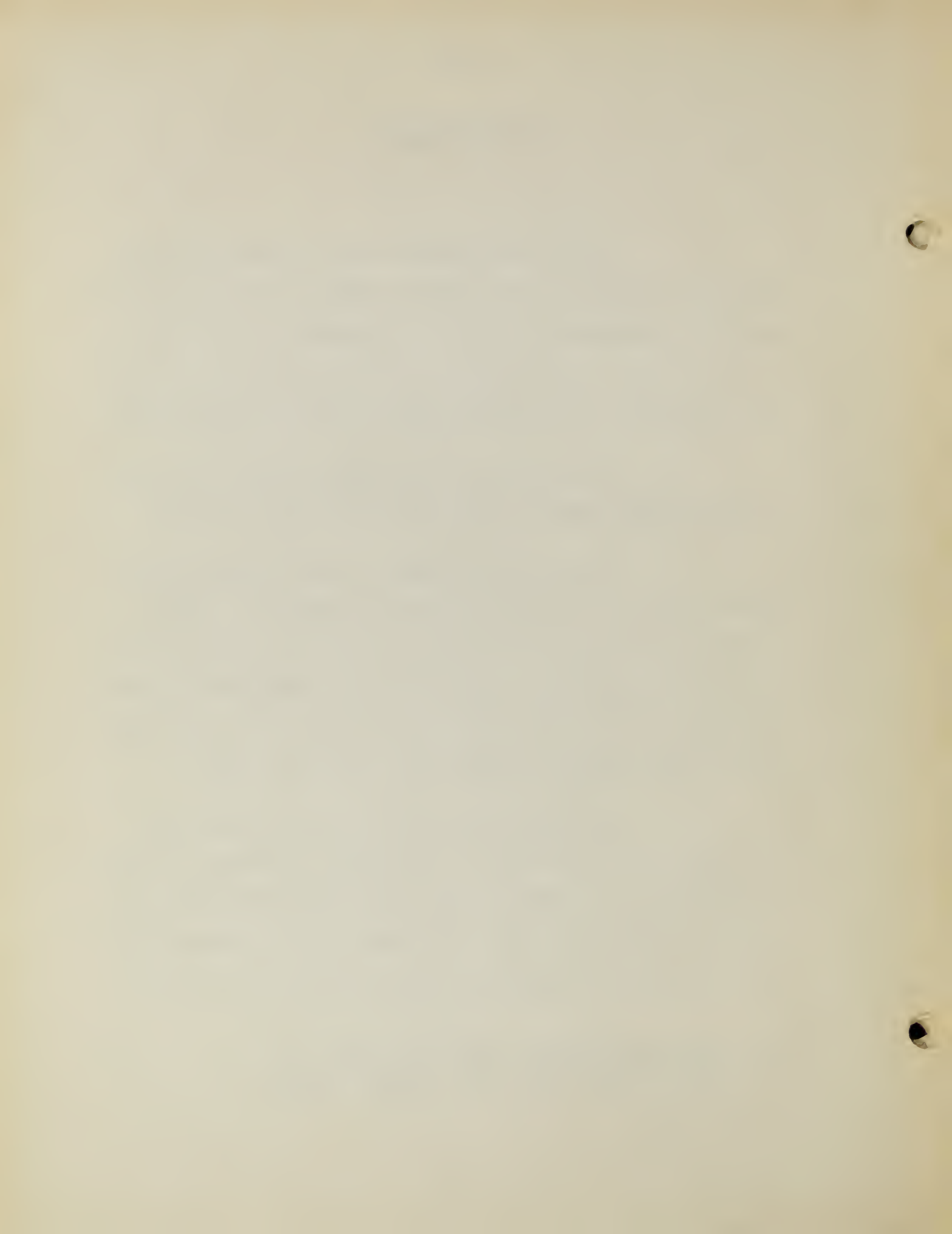
The pyrrole used in the following analyses was all prepared by the method of Blicke and Powers which has been described in detail in reference (7) in the historical part. The pyrrole so obtained varied in its purity from 80 % to 85 % after washing with acid and alkali.

The product of the Eastman Kodak Co., supposedly pure, gives on analysis a purity of but 90 %.

All the above figures were obtained by Dr. Holmes and he in turn succeeded in obtaining a product which is 95 % pure, using KOH to form the K salt in the purification process. This method is described in detail on page 2. This 95 % product was obtained but once, most of the other samples being from 1 % to 2 % lower.

All determinations of pyrrole were made by titration of the pyrrole, dissolved in 200 cc. of water containing 5 cc. ammonia water, with standard iodine solution. A precipitate of tetraiodopyrrole is obtained and the end point is detected by using starch as an outside

(7) Blicke and Powers: C.A. 22, p.778.
Ind. and Eng. Chem. 19, p.1334-5 (1927).



indicator. The characteristics of the reaction and the method of calculating the purity of the pyrrole are described in detail in the historical section on page 8.

Pyrrole from Glutaric Acid

On heating glutamic acid to 180° - 190° C. there is produced pyroglutamic acid. This acid on stronger heating gives a small amount of pyrrole. (19) Dr. Holmes investigated this process and found it to be of no value.

Pyrrole from Succinimide

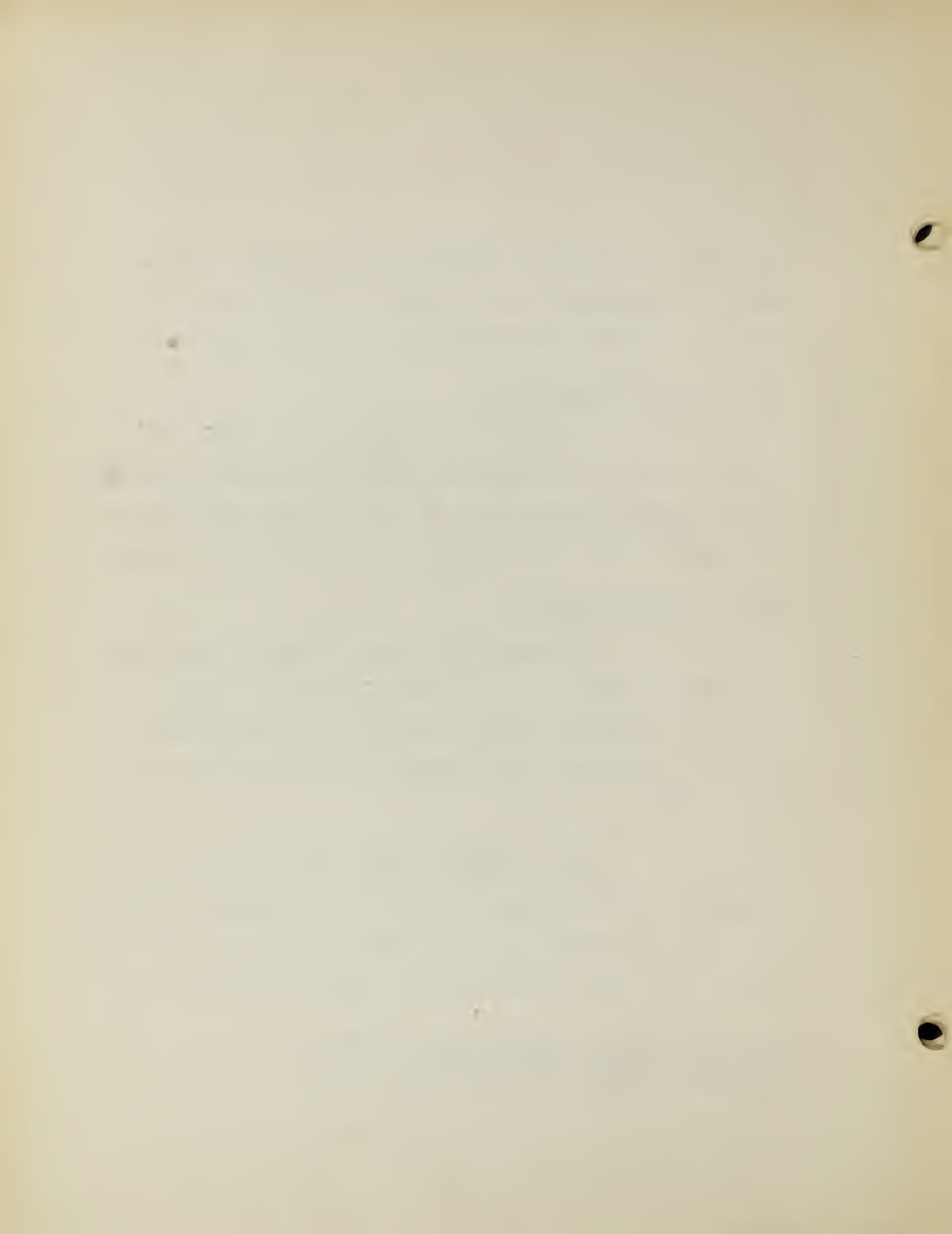
When succinimide is heated with zinc dust in a small retort a small amount of pyrrole is formed. (20) This process on investigation gave hardly enough pyrrole to produce a red coloration with a pine chip moistened in HCl.

It is thus apparent that, although these processes of obtaining pyrrole are of theoretical interest, they have no practical value in preparing pyrrole on a large scale. Michelman (21) mentions a method of preparing pyr-

(19) Ber. 15, 1342 (1882) Ludwig Haitinger.

(20) Ber. 13, 877 (1880) Bell.

(21) Ind. and Eng. Chem. 17, 471-2 (1925).



role from the destructive distillation of scrap leather which may be of commercial importance.

Purification by Means of K Salt Formation

Took 70 gms. of pyrrole and added an equal volume of toluene. Added 60 gms. of KOH and refluxed in a copper retort for about an hour. Separated the brown crystals which floated in the upper layer. Washed with ether and hydrolyzed. Distilled with steam. Separated the pyrrole by means of a separatory funnel. Dried overnight over KOH and fractionally distilled taking the liquid which boiled steadily at 129° C. (uncorrected). This was titrated with iodine solution.

Wt. Sample	cc. 0.509 I Sol.	% Pyrrole
0.1438	30.49	92.0
0.1700	35.24	91.9

Pyrrole exhibits very peculiar properties. It boils steadily at a constant boiling point, giving a clear homogeneous distillate. Yet on analysis the apparently pure product falls short of 100 %.

Formation of Potassium Salt in the Cold

A sample of pyrrole which had a purity of 90 % was allowed to stand three weeks over finely pulverized KOH. A dark solid formed on this which was the K salt of pyrrole. This was hydrolyzed and separated and dried over NaOH. Titration with iodine gave a low value:

Wt. Pyrrole	cc. I ₂	% Pyrrole
0.1436 gm.	29.06	86.0

There was not enough pyrrole for more than one analysis. This would show that the impurity in pyrrole reacts with potassium in the cold at a greater rate than pyrrole itself.

The original pyrrole standing three weeks alone analyzed as follows:

Wt. Pyrrole	cc. I ₂	% Pyrrole
0.1274	26.50	88.4
0.1290	26.90	88.6

This value was greater than the other by about 2.5 %, although the pyrrole was much darker.

Purification by Recrystallization

A sample of pyrrole which had darkened on standing was distilled. The clear colorless distillate was then frozen by cooling in a mixture of CaCl and ice (-26° C.).

The crystals were separated and allowed to melt and then titrated with iodine. The results:

Wt. Pyrrole	cc. 0.519 I	% Pyrrole
0.1397	29.12	85.8
0.1444	30.22	85.8

This method gives a purification of but 1 % on three successive crystallizations and would obviously require an infinite number to approach anywhere near 100 %, with a constant loss of material at each crystallization.

Purification by Distillation in Vacuo

A sample of crude pyrrole prepared by the ammonium mucate process was washed first with acid and then with alkali. This was refluxed in an iron retort with KOH for 45 minutes. The K salt so formed was washed with ether, allowed to stand over night and then hydrolyzed. The liberated pyrrole was distilled with steam and separated from the water with a separatory funnel. It was then dried over night with NaOH and distilled in vacuo. The results following were obtained: boiling point 43°-47° C. (18 mm.);

Wt. Pyrrole	cc. 0.508 N I	% Pyrrole
0.1698	36.13	90.5
0.1752	37.60	91.2

A disadvantage of using KOH is that but 10 % of the reacted pyrrole is recovered.

Pyrrole from Bone Oil

Distilled about two quarts of bone oil taking the fraction between 80° and 150° C.. Washed with alkali to remove acids and then with acid to hydrolyze nitriles and also to remove pyridine bases. Finally washed with water and distilled, taking the portion between 120° and 140° C.. Refluxed this with KOH. Separated the dark brown solid and washed with ether. Hydrolyzed. A thin film of oil remained which on drying with NaOH and distillation was too small for analysis. This further illustrates the fact that the use of the K salt for purification is of no use when dealing with small amounts of material.

Effect of Oxygen on Pyrrole

A sample of freshly distilled pyrrole which analyzed as 87.2 % pure was treated with a stream of oxygen



gas for five hours. The clear solution became first yellow, then brown, and finally black. However, upon analysis the change was found to be very slight.

Wt. Pyrrole	cc. I sol.	% Pyrrole
0.1440	29.36	87.0
0.1436	29.30	87.0

The change in color is evidently due to the formation of colloidal pyrrole black. A similar process takes place on exposure to the air, but it is not so rapid.

Summary

The purest pyrrole yet obtained is produced by hydrolyzing the K salt and then further purifying by fractional crystallization. This gives a purity of from 92 % to 94 %.

Recrystallization at the freezing point increases the purity but 1 %, giving a maximum of 86 %.

Distillation in vacuo has no apparent advantage. The product so obtained is 91 % pure.

The formation of the K salt at room temperature gives the same results as when formed at the boiling point.

The distillation of glutamic acid and the reduction of succinimide give but traces of pyrrole.

The ammonium mucate process gives a good yield, running as high as 50 %. This yield is obtained only when glycerine is added to the ammonium mucate.

We have every reason to believe that, with the methods of refinement used, the purest pyrrole possible has been produced.

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- (12) Bernardo Oddo; C.A. 5. p. 686; Gazz. Chim. Ital. 39, p.649-59.
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- (20) Bell; Ber. 13, p.877 (1880).
- (21) Ind. Eng. Chem. 17, p.471-2 (1925) Michelman.

The above abbreviations are standard and are authorized by the American Chemical Society.

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