Electrosynthesis of Glycamines

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1-Amino-1-deoxypentitols and 1-amino-1-deoxyhexitols were obtained by electroreduction of the corresponding oximes of D-arabinose, L-arabinose, D-ribose, D-xylose, D-lyxose, D-glucose, D-mannose, and D-galactose. These oximes were prepared *in situ* by treatment of the respective aldoses with hydroxylamine in an acetate buffer of pH from 4 to 6, or directly with hydroxylammonium acetate. The electrolysis was carried out in a divided electrolyzer on a mercury working cathode and an auxiliary anode separated by a cation-selective membrane.

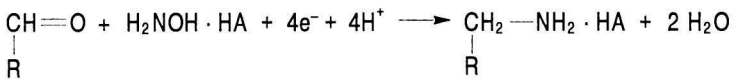
Although some attention has been paid to develop the synthesis of glycamines since the beginning of this century, still optimal economic routes for their preparation have not been worked out. The most frequented preparation of glycamines is based on the catalytical reductive alkylation of ammonia with monosaccharides [1—3] and alternatively, by catalytic hydrogenation of the respective oximes [4], hydrazones [5] or phenylhydrazones [6]. The required product synthesized according to the first method was accompanied with four by-products [7]. Also electroreduction of small amounts (0.5—1.0 g) of monosaccharide oximes was reported in the pH range from 6 to 7, *i.e.* out of the optimal pH values for formation of oximes and their electroreduction [9—11]. The noticeable position of glycamines as intermediates in organic and pharmaceutical chemistry stimulated us to optimize the electrochemical preparation method.

RESULTS AND DISCUSSION

The rate of formation and equilibrium of oximes being formed during the reaction of carbonyl compounds with hydroxylamine depend on the pH value of the medium and acid-base properties of the reactants. Whereas the reaction rate of oxime formation reveals a maximum in an acid medium [9—13], values of equilibrium constants of oxime formation rise with the increasing pH value of the medium and reach maxima in the alkaline region [14]. As known, only protonized forms of oximes are capable of electrochemical reduction [9, 10, 15—17] and therefore, it was necessary to choose such pH values of the medium as to attain optimum among the formation rate, equilibrium value and protonization stage of the oxime. As it follows, it would be useless to start from oximes and carry out electroreductions out of the optimal pH region. The half-wave potential values of oximes and hydroxylamine approximate with the rising pH value and the polarographic wave heights of oximes drop; consequently, influence of decreasing acidity of the medium of pH greater than 6 [8] is unfavourable. Thus, electroreduction of the D-glucose oxime proceeds at half-wave potentials by 400 mV, 300 mV, and 100 mV more positive than with hydroxylamine at the respective 3.6, 4.6, and 5.6 pH values. The polarographic wave of D-glucose oxime decreases at pH 4.6 and 5.6 to 80 % and 25 %, respectively, when compared with that at pH 3.6.

Aldose oximes were prepared usually by dissolving the appropriate aldose in aqueous acetate buffer of pH 4.6 of sufficient capacity to which hydroxylammonium salts (sulfate, chloride) were added. Formation of oximes is reflected in a decrease of the pH values due to replacement of the more basic hydroxylamine by the five orders less basic oxime. Basicity of hydroxylamine expressed by the pK_a value of the conjugated acid is 6.0, that for acetone oxime is 0.99 only [18]. The pH value of the medium was adjusted by addition of sodium hydroxide to the optimal range from 4 to 6. Equilibrium of the oxime formation attained after several hours was manifested by a constant pH value. It is advantageous to use hydroxylammonium acetate, fulfilling all functions of an acetate buffer and a better isolation of the glycosamine as well.

The electroreduction takes place in a divided electrolyzer, the cathodic compartment being separated from the anodic one by a cation-selective membrane. Advantage of this arrangement is that protons generating in the anodic section and migrating through the cation-selective membrane into the cathodic section are consumed in the four-electron reduction of oximes to glycamines (Scheme 1), so that only acid, necessary to neutralize the glycamine formed, has to be added ei-



R = saccharide residue
HA = acid

Scheme 1

ther automatically (pH-statically) or sporadically in greater amounts.

Formation of both the aldose oximes from the starting compounds and glycamines by electroreduction of oximes was monitored by analytical polarographic and chromatographic methods. Formation of oximes was monitored polarographically in a formate buffer of pH 3.6 and consumption of hydroxylamine in a carbonate buffer of pH 10. Both processes can also be monitored, due to a greater mobility of oximes and a lower mobility of glycamine salts, by paper chromatography in acetone—n-butanol—water (φ_r = 7 : 2 : 1).

Completeness of the chemical and electrochemical processes of glycamine formation and mainly the possible origination of by-products [7] are the determining factors regarding the yield and quality of glycamines. Our improvement of electroreduction afforded glycamines in high yields and purity. The reactivity of glycamines *via* Schiff bases was quite different; 1-amino-1-deoxyarabinitols react easily with benzaldehyde to give colourless crystalline 1-benzylidenamino-1-deoxyarabinitols, whereas the reactivity of benzaldehyde is insufficient to produce the analogous 1-benzylidenamino-1-deoxy-D-ribitol and -D-xylitol, for which the more reactive salicylaldehyde had to be used. This fact might be rationalized by a different conformation of the sugar moieties [19].

EXPERIMENTAL

As already mentioned, the electrosynthesis of glycamines was carried out in a divided electrolyzer having the cathodic compartment separated from the anodic one by a cation-selective membrane. The working electrode was constituted by an approximately 1 cm layer of mercury at the bottom of a 2 dm^3 beaker of 13 cm i.d. An 800 cm^3 glass tube of 9 cm i.d. passing through a nylon stopper into the beaker was equipped with a cation-selective membrane at its bottom. The auxiliary electrode made of platinum-coated titanium had the form of a 15 cm high cylinder of 5.5 cm i.d. The distance between the mercury surface of the cathodic section and the cation-selective membrane separating the anodic compartment was about 3 cm. The stopper had, in addition to the mean hole housing the anodic compartment, further ones for glass electrode measuring the pH out of the influence of electric field [20], for reference electrode, for withdrawing samples for analytical monitoring and an inlet for addition of acid. Catholyte was the reaction solution, anolyte 0.2 M-H_2SO_4. Cooling was provided by an immersion glass cooler localized inside the anode. Magnetic stirrer assured vigorous stirring of the mercury surface. Source for the DC current was the loading device NB 20 C. The classic polarograph LP 7 served for polarographic analyses and Titrator TTT 2 for monitoring the pH values of the medium. Optical rotation was measured with a Perkin—Elmer, model 241 polarimeter; the m.p. values are uncorrected.

1-Amino-1-deoxy-D-arabinitol

Hydroxylammonium sulfate (61.5 g; 0.75 mol) was added to D-arabinose (75 g; 0.5 mol) dissolved in 1 M acetate buffer of pH 4.6 (500 cm^3). Formation of the oxime was accompanied with a decrease of the pH value, which was adjusted with aqueous sodium hydroxide (40 g) to 5.6. The solution, filled up to 700 cm^3 and allowed to react overnight, was poured into the cathodic compartment of the electrolyzer; the anodic one was filled with 0.2 M-H_2SO_4 in such an amount so as both surfaces were at the same level. The electroreduction was carried out at 25 °C with stirring. The initial current density 2.5 A dm^{-2} was reduced during the reaction to 0.8 A dm^{-2} and the adjusted pH value (5.6) was maintained pH-statically by an automatic addition of 5 M-H_2SO_4. The completely reduced mixture was neutralized with sodium hydroxide to pH 7. Additional sodium hydroxide (30 g; 0.75 mol) was added to release 1-amino-D-arabinitol and ammonia originating by reduction of the excess of hydroxylamine. The glycamine was precipitated with benzaldehyde (55 cm^3, 57.4 g; 0.54 mol) as 1-benzylidenamino-1-deoxy-D-arabinitol. The precipitated crystals were filtered off, washed first with water to SO_4^{2-} negative reaction of the filtrate and then with ether and dried in air. Yield 102 g (85.3 %) of 1-benzylidenamino-1-deoxy-D-arabinitol.

1-Amino-1-deoxy-D-arabinitol was freed from the 1-benzylidenamino derivative (50 g) by distillation with steam and the residue was crystallized from methanol. Yield 28.5 g (90.2 %), m.p. = 95—97 °C, [α](D, ρ = 40 g dm^{-3}, H_2O) = + 3.8°; Ref. [3] gives m.p. = 114—120 °C (decomp.), [α](D) = + 4°.

1-Ammonium-1-deoxy-L-arabinitol Chloride

Concentrated hydrochloric acid (42 cm^3; 0.48 mol) was added gradually to a stirred and refluxed solu-

tion of 1-benzylidenamino-1-deoxy-L-arabinitol (102 g; 0.46 mol) in water (80 cm^3), prepared analogically as its D-enantiomer. After 15 min the cooled upper layer (benzaldehyde, 42 cm^3) was separated and the aqueous one extracted with ether (2 × 30 cm^3) was heated to 65 °C. Methanol (450 cm^3) was added and the clear solution was left standing in a refrigerator. Yield 69 g (73.6 %) of the title compound. The filtrate after separation of crystals was concentrated to a sirupy consistence; addition of methanol (40 cm^3) afforded another 9.3 g (9.9 %), so that the total yield of 1-ammonium-1-deoxy-L-arabinitol chloride was 78.3 g (83.5 %), m.p. = 134—136 °C, $[\alpha](D, \rho = 10\ g\ dm^{-3}, H_2O) = -13.2°$.

1-Ammonium-1-deoxy-D-xylitol Chloride

Hydroxylammonium sulfate (61.5 g; 0.75 mol) was added to a solution of D-xylose (75 g; 0.5 mol) in 1 M acetate buffer of pH 4.6 (500 cm^3). The pH value was adjusted with NaOH (23 g) to 4.6 and the mixture was electroreduced as in the preceding experiment, but at 4.0 A dm^{-2} current density, which was lowered to its half at the end-stage. After 11 h, the solution was made alkaline with NaOH to liberate 1-amino-1-deoxy-D-xylitol and ammonia. The mixture was evaporated to a sirup under reduced pressure and ethanol (300 cm^3) was poured into the ammonia-removed residue. The sirup was then heated and allowed to stand, and the separated sodium sulfate and sodium acetate, making the isolation difficult, were filtered off. The sirup, from which the substantial portion of salts was removed, was dissolved in water (300 cm^3) and then salicylaldehyde (60 cm^3, 68.8 g, 0.56 mol) was introduced with stirring. The separated yellow 1-deoxy-1-salicylidenamino-D-xylitol was filtered off, washed with water and ether and dried in air. Yield 105.5 g (82.7 %), m.p. = 124—128 °C.

1-Ammonium-1-deoxy-D-xylitol chloride was prepared from the salicylidene derivative dissolved in water (100 cm^3) by a gradual addition of concentrated hydrochloric acid (38 cm^3; 0.43 mol) to the refluxing solution in a nitrogen atmosphere. The salicylaldehyde (40 cm^3) released after 15 min was separated from the cooled mixture and the aqueous layer, extracted with ether (2 × 30 cm^3) was heated to 65 °C. Methanol (400 cm^3) was then added and the mixture was left crystallizing as in the preceding experiment. Yield 69.7 g (79.3 %), m.p. = 139—140 °C, $[\alpha](D, \rho = 10\ g\ dm^{-3}, H_2O) = -12.3°$; Ref. [4] reports m.p. = 139—140 °C.

1-Ammonium-1-deoxy-D-lyxitol Bromide

Sodium hydroxide was added to the solution of D-lyxose (75 g; 0.5 mol) and hydroxylammonium sulfate (61.5 g; 0.75 mol) in 1 M acetate buffer of pH 4.6 (500 cm^3) to keep the pH value at 4.6. The solution was electroreduced for 12 h at 4 A dm^{-2} initial current which was lowered to its half at the end. The solution was then worked up as described in the preceding experiment with the same amounts of ethanol, water and salicylaldehyde. Yield of 1-deoxy-1-salicylidenamino-D-lyxitol was 109.4 g (85.7 %), m.p. = 182—183 °C. It was reported [4] that 1-ammonium-1-deoxy-D-lyxitol chloride cannot be obtained in crystalline form and therefore we isolated it as bromide as follows: hydrobromic acid (48 %, 52 cm^3, 77.5 g; 0.46 mol) was added gradually to a stirred solution of 1-deoxy-1-salicylidenamino-D-lyxitol (109.4 g; 0.43 mol) in water (100 cm^3) and the mixture was heated to 100 °C. Salicylaldehyde (41 cm^3) separating from the aqueous layer of 1-ammonium-1-deoxy-D-lyxitol bromide after 15 min of heating was removed and the aqueous layer extracted with ether (2 × 30 cm^3) was concentrated. The residue was dissolved in methanol (200 cm^3) with heating and the crystals separating on cooling were filtered off. The second crop of this bromo derivative was obtained after evaporation of the mother liquor to 70 cm^3. Combined yield of the title product was 97.8 g (84.3 %), m.p. = 103.5—104.5 °C, $[\alpha](D, \rho = 10\ g\ dm^{-3}, H_2O) = +3.5°$.

1-Amino-1-deoxy-D-ribitol

To D-ribose (75 g; 0.5 mol) dissolved in aqueous hydroxylamine (19.8 g, 0.6 mol, 500 cm^3) concentrated acetic acid was added to adjust the pH value to 6. Decrease of the pH value due to formation of the oxime stopped at 3.8 already after 1 h and remained constant to the next day. The mixture filled up with water to 650 cm^3 was electroreduced as in the preceding experiments without the pH of the mixture being somehow influenced. 1-Amino-1-deoxy-D-ribitol, originating during the reduction enhanced the pH value of the medium and therefore greater amounts of concentrated acetic acid had to be added to maintain the pH within 4 and 6, preferentially within 4.5 to 5.5. The solution was desalted after the 14 h lasting reduction on a strong basic anion exchanger IRA 420, concentrated under diminished pressure and freeze-dried to afford the sirupy 1-amino-1-deoxy-D-ribitol (70.5 g, 93.3 %), $[\alpha](D, \rho = 40\ g\ dm^{-3}, H_2O) = -1.5°$. Ref. [3] reports $[\alpha](D)$ of the sirup as being + 5°.

1-Amino-1-deoxy-D-glucitol

The 20 h lasting reaction of D-glucose (90 g; 0.5 mol) with hydroxylammonium acetate (1.5 M, 0.75 mol, 500 cm^3) of pH 5.4 resulted in the change of pH decreasing to 4.2. This solution was electrolyzed

at 3.4 A dm^{-2} for 10 h, then a further amount of hydroxylammonium acetate (1.5 M, 0.25 mol, 166.7 cm^3) was added and the mixture was allowed to react for 2 h. The current was then switched on and the electroreduction continued at 1.7 A dm^{-2} for 6 h. The aqueous solution of 1-amino-1-deoxy-D-glucitol, desalted over the strong basic ion exchanger IRA 420, was concentrated and the residue was crystallized from methanol to yield 83.4 g (93 %) of crystalline product of m.p. = 131.5—133 °C, $[\alpha](D, \rho = 40 \text{ g dm}^{-3}, H_2O) = -7.2°$; Refs. [4, 21] report m.p. = 126.5—128.5 °C, $[\alpha](D) = -6.9°$.

1-Amino-1-deoxy-D-galactitol

The solution of D-galactose (80 g; 0.5 mol) and hydroxylammonium sulfate (61.5 g; 0.75 mol) in 1 M acetate buffer of pH 4.6 was adjusted to pH 5 with sodium hydroxide; this value was kept constant during the electroreduction (11 h) pH-statically. The mixture was then neutralized, 1-amino-1-deoxy-D-galactitol freed by addition of sodium hydroxide as in the preceding experiments was converted with benzaldehyde (55 cm^3, 57.4 g, 0.54 mol) to the corresponding benzylidenamino derivative, which was filtered off and washed with water to the sulfate-negative reaction of the filtrate. Yield 102.6 g (76.2 %), m.p. = 191—193 °C. The benzylidene derivative (50 g) was steam-distilled to give 1-amino-1-deoxy-D-galactitol (30.6 g, 91.0 %), m.p. = 148.5—150 °C (dilute methanol), $[\alpha](D, \rho = 40 \text{ g dm}^{-3}, H_2O) = -1.5°$. Ref. [7] reports m.p. = 143—145 °C, $[\alpha](D) = -1°$.

1-Amino-1-deoxy-D-mannitol

Hydroxylammonium chloride (52.1 g; 0.75 mol) was added to the solution of D-mannose (90 g; 0.5 mol) dissolved in 1 M acetate buffer of pH 4.6 (500 cm^3). The insoluble oxime precipitated immediately after addition of sodium hydroxide (23 g) and therefore the electroreduction began already at pH 4. The pH value increased to 6 during the reduction, whereas the precipitate started to disappear due to formation of 1-amino-1-deoxy-D-mannitol. The pH was kept at lower value than 6 by adding 5 M-H_2SO_4 at the end of this reaction lasting 11 h. The mixture was then neutralized, the product was liberated with sodium hydroxide and converted into its benzylidene derivative with benzaldehyde (55 cm^3, 57.4 g, 0.54 mol) as described previously. The yield of benzylidenamino-1-deoxy-D-mannitol was 109.5 g (81.3 %); steam distillation of 50 g afforded the title product in a 87.4 % yield (29.3 g), m.p. = 136.0—137.5 °C (dilute methanol), $[\alpha](D, \rho = 40 \text{ g dm}^{-3}, H_2O) = -2.5°$; Ref. [3] reports m.p. = 134—135 °C (decomp.), $[\alpha](D) = +1°$.

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