p-benzoquinone, for example, owes its strength as an oxidizing agent not so much to a particularly active carbonyl group, but rather to the tendency of its reduction product to rearrange to a benzenoid system.

Additional evidence has been given to support the supposition that the alcohol–ketone–aluminum *t*-butoxide systems come to a true equilibrium. The technique and procedures for equilibration and analysis of these reaction mixtures have been improved.

The lack of correlation between the depolarization potential of a carbonyl compound at a dropping mercury cathode and its true oxidation potential has been demonstrated.

MADISON, WISCONSIN RECEIVED AUGUST 19, 1940

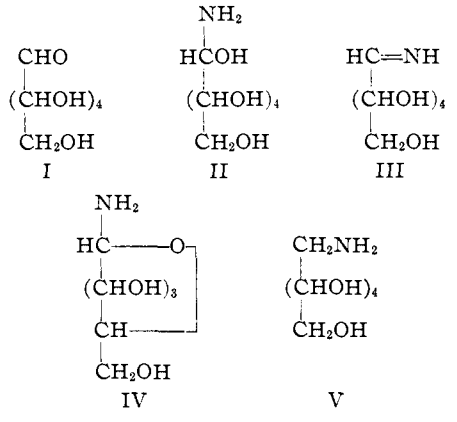
[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

d-Glucamine from *d*-Glucose

BY WINSTON WAYNE[1] AND HOMER ADKINS

The success realized in this Laboratory three years ago in the direct preparation of primary amines by the hydrogenation over Raney nickel of an aldehyde or ketone in an ammonia–methanol solvent, prompted an extension of the method into the sugar series.[2] The present paper is concerned with the preparation of glucamine from glucose.

The aldehyde form of *d*-glucose, I, may add ammonia to give *d*-glucoseammonia, II, which may then lose water to give *d*-glucoseimine for which both an imine, III, and a pyranose, IV, structure have been proposed. The hydrogenation of glucoseimine or the hydrogenolysis of glucoseammonia would give *d*-glucamine, V.



Glucamine was first prepared by the sodium amalgam reduction of glucoseoxime.[3] Later Neuberg and Marx[4] used calcium turnings instead of sodium amalgam. Roux in an excellent review paper[5] has described the purification of the compound and its physical and chemical properties. Ling and Nanji[6] reported the hydrogenation over nickel of glucose-ammonia to glucamine. They also used electrolytic reduction and aluminum amalgam. A patent was issued to Flint and Salzberg covering the hydrogenation over nickel of monosaccharides in the presence of ammonia.[7] It is difficult to evaluate these various processes for data are lacking as to the purity of the product. In fact our experiments soon showed that the difficulty in obtaining glucamine was not in the hydrogenation stage but in the isolation of the compound.

It seemed desirable therefore to start with pure glucoseimine (III or IV) and thus perhaps avoid some of the reactions and products possible with a mixture of glucose and ammonia. Attempts were therefore made to repeat the preparation according to Muskat,[8] who obtained glucoseimine by dissolving glucose in liquid ammonia, evaporating the excess ammonia, washing the product with alcohol and drying. The material obtained differed greatly in physical characteristics from the *d*-glucoseimine prepared in the usual manner and from the material reported by Muskat.[9]

(1) Research assistant on funds from the Wisconsin Alumni Research Foundation.

(2) This method was apparently first used by C. F. Winans for the preparation of furfurylamines from furfural. His U. S. Patent 2,109,159 (1938) was issued after the completion of the experimental work described by Schwoegler and Adkins, THIS JOURNAL, **61**, 3499 (1939).

(3) Maquenne and Roux, *Compt. rend.*, **132**, 980 (1901).

(4) Neuberg and Marx, *Biochem. Z.*, **3**, 539 (1907).

(5) Roux, *Ann. chim. phys.*, [8] **1**, 77 (1904).

(6) Ling and Nanji, *J. Chem. Soc.*, **121**, 1682 (1922).

(7) Flint and Salzberg, U. S. Patent 2,016,962, Oct. 8, 1935.

(8) Muskat, THIS JOURNAL, **56**, 693 (1934).

(9) *d*-Glucoseimine prepared by the method of Lobry de Bruyn was very slightly hygroscopic and had a m. p. of 130–131°; $[\alpha]^{25}D$ +21.0 after 15 min.; +22.6 after 24 hr. (*c*, 4; H_2O). The material obtained by Muskat's procedure was very hygroscopic and had a m. p. of 49–51°; $[\alpha]^{25}D$ +26.1 after 20 min.; + 20.1 after 24 hr. (C, 5.5; H_2O). It will be observed that the specific rotations of the

Glucoseimine was prepared by a modification of the Lobry de Bruyn method in good yield and quality.[10] However, upon hydrogenation this compound behaved just as did an equivalent amount of glucose and ammonia. It was found that the best method for isolating glucamine was as the benzal derivative, and that it was just as easy to obtain a good product from the hydrogenation of glucose and ammonia as it was in the cases where glucoseimine had been obtained as a pure compound. The yield of glucamine—isolated and weighed as benzalglucamine—was about 26% of the theoretical amount based upon the compound hydrogenated. In one hydrogenation a higher yield of glucamine was obtained from glucoseimine, but this result could not be duplicated. The yield of glucamine based upon glucose was only 12% in the case of glucoseimine since the latter was obtained in 46.5% yield from glucose. The direct hydrogenation of glucose and ammonia in methanol thus gives more than twice as good yields as does the hydrogenation of glucoseimine and avoids the rather laborious preparation of that compound. Glucoseoxime was also hydrogenated to glucamine under conditions similar to those noted above, but the yield of glucamine was only 15% based upon the oxime or 8% based upon glucose.

It is thus clear that the best method for obtaining glucamine by catalytic hydrogenation so far reported is as follows.

The reactants, glucose (0.11 mole), dry ammonia (0.55 mole) were made up to 120 ml. with dry methanol, and shaken for thirty minutes under a pressure of 155 atm. of hydrogen and ammonia. The mixture was then heated within twenty minutes to 100° where hydrogenation began. The temperature was allowed to rise to 115° but no higher, and the rocking of the reaction vessel continued until the adsorption of hydrogen ceased after forty to sixty minutes. The drop in pressure in the reaction vessel was considerably greater than corresponded to the absorption of one mole of hydrogen per mole of glucose. Presumably this was on account of the decrease in the pressure of ammonia, although it may be in part due to hydrogenolysis.

The product, after being filtered through asbestos into a 500-ml., round-bottomed flask, was concentrated without ebullition at the water pump at a bath temperature of 50-60° to remove the solvent and ammonia. Except in the case of *d*-glucoseoxime the product was a light brown, semi-crystalline solid (18–20 g.). The material in the still-head and clinging to the walls of the flask was washed to the bottom by refluxing with absolute methanol (25 to 30 ml.). Benzaldehyde, which had been rendered free of benzoic acid in the usual manner and stored under nitrogen in the presence of a few milligrams of hydroquinone, was added in a molecular amount twice that of the original material hydrogenated. After attaching a condenser set for distillation, the flask was heated with a Wood's metal bath which was held in the vicinity of 100° while the methanol distilled. After distillation had nearly stopped the bath was rapidly heated to 180 to 190° and held there for two to three minutes while the reaction mixture boiled. The bath was then removed and after the dark brown sirup had cooled somewhat it was diluted with dry methanol (50 to 75 ml.), whereupon it crystallized. After cooling in an ice–salt mixture, the yellow brown solid was filtered and the dark brown filtrate concentrated without ebullition at the water pump, the bath temperature eventually reaching 100°, whereby most of the excess benzaldehyde was removed. The black residue was taken up in a small amount of absolute methanol and after cooling, scratching and seeding a small second crop of crude benzalglucamine was obtained. The crude material was purified by two or three recrystallizations from dry methanol using Norit. The mother liquids were concentrated without ebullition at the water pump at a bath temperature of 40 to 50°, recrystallizing the material obtained and again working up the mother liquors to give a total yield of 7.8 g. The benzalglucamine crystallized from dry methanol as clusters of fine, light cream needles with m. p. 161.5–162.5° with slight decomposition. Roux reported the melting point as 162 to 163°.

The hydrolysis of the benzalglucamine and separation of the products was accomplished by steam-distillation as suggested by Roux. Certain precautions were taken during the hydrolysis of the benzalglucamine to prevent the benzaldehyde formed from being oxidized to benzoic acid before it was removed and to prevent the glucamine from being contaminated with carbon dioxide. A 500-ml., round-bottomed flask was fitted with a gas inlet tube, a mechanical seal stirrer and a downward condenser by means of ground-glass joints. Distilled water (275 ml.) was placed in the flask and heated to boiling, by means of an oil-bath held at 170°. The solution was stirred and a steady stream of nitrogen passed over the surface. After dissolved oxygen was removed (10 to 20 ml. of distillate was collected) the distillation was interrupted, the finely ground benzalglucamine (8 g.) was quickly added and the distillation resumed. The distillation was very rapid, 100 ml. of distillate being collected in fifteen minutes, and was continued until about 225 ml. of distillate was received. The flow of nitrogen was then stopped and the remainder of the water removed under the reduced pressure of a water pump with continued stirring, without ebullition, and with the heating bath at 90°. When the liquid was practically gone and the contents of the flask had started to solidify, the evaporation was stopped and the flask quickly transferred to a vacuum desiccator charged with phosphorus pentoxide. After being dried under reduced pressure, the glucamine was obtained in quantitative yield (5.4 g.) as a

two substances changed with time in opposite directions. Muskat gave a m. p. of 121°; $[\alpha]^{26}D$ +17.6 (0.048 g. in 5 cc. H_2O) for his compound. While the physical characteristics of *d*-glucoseimine as described in the literature have varied somewhat, no variation of this degree has been reported before. The only insight to the structure of the compound obtained in attempting to follow Muskat's procedure is that it yields *d*-glucamine upon catalytic hydrogenation in the presence of ammonia.

(10) Lobry de Bruyn, *Rec. trav. chim.*, **14**, 93 (1895).

white, amorphous appearing solid tinged with yellow, m. p. 123–125°; neut. equiv. 181, 183; $[\alpha]^{25}D$ −7.2 (*c*, 3.7; H_2O). A sample of the glucamine (2.6 g.) was dissolved in the least possible amount of hot absolute methanol, filtered hot, cooled in an ice–salt mixture and the curdy precipitate quickly filtered, pressed as dry as possible and dried *in vacuo* over phosphorus pentoxide. The white solid (2.02 g.) softened at 123° and melted indistinctly at 127–128°; $[\alpha]^{25}D$ −7.5 (*c*, 2.7; H_2O). The neut. equiv. was found to be 179 to 180° as compared with a value of 181 calculated for *d*-glucamine. The methanol filtrate was concentrated to yield an additional 0.33 g. of a slightly yellow solid, m. p. 127–128°. Roux gives for *d*-glucamine m. p. 128°, $[\alpha]^{15}D$ −7.9 (*c*, 10; H_2O).

It seems unnecessary to detail the long series of experiments which were made in attempting to obtain pure glucamine. No definite information has been gained through them with respect to products of the hydrogenation other than glucamine. The hydrogenation goes smoothly and the neutral equivalent of the crude product indicates that 80% or more of the glucose has been converted to basic compounds. The use of the methods recommended by Roux and by Flint and Salzberg did not give us products which were pure, although it is rather simple to obtain a product in good yield which has a neutral equivalent in the vicinity of 200. Such products are unquestionably mixtures.

Summary

d-Glucose in a methanol–ammonia solution reacts smoothly with hydrogen over Raney nickel at 100–115° at 150 atm. within less than an hour, to give a mixture of products, from which *d*-glucamine may be separated in 26% yield as the benzal derivative. Pure *d*-glucamine may be obtained quantitatively by the hydrolysis of the benzal derivative.

MADISON, WISCONSIN RECEIVED AUGUST 26, 1940

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

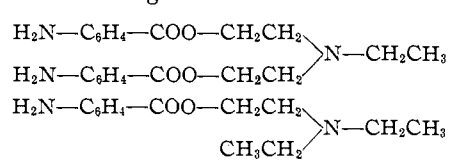
Local Anesthetics in the Naphthalene Series[1]

BY F. F. BLICKE, H. C. PARKE AND E. L. JENNER

A short time ago[2] we described the preparation of twenty-one dialkylaminoalkyl esters of 3-, 4-, 5- and 6-amino-1-naphthoic acids. A number of these have been shown[3] to be strong local anesthetics.

In view of the very favorable properties of many esters in this series and in particular of β-diethylaminoethyl 4-amino-1-naphthoate, the naphthalene analog of procaine, our study has been extended to include certain dialkylaminoalkyl and dialkylaminoalkoxyalkyl[4] esters of 4-amino-1-naphthoic, 5-amino-1-naphthoic and 5-amino-2-naphthoic acids. Furthermore, a number of dialkylaminoalkylamides[5] of 4-amino-1-naphthoic acid have been prepared.[6]

In addition we have synthesized the di-4-aminobenzoyl derivative of ethyldi-β-hydroxyethylamine. Its relationship to procaine is apparent from the following formulas



Procaine

The esters and amides were obtained by interaction of the required dialkylamino alcohol or dialkylaminoamine and the nitro acid chloride with subsequent reduction of the nitro group in the nitro ester or nitro amide.

The hydrochlorides of the esters and amides have been tested pharmacologically by L. W. Rowe in the Parke, Davis and Company Laboratories and a detailed report will be published by him in another journal. All of the compounds exhibited activity to some degree but the amides were found to be much less satisfactory as local anesthetics than the esters.

The di-4-aminobenzoyl derivative of ethyldi-β-hydroxyethyl-amine[7] is a weak anesthetic.

(1) We wish to express our indebtedness to Parke, Davis and Company, whose support made this investigation possible.

(2) Blicke and Parke, THIS JOURNAL, **61**, 1200 (1939).

(3) Rowe, *J. Am. Pharm. Assoc.*, **29**, 241 (1940).

(4) Ruberg and Shriner (THIS JOURNAL, **57**, 1581 (1935)) have shown that dialkylaminoalkoxyalkyl esters of 4-aminobenzoic acid are strong local anesthetics.

(5) A few alkyl- and dialkylamides of 4-aminobenzoic acid have been found by Wenker (*ibid.*, **60**, 1081 (1938)) to exhibit local anesthetic activity. The β-diethylaminoethylamide of 2-butoxyquinoline-4-carboxylic acid (nupercaine) has been on the market for some years.

(6) We wish to call attention to the recent publications of Cook and Hill (*ibid.*, **62**, 1995, 1998 (1940)) who have discovered the local anesthetic activities of esters of 2-dialkylamino-3-hydroxy- and 1-dialkylamino-2-hydroxy-1,2,3,4-tetrahydronaphthalenes.

(7) Pyman (*J. Chem. Soc.*, **93**, 1796 (1908)) stated that the corresponding dibenzoyl compound has very little local anesthetic action; the dibenzoyl derivative of methyldi-(γ-hydroxypropyl)-amine, likewise, seems to be only slightly active (Wichura, *Z. exptl. Path. Therap.*, **20**, 11 (1919)).