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The synthesis of 1-DIAZO-2, 3, 4, 5, 6-pentahydroxyhexane and its derivatives

BOSTON UNIVERSITY

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Thesis

THE SYNTHESIS OF 1-DIAZO-2,3,4,5,6-PENTAHYDROXYHEXANE AND ITS DERIVATIVES

by

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of Master of Arts.

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ACKNOWLEDGEMENT

I wish to express by gratitude to Professor J.P.Mason for his kindness and consideration.

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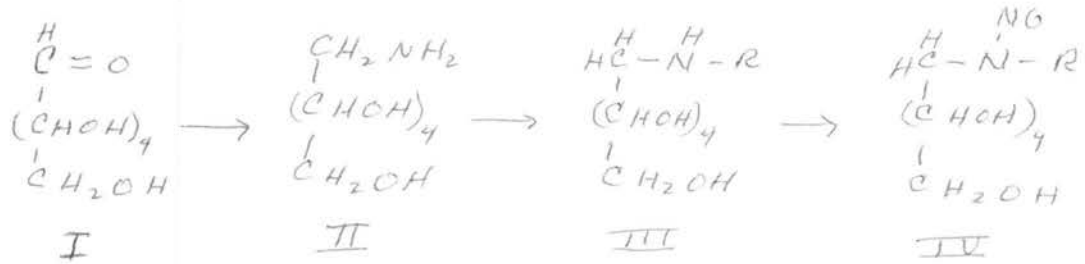
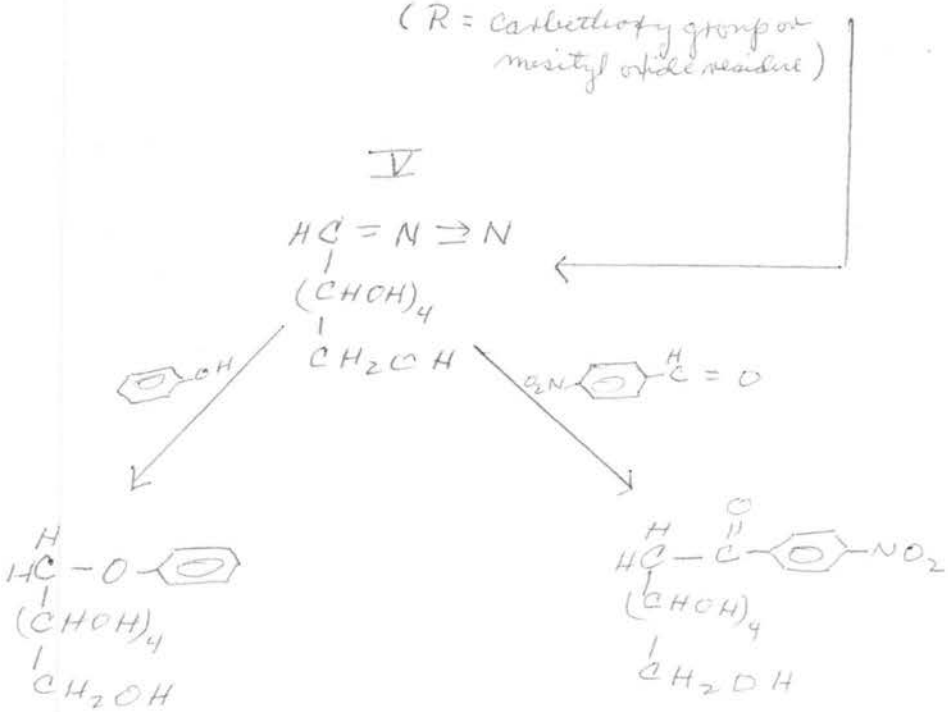
Part III -

INTRODUCTION

The synthesis of 1-diazo-2,3,4,5,6-pentahydroxyhexane was investigated via the following reactions:



I → II → III → IV



The main problem involved in this work was to find a feasible route to the amine and subsequently to the diazo compound. Actual isolation of the diazo compound was not attempted, as it was suspected to be quite unstable. Therefore, the diazo compound was identified by the product of its reaction with a phenol.

An important aspect of this work is the possibility of using the diazo compound as a solubilizer for medicinal drugs. Since the nitroso compound can be decomposed catalytically (hydroxyl ions) to generate the diazo compound which in turn reacts with phenols, carboxylic acids, and aldehydes with the loss of nitrogen, it should be possible to effect the solubility of any water insoluble drug containing the aforementioned groups. The product obtained should be physiologically safe in that when it is hydrolyzed by the system, a polyhydroxy compound related to carbohydrates would be left which would probably be harmless to any biological system.

The following thesis is divided into three parts. Part I deals with attempts at a preparation of compound III from compound I. Part II considers different syntheses of compound II from compound I. Part III deals with the preparation of compound V and its derivatives from compound IV.

PART I

Attempted Preparations of Polyhydroxyalkylurethane Compounds

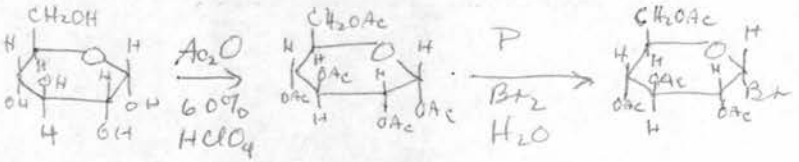
A. Discussion

One of the early routes investigated as a possible means of diazo synthesis involved preparing urethane derivatives of tetra-O-acetyl-α-D-glucopyranosyl bromide. The chief means employed involved:

1. Reaction of the tetra-O-acetyl-α-D-glucopyranosyl bromide with the sodium salt of urethane.
2. Condensation of the tetra-O-acetyl-α-D-glucopyranosyl bromide with silver cyanate to form the isocyanate which, when refluxed with absolute ethanol, should form the urethane product.

For both these methods a large amount of tetra-O-acetyl-α-D-glucopyranosyl bromide was prepared.[1,2]

Section I. The Preparation of Tetra-O-acetyl-α-D-glucopyranosyl Bromide.



The procedure followed in this synthesis is directly that of M.Barczai-Martos and F. Korosy.[1]

To a mixture of 400 ml. of acetic anhydride and 2.4 ml. of 60 percent perchloric acid, 100 g. of anhydrous D-glucose

(Baker Analyzed) was added over a period of 30 minutes. The temperature was kept at 30-40° C to avoid caramelization and to maintain a steady reaction rate. After cooling the solution in ice, 30 grams of red phosphorus was added. This was followed by the gradual addition of 180 g. (60 ml.) of bromine while keeping the temperature below 20° C and constantly stirring the mixture.

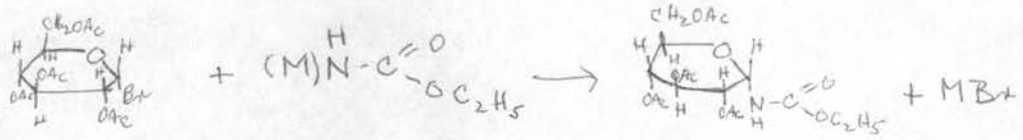
With careful mixing and cooling, 36 ml. of water (90 percent of the theoretical) was introduced over a 30 minute period. The stoppered vessel was kept at room temperature for two hours and 300 ml. of chloroform was added. After pouring the mixture into 800 ml. of ice water, the chloroform layer was separated, filtered to remove the excess phosphorus, and washed three times with equal volumes of ice water. The water in turn was extracted with 30 ml. of chloroform. A final extraction of the chloroform with a saturated sodium bicarbonate solution adjusted the pH of the chloroform layer to six.

The yellow solution was dried and decolorized simultaneously (for one hour) with calcium chloride, 5 g. of charcoal and 0.5 g. of sodium bicarbonate. This procedure was repeated and the solution was evaporated to dryness on a steam bath under vacuum keeping the temperature below 60° C. The hard crystalline residue was dissolved in anhydrous ether, but on cooling gave impure crystals melting at 84-6° C, with excess Norit still in the mother liquor. Therefore the mixture was redissolved in a liter

of ether, filtered through Supercel and left to crystallize. On cooling, feathery crystals separated from the liquor which melted sharply at 85°C. (literature: m.p. 87°C) These crystals, on drying, proved to be unstable. The product began turning dark brown. A gas was emitted which had an unpleasant odor similar to that of acetic acid and which fogged when breathed upon as hydrogen bromide. It was concluded that the gas could possibly be acetyl bromide and the solid was recrystallized and kept under ether until used. The yield obtained was 92 percent. (literature: 85%)

Section II. Attempted Reactions of Tetra-O-acetyl-α-D-glucopyranosyl Bromide Leading to the Urethane Derivatives.

Method 1. The Reaction of Metal Urethides with Tetra-O-acetyl-α-D-glucopyranosyl Bromide



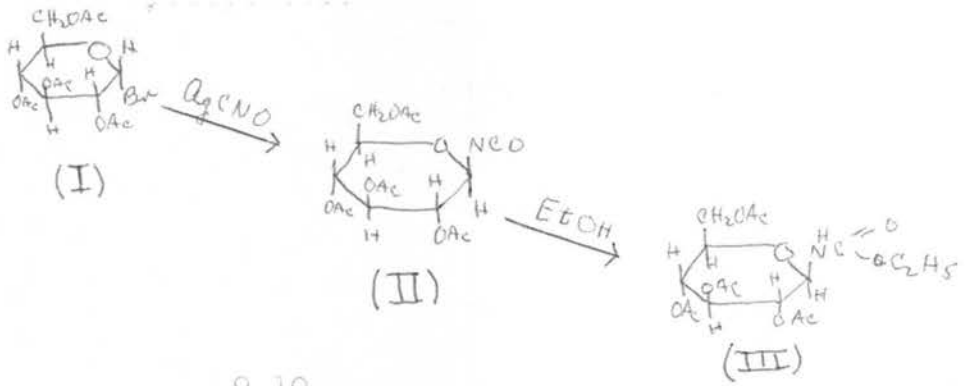
(where M is the metal of the urethide)

This plan involved the preparation of the urethane derivative of tetra-O-acetyl-α-D-glucopyranosyl bromide as a means of sidestepping the amine formation and proceeding directly to the carbamate derivative which could then be nitrosated in a procedure analogous to that of the amine. The choice of metal (M) for the urethane derivatives included the following possibilities. The potassium,[3,4] sodium,[6-8] silver,[3-4] and mercury[8] salts are known. The potassium salt was found only in the hydrated form, $KNHCO_2CH_2CH_3 \cdot 2\ H_2O$. The reaction was carried out using sodium urethide. The procedure of B.Kraft[6] was followed almost exactly.

Ten grams (0.11mole) of ethyl carbamate were dissolved in 70 ml. of anhydrous ether to give a clear solution. Nine and three tenths grams (0.11 mole) of sodium were added slowly to the ethereal solution of ethyl carbamate and as the sodium reacted, a white solid separated out. The reaction was continued overnight and 10 g. of white, powdered sodium urethide was obtained (82 percent yield).

The first reaction medium chosen was a water system, but it was found that the sodium salt hydrolyzed in water and no reaction took place. The next solvent chosen was N,N-dimethylformamide in the hope that it would afford a convenient means of measuring the progress of the reaction as sodium chloride is insoluble in this solvent and should separate out as formed. However, no product separation occurred during this reaction and on evaporation to dryness, a yellow-orange syrup remained which proved to be a mixture of the starting materials. Some work was done repeating the reaction in alcoholic solvents but the sodium salt was unstable in these media and reaction did not occur. A similar investigation of the mercuric salts of urethane also gave no results.

Method 2. Attempted Condensation of Tetra-O-acetyl-α-D-glucopyranosyl Bromide with Silver Cyanate and Consequent Formation of the Urethane Derivative.



(I) (II) (III)

The Fischer[9,10] preparation of the isocyanate involves

condensing the bromo compound (I) with silver cyanate to form the isocyanate (II) which, Fischer states, separates as a resin-like gum. This isocyanate on refluxing with a large excess of absolute ethanol takes up a mole of ethanol to form the carbamate structure (III). The silver cyanate used was prepared by making saturated solutions of silver nitrate and of potassium cyanate, filtering the solutions to remove any undissolved salt and combining them. Immediately a white curdy precipitate of silver cyanate appeared which was filtered under vacuum.

$$AgNO_3 + KCNO \xrightarrow{H_2O} KNO_3 + AgCNO\downarrow$$

Several experiments were run varying the solvents and the isolation procedure but all resulted in impure, dark syrups or gums. The following is the general experimental procedure followed:

Twenty four and five tenths grams (0.06 mole) of tetra-O-acetyl-α-D-glucopyranosyl bromide were dissolved in 100 ml. of dry xylene. Seven grams of dry silver cyanate was added and the solution heated on a steam bath with constant stirring. After 20 minutes the bottom of the previously clear solution became yellow. After heating for one hour the remaining three grams of silver cyanate (making a total of 0.06 mole) were added. The heating was continued for an additional hour. The liquid was separated from the gray silver bromide precipitate by

filtration and 60 ml. of ethyl acetate were added to extract the remaining silver salts. The solution of xylene and ethyl acetate was poured into one liter of petroleum ether to precipitate the isocyanate. After two days of refrigeration, a gummy white substance was deposited on the bottom of the vessel.

The liquid was decanted from the isocyanate material and a large excess of absolute ethanol was added. This solution was refluxed for four hours and then poured into a large amount of hot water to precipitate the N-carbethoxy-tetra-O-acetyl-α-D-glucosamine-1. The solution became cloudy and after some time an oily layer formed. Some benzene was added to the solution and a dark white gum formed at the interphase. Azeotropic distillation with benzene failed to yield a solid product and a portion of the water solution was evaporated to dryness, leaving a brown syrup. The original reference states that the carbamate derivative crystallizes from the mother liquor if left for a few days. No crystalline product was isolated from this reaction.

The second experiment which was carried out was very similar to the previous but employed N,N-dimethylformamide (DMF) as a solvent rather than xylene. Recent studies[36] have shown that DMF acted as a catalyst even in small amounts in

reactions where the splitting off of silver halides was involved. The procedure followed was identical to the previous condensation with silver cyanate, but in this case solid particles separated from the solution even before the heating was begun. The solid material was removed and an excess of absolute ethanol added. Initially gray solid separated out as the ethanol was added, but this proved to be silver bromide. When all the silver bromide had been removed, excess absolute ethanol was added and the mixture refluxed as in the previous case. No solid carbamate product was found either upon the water dilution, azeotropic distillation, on standing in benzene or on evaporation to dryness.

The third and last run involved xylene as the solvent, but after reaction and removal of silver bromide the yellow solution was divided into two fractions.

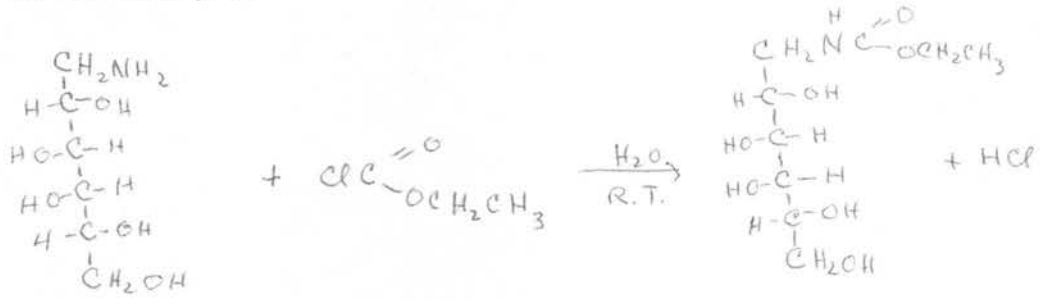
Fraction I was treated in the regular way and all efforts to crystallize the carbamate product were futile.

Fraction II was treated with excess ethanol immediately (without isolation of the isocyanate resin) and refluxed for several hours. An azeotropic benzene-ethanol distillation gave no solid product and evaporation to complete dryness gave a brown syrup.

The carbamate derivative could not be isolated in any pure form, and all the various fractions obtained from these experiments yielded no solid product after several months of standing at room temperature.

Section III. Alternate Procedure for the Synthesis of a Carbethoxy Derivative of Galactamine. The Preparation of N-carbethoxygalactamine-1.

In order to obtain the desired product, N-carbethoxy-galactamine-1 a small amount of galactamine (1-amino-1-desoxy-dulcitol) prepared according to the method of Kagan (see Part III B) was allowed to react with ethyl chloroformate and a white solid product isolated which melted at 182-3°C.



Experimentally, an aqueous solution of the amine was kept at room temperature with constant stirring. As the stoichiometric amount of ethyl chloroformate was added from a dropping funnel, sufficient sodium hydroxide (10 percent solution) was added to neutralize any amine hydrochloride formed during the reaction. When the pH of the solution remained constant the mixture was allowed to stir for one hour to insure completion of the reaction. The volume of solution was evaporated to dryness and the white crystalline material was recrystallized from absolute methanol. After three recrystallizations from absolute methanol an analytical sample was produced, which

melted at 182-2.5° C. Yield: 78%.

Analysis for $C_9H_{19}NO_7$

Calculated: C = 42.68%; H = 7.50%; N = 5.53%

Found : C = 42.65%; H = 7.36%; N = 5.54%

PART II

The Preparation of 1-Amino-1-desoxy-D-sorbitol (Glucamine)

A-1. Literature Review

Glucamine was first prepared by Maquenne and Roux[13] in 1901. These workers obtained a 25 percent yield by reducing glucosoxime using three percent sodium-amalgam. A similar reduction was carried out by Neuberg and Marx[14] in 1907 which resulted in a low yield of material. At this time the structure of the product was still unknown.

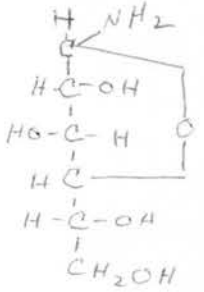
In 1922, Ling and Nanji[15] reduced a methanolic solution of glucose which was saturated with ammonia. The reduction was effected by three different methods:

a) by hydrogenation using a Palladium catalyst

b) by chemical reduction with aluminum amalgam

c) by electrolytic reduction.

All three methods gave an amine product identical to that of earlier workers. Ling and Nanji made the condensation product of the amine with formaldehyde and sodium bisulfite[37] and concluded that the product was a primary amine of the following structure:



Later workers prepared glucamine by glucose reduction in alcoholic ammonia solution.[16,17] In 1950 Holly[18] prepared

glucamine in 54 percent yield by using liquid ammonia, H_2, and a Raney nickel catalyst under high temperature and pressure.

More recent methods of preparation have involved reduction of the phenyl osazone[19] and catalytic reduction with hydrazine[20] using high temperature and pressure and a Raney-type catalyst.

A-2. General Discussion

Experimentally, four different methods were tried to prepare glucamine. The first involved the preparation of the oxime of glucose (see Part II-B, Section I) which was found to be quite difficult to obtain in a pure form and was subsequently abandoned as a feasible route to the amine.

Method II was one of Irving Muskat,[21] in which glucose was dissolved in liquid ammonia (see Part II-B, Section II). The yield was reported as quantitative, but the mechanism of the reaction was not clearly known. This experiment was repeated twice and no amine was isolated as had been previously described by Muskat.

Method III involved a known laboratory preparation of Kagan[22] and co-workers (see PartII-B, Section III). In this procedure glucose is condensed with benzylamine and the condensation product is hydrogenated with platinum catalyst. The resulting N-benzyl derivative is then hydrogenolyzed with hydrogen and a palladium catalyst. The product obtained is quite impure and trouble was encountered with solvation.

Method IV (see Part II-B, Section IV) was a patented method of R.U.Lemieux[23] using glucose, hydrazine and Raney

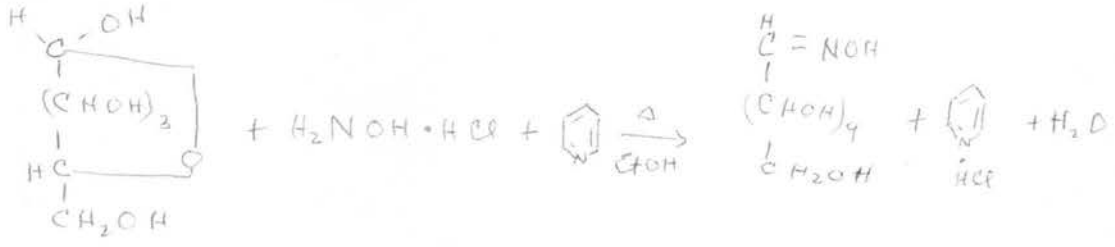
nickel at a moderately high temperature and pressure. The main problem here was a large amount of contaminant, thought to be D-sorbitol, in the glucamine product.

B. Experimental Procedure Leading to the Preparation of Glucamine

Section I. The Preparation of Glucosoxime

I-a: Discussion

Glucosoxime was first prepared by H. Jacobi[24] in 1891 using glucose and hydroxylamine sulfate in aqueous solution. After a period of seven days (three days reaction time and four for product separation) the oxime was obtained as a dark syrup which yielded colorless crystals in three days. The yield was 70 percent based on glucose and the product obtained was fairly pure (136-7°C). Oximes have also been prepared by various standard methods involving the aldehyde and hydroxylamine hydrochloride. Since the oxime is quite soluble in water and only slightly soluble in alcohol, 95 percent ethanol was used as a solvent. The reaction employed was the following:



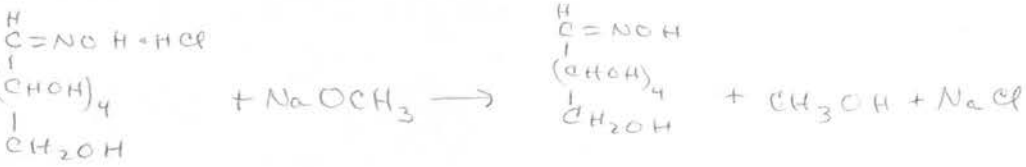
I-B. Experimental Procedure

A mixture of 18.0 g. (0.10 mole) of D-glucose (anhydrous, 'Baker Analyzed' - used as received), 16.6 g. (0.25 mole) of hydroxylamine hydrochloride (Matheson, Coleman and Bell) 100 ml. of 95 percent ethanol and 50 ml. of pyridine was refluxed on a steam bath for 2.5 hours. The solvent was partially removed by an air jet at room temperature but attempts to evaporate to dryness were futile. After four days of evaporation under vacuum on a mechanically rotated round-bottomed flask, supported over a steam bath, a white solid separated from the amber syrup. The entire product (both crystalline and syrup) was dissolved in methanol and on concentration yielded 2.3 g. of white solid material which gave a positive silver nitrate test for chloride ion, and sintered at 285°C. This white solid product was thought to be either gluconitrile or glucosoxime hydrochloride. The former possibility was eliminated since the product on refluxing with alkali gave a negative test with Nessler's Reagent,[25] indicating that no ammonia was formed, and the literature revealed a variable melting point for gluconitrile[26] of 120°C when re-crystallized from ethanol, and 145°C from acetic acid. Support for the oxime hydrochloride is a positive silver nitrate test and reaction in methanol (with sodium methoxide) to give a white crystalline product with a melting point of 156°C (lit: for oxime: 156°C).

Two grams (0.008 mole) of the suspected hydrochloride was dissolved in the stoichiometric amount of 10 percent sodium methoxide (prepared by the method of Fieser and

Fieser

Fieser[27]). After heating, the solution was left to cool and 1.54 g. of a white crystalline material was collected which melted at 136°C and was thus assumed to be glucosoxime, obtained according to the following reaction:



The mother liquor of the oxime hydrochloride, an amber syrup, was shaken with Norit several times but still retained the same amber coloration. The syrup was dissolved in a benzene-methanol solution. This was distilled for seven hours, the azeotrope distilling at 58°C. Excess benzene was added until the methanol was completely removed. The product did not crystallize but appeared in the form of a thick syrup which was placed in a vacuum desiccator over calcium chloride. This syrup eventually began crystallizing after twelve months.

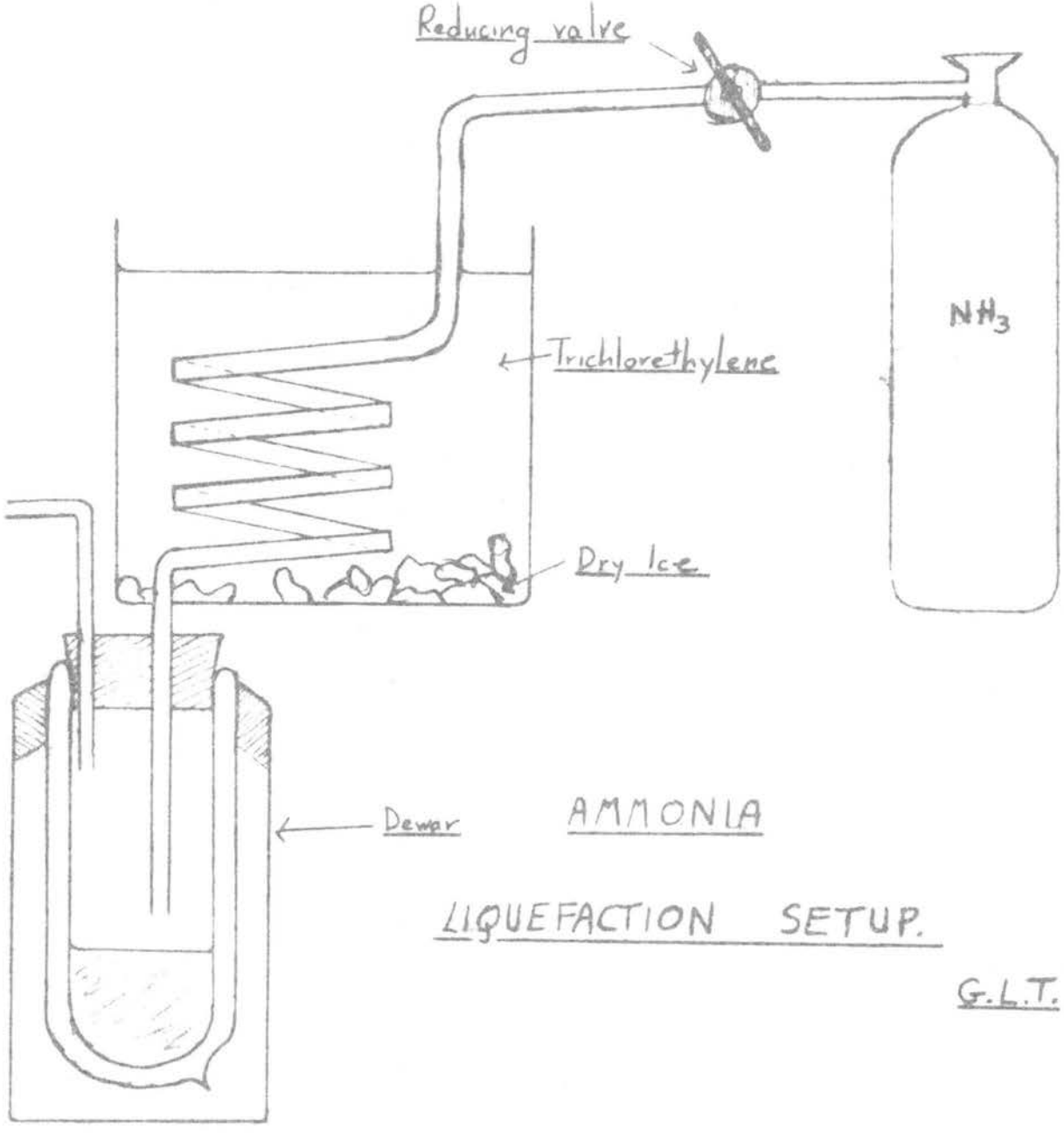
Three percent sodium amalgam had also been prepared[27] to reduce the oxime product to glucamine, but since only 1.54 g. of oxime were obtained from 20 g. of glucose the method was abandoned since the difficulty of isolation of pure material showed the unfeasibility of this method.

Section II. The Preparation of Glucamine by the Procedure of Irving Muskat[21]

II-a. Experimental

Five grams of D-glucose (anhydrous - Merck - used as received) was inserted into an eight inch test tube which had been etched at the 25 ml. level. The test tube was immersed in a Dewar vessel containing a trichloroethylene - Dry Ice bath at -45°C. Twenty five milliliters of liquid ammonia (Dupont - anhydrous ammonia) were introduced into the sample in the following way.

Due to the size of the tank, the most convenient method of obtaining the ammonia in the liquid form was to condense the gaseous anhydrous ammonia through a series of coils (kept at -35°C with trichloroethylene and solid carbon dioxide) under a pressure of 2-3 p.s.i. of ammonia gas (see Figure 1). The test tube was kept in the Dewar vessel overnight at -60°C to allow the reaction to proceed to completion. The ammonia



AMMONIA

LIQUEFACTION SETUP.

G.L.T.

Fig 1

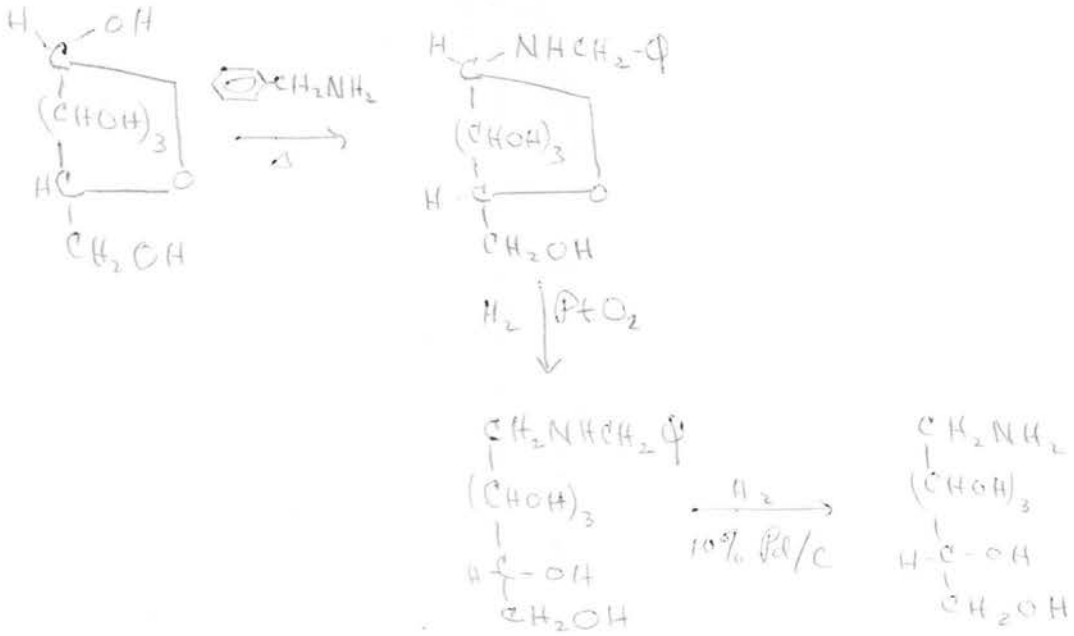
was then allowed to evaporate slowly and a clear syrup remained. Upon addition of absolute ethanol the syrup changed to a milk-white taffy-like semi-solid which after hours of repeated trituration remained in the same form. According to the literature, trituration with absolute ethanol should produce white crystals of glucamine.

Fractions of the white material were refluxed with ethanol and methanol. The syrup showed a greater solubility in methanol than in ethanol, and, on standing, the ethanol solution produced a white solid which reverted to the syrup form on exposure to air. The methanol solution was combined with benzene and distilled. The azeotrope distilled at 58°C and excess benzene was added until only benzene remained. White solid particles separated from the benzene layer but these also were unstable. A benzene-ethanol distillation of the ethanol fraction left a residue which was a yellow oil, but did not crystallize. Thus a positive identification of the amine was not realized since none of the material isolated showed sufficient stability for a melting point. This method was also abandoned for that of Kagan(see next section).

Section III. The Preparation of Glucamine by the Method of Kagan[22]

III-a Discussion

The synthesis of glucamine by the method of Kagan, Rebenstorf and Heinzelman employs the following reactions:

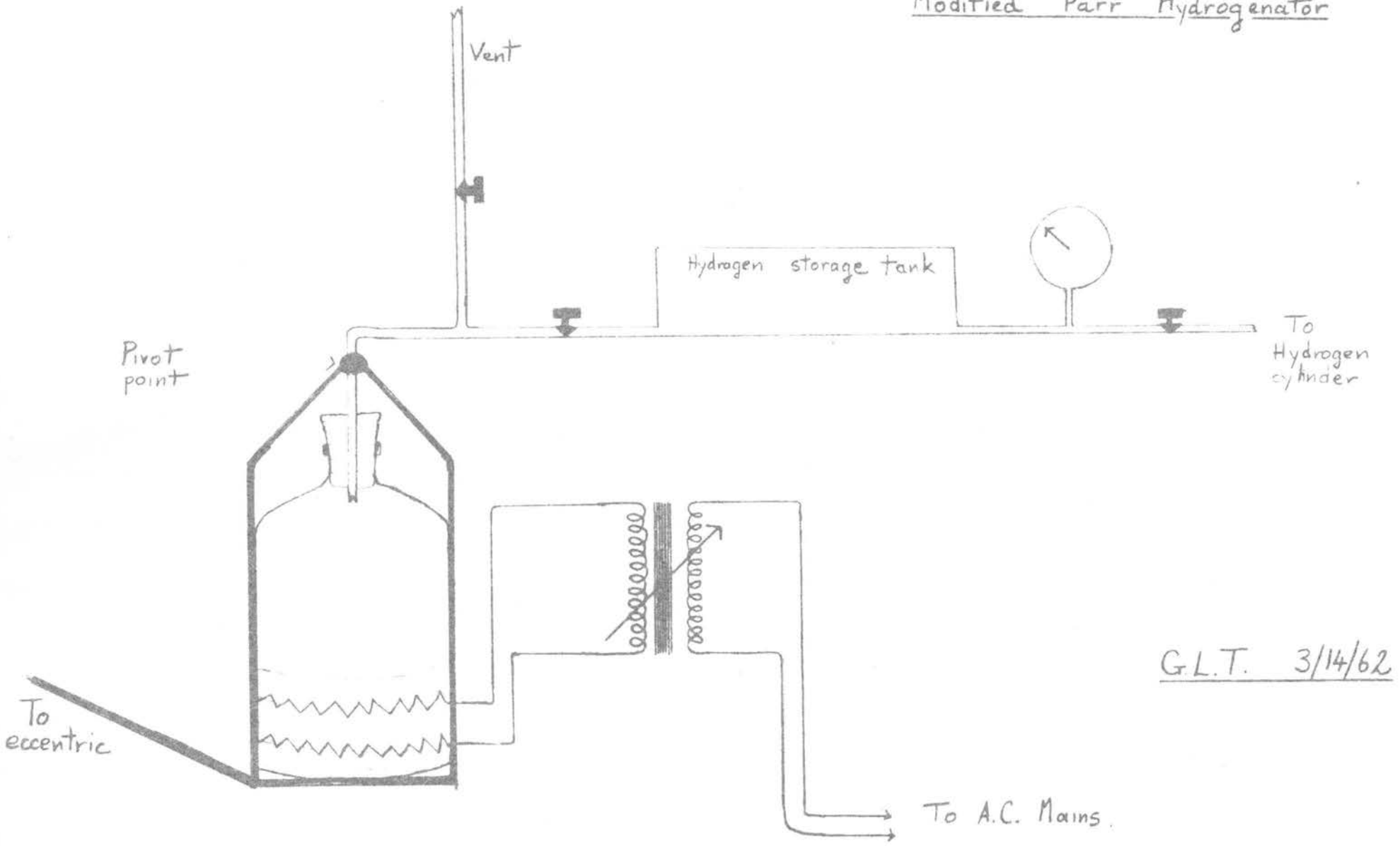


Anhydrous D-glucose is condensed with benzylamine and the product is hydrogenated using platinum oxide (Matheson, Coleman and Bell) at a moderate temperature and pressure. The resulting N-benzyl-glucamine is then hydrogenolyzed at 20 - 50 p. s. i. at 50°C with 10 percent palladium-on-charcoal.

The reactions were carried out in a Paar hydrogenator (Paar Instrument Co., Moline, Illinois: Item 3811, Pressure Reaction Apparatus) as described in Fig. II. The reaction vessel was fitted with electrothermal heating tape and the temperature was controlled by means of a variable powerstat (Superior Electric Co., Bristol, Connecticut, USA) which had previously been calibrated in the 30° - 50°C temperature range.

In each platinum oxide hydrogenation, the quantity of catalyst was reduced from one half to one third the recommended amount and it was found that as long as the catalyst was kept moist with

Schematic of Modified Parr Hydrogenator



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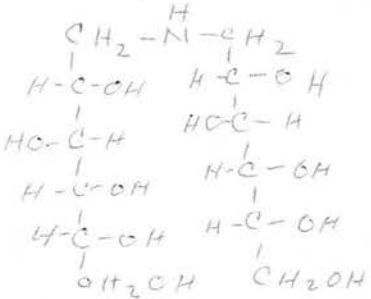
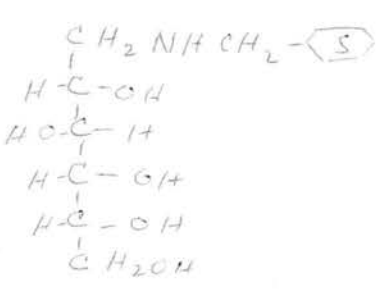
ethanol or methanol it retained its activity and could be re-used several times. A slight delay of three to four hours for crystallization was experienced with the reduced amount of catalyst. In removing the catalyst a filtering aid such as Supercel was used since portions of the finely divided metal remained in the mother liquor.

Some contaminants of the glucamine reaction appear to be didulcitylamine (I) and cyclohexylmethylglucamine(II).



(I)



(II)

Although the product obtained possessed the same physical properties as that of Kagan et al., it was found by analysis that the main product was still the N-benzylglucamine which had not been hydrogenolyzed.

Analysis:

calculated for amine, $C_6H_{15}NO_5$: C = 39.77%; H=8.34%; N=7.73%

Calculated for N-benzylamine, $C_{13}H_{21}NO_5$:

C = 57.6% ; H = 7.76%; N = 5.18%

Found: C = 55.12% ; H = 7.72% ; N = 5.20%

The analysis corresponds to a mixture of approximately twenty percent of the glucamine and eighty percent of

N-benzylglucamine which was not hydrogenolyzed. During repeated runs varying solvent-solute ratio, amount of catalyst, and time of hydrogenolysis, similar results were obtained. Kagan and co-workers did not have an analysis on glucamine and had not yet devised a purification procedure.

A procedure for separation through the Schiff base using o-salicylaldehyde was attempted, but this proved inadequate as the final product was still found to contain some contaminant thought to be D-sorbitol.

Since there was no complete separation even after the Schiff base procedure the plan was altered to begin with galactose since this was obtainable in a pure form by the above method and would also give the desired final product. The average overall yield of glucamine product (mixture) from glucose is 25.6 percent. The actual yield of pure glucamine is approximately 15 percent.

III-b. Experimental Preparations:

1) Preparation of N-benzylglucamine

Twenty five grams (0.14 mole) of D-glucose (anhydrous, Baker Analyzed - used as received), 15 g. (0.14 mole) of benzylamine (b.p.56-7° C/5mm; Matheson, Coleman and Bell) and 7.5 ml. of water were heated in a water bath at 60° C until the solution process was complete. Overheating such as heating directly on a steam bath caused gelation

of the mixture. Twenty five ml. of absolute methanol were added with continuous shaking and, once the mixture was cooled, the volume of the solution was adjusted to 250 ml. with methanol.

One gram of platinum oxide (Adams' Catalyst, Matheson, Coleman and Bell) was inserted into the reaction vessel which had previously been flushed with nitrogen since the catalyst was explosive in the presence of methanol vapors and in a pure hydrogen atmosphere. The 250 ml. of solution was hydrogenated with constant agitation at 40-45 p.s.i. and 50°C. for a period of 15 hours. The product was dissolved in 750 ml. of methanol and heated on the steam bath until all of the crystalline product had dissolved. The catalyst was filtered off but kept moist and stored under methanol and the filtrate was filtered through Supercel to remove last traces of catalyst. The resulting yellow solution was concentrated to 500 ml. and allowed to cool to room temperature. A white crystalline product appeared in two days with a melting point of 136-9°C (same as the literature).

Average yield (14 runs): 27.5 g.; 72% yield (67% literature yield)

2) Hydrogenolysis of N-benzylglucamine to Glucamine

Twenty five grams of N-benzylglucamine was suspended in 250 ml. of 95 percent ethanol and 3 g. of 10 percent palladium on powdered charcoal (Matheson, Coleman and Bell - used as received) were added. The mixture was hydrogenated

at 50° C and 50 p.s.i. for two hours.

The product was then diluted to 500 ml. with methanol and heated on a steam bath until the supernatant liquor was clear (toluene is driven off at this stage). The catalyst was removed by filtration and stored under methanol. The filtrate was re-filtered through Supercel and allowed to cool at room temperature.

Yield: 10.0 g. m.p. 126-7° C

55 percent from N-benzylglucamine

25.6 percent from glucose

Since the previous analysis showed that the 10 gram product of the hydrogenolysis procedure was approximately 20 percent pure, a method of separation was effected by condensing the amine product with salicylaldehyde in water solution.

3) Purification Method Involving the Schiff Base

Two grams of the amine mixture (0.011mole if pure glucamine) was dissolved in a minimum amount of water and set in an ice bath while being stirred constantly. Then 1.5 g. (0.011 mole) of salicylaldehyde (Fisher Scientific Co.) were added from a dropping funnel. A small amount of aqueous ethanol was added to bring the salicylaldehyde into solution since it is insoluble in water. After one hour a yellow precipitate appeared which had a melting point of 175-7° C. A total of 0.8g. (0.0028 mole) of this product was collected.

The yellow product was suspended in ether and stirred for ten minutes to remove excess salicylaldehyde, and dried in a desiccator over calcium chloride. Since two grams of the amine mixture , 0.011 mole if it were pure glucamine, formed only 0.0028 mole (0.8 g.) of the salicylaldehyde derivative the mixture was taken as approximately 25 percent pure glucamine.

The Schiff base was then suspended in 250 ml. of water and 2 ml. of concentrated hydrochloric acid (12 M) was added for hydrolysis. After stirring the mixture for 10 minutes on a steam bath the solution was cooled and extracted three times with 125 ml. portions of methylene chloride to remove the salicylaldehyde. The aqueous solution was vacuum distilled to dryness and the glucamine hydrochloride dissolved in 400 ml. of water and passed through a hydroxide cycle resin (Dowex - 3; Baker Analyzed) until the pH of the effluent was neutral. The water solution was again vacuum distilled to dryness and the white solid dissolved in methanol to crystallize. Repeated re-crystallizations were necessary since the amine product was quite hydrated. The volume of methanol was decreased and excess ether added. Approximately 0.7 g. of white solid was collected and dried in a vacuum desiccator. The product melted from 119-125°C and sintered at 112°C, which may be attributed to a slight amount of sorbitol contaminant.

Section IV. The Preparation of Glucamine by the Method of Lemieux[23]

IV-a Discussion

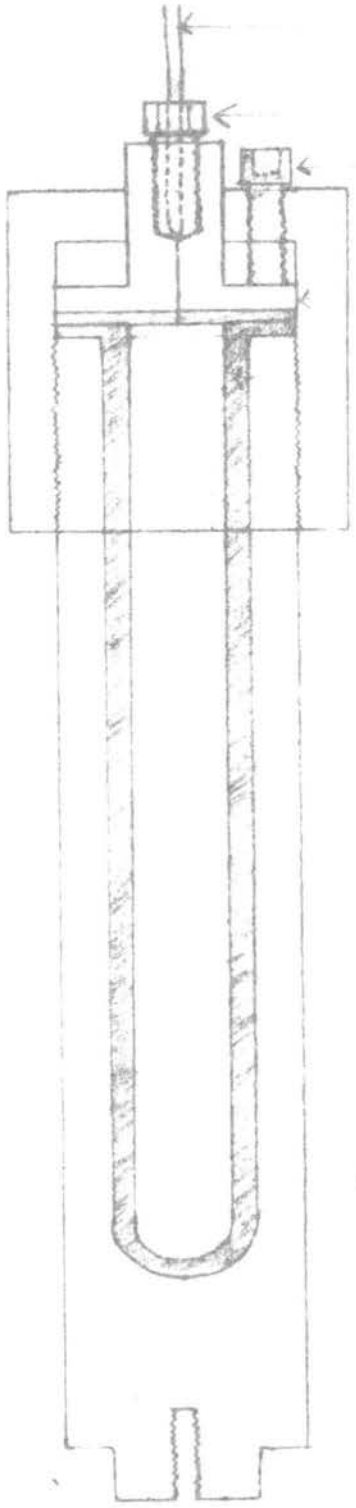
R.U.Lemieux patented a method of preparation of amino sugars in 1958, which did not appear (and has not since) in the chemical journals. This method is a bomb reaction at 1500 p.s.i. of hydrogen and 90°C involving catalytic liquid phase hydrogenation of aliphatic hydroxy aldehydes in the presence of hydrazine. The reported yield averaged 83 percent (determined by titration - one assumes hydrochloric acid - titrant not stated) and gives a very unsatisfactory analysis for nitrogen (only element analyzed for). This seemed to suggest a large amount of impurity present.

IV-b Experimental

The Raney catalyst was first prepared by boiling 1.25 g. of Raney nickel catalyst powder with excess concentrated sodium hydroxide for two hours. As the water evaporated, more water was added, and the final solution was decanted, the solid washed with water and used as prepared.

The reaction vessel was a high pressure bomb (American Instrument Co., Cat. No. 406-OIM) see Fig. III. In a 250 ml. Erlenmeyer flask were dissolved 10 g. of D-(+)-glucose (Baker

Detail of Microbomb showing Teflon liner.



SCALE
2" = 1"

Microbomb
CAT - 406 - 35D
Ser - E-1472 EPMS.

G.L. TAYLOR
BOSTON - 1962

Fig. 3

Analyzed), 30 ml. of water and 5 ml. (molar excess) of hydrazine (Hydrazine Hydrate, 85 percent in water, Technical, Matheson, Coleman and Bell). The Raney nickel catalyst was added to this mixture and the contents rinsed into the bomb with small amounts of water. The bomb used only had a total capacity of 100 ml. and with the excessive foaming of the catalyst, the amount of reactants was the maximum the vessel could accept. The reaction was maintained at 1500 p.s.i. of hydrogen and 90°C for five hours. The catalyst was then filtered off, the solution shaken with Norit and run through a hydrogen ion exchange resin column (Dowex 50W-X8; a strongly acidic cation exchange resin; Baker Analyzed) to remove the finely dispersed nickel. The effluent, still tinged with green, was evaporated to dryness and the solid dissolved in a small amount of methanol. When crystallization did not seem realizable, a large amount of ethyl ether was added to the methanol solution and on cooling in the refrigerator, a moderate amount of round, star-like crystals formed on the bottom of the flask. These crystals were thought to contain a large amount of D-sorbitol due to a sintering at 112°C when melting. The Schiff base purification described in Section III was repeated, However the final product still appeared to be contaminated with sorbitol.

Further work on glucamine was abandoned and galactose was selected as a new starting material.

PART III

The Preparation of 1-Amino-1-desoxy-D-dulcitol and its Subsequent Reactions Leading to 1-Diazo-2,3,4,5,6-pentahydroxyhexane.

Section I - The Preparation of 1-Amino-1-desoxy-D-dulcitol (GALACTAMINE)

I-a General Discussion.

The procedure followed in this preparation is that of Kagan, Rebenstorf and Heinzelmann[22] previously described in Part II, Section III. D-(+)-galactose was used rather than D-(+)-glucose, and a cleaner final product of amine was obtained with a slightly higher over-all yield. Greater difficulty was encountered in dissolving the D-(+)-galactose in the initial condensation with benzylamine than was experienced with D-(+)-glucose. The hydrogenated condensation product, N-benzylgalactamine, required a much greater period of time to re-dissolve in methanol for crystallization.

The hydrogenolysis product, a mixture of galactamine and N-benzylgalactamine was separated by forming the Schiff base of the amine with o-salicylaldehyde.

I-b Experimental Procedure

1) The Preparation of N-benzylgalactamine

Twenty five grams (0.14 mole) of D-(+)-galactose (anhydrous, 'Baker Analyzed' - used as received),

15 g. (0.14 mole) of benzylamine (b.p. 95-7°C/5mm; Matheson, Coleman and Bell) and 7.5 ml. of water were heated in a water bath at 50°C until the galactose was completely dissolved. Twenty five milliliters of methanol was added with continuous shaking and, once the mixture was cooled, the volume was adjusted to 250 ml. with methanol.

One gram of platinum oxide (Adams' Catalyst, Matheson Coleman and Bell) was inserted into the reaction vessel under a nitrogen atmosphere. The methanol solution was hydrogenated with constant agitation at 40-45 p.s.i. and 50°C for a period of fifteen hours. The product was diluted to 750 ml. with methanol and heated on the steam bath until completely dissolved. The catalyst was filtered off and stored under methanol and the filtrate was filtered through Supercel to remove finely dispersed catalyst. The resulting clear solution was concentrated to 500 ml. and allowed to cool to room temperature. A white crystalline product appeared, melting at 150-154°C (literature: 151-7°C). Average Yield (8 runs): 20 g., 52.6% yield

(64% literature yield).

2) Hydrogenolysis of N-benzylgalactamine.

Twenty five grams of N-benzylgalactamine was suspended in 250 ml. of 95% ethanol and three grams of 10% palladium on powdered charcoal (Matheson, Coleman and Bell - used

as received) was added. The mixture was hydrogenated at 50°C and 40-50 p.s.i. for two hours.

The product was then diluted to 500 ml. with methanol and heated on the steam bath until it was completely dissolved. The catalyst was removed and the filtrate cleaned with Supercel and allowed to cool to room temperature. The product obtained melted at 142-145°C (literature for amine m.p. 143-5°C) and was found to be a mixture of galactamine and N-benzylgalactamine. Therefore the mixture was separated by forming the salicylaldehyde derivative as follows:

Fourteen grams of the amine mixture (0.08 mole if pure amine) was dissolved in a minimum amount of water and set in an ice bath while being stirred constantly. Then 12.0 g. (0.08 mole) of salicylaldehyde (Fisher Scientific Co.) were added from a dropping funnel. A small amount of aqueous ethanol was added to bring the salicylaldehyde into solution.

After one hour nine grams of the yellow C-salicylaldehyde derivative of galactamine was collected, which melted at 199-200°C. A small amount was recrystallized several times from absolute methanol for analysis.

Analysis for $C_{13}H_{19}NO_6$

Calculated: C = 54.73%; H = 6.71%; N = 4.91%

Found : C = 54.36%; H = 6.58%; N = 4.80%

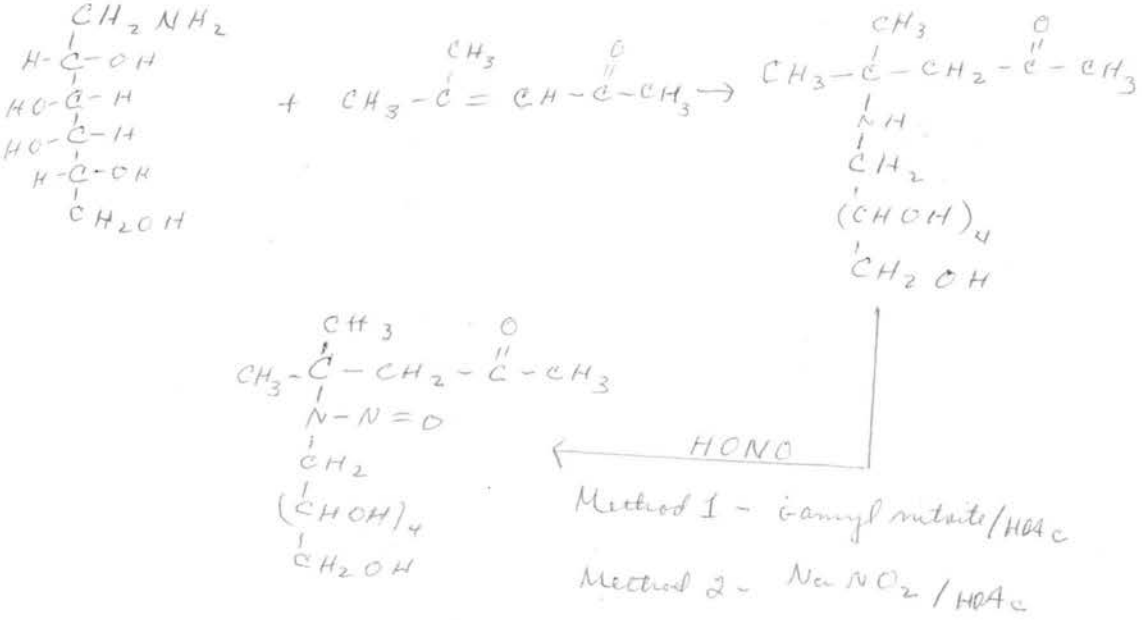
Average yield of galactamine:

(Calculated on the stoichiometric basis of amount of Schiff base formed by amine product mixture)

average of 8 runs: 5.75 g.; (23% overall yield from galactose)

The Schiff base was then suspended in 500 ml. of water and 20 ml. of concentrated hydrochloric acid (12 M) was added for hydrolysis. After stirring the mixture for 10 minutes on a steam bath the solution was cooled and extracted three times with 125 ml. portions of methylene chloride to remove the salicylaldehyde. The aqueous solution was vacuum distilled to dryness and the galactamine hydrochloride dissolved in 1 liter of water and passed through an hydroxide cycle ion exchange resin (Dowex-3; 'Baker Analyzed') until the pH of the effluent was neutral. Initially, the pH of the effluent was approximately 9.5 but the solution gave a positive test for chloride ion with silver nitrate. This solution was again run through a second hydroxide ion column, but still emerged with some unchanged hydrochloride. It appears that no matter how slowly the mixture is run through an exchange column(with a large excess of ion exchange resin) it is difficult to effect complete ion exchange. The product gave a melting point of 137-9°C and was used with the small amount of hydrochloride contamination for the subsequent steps in the synthesis.

Section II - The Preparation of 4,4-Dimethyl-N-nitroso-5-aza-7,8,9,10,11-pentahydroxy-2-undecanone from the Addition Product of Galactamine to Mesityl Oxide.[29,30]



II-a General Discussion

The method followed in this section is similar to that of Jones and Kenner.[29,30] Initially, the amine is condensed with mesityl oxide at room temperature and the resulting product is then nitrosated.

Two different nitrosating agents were employed in this synthesis. The first experiment involved using iso-amyl nitrite, and gave no evidence of reaction. A

second method involving sodium nitrite as the nitrosating agent was subsequently employed.

Method I - The Addition of Galactamine to Mesityl Oxide

In a 500 ml. round-bottomed three-necked flask, provided with a magnetic stirrer and dropping funnel was inserted 2.36 g.(0.015 mole) of galactamine dissolved in 100 ml. of water. An excess amount of mesityl oxide (3 ml. - 0.03 mole) was added with constant stirring over a period of one hour. The mixture was left stirring for two additional hours to insure completion of the reaction. The yellow water solution was extracted three times with ether to remove any excess mesityl oxide, and shaken with Norit to remove impurities. The resulting filtrate was vacuum distilled to dryness at room temperature. The product was an orange syrup which appeared to be slightly soluble in aqueous ethanol but completely soluble only in water.

A small sample of this syrup was therefore dissolved in the minimum amount of water necessary to effect solution, and a large excess of acetone was added to the solution. A very small amount of white material precipitated (m.p. 145-8°C) which on analysis proved to be the unreacted amine hydrochloride contaminant with one molecule of water of crystallization.

Analysis:

calculated for $C_6H_{16}NO_5Cl \cdot H_2O$:

C = 30.50%; H = 7.65%; N = 6.1%; Cl = 15.0%

Found: C = 30.52%; H = 7.60%; N = 6.01%; Cl = 14.85%

The mother liquor (water-acetone pair) was evaporated to dryness and again yielded an orange syrup. Repeated attempts at isolation of a solid mesityl oxide addition product using a water-acetone solvent pair gave no results. Various other solvent pairs such as ethanol-ethyl acetate, and ethanol-ethyl ether also proved futile.

Various runs were made with galactosmine and mesityl oxide varying the time and temperature of reaction. Addition at temperatures up to 60°C yielded the same orange syrup as product. Above 60°C the solution became quite dark and a black tar-like material resulted.

The only solid material isolable from the reaction product is the small amount of unreacted galactosmine hydrochloride hydrate.

Nitrosation using Amyl Nitrite.

Four grams of the syrup obtained from the reaction of galactosmine with mesityl oxide was re-dissolved in 200 ml. of water and inserted into a round-bottomed three-necked flask, equipped with a magnetic stirrer. After flushing the vessel out with nitrogen and neutralizing the solution to a pH of seven with glacial acetic acid, 5 ml. (0.04 mole)of amyl nitrite (K & K Chemicals, used as received), 5 ml. of water and 5 ml. of glacial acetic acid were added at once with continuous

stirring. No temperature change was observed, and the reaction was allowed to continue overnight in the stoppered vessel. The resulting straw-colored solution was extracted several times with ethyl ether to remove unreacted amyl nitrite, cleaned with Norit, and evaporated to dryness. The resulting syrup was found to be soluble only in water and a water-acetone solvent pair yielded a small amount (approximately .25 ml.) of a brown oil which crystallized in the solvent but reverted to an oil on exposure to the atmosphere. Attempts to clean the oil by extraction with ether were futile and it was concluded that nitrosation had not occurred to any appreciable extent.

The Addition of Galactamine to Mesityl Oxide

Method 2 - The procedure followed is similar to that of M. Berenbom and U.S. Fones[28] for the preparation of diazomethane.

In a 500 ml. round-bottomed three-necked flask equipped with a mechanical stirrer, was inserted 19.7 g. (0.11mole) of galactamine in 250 ml. of water. Thirteen milliliters (0.11mole) of mesityl oxide were added over a period of two hours with constant stirring. The reaction was allowed to continue overnight. A sample was extracted with a pipette, and shaken with ethyl ether to remove excess mesityl oxide. On evaporation to dryness, the sample formed brown star-like clusters which were too gummy for identification by means of a melting point. Repeated attempts at isolation of solid material using a water-acetone solvent pair yielded only small amounts of unreacted galactamine hydrochloride and orange syrups of the concentrated mother liquor. The subsequent nitrosation was carried out on this syrup product.

Nitrosation with Sodium Nitrite:

The remaining solution of the mesityl oxide addition product was neutralized to a pH of seven with glacial acetic acid. Then fourteen grams (0.2mole) of sodium nitrite, 10 ml. of glacial acetic acid and 20 ml. of water were added at once with constant

stirring. The temperature began to rise immediately, the solution began foaming and evolution of a small amount of brown gas was observed. The reaction vessel was immediately cooled to 0°C in an ice-salt bath and kept at that temperature for one hour. The solution was then kept in a water bath at 35°C for an additional hour. Finally the reaction was allowed to continue overnight at room temperature.

The resulting orange solution was extracted with ether several times, decolorized to a light yellow solution with Norit and vacuum distilled at room temperature to a thick yellow syrup.

This syrup still contained sodium and acetate ions from the nitrosation procedure. Initially, extraction of inorganic ions by means of an ion exchange column was rejected since when N-nitroso-N-benzylglucamine, prepared by the action of sodium nitrite and glacial acetic acid on N-benzylglucamine, was run through a hydrogen ion exchange resin (Dowex 50W-X8; a strongly acidic cation exchange resin; Baker Analyzed) the nitroso compound adhered to the column and seemed to decompose.

In order to remove as much of the inorganic residue as possible without reverting to ion exchange, the syrup was triturated in the minimum amount of absolute ethanol necessary for solution. The nitroso syrup was completely soluble only in water, and formed a turbid solution after repeated trituration in absolute ethanol. The inorganic salts were removed by filtration and the ethanol mother-liquor was concentrated to half of its original volume. Addition of acetone to this ethanol

solution produced a fluffy white solid which was quite hygroscopic and reverted to a sticky white gum when exposed to the atmosphere. This substance gave a negative test for chloride ion with silver nitrate and thus could not be the amine hydrochloride contaminant extracted from the mesityl oxide addition product. Any analysis obtained would be only an approximate indication owing to the extreme hygroscopicity of the sample and the possibility of sodium acetate being co-precipitated with this solid. The analysis showed a large amount of sodium ions in the residue. An ash residue was given for the carbon and hydrogen which when applied as a correction factor gave:

C = 44.5% ; H = 9.0%

calculated for $C_{12}H_{22}N_2O_7$

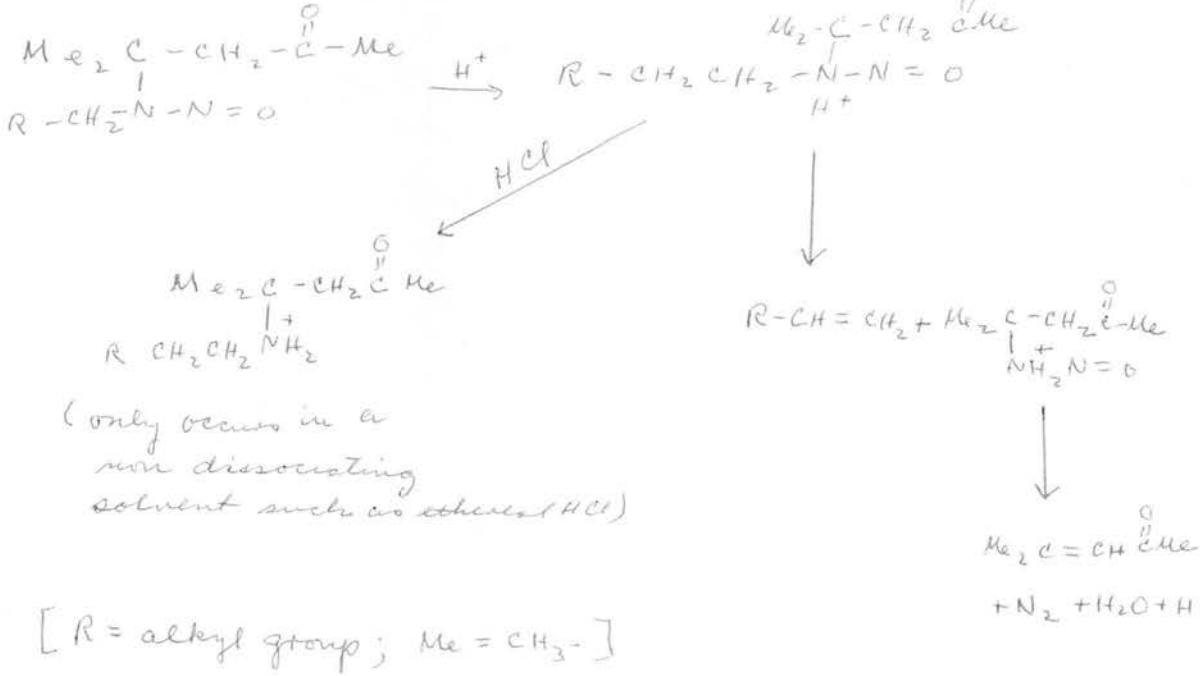
C = 42.1% ; H = 7.18% N = 9.15%

The percentages for carbon and hydrogen would be expected to be greater than the calculated amounts due to the possible decomposition of the acetate ion. The nitrogen analysis was low, but valueless, since the analysts stated that a large amount of ash was found, but gave no weight of the ash residue.

Since compounds of this type, nitroso-β-alkylamino-ketones are readily decomposed by heat[30] usually resulting in olefin formation, at no stage in this work was any crystallization or reaction attempted which would involve

temperatures higher than room temperature.

Jones and Kenner, in their study of the catalytic decomposition of N-nitroso-β-alkylamino-ketones[30] found that these nitroso compounds exhibited decomposition in the presence of concentrated mineral acid in the following way:



[R = alkyl group; Me = CH_3-]

The resulting nitroso syrup was reacted (see Section IV) in two ways. One half was run through a hydrogen ion exchange resin (Dowex 50W-X8; a strongly acidic cation exchange resin; Baker Analyzed) and evaporated to dryness at room temperature. The resulting yellow syrup gave only small amounts of the white hygroscopic material previously obtained from an ethanol-acetone pair. No analysis was possible on this material since it could not be isolated from the mother liquor in a semi-stable condition.

The second half of the syrup was purified for subsequent reactions solely by trituration in absolute ethanol and removal of the resulting inorganic residue.

Both fractions (material run through ion exchange resin and material triturated in ethanol) reacted in a similar manner and seemed to give identical products.

The inherent instability of this compound made it impossible to prepare any derivatives. The subsequent alkaline decomposition of the nitroso compound to a diazo compound was carried out with the material in syrup form.

Section III - Attempted Preparation of N-Nitroso-N-carbethoxy-galactamine-1.

III-a. Discussion.

In 1919, E.A.Werner published an article on the nitrosation of mono-substituted ureas.[31] He concluded that the interaction of the mono substituted ureas and nitrous acid could result either in the production of an N-nitroso derivative or in complete disruption of the molecule. He further states that "the tendency to form a nitroso-derivative falls as the electropositive character of the hydrocarbon radical diminishes."

Nitrosation of N-carbethoxy derivatives of amines would be expected to follow, analogous to the mono substituted ureas, with production of an N-nitroso-N-carbethoxy derivative.

III -b. Experimental Procedure.

In a 250 ml. round-bottomed three-necked flask equipped with a mechanical stirrer was inserted 0.25g. (0.001 mole) of N-carbethoxygalactamine-1 (previously prepared - see Part I, Section III - analyzed, m.p.182-2.3°C).

Fifty milliliters of water was added and the solution stirred until all the material had dissolved. The flask was placed in an ice bath at 0°C and 0.1g. (excess) of sodium nitrite, 2ml. of glacial acetic acid, and 2 ml. of water were added consecutively with constant stirring.

No change in temperature occurred. The mixture was allowed to react for four hours. The final solution was vacuum distilled to dryness at room temperature, and re-dissolved in hot, aqueous (90%) ethanol.

The crystalline product obtained melted at 180-2°C. A mixed melting point on this material and original starting material showed no depression. Two tenths grams of N-carbeth-oxygalactamine-1 was recovered.

Nitrosation at Room Temperature.

The procedure followed was the same as that above, except that the substances were allowed to react at room temperature. No temperature change occurred, and evaporation to dryness gave only starting material and sodium acetate.

Nitrosation at Elevated Temperatures.

The above procedure was followed and reaction was allowed to proceed as follows:

1) Reaction was carried out in a water bath at 50°C. No reaction seemed to occur and no product other than starting material was isolated.

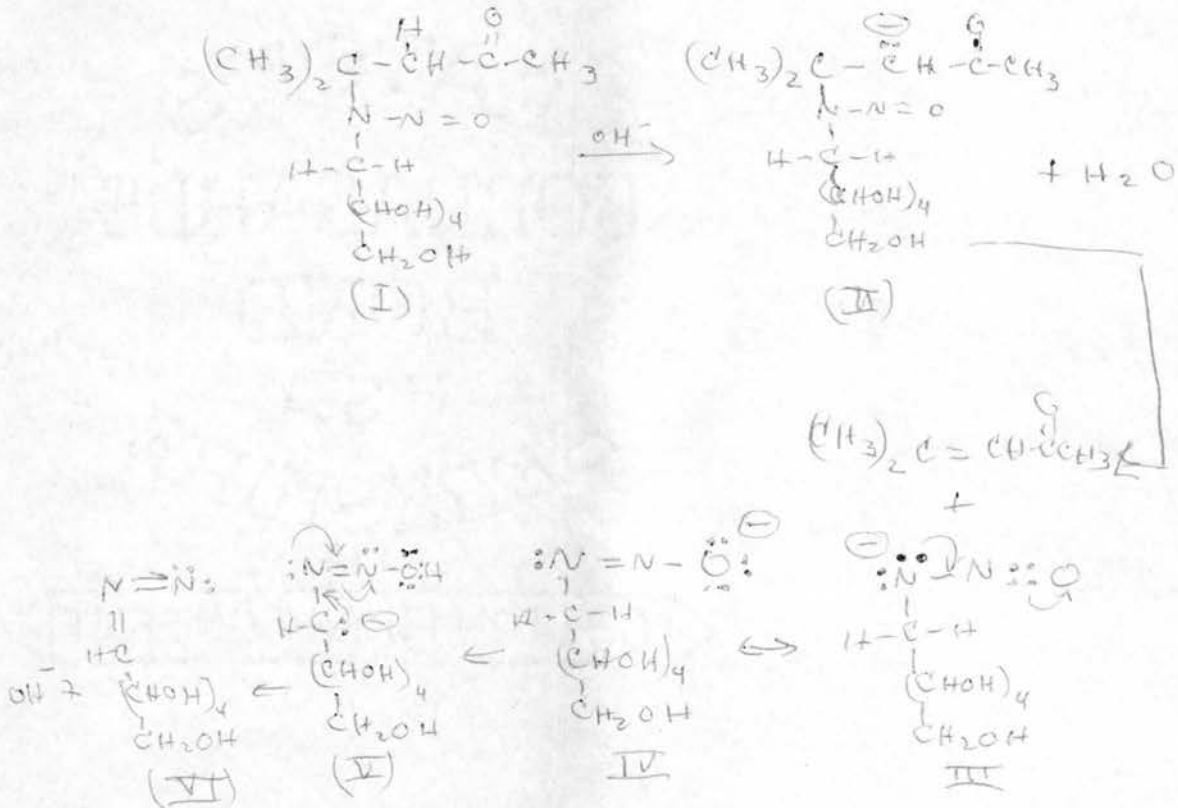
2) Reaction at 70°C. No reaction, and only starting material isolated.

3) The flask was heated on a steam bath at 97°C, but again no product was isolated.

No further nitrosations at higher temperatures were performed, as the product would probably decompose on forming, if reaction was carried out at temperatures above 100°C.

Section IV - Preparation of 1-Diazo-2,3,4,5,6-pentahydroxy-hexane by Catalytic Decomposition of 4,4-Dimethyl-N-nitroso-5--aza--7,8,9,10,11-pentahydroxy-2-undecsnone. Reactions of the Diazo Compound formed with Aldehydes and Phenols.

IV-A Discussion.



The above mechanism for the formation of diazo alkanes from the corresponding N-nitroso compound is an adaptation of a mechanism for the formation of bis-diazo alkanes suggested by C.M.Samour in his doctoral dissertation on bis-diazo alkanes.[32]

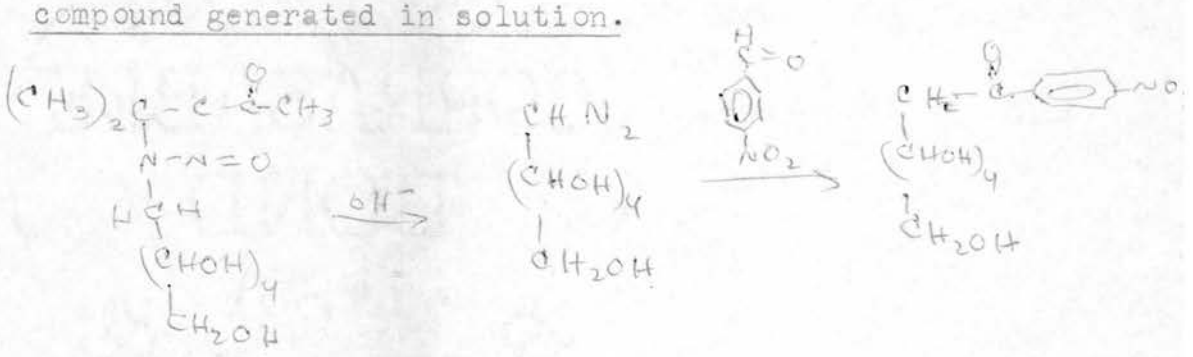
Since compounds of type I can be decomposed by OH^-,

the suggested mechanism involves loss of the acidic hydrogen alpha to the carbonyl group (II) which gives structure III and mesityl oxide. Structure III is in resonance with structure IV. In the latter structure an alpha hydrogen atom rearranges to form structure V. The formation of V is supported by work carried out by A.Hantzsch and M.Lehmann on hydrolysis of N-nitrosomethyl-urea with concentrated alkalai.[33] Compound V can lose an OH^- to give compound VI.

Since the diazo compound VI would be expected to be quite unstable, no attempt was made to isolate it, but rather it was allowed to react immediately with aldehydes or phenols in solution.

IV-B Experimental Procedure.

1. - Reaction of p-nitrobenzaldehyde with the diazo compound generated in solution.



In a 250 ml. three-necked flask provided with a stirrer and a thermometer was introduced an ethanolic solution of 0.4g. (excess) of p-nitrobenzaldehyde (Eastman Kodak Co.) and 0.5g. of the N-nitroso syrup (see PartIII, Section II, Method 2).

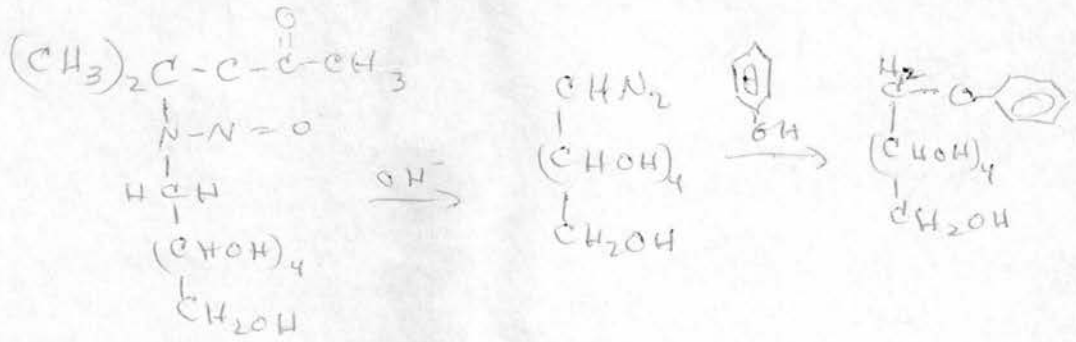
The nitroso syrup had been previously triturated with absolute ethanol to remove the inorganic salts, and the resulting ethanol solution (approximately 150 ml.) was admixed with p-nitrobenzaldehyde.

To the resulting solution at 29°C (room temperature) was added a pellet of sodium hydroxide. The solution immediately became orange in color, and in one minute the color deepened to red. The temperature after four minutes reaction time was 31.5°C. The solution became a deep violet-brown and particles began collecting on the walls of the flask. The reaction was allowed to continue for two hours and the solution was left at 4°C overnight.

The solid particles, on filtration, suddenly contracted and formed a purple tar-like mass as they became dry. This mass was soluble only in water and did not prove obtainable from water-acetone or other solvent pairs. The experiment was repeated and the solid was not allowed to dry on the funnel. However these too formed a tar-like substance in solution and isolation of any pure product of this reaction was not realized.

The reaction did serve to lend some evidence of an N-nitroso intermediate, as similar color changes and temperature rises were observed by Dr. Samour in reacting an N,N-dinitrosoalkane with p-nitrobenzaldehyde.[32]

2. - Reaction of Phenol with the Generated Diazo Alkane



Procedure 1.

In a 500 ml. flask fitted with a thermometer and stirring device was inserted a solution of 10g.(0.03 moles) of the N-nitroso compound in 100 ml. of water.

The temperature of the solution was initially 28° C. Two pellets of sodium hydroxide were added and the solution was stirred continuously. After one minute of reaction, the inside walls of the vessel became cloudy and the solution went from a yellow to a deep brown color. The final temperature after ten minutes was 31° C.

Three and one half grams (excess) of phenol was added to the solution and the color changed immediately from a red-brown to a milky, dense tan color. After seven minutes of reaction the solution became clear and retained its tan coloration. The final temperature of the solution was 31.5° C.

After an additional hour of reaction time, the solution was vacuum distilled at room temperature to a

brown syrup which was soluble only in water and quite hygroscopic. This syrup was derivatized as described in the discussion which follows.

Procedure 2.

This procedure was identical to the previous except that the solvent used was absolute ethanol. The N-nitroso syrup (0.3 g.) was triturated in absolute ethanol and a pellet of sodium hydroxide was added to the solution. The solution turned cloudy quite quickly and after three minutes reaction the temperature had increased by 2°C. An alcoholic solution of phenol (0.2 g., excess) was added slowly with stirring and the temperature increased by one degree Centigrade.

After stirring for three hours the volume of the reaction mixture was concentrated by vacuum distillation at room temperature to a yellow syrup. A small amount was dissolved in ethanol and a large excess of ethyl ether was added. No crystals or precipitate was isolated. A water-acetone pair produced a tiny portion of crystals in a period of three weeks. Analysis showed a large amount of inorganic residue (some sodium acetate from the nitrosation step which remained dissolved in the ethanol solution), and thus gave poor values for carbon and hydrogen, but nitrogen analysis showed 0.0% nitrogen in the sample. The crystals charred at 165-70°C with no melting or further decomposition. The experiment was repeated twice, but none of the

syrups obtained yielded any crystalline product when treated in a similar manner.

The syrup product obtained from both procedures was used to make derivatives for analysis.

Derivatives attempted.

1. - The benzoate derivative, made by the method of Shriner, Fuson and Curtin[34] gave evidence of reaction (a large quantity of heat evolved) but no solid product, merely a gummy oil. Attempts to purify and crystallize this gum were futile.

2. - The 3,5-dinitrobenzoate derivative was prepared according to the method of Cheronis and Entrikin[35], The final benzene-ether solution was washed with dilute sodium hydroxide, dilute hydrochloric acid, and water. The benzene-ether layer was evaporated to dryness and the resulting solid material was dissolved in boiling absolute ethanol. Water was added until a slight turbidity persisted and the solution was left to cool in the refrigerator. After two days, a yellow solid material melting at 136-8°C was collected. After several re-crystallizations some material was obtained melting at 137-9°C, and another sample 135-6°C. Both samples were sent for analysis.

The tetra (3,5-dinitrobenzoyl) derivative crystallizes with three moles of benzene per mole of material.

Analyses on both samples are given below:

Calculated for $C_{40}H_{26}N_8O_{26}\cdot 3C_6H_6$

C = 54.8%; H = 3.46%; N = 8.80%

Found:

Sample 1: C = 54.37%; H = 3.19%; N = 8.92%

Sample 2: C = 55.17%; H = 3.60%; N = 8.14%

Sample 1 - m.p.137-9°C ; Sample 2 - m.p.135-6°C

Further recrystallizations did not change the melting point on either sample.

3 - The acetate derivative was prepared by suspending the syrup of the phenol reaction in pyridine and adding acetic anhydride with constant stirring. A large quantity of heat was evolved and the solution became red-brown. After the reaction was left to preceed for two hours, the volume of solution was decreased (by means of an air jet) and the solution was poured into a large volume of water. A thick brown paste resulted which did not crystallize upon trituration. Various solvents and solvent pairs such as ethanol-water, ethyl acetate-petroleum ether, ethyl acetate-water etc., gave no crystalline material. When dissolved in benzene and petroleum ether was added, a small amount of white product appeared which reverted to a brown syrup when taken out of the solution.

The syrup was triturated in water to remove any excess acetic acid and dissolved in ethyl ether. As much remaining water as possible was removed by means of a separatory funnel, and the ether solution was filtered and evaporated to dryness at room temperature. The resulting clear gold colored syrup was sent for analysis.

Analysis showed that the penta-acetyl derivative crystallizes with three moles of water per mole of material in analogous fashion to the nitrobenzoyl derivative, which crystallized with three moles of benzene per mole of material. The presence of three molecules of water of crystallization is easily proved by heating the sample in an air oven at 125°C for one hour. The loss in weight, about eleven percent, corresponds closely to that required by the loss of three moles of water of crystallization per mole of penta-acetate.

Calculated for $C_{22}H_{28}O_{11} \cdot 3H_2O$:

	C = 50.5%;	H = 6.49%;	N = 0.0%
Found:	C = 50.01%;	H = 6.18%;	N = 0.83%

The small percentage of nitrogen is bothersome, but can be attributed to contamination either by the acetylation solvent (pyridine) or by unchanged nitroso material, 4,4-dimethyl-N-nitroso-5-aza-7,8,9,10,11-pentahydroxy-2-undecanone. However, the fact that the nitrogen content

of the product is only a fraction of a percent does indicate that the greater part of the nitroso intermediate must have reacted, since the starting material contains 9.15% nitrogen.

If we make the assumption that the nitrogen in the product is entirely due to contamination by 8.3% of nitroso intermediate, we observe much better analytical agreement.

Calculated for mixture: 92% of desired penta-acetyl derivative
8% nitroso intermediate

C = 50.27%; H = 6.51%; N = 0.73%

Observed:

C = 50.01%; H = 6.18%; N = 0.83%

In order for the nitrogen percentage to correspond to one gram atom of nitrogen per formula, the compound would have to have a molecular weight of 1,690, or roughly six times the molecular weight of the ether product.

Conclusions:

The synthesis of these compounds would present less difficulty if the hydroxyl groups are protected from the beginning. The main problem is in the identification of the compounds, since most of them are obtained in syrup form.

The feasibility of the synthesis is limited by the difficulty of isolation and by the low yield of pure galactosamine.

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