THE REDUCTION OF AMINOSORBITOL HYDROCHLORIDE WITH HYDRIODIC ACID

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Inasmuch as attempts at the reduction of glucosaminic acid to optically active norleucine have met with great difficulties, it was decided to select a different approach to the solution of the problem of the configuration of glucosamine; namely, the conversion of glucosamine into 2-aminopentahydroxyhexane[1] (2-aminosorbitol) in the hope that by reduction with hydriodic acid the hydroxyamine would be converted into 2-aminohexane. Thus a direct answer to the configuration of *d*-glucosamine would be furnished, since the configuration of 2-aminohexane has been correlated by Levene and Mardashew[2] to that of 2-aminocaproic acid. The work has not yet been completed but the results so far obtained are reported here in view of the activities of other laboratories on the question of the configuration of *d*-glucosamine.

The product so far obtained by reduction with aqueous hydriodic acid has the composition of 2-aminohexene oxide; on acetylation it forms a monoacetyl derivative which no longer possesses a free amino group but on deacetylation the amino group becomes free again. This acetylated substance possesses no ethylenic linkage and is not a double molecule formed by union of 2 monohydroxyaminohexane molecules, since a molecular weight of 166 was obtained by the Rast method. The composition of of the substance, therefore, is $C_6H_{13}ON \cdot HCl$.

Further reduction of this substance is now in progress. Also, other methods of arriving at the configuration of the 2-aminopentahydroxyhexane are now in progress.

[1] Levene, P. A., and Christman, C. C., *J. Biol. Chem.*, **120**, 575 (1937).

[2] Levene, P. A., and Mardashew, S., *J. Biol. Chem.*, **117**, 707 (1937).

It may be mentioned that reduction of the hexaacetate of 2-aminopentahydroxyhexane with hydriodic acid in glacial acetic acid resulted in a 2-aminomonohydroxyhexane directly and its acetate by acetylation of the substance from the mother liquor. Unfortunately the yield was so small that the experiment could not be repeated with sufficiently consistent success to warrant further experimentation.

EXPERIMENTAL

Treatment of Aminosorbitol Hydrochloride with Hydriodic Acid—A solution of 5 gm. of aminosorbitol hydrochloride[1] in 60 cc. of hydriodic acid (sp. gr. = 1.70) was heated in a sealed tube during 5 hours at a temperature of 125°. The furnace and tube were allowed to cool for 18 hours, after which the tube was opened and the contents diluted with water to 180 cc.

The solution, containing much free iodine, was evaporated under diminished pressure to about 75 cc. and then diluted to 1000 cc. with water. The major portion of the free iodine and hydriodic acid was removed by adding lead carbonate and then filtering off the lead salts. (In this and in all the following operations the precipitates were shaken with water and then filtered, the filtrates being combined with the original filtrate.) The remainder of the iodine and hydriodic acid was removed with silver carbonate in the presence of free sulfuric acid. After removal of all the silver and lead ions with hydrogen sulfide, the solution was made alkaline and steam-distilled into dilute hydrochloric acid. The distillation was continued until the distillates were no longer alkaline to red litmus paper. The acid solution of the distillate was evaporated under diminished pressure to a sirup, which was dried by repeated addition and concentration of benzene and absolute ethyl alcohol. The dried sirup was dissolved in absolute ethanol, filtered from the ammonium chloride, and an equal volume of ether added to the filtrate. More ammonium chloride separated out after standing in the refrigerator overnight and this was also filtered off. The sirup obtained by concentration of this filtrate was used in the next experiment.

Preparation of Crystalline Chloroplatinate from Reaction Product Obtained by Treatment of Aminosorbitol Hydrochloride with Hydriodic Acid—The dried sirup from the previous experiment was

dissolved in a small volume of absolute ethanol and an excess of chloroplatinic acid added. Ammonium chloroplatinate, if present, was removed by filtration and the filtrate concentrated to half its volume in a vacuum desiccator.

In this way a crop of crystals was obtained which were recrystallized by dissolving in warm absolute ethanol, filtering, and then allowing the filtrate to evaporate spontaneously in a desiccator. The average yield obtained in several experiments was about 1.5 gm. (from 5 gm. of aminosorbitol hydrochloride).

This chloroplatinate had a composition which agreed fairly well with that calculated for the chloroplatinate of an aminohexene oxide. However, the analytical data varied with different preparations (indicating the presence of other material). By repeated careful recrystallization a product was obtained which had the following composition.

4.780 mg. substance: 3.902 mg. CO_2 and 1.895 mg. H_2O

$C_{12}H_{28}O_2N_2PtCl_6$.	Calculated.	C 22.48, H 4.5
	Found.	" 22.26, " 4.4

Preparation of 2-Aminohexene Oxide Hydrochloride—9 gm. of the once recrystallized chloroplatinate (from the previous experiment) were dissolved in 100 cc. of warm water. Hydrogen sulfide was passed into the solution for 3 hours and the mixture allowed to stand overnight in the presence of hydrogen sulfide. The platinum sulfide was removed by filtration and well washed with warm water. The combined filtrates were concentrated to 25 cc., treated with charcoal, and then filtered.

This filtrate was concentrated to a dry crystalline mass which was dried further by frequent addition and evaporation of benzene and absolute alcohol. The product was obtained in the pure state by recrystallizing from a small volume of absolute ethanol. Yield 2.0 gm. All the mother liquors were concentrated to dryness. Yield 1.4 gm.

The pure substance had a melting point of 217–218° and a specific rotation of $[\alpha]_D^{25} = \frac{-0.30° \times 100}{2 \times 2.54} = -5.9°$ (in absolute ethanol). It is soluble in alcohol and water but practically insoluble in ether, acetone, chloroform, and pentane.

The compound had a composition agreeing with that of 2-aminohexene oxide hydrochloride.

3.981 mg. substance: 6.914 mg. CO_2 and 3.330 mg. H_2O
6.078 " " : 0.498 cc. N_2 (748 mm. at 28°)
7.478 " " : 4.90 cc. 0.01 N $AgNO_3$
$C_6H_{13}ON \cdot HCl$. Calculated. C 47.49, H 9.3, N 9.20, Cl 23.08
Found. " 47.36, " 9.36, " 9.14, " 23.26

Attempted Catalytic Hydrogenation of 2-Aminohexene Oxide Hydrochloride—200 mg. of crystalline 2-aminohexene oxide hydrochloride dissolved in 30 cc. of absolute ethanol were shaken with Adams' catalyst and hydrogen for several hours. The catalyst was removed by filtration and the filtrate concentrated to about 4 cc. Unchanged starting material was isolated from this solution by the addition of ether, as indicated by the melting point (217–218°) and analysis, thus indicating the presence of an oxygen ring and the absence of any double bonds.

Acetylation of 2-Aminohexene Oxide Hydrochloride—Pure 2-aminohexene oxide hydrochloride (0.6 gm.) was refluxed for 2 hours with 10 cc. of acetic anhydride and 1 gm. of freshly fused sodium acetate. The mixture was allowed to stand overnight at room temperature and then concentrated to dryness under reduced pressure. All traces of acetic anhydride and acetic acid were removed by repeated concentrations with the addition of small volumes of benzene.

The crystalline mass was now treated with 15 cc. of chloroform and filtered. The filtrate was dried with sodium sulfate and concentrated to a dry mass of crystals. The product was recrystallized by dissolving in an acetone-ether mixture and then adding a small volume of pentane. Yield 0.55 gm. The substance was pure after three such recrystallizations and had a melting point of 142–143°. It had the following specific rotation.

$$[\alpha]_D^{26} = \frac{+0.29° \times 100}{2 \times 3.56} = +4.1° \quad \text{(in absolute ethanol)}$$

The substance showed no perceptible rotation in chloroform solution. It is soluble in acetone, ether, chloroform, water, and benzene but is practically insoluble in pentane.

The material had a composition agreeing with that of an N-acetylaminohexene oxide. It contained no free amino nitrogen and a Rast molecular weight determination gave a value of 166, which is in accord with the calculated value of 157.

4.594 mg. substance: 10.310 mg. CO_2 and 3.897 mg. H_2O
5.994 " " : 0.455 cc. N_2 (759 mm. at 25°)
5.402 " " : 3.371 " 0.01 N $Na_2S_2O_3$*

$C_8H_{15}O_2N$.	Calculated.	C 61.14, H 9.6, N 8.9, $COCH_3$ 27.39
	Found.	" 61.20, " 9.5, " 8.7, " 26.83*

Action of Hydrogen Iodide in Glacial Acetic Acid on Aminosorbitol Hydrochloride—Two sealed tubes, each containing 5 gm. of aminosorbitol hydrochloride, 0.5 gm. of phosphonium iodide, and 40 cc. of a solution composed of equal parts by weight of dry hydrogen iodide and dry glacial acetic acid, were heated at 125° for 5 hours. The materials were united and the product isolated in the same way as in the previous experiment with hydriodic acid.

The dried, steam-distilled sirup was treated with chloroplatinic acid but only about 0.2 gm. of crystalline chloroplatinate was obtained.

Action of Hydrogen Iodide in Glacial Acetic Acid on 2-Aminosorbitol Hexaacetate[1]—To 6 gm. of pure 2-aminosorbitol hexaacetate were added 25 cc. of a solution composed of equal parts by weight of dry hydrogen iodide and glacial acetic acid, and the mixture sealed in a bomb tube. After heating at 125° during 4 hours and then cooling in the furnace for 12 hours, the tube was opened and the contents diluted with 150 cc. of water.

Sulfur dioxide was passed into the solution until all the free iodine had been consumed. The excess sulfur dioxide was removed by aspirating with air and the sulfuric acid was removed quantitatively by the addition of barium hydroxide solution. This solution was then concentrated to dryness under diminished pressure at 40°, and the residue was dissolved in 100 cc. of methyl alcohol and reduced with hydrogen and Raney's catalyst.

When the reduction was complete, the catalyst was removed by filtration and the methyl alcohol solution steam-distilled in alkaline solution until the final distillate was no longer alkaline to red litmus. The distillate was collected in a solution of hydrochloric acid in order to prevent the loss of the volatile free base.

* This substance has the acetyl group bound so firmly to the nitrogen that the time of digestion in the acetyl determination had to be increased (from 3) to 6 hours. This is the first compound which Dr. Elek has found to require more than 3 hours for completion of the deacetylation.

The acid distillates were then concentrated to dryness under reduced pressure at 40° and a small amount of crystalline material was obtained by dissolving the partially crystalline residue in acetone and then adding ether. Yield 0.05 gm. This was recrystallized twice from acetone and then melted at 86–88°.

The substance had the following composition.

4.299 mg. substance: 7.302 mg. CO_2 and 3.995 mg. H_2O; 2% ash
5.120 " " : 0.394 cc. N_2 (760 mm. at 27°)
$C_6H^{15}ON \cdot HCl$. Calculated. C 46.9, H 10.45, N 9.12
Found (ash-free). " 47.1, " 10.5, " 8.92

The acetone-ether mother liquors were combined and evaporated to dryness. The dry sirup was refluxed for 1 hour with a mixture of anhydrous sodium acetate and acetic anhydride, and then kept at room temperature for 1 day. This mixture was now concentrated to dryness and the product extracted with chloroform. The chloroform extract was washed with three small portions of water and then dried with anhydrous sodium sulfate.

The product partly crystallized after the removal of the chloroform and was completely crystallized from ether and pentane. Yield 0.25 gm. After one more recrystallization from ether and pentane the substance melted at 77–78° and had the following specific rotation.

$$[\alpha]_D^{26} = \frac{+1.62° \times 100}{1 \times 4.08} = +39.7° \quad \text{(in chloroform)}$$

This material had the following composition.

4.416 mg. substance: 9.590 mg. CO_2 and 3.790 mg. H_2O
6.420 " " : 6.36 cc. 0.01 N $Na_2S_2O_3$
$C_{10}H_{19}O_3N$. Calculated. C 59.9, H 9.5, $COCH_3$ 42.8
Found. " 59.2, " 9.6, " 42.6