The oxidation of uric acid with potassium chlorate and hydrochloric acid, pt I. : the preparation of alloxan and alloxantin, pt. II
by Morse R Waldorf

A THESIS Submitted in partial fulfillment of the requirements for the Degree of Master of Science in Chemistry
Montana State University

Abstract:
Alloxantin has been prepared from uric acid and the effects of different quantities of reagents has been studied. An average yield Of 12.7 grams alloxantin has been obtained from all runs, and an average of 14.5 grams alloxantin from runs in which conditions were most favorable for its preparation.

A possible new method for the preparation of alloxan directly from uric acid has been found, although more work along this line is necessary.

In, brief, certain conclusions may be drawn - 1. Temperature must be kept below 35°C.

2. Amounts of $KClO_3$ less than theoretical may be used.

3. Increasing the ion concentration does not materially aid the formation of alloxan during oxidation, while increase during the ruduction materially lowers the yield.

4. The Solution of alloxantin tends to become supersaturated. 5. Mechanical stirring both during the oxidation and during the reduction is beneficial.

6. There is no "burning up" of the uric acid during the oxidation to form. CO_2 and H_2O.

7. The addition of the $KClO_3$ in solution is more conducive to gentle oxidation and helps avoid the effect of "local" oxidation as. when the solid $KClO_3$ is used. The $KClO_3$ is added in a part of the water ordinarily added to the uric acid.

THE OXIDATION OF URIC ACID WITH POTASSIUM CHLORATE AND HYDROCHLORIC ACID.

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THE PREPARATION OF ALLOXAN
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I. INTRODUCTION

One of the earliest researches on uric acid was that of Liebig and Wöhler in 1838, in which it was shown that the acid and its derivatives may be considered as derived from barbituric acid, $C_4H_4O_3N_2$, the ureide of malonic acid. Of these derivatives of uric acid, those which may be considered as derived from the condensation of one molecule of urea with one molecule of a dibasic acid, thus giving rise to cyclic ureides, are the most important. Of these cyclic ureides, one of the most important is alloxan, or mesoxalyl urea, obtained by the oxidation of uric acid by cold nitric acid:

$$C_5H_4O_3N_4 + H_2O + O \longrightarrow C_4H_2O_4N_2 + CO(NH_2)_2$$

Alloxan is of considerable importance on account of its ready transformation into other ureides, one of which is alloxantin, $C_8H_4O_7N_4 \cdot 3H_2O$, a compound in which one of the water molecules is probably considered as constitutional.

$$2\ C_4H_2O_4N_2 + 2(H) \longrightarrow C_8H_4O_7N_4 + H_2O$$

Alloxantin was first prepared by Liebig and Wohler in

1838 by the reduction of alloxan with stannous chloride.[1] E.Fischer prepared alloxantin somewhat later by the reduction of alloxan with hydrogen sulphide.[2]

Uric acid, when oxidized with well-known oxidizing agents, yields various oxidation products. Under varying conditions, parabanic acid, $C_3H_2O_3N_2$, and alloxan, $C_4H_2O_4N_2$, are formed. The oxidation products depend largely upon two factors,(1) the oxidizing agent used, and (2) the nature of the solution, i.e.,whether acidic, basic, or neutral, the latter factor being the more important.[3]

Alloxan, once formed in solution, is difficult to remove in the solid state due (1) to the presence of the oxidizing agent employed and which remains in the solution, and (2) to the instability of the alloxan itself. Alloxan often reacts with excess oxidizing agents to form explosive mixtures, particularly during the usual process of evaporation under reduced pressure to remove the excess solution. For this reason it is not considered advisable to attempt to obtain the alloxan from the solution once it is formed. Several instances are recorded in the literature in which alloxan kept in glass containers has exploded while on the work shelf, due to the decomposition into carbon dioxide and water, the

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[1] Liebig and Wohler, Ann. 26, 266, (1838)
[2] E.Fischer, Ann. 215, 258,(1882)
[3] Biltz and Schauder, Jour.Prakt.Chem. 106, 108-72 (1923)

gas formed being unable to escape and the pressure created being of sufficient amount to break the glass.[4]

Due to this instability of the alloxan, and the difficulty frequently encountered during its preparation directly from uric acid, it is advisable to first prepare the reduction product of alloxan, alloxantin, which can be more easily separated in the solid state and which can be readily transformed into alloxan by direct oxidation.

Under proper conditions, alloxan in solution may be reduced to form alloxantin. The most satisfactory agent for this reduction to alloxantin has been found to be hydrogen sulphide, though Liebig and Wohler and others[5] recommend the use of stannous chloride. Hydrogen sulphide is more satisfactory than sulphur dioxide because it has a greater reduction potential than the latter.

At the suggestion of Dr.O.E.Sheppard and under his personal supervision, a series of experiments were performed to determine, if possible, the factors influencing the yields of alloxantin obtainable from alloxan prepared from uric acid, while still in solution.

The publication " Organic Synthesis" refused to publish a method, of Dr.Sheppard and W.W.Hartman, for the pre-

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[4] Bogert and Wheeler, J.A.C.S. 32, 809, (1910)
Franklin " 32, 1362,(1910)
Gortner " 33, 85, (1911)

[5] Liebig and Wohler, loc. cit.

paration of alloxan from alloxantin, for two reasons, (1)No satisfactory method was available for the preparation of alloxantin, and (2)The list price of alloxantin in the Eastman Kodak Company's catalog of Organic Chemicals is somewhat higher than the list price of alloxan.

Dr.C.S.Marvel, of the "preparations staff" of "Organic Synthesis" gave the following results from tests run at the University of Illinois using C.P. uric acid--

Run No.1 - 30 gr. uric acid ----- 9 gr. alloxantin
2 - 30 " " " ----- 12 " "
3 - 300 " " " ----- 86 " "
4 - 30 " " " ----- 17 " "
5 - 120 " " " ----- 32 " "

These results show an average yield of 10.9 grams of alloxantin from 30 grams of uric acid, and very poor consistency in the yields obtained.

The directions for the preparation of alloxantin in general use are those of Vanino.[6] In brief, they are as follows--

Place 15 grams of uric acid, 30 grams of concentrated HCl and 40 cc. of distilled water in a round bottom flask. Heat to 30°C. and add in small quantities 4 grams of $KClO_3$ during 45 minutes. Filter if necessary and add 30 cc. of water. Saturate the solution with hydrogen sulphide. Crystals of alloxantin and sulphur are formed. Filter and wash the pre-

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[6] Vanino, Preparativ Chemie, Vol.II,page 233.

cipitate with cold water. Dissolve the alloxantin in boiling water and filter to remove the insoluble sulphur. Cool the filtrate, and alloxantin separates out in the form of white needles and prisms.

The work done, then, has been a study of these directions. It was desired to prepare alloxantin in more satisfactory yields, and if possible, to find a method for the preparation of alloxan directly from uric acid; a method lacking the difficulties encountered when the alloxan remained in solution after oxidation.

II. DISCUSSION OF RESULTS

Alloxantin was prepared following the directions of Vanino, but different variables were studied-[7]

1/ Temperature - Control of the temperature of the oxidation of the uric acid and the reduction of the alloxan to discover the most satisfactory temperature for the greatest yield.

2/ Acid Concentration - Various acid concentrations were tried with the hope that an optimum oxidation potential to give the maximum yield of alloxan could be discovered.

3/ Amount of Oxidizing Agent - The quantity of $KClO_3$ used for the oxidation of the uric acid to alloxan was varied, with the view of studying the effect on the oxidation of the following-
   a. Theoretical amount
   b. Slight excess
   c. Slight amount less than theoretical

4/ Addition of Hydrogen Sulphide - A study of the amounts and methods of addition (rate, time, etc.) with the hope that this would give a better insight into the reduction of alloxan to form alloxantin.

5/ Dilution Prior to Reduction - The effect of the

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[7] In each case, the procedure and quantities of starting materials were the same. See EXPERIMENTAL PART- REGULAR RUN.

water or acid added prior to the addition of the hydrogen sulphide was studied in order to find the concentration of the acid necessary for the maximum reduction of the alloxan.

These variables will be discussed-

TEMPERATURE - The runs made with no control of the temperature showed that above 35°C. the yield of alloxantin was materially lowered, while below 35°C. no great difference was apparent, though a longer time was required for the completion of the oxidation reaction.

TABLE I

Run	Temp.	Time	Yield of Alloxantin
1	30-35°	1 hr.	17 grams
2	55	½ hr.	9 "
3	20	2 hr.	15 "
4	20	1 hr.	10 "

Note that in Run 4, the time element enters into the consideration of the final yield. At lower temperatures than 35°C. it is essential to allow enough time for the reaction to go to completion.

ACID CONCENTRATION - The oxidizing action of the $KClO_3$ is speeded up in the presence of excess HCl. More acid should aid the action of the $KClO_3$ on the uric acid, giving more complete oxidation and less time should be required for the reaction.

With this in mind, various amounts of HCl were added before the oxidation of the uric acid, and the effect of the acid concentration was noted. It was during these runs that it was found possible to prepare alloxan directly from uric acid. The method is described in another part of this paper.

TABLE II

Run	Grams HCl	Grams H_2O	Yield
A	100	40	15 gr. alloxan
B	80	60	14 " "
C	80	60	12 " "

On saturating the filtrate from the above the hydrogen sulphide, no appreciable amount of alloxantin was formed. Thus it will be seen that the presence of HCl in excess of the amount in Vanino's directions does nothing more than throw the alloxan out of solution as fast as it is formed.

AMOUNT OF OXIDIZING AGENT - The theoretical quantity of $KClO_3$ necessary for the oxidation of 30 grams of uric acid to alloxan is 7.25 grams. The Vanino directions call for 8.0 grams of $KClO_3$. It was thought that the excess $KClO_3$ was possibly being used to further oxidize the alloxan to parabanic acid. Three runs were made to determine the yields of alloxantin from 30 grams of uric acid, using a theoretical amount, a slight excess, and a slight amount less than the theoretical of the oxidizing agent.

TABLE III

Run	Temp.	Grams $KClO_3$	Yield	Grams uric acid not acted upon
18	25-30°	7.25	16 gr.	3.00
19	"	7.25	16 "	2.50
20	"	6.75	17 "	3.00

This would indicate that an amount of oxidizing agent less than the theoretical is entirely satisfactory for the oxidation to alloxan, even though the entire amount of the uric acid was not acted upon.

ADDITION OF HYDROGEN SULPHIDE - Since no particularly good means was available for accurately measuring the amount of hydrogen sulphide added during the reduction of the alloxan, a time factor was employed. A strong current of the gas was passed through the alloxan solution for 15-20 minutes in each case and the effects were noted. When the solution, after reduction and filtration, was allowed to stand overnight in an atmosphere of hydrogen sulphide, no more alloxantin was precipitated. Even with the hydrogen sulphide being added under a pressure of six or more inches of water, the yield of alloxantin was not increased.

TABLE IV

Run	Yield	Pressure
5	16	6" water
7	17	atmospheric

It is the opinion of the writer that the chief difficulty encountered during the preparation of alloxantin is the lack of complete reduction of the alloxan, since in every case, a portion of the liquid remaining after reduction with hydrogen sulphide, when applied to the skin gave the red coloration typical of alloxan. Further addition of hydrogen sulphide did not precipitate the alloxantin which should have been obtained from this alloxan.

In addition to this, a run was made on alloxan prepared from alloxantin by oxidation with fuming nitric acid. The conditions of acidity and the presence of KCl and water were followed as closely as possible, on the basis of a regular run made on uric acid. After passing in the hydrogen sulphide in the same manner as in regular runs, the alloxantin was filtered off, separated from the precipitated sulphur and allowed to settle overnight. The amount of alloxan taken for this run was 5.0 grams. The theoretical yield of alloxantin from 5.0 grams of alloxan monohydrate is 4.1 grams. Yield obtained was 2.0 grams or 50% of the theoretical.

$$\underset{\text{alloxan monohydrate}}{2\ C_4H_2O_4N_2{:}1\ H_2O} + H_2 \longrightarrow \underset{\text{alloxantin}}{C_8H_4O_7N_4} + H_2O$$

$$\frac{2 \times 160.0}{268} = \frac{5}{X}$$

<u>DILUTION PRIOR TO REDUCTION</u> - With the hope that a variation of the H^+ ion concentration during the reduction would give a more satisfactory yield of alloxantin, various amounts of

HCl and also of H_2O were added prior to reduction. It will be seen from Table V that an increase of HCl materially lowers the yield, as do amounts of water in excess of 150 cc. Vanino recommends 30 cc. water for 15 grams of uric acid. Dilution with water up to amounts of 150 cc. show no effect on the yield.

TABLE V

Run	Reagent added	Yield Alloxantin
9	300 cc. H_2O	11 gr.
10	150 cc. "	16
11	200 cc. "	14
12	100 cc. "	16
14	50 cc. HCl	8
15	100 cc. "	6
16	40 cc. "	10
17	80 cc. "	12

In runs 9-12 inclusive, the water added(total volume) included 60 cc. regularly added.

SUPERSATURATION OF SOLUTION BY ALLOXANTIN - In each case observed, the dissolved alloxantin showed a marked tendency to supersaturate the solution and only by prolonged stirring after cooling was this overcome. Though the solubility of alloxantin as given by Biilmann and Bentzon[8] is .2886 grams per 100 grams of water, as high as 11 grams (Run 9) were recovered from 1 liter of solution after vigorous stirring and scratching the sides of the beaker.

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8. Biilmann and Bentzon, Ber. 51, 522,(1918)

III. EXPERIMENTAL PART

PREPARATION OF ALLOXANTIN - REGULAR RUNS.

Throughout this paper, the term "regular runs" has been used to denote runs made in the following manner and upon which various amounts of reagents were used in order to study their effect on the yield of alloxantin.

To 30.0 grams of uric acid, 60.0 grams concentrated HCl and 80 cc. distilled water, in a 500 cc. round bottom flask, was added in small amounts, 8.0 grams of powdered $KClO_3$. The addition was made during 45 minutes to one hour, the temperature being kept below 35°C. When the reaction was complete, as shown by the solution of the solid, it was filtered, if necessary, and diluted with 60 cc. of water. Then a strong stream of H_2S was added, and soon the crystals of alloxantin and sulphur were precipitated. After 15-20 minutes'addition of the H_2S, the mass of crystals was cooled and filtered on a suction filter. The mass was washed with cold water and the solid placed again in the flask and boiling water was added to dissolve the alloxantin. The water was not boiled while in contact with the alloxantin, since too strong heating tends to decompose the alloxantin. A small amount of decolorizing carbon was added to insure a white product and the mixture was filtered to remove the sulphur and carbon. In all, 400 cc. of water was used for the extraction of the alloxantin. The filtrate containing the alloxantin was cooled overnight and the alloxantin came down in the form of white needles and prisms. Stirring after cooling materially aided in the counteracting of the tendency of the alloxantin to supersaturate the solution. The product was dried over sulphuric acid. In order to obtain more perfect mixing of the reagents, a motor stirrer was used in all these runs, both during the oxidation and during the reduction.

The uric acid used in all these experiments was C.P. Eastman product, one kilogram of which was given by the Eastman Kodak Company to the Montana State College Department of Chemistry for this work. The concentrated HCl and the $KClO_3$ used were C.P. and the water was regularly distilled.

For all runs made, 30.0 grams of the uric acid was taken, thus doubling the amounts of all the reagents in the Vanino directions.

The motor stirrer used was a small electric motor, having an r.p.m. of 1800. The stirring device proper was constructed of Pyrex glass tubing in the form of a T having three holes, one placed in the center of the cross member, providing in this manner more active mixing of the materials. The stirrer was held in the flask by means of a glass bearing slightly larger than the stirrer, through the stopper, and no lubrication was found necessary. Heat of contact proved too great for the use of vaseline as a lubricant, and a heavy stop-cock grease, Lubriseal, was found ver y satisfactory tho not essential.

Control of the speed of the motor was accomplished by means of a "salt-cell" rheostat. Into a glass jar was fitted a stopper containing two carbon electrodes, one of which was moveable. By varying the concentration of the salt solution, the speed of the motor was easily controlled. After long continuous use, the solution in the cell often heated sufficiently to cause the speed of the motor to rise, when it was merely necessary to decrease the electrode surface by raising the moveable electrode out of the solution a little way.

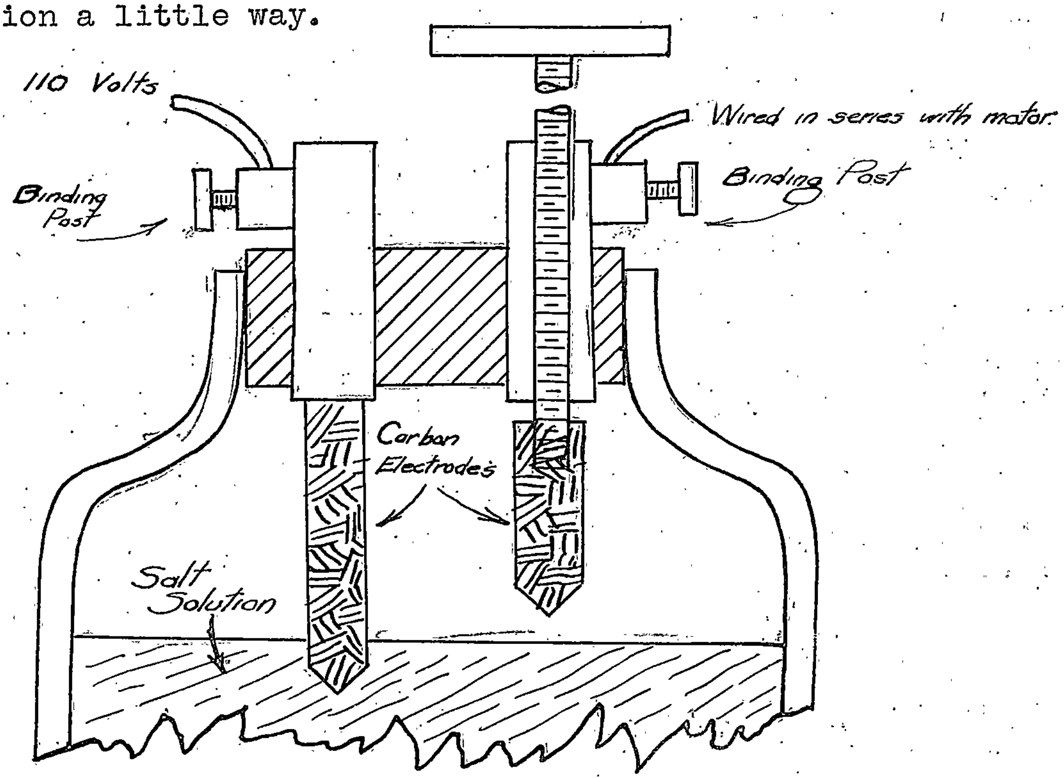

Figure 1

Diagram of Salt-Cell Rheostat.

Loaned for this work by Dr.W.M.Martin of the Montana Experiment Station,Bozeman,Montana.

EFFECT OF NOT CONTROLLING THE TEMPERATURE.

The mixture of uric acid and HCl tends to heat rapidly when the $KClO_3$ is added. To test whether this heating caused any decomposition into carbon dioxide and water(of the uric acid),a run was made as follows-

"Regular" quantities of uric acid, HCl and water were used and the gases generated during the reaction were drawn through a series of gas-washing bottles,(1) two bottles of KI solution in carbon tetrachloride,CCl_4, to absorb the chlorine gas liberated, and (2) a weighed bottle of NaOH solution. The entire amount of $KClO_3$, 8 grams, was added rapidly and the solution became clear in about 5 minutes, showing complete oxidation of the uric acid. The temperature rose rapidly to a maximum of 65°C. The weighed NaOH bottle gained only .08 grams, a quantity far too small to be considered as carbon dioxide coming from any "burned up" uric acid. On reduction, the solution yielded 11.0 grams of alloxantin, a smaller amount than usual due to the probable formation of parabanic acid. This was run No. 13.

A second run,No.23, gave 9.0 grams of alloxantin, and in this case the entire amount of the $KClO_3$ was added at once; the oxidation was complete in 4 minutes.

SOLUBILITY OF ALLOXAN.

Biilmann and Bentzon[9] determined the solubility of

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[9]. Biilmann and Bentzon, loc.cit.

alloxantin alone and of alloxantin in the presence of various amounts of alloxan. They found the solubility in water to be .2886 parts of alloxantin per 100 parts of water, but gave no data on the solubility of alloxan itself.

The solubility of alloxan in water at 25°C. has been determined during the course of this work.

EXPERIMENTAL PART.

Preparation of Alloxan:

57.0 grams of finely crystalline alloxantin and 80 cc. of water were placed in a large beaker fitted with a mechanical stirrer and the contents brought to a temperature of 50° C. on a water bath. Then 8 cc. of fuming nitric acid (sp.gr. 1.52) were added in a fine stream, keeping the temperature at 55°C. After the nitric acid had been added, and the temperature regulated at 55°C., the stirrer was stopped. Soon a vigorous reaction took place and large quantities of oxides of nitrogen were evolved. The beaker and contents were heated to 65°C. for about ten minutes, when the solid was nearly all in solution. The reaction mixture was placed in a large beaker and cooled overnight at about 0°C. or below. The large crystals of alloxan tetrahydrate were filtered off and sucked as free from water as possible, and then washed with ice water. These crystals were recrystallized three times from boiling water, but were not boiled with the water. After the third recrystallization, the material was placed over concentrated sulphuric acid for several days. The product was a white powder, the monohydrate, which decomposed about 169°C.

Solubility of Alloxan:

In small bottles fitted with ground glass stoppers was placed 20 cc. of distilled water and more than enough alloxan (15 grams) to completely saturate the solution. The bottles and contents were placed in a water bath carefully regulated to 25°C. and allowed to remain for two days. A portion of the supernatant liquid was pipetted off and taken to dryness under reduced pressure. At a pressure of 8 inches of mercury the solution boiled at 35-40°C. After it was dry, the small distilling flask (50 cc.) used was placed over concentrated sulphuric acid and taken to constant weight.

The results follow-

Ten cc. of solution-	
Wt. of flask and alloxan	24.2326 grams
Wt. of flask	21.0060
Wt. of alloxan in 10 cc.	3.2266
Five cc. of solution-	
Wt. of flask and alloxan	22.6215 grams
Wt. of flask	21.0060
Wt. of alloxan in 5 cc.	1.6155
" " " " 10 cc.	3.2310

Hence the solubility of alloxan in 100 parts (grams) of solution is- $\frac{(3.2266 \text{ plus } 3.2310)}{2}$ x 10 equals 32.288 grams.

NEW METHOD FOR THE PREPARATION OF ALLOXAN.

Vanino[10] gives a method for the preparation of alloxan by the oxidation of uric acid by chlorine in the presence of acetic acid.

It was found during these experiments that alloxan was thrown out of solution in the presence of an excess of HCl.

30 grams of uric acid, 100 cc. of concentrated HCl, and 40 cc. of water were placed in a round bottom flask fitted with a mechanical stirrer. 9 grams of $KClO_3$ were added in small amounts, keeping the temperature about 25°C. After about two hours constant mixing, the white solid was filtered through a suction filter and sucked as dry as possible. The solid readily dissolved in water. A test portion placed in a test tube with water and heated dissolved at once, showing that the uric acid,which is insoluble in water, had been oxidized. The solid could not have been parabanic acid, since this is soluble only 4.7 parts per 100 parts of water. If the test portion did not readily dissolve, the entire solid portion was again agitated for a longer period, using the same filtrate again, since it contained sufficient oxidizing agent. When the test portion showed the oxidation reaction was complete (solubility) the entire solid after filtering was placed in a dessicator over NaOH to remove the

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[10] Vanino, loc.cit. page 235

remaining HCl, and later dried over concentrated sulphuric acid. The solid had a decomposition point of about 170°C.

Three runs, A, B, and C, were made, and yields of 14-15 grams were obtained. This method may have possibilities although lack of materials and time prohibited further work along this line.

Obviously it is desireable to prepare alloxan directly from uric acid, thus eliminating the reduction to alloxantin and the subsequent reoxidation to alloxan. Further study of this reaction should undoubtedly prove of value.

TABLE SHOWING ALL RUNS.

Run	Yield of Alloxantin	Temp.	Time of Oxidation	Grams $KClO_3$	HCl added Before Ox.	HCl added Before Red.	H_2O added Before Red.
1	17 gr.	35°C.	1 hr.	8	60 cc.	none	60 cc.
2	9	55	30 min.	8	"	"	"
3	15	20	2 hr.	10	"	"	"
4	10	25	1 hr.	8	"	"	"
5	16	30	1 hr.	8	"	"	"
6	17	30	1 hr.	8	"	"	"
7	17	20	2 hr.	9	"	"	"
8	19.5	20	2 hr.	9	"	"	"
9	11	30	1 hr.	8	"	"	300 cc.
10	16	30	1 hr.	8	"	"	150 cc.
11	14	30	1 hr.	8	"	"	250 cc.
12	16	30	1 hr.	8	"	"	100 cc.
13	11	no control	5 min.	8	"	"	60 cc.
14	8	30	1 hr.	8	"	50 cc.	none
15	6	30	1 hr.	8	"	100 cc.	none
16	10	30	1 hr.	8	"	40 cc.	none
17	12	30	1 hr.	8	"	80 cc.	none
18	16	30	1 hr.	7.25	"	none	60 cc.
19	16	30	1 hr.	7.25	"	"	"
20	17	30	1 hr.	6.75	"	"	"
21	13	30	1 hr.	8	"	"	"
22	13.5	30	1 hr.	8	"	"	"
23	9	no control	4 min.	8	"	"	"
A	15 alloxan	25	2 hr.	9	100 cc.	"	"
B	14 alloxan	25	2 hr.	8	80 cc.	"	"
C	11.5 alloxan	25	2 hr.	8	80 cc.	"	"

IV. SUMMARY

Alloxantin has been prepared from uric acid and the effects of different quantities of reagents has been studied. An average yield of 12.7 grams alloxantin has been obtained from all runs, and an average of 14.5 grams alloxantin from runs in which conditions were most favorable for its preparation.

A possible new method for the preparation of alloxan directly from uric acid has been found, although more work along this line is necessary.

In brief, certain conclusions may be drawn -

1. Temperature must be kept below 35°C.

2. Amounts of $KClO_3$ less than theoretical may be used.

3. Increasing the H^+ ion concentration does not materially aid the formation of alloxan during oxidation, while increase during the ruduction materially lowers the yield.

4. The solution of alloxantin tends to become supersaturated.

5. Mechanical stirring both during the oxidation and during the reduction is beneficial.

6. There is no "burning up" of the uric acid during the oxidation to form CO_2 and H_2O.

7. The addition of the $KClO_3$ in solution is more conducive to gentle oxidation and helps avoid the effect of "local" oxidation as when the solid $KClO_3$ is used. The $KClO_3$ is added in a part of the water ordinarily added to the uric acid.

The writer here wishes to express his appreciation and thanks to Dr.O.E.Sheppard for his guidance and personal inspiration during the course of this work.

Waldorf, M. R.

The oxidation of uric acid with potassium chlorate and hydrochloric acid.