

Synthesis of D-glucosaminic acid *

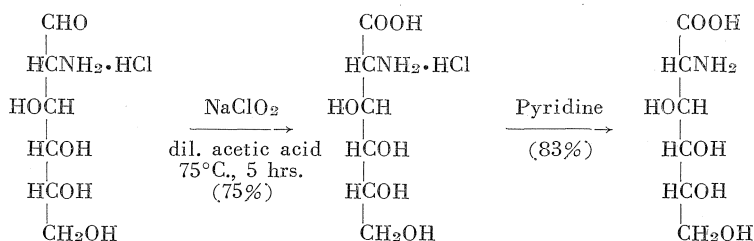
By

MITUO EBATA

(Received September 5, 1955)

It is well known that D-glucosamine hydrochloride can be oxidized to D-glucosaminic acid hydrochloride by appropriate oxidizing agents. Thus, E. Fischer¹⁾ performed the oxidation with bromine and obtained a 20-40% yield of the product. Pringsheim²⁾, on the other hand, employed Ag₂O as an oxidizing agent and succeeded in producing a yield of 54%. However, the yields of the hexosaminic acid in these two methods can not be conceived of to be very high.

We have recently been able to show that sodium chlorite, if it is used in slightly acidic media, is an excellent for the oxidation of D-glucosamine hydrochloride to D-glucosaminic acid hydrochloride; the yield of product being as high as 75%. Free D-glucosaminic acid could readily be obtained in 83% yield by treating the hydrochloride with pyridine and alcohol.



In order to increase the yield of the hexosaminic acid it is important to eliminate the possible deamination of D-glucosamine due to oxidizing agents. This is especially true when chlorite is used as the oxidizing agent, since Wieland *et al.*³⁾ have shown that glutamic acid is oxidatively deaminated to α -ketoglutaric acid by the action of chlorite in alkaline solution. It has, however, been known that the oxidizing power of chlorite in acidic media can be successfully used in removing impurities from crude preparations of glutamic acid⁴⁾. Therefore, we decided to choose dilute acetic acid as the reaction medium so as to minimize the undesirable deamination reaction. It was indeed found that no appreciable deamination took place in the acetic acid medium when a theoretical amount (0.5 mole) of chlorite was employed. When, however,

* Presented at the Meeting of Hokuriku Division of the Chemical Society of Japan, October, 1954, at Toyama.

** Department of Chemistry, Faculty of Science, Kanazawa University.

excess amounts of the oxidizing agent were used, the formation of some sirupy by-products was observed. It is not yet certain if these by-products were formed by the deamination. Glucose was found not to be attacked by chlorite under similar conditions.

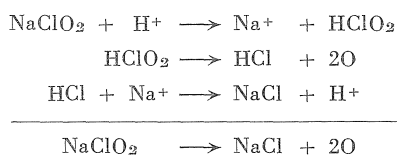
In Table I are summarized typical results of the oxidation experiments in which 0.5-0.6 mole equivalents of chlorite were used in dilute acetic acid for 1 mole equivalent of D-glucosamine hydrochloride. In each experiment listed in the table the mixture was heated to 80-90°C for 30 minutes at the end of the reaction to assure

Table I
Oxidation of D-glucosamine hydrochloride under various conditions

D-Glucosamine hydrochloride	Amount of sodium chlorite	Volume of reaction mixture	Temp.	Time	D-Glucosaminic acid hydrochloride	Yield
g.	g. (mole)	ml.	°C	hr.	g.	%
10	2.5 (0.50)	63	20	24	8.0	74
10	2.5 (0.50)	57	20	24	8.4	79
10	2.7 (0.60)	47	20	24	6.7	63
20	5.8 (0.60)	56	75	2	16.3	75
50	13.5 (0.55)	140	20	40	40.3	75
100	29.0 (0.60)	280	20	24	76.0	71
100	29.0 (0.60)	280	75	5	78.0	73

the complete oxidation. As can be seen, the yields of D-glucosaminic acid hydrochloride were 63-79% under the condition employed. Of course, longer periods of time were required at lower temperatures to complete the reaction.

The oxidizing power of sodium chlorite in acidic solutions may be expressed by the following equations:



As is indicated in these equations, a relatively large amount of sodium chloride is accumulated during the oxidation in the reaction mixture. This may interfere the isolation of product and consequently lower its yield. This consideration led us to an attempt to use chlorine dioxide (ClO_2), instead of sodium chlorite, as an oxidizing agent.

Chlorine dioxide was generated from sodium chlorite by a mixture of acetic acid and acetic anhydride, absorbed in a suitable amount of water, and used like sodium chloride solution in the above experiments. By the use of such a solution as an oxidizing agent, the isolation procedures of D-glucosaminic acid hydrochloride became

easier owing to the absence of sodium chloride in the reaction mixture. On the other hand, a larger amount of sodium chlorite was required for this purpose. Furthermore, any appreciable differences in the yields of product could be observed between the oxidation with sodium chlorite and that with chlorine dioxide solution. Table II shows some examples of results obtained by the use of chlorine dioxide solution.

Table II
Oxidation of *D*-glucosamine hydrochloride with chlorine dioxide solution.

D-Glucosamine hydrochloride	Chlorine dioxide	Volume of reaction mixture	Temp.	Time	D-Glucosaminic acid hydrochloride	Yield
g.	g. (mole)	ml.	°C	hrs.	g.	%
10	1.75 (0.55)	37	20	24	3.2	78
10	1.75 (0.55)	45	20	24	7.0	65
10	1.75 (0.55)	40	70	2	7.5	70

In all the experiments described above, unchanged *D*-glucosamine hydrochloride after the first oxidation procedure was collected and subjected to a second oxidation. The yields recorded in Tables I and II represent the total amount of *D*-glucosaminic acid hydrochloride obtained in the both oxidations.

Experimental

Sodium Chlorite—"Silblite" manufactured by Hodogaya Soda Co. Ltd., was used without purification. The purity of this preparation was 85.4% and the main impurity was sodium chloride.

D-Glucosaminic acid hydrochloride—(a) 100 g. of *D*-glucosamine hydrochloride and 200 ml. of water were placed in a 500 ml. three-necked flask. The content was heated until the hexosamine chloride was dissolved. To the solution were added 10 ml. of glacial acetic acid, and the mixture was kept at 75°C with stirring throughout the reaction. 29 g. of sodium chlorite (85.4% purity) in 70 ml. of water were then added dropwise to the reaction mixture. After 5 hours of reaction, the temperature was raised to 90°C with the aid of a steam bath and stirring was continued for another 30 minutes. The mixture was then concentrated to dryness under reduced pressures, and the residue was dissolved in 120 ml. of water. When the solution was kept at room temperature for several hours, about 30 g. of unchanged glucosamine hydrochloride were precipitated which were removed by filtration. *D*-Glucosaminic acid hydrochloride was obtained from the filtrate by concentration to dryness under reduced pressures. The crude hydrochloride was recrystallized from water to remove sodium chloride. The unchanged hexosamine hydrochloride was again oxidized by the same procedure. The yield of *D*-glucosaminic acid hydrochloride was 75%.

Analysis	C	H	N	Cl
found	32.17%	6.36%	6.03%	14.81%
calcd. for C ₆ H ₁₄ O ₆ NCl	31.23	6.12	6.08	15.37

(b) 1.75 g. of chlorine dioxide, generated from sodium chlorite by a mixture of acetic acid and acetic anhydride (1;1), were absorbed in 40 ml. of water at 0°C. This solution was added to 40 ml. of an aqueous solution containing 10 g. of D-glucosamine hydrochloride and 2 ml. of acetic acid, and the mixture was allowed to stand at 20°C for 24 hours. It was then heated to 90°C for 30 minutes. The isolation of the product was as above. The unchanged material was subjected to a second oxidation at 20°C for 24 hours and treated as above. The yield of the product was 78%.

D-Glucosaminic acid—10 g. of D-glucosaminic acid hydrochloride were dissolved in 15 ml. of water and 3.5 g. of pyridine were added. When 30 ml. of 99% alcohol were poured to the mixture, free D-glucosaminic acid was precipitated. This was collected, washed with alcohol, and dried *in vacuo*. Yield, 7.0 g. (83%).

Analysis	C	H	N
found	36.22%	6.73%	7.26%
calcd. for C ₆ H ₁₃ O ₆ N ₆	36.92	6.66	7.18

Thanks are due to Dr. J. Noguchi, Professor of the Division of Organic Chemistry, Department of Chemistry, for his kind guidance and valuable advice throughout this work.

The author is also indebted to Dr. H. Yuki, Faculty of Science, Osaka University, for the carbon and hydrogen analyses.

References

- 1) E. Fischer, and F. Tiemann, Ber., 27, 138 (1894)
- 2) H. Pringsheim, and G. Ruschmann, Ber., 48, 680 (1915)
- 3) T. Wieland, C. Vogelbach, and H. J. Bieling, Ann, 561, 116 (1948)
- 4) H. W. Dorn, U. S. 2,419,255 Apr. 22 (1947)