[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Sodium Borohydride as a Reducing Agent in the Sugar Series[1]

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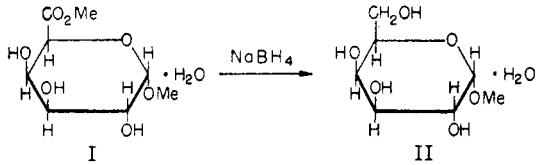
Sodium borohydride has been employed in aqueous solution to effect the following reductions: D-lyxono-γ-lactone to D-lyxose (or D-arabitol); D-glucuronate and D-galacturonate salts to L-gulono-γ-lactone and L-galactono-γ-lactone, respectively; methyl (methyl α-D-galactopyranosid)-uronate (I), its β-D-anomer and methyl (methyl D-glucopyranosid)-uronate to the methyl pyranosides of α-D-galactose (II), β-D-galactose and α-D-glucose, respectively.

Sodium borohydride[3,4] has been stated[5-9] to be a useful reducing agent in the sugar series. In continuation of our previously recorded[5] preparative work, we report herein the reduction with this reagent of D-lyxono-γ-lactone to D-lyxose or, alternatively, to D-arabitol. In combination with our published[10] simplified procedure for the preparation of D-lyxono-γ-lactone from D-galactose, the rare pentose D-lyxose thus becomes relatively available. Turning our attention to the uronic acids, we find that their salts may be employed in the reduction of their aldehyde groups; thus the D-glucuronate and D-galacturonate ions yielded L-gulonic acid and L-galactonic acids, respectively. In all these cases the yields of isolated products of good purity were in the range 20–30% but the ease of operation nevertheless makes the procedure of interest. The methyl ester glycosides of the uronic acids were reducible to the glycosides of the corresponding hexoses, methyl (methyl α-D-galactopyranosid)-uronate (I, monohydrate), its β-D-anomer and methyl (methyl D-glucopyranosid)-uronate giving good yields of methyl α-D-galactopyranoside (II, monohydrate), methyl β-D-galactopyranoside and methyl α-D-glucopyranoside, respectively. This type of conversion has been effected in low yield (10%) with sodium amalgam[11] and on the methyl ethers or acetates with lithium aluminum hydride[12,13] or with high pressure catalytic (copper chromite) hydrogenation.[14] It should be useful in the determination of structure of oligosaccharides and polysaccharides containing uronic acid units.



I II

Experimental

Reduction of D-Lyxono-γ-lactone to D-Lyxose.—A solution of sodium borohydride (1.0 g.) in 25 ml. of water was added to a solution of D-lyxono-γ-lactone[10] (10.0 g.) in 100 ml. of water over a period of 15 min. at 0–2°, and at *p*H 3–4 maintained by adding dilute acetic acid. After an additional 10 min. the solution was made slightly acidic with dilute acetic acid, diluted with 1 volume of water and passed through columns of the ion exchange resins Amberlite IR-120[15] and Duolite A-4.[16] The sirup (6.7 g.) obtained from the effluent on solvent removal under reduced pressure was crystallized from absolute ethanol; yield 2.1 g. (21%), m.p. 114–115°, $[\alpha]^{27}D$ −13.5° (*c* 4, water, final). One recrystallization from absolute ethanol gave pure material; m.p. 117–118°, $[\alpha]^{30}D$ −14° (*c* 3, water, final, upward mutarotation) in agreement with the values cited by Haworth and Hirst[17] for β-D-lyxose.

Reduction of D-Lyxono-γ-lactone to D-Arabitol.—D-Lyxono-γ-lactone[10] (5.0 g.) in 25 ml. of water was reduced with sodium borohydride (1.0 g.) in 20 ml. of water at room temperature by essentially the same procedure as described[5] for the reduction of D-gluco-D-*gulo*-heptono-γ-lactone to *meso*-gluco-*gulo*-heptitol. After reaction the solution was acidified with dilute acetic acid and passed through the columns of Amberlite IR-100-H[15] and IR-4-B.[15] The viscous sirup (3 g.) obtained from the effluent on solvent removal under reduced pressure was crystallized from absolute ethanol; yield 1.3 g. (25.5%), m.p. 97–98°. Pure D-arabitol was obtained on recrystallization from absolute ethanol, m.p. 102–103°, $[\alpha]^{27}D$ +9° (*c* 5, saturated aqueous borax solution) in agreement with the constants (m.p. 103°, $[\alpha]^{20}D$ +7.7° in borax solution) cited by Ruff.[18]

Reduction of Sodium D-Glucuronate to L-Gulono-γ-lactone.—A solution of sodium borohydride (0.6 g.) in 15 ml. of water was added during 10 min. at room temperature (25–35°) to a mechanically stirred solution of sodium D-glucuronate monohydrate[19] (3.0 g.) in 25 ml. of water. During the reduction the solution was kept at *p*H 7–8 by adding *N* HCl. After an additional 10 min. the excess sodium borohydride was neutralized with *N* HCl. The reaction mixture showed no reduction toward Fehling solution. An amount of 10 ml. of *N* HCl was then added to the solution which was dewatered under reduced pressure at 80–90°. The residue was dissolved in water and this solution was again dewatered under reduced pressure at 80–90°. The lactone obtained was extracted from the residue with hot absolute ethanol and the solvent was removed under reduced pressure. The resultant sirup was dissolved in 50 ml. of water and was passed through successive ion exchange columns of Amberlites IR-100-H[15] and IR-4-B.[15] The effluent was concentrated under reduced pressure to a sirup which was crystallized by trituration with absolute ethanol; yield 0.68 g. (30%), m.p. 178–180°, $[\alpha]^{25}D$ +51.4° (*c* 3, water, initial). Pure L-gulono-γ-lactone was obtained on recrystallization from absolute ethanol; m.p. 183–185°, $[\alpha]^{22}D$ +55° (*c* 2, water, initial), in agreement with reported[20] values.

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Reduction of D-Galacturonate Ion to L-Galactono-γ-lactone.—The hexahydrated sodium calcium mixed salt of D-galacturonic acid[21] was reduced with sodium borohydride by the procedure described above for sodium D-glucuronate. A solution of sodium borohydride (1.0 g.) in 40 ml. of water was added to a suspension of sodium calcium D-galacturonate hexahydrate (5.0 g.) in 50 ml. of water at room temperature under slightly basic conditions. At the end of the reaction the solution became almost clear and was then acidified with dilute HCl. Lactonization was achieved as described above for L-gulono-γ-lactone and the lactone was extracted with hot absolute ethanol. The sirup obtained from the ethanolic solution was dissolved in water and passed through the ion exchange columns. The sirup from the effluent was dissolved in a small amount of absolute ethanol and was crystallized by seeding with L-galactono-γ-lactone; yield 0.85 g. (24%), m.p. 132–133°, $[\alpha]^{26}D$ +73.4° (*c* 3, water, initial). Recrystallization from absolute ethanol gave pure material; m.p. 134–135° with sintering at 128°, $[\alpha]^{22}D$ +77° (*c* 4, water, initial) in agreement with recorded[22] values.

Reduction of Methyl (Methyl α-D-Galactopyranosid)-uronate Monohydrate (I) to Methyl α-D-Galactopyranoside Monohydrate (II).—A solution of methyl (methyl α-D-galactopyranosid)-uronate monohydrate[23–25] (0.50 g.) in 5 ml. of water was added dropwise to a stirred solution of sodium borohydride (0.20 g.) in 3 ml. of water at room temperature (25–35°) during a period of 5 min. After stirring for an additional 10 min., the reaction mixture was acidified with dilute acetic acid, diluted with 2 volumes of water and passed through columns of Amberlite IR-100-H[15] and IR-4-B.[15] The effluent was concentrated under reduced pressure to a sirup. The sirup (0.4 g.) was dissolved in 10 ml. of water and 20 ml. of 0.2 *N* $Ba(OH)_2$ was added. After standing at room temperature (28–30°) for 4 hr., the alkaline solution was deionized by passage through columns of Amberlite IR-100-H and IR-4-B. The effluent was concentrated under reduced pressure to a sirup which was crystallized from absolute ethanol and ether; yield 0.27 g. (61%), m.p. 104–106°, $[\alpha]^{27}D$ +170° (*c* 0.5, water). Pure methyl α-D-galactopyranoside monohydrate was obtained on recrystallization from the same solvent; m.p. 108–109°, $[\alpha]^{25}D$ +177° (*c* 3, water) in agreement with recorded[26–28] values. The X-ray powder diffraction diagram of this substance was exactly identical with that of an authentic specimen. The principal lines are 7.08[29]–15,[30] 6.10–20, 5.27–100, 4.57–80, 4.35–30, 3.97–50, 3.53–25, 3.20–30, 2.32–30.

This reaction was repeated except that the addition of the reducing agent was made at 5–10° during 20 min. and the reaction was maintained at this temperature for 20 min. before acidification; yield 45 or 70% on correction for a 36% recovery of starting material (recrystallized from 95% ethanol) obtained from the ion exchange effluent material before saponification.

Reduction of Methyl (Methyl β-D-Galactopyranosid)-uronate to Methyl β-D-Galactopyranoside.—Methyl (methyl β-D-galactopyranosid)-uronate, first described by Ehrlich and Guttmann,[23] was obtained on concentrating the mother liquor from the preparation of the α-D-anomer according to the method of Jones and Stacey.[25] This substance (0.50 g.) was reduced with sodium borohydride (0.20 g.) in the same manner as described above, in the first instance, for the anomer and the product was isolated in the same manner; yield 0.28 g. (64%), m.p. 175–176°, $[\alpha]^{24}D$ −0.8° (*c* 3, water). One recrystallization from absolute ethanol gave pure methyl β-D-galactopyranoside; m.p. 177–178°, $[\alpha]^{27}D$ −0.6° (*c* 2.5, water) in agreement with recorded[27,31] values.

Reduction of Methyl (Methyl D-Glucopyranosid)-uronate to Methyl α-D-Glucopyranoside.—A crude sirupy preparation[32] of methyl (methyl D-glucopyranosid)-uronate (0.50 g.) in 5 ml. of water was reduced with sodium borohydride (0.20 g.) in 3 ml. of water as described above for the corresponding derivatives of D-galacturonic acid with omission of the hydrolysis with alkali. Crystals were obtained from absolute ethanol; yield 0.16 g. (37%), m.p. 164–165°, $[\alpha]^{30}D$ +151° (*c* 1, water). Further recrystallization from absolute ethanol gave pure material; m.p. 164.5–165.5°, $[\alpha]^{30}D$ +155° (*c* 0.9, water) in agreement with recorded[33] values for methyl α-D-glucopyranoside.

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Role of Neighboring Groups in Replacement Reactions. XIX. Polarimetric Acetolysis Rate of *trans*-2-Acetoxycyclohexyl *p*-Toluenesulfonate

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The polarimetric and titrimetric rates of acetolysis of *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate have been shown to be equal. This shows that internal rearrangement does not accompany solvolysis as in other cases of neighboring group participation. The absence of the internal phenomenon in the present case, ascribed to the special nature of the neighboring acetoxy group, supports the "internal return" interpretation for the observed internal rearrangements.

So-called internal rearrangements accompany solvolysis in cases of allylic, homoallylic and Wagner–Meerwein rearrangements. These have been observed, for example, in acetolysis of α,α-dimethylallyl chloride,[1] *exo*-norbornyl *p*-bromobenzenesulfonate,[2] 3-phenyl-2-butyl *p*-toluenesulfonate,[3a,b] 2-phenyl-1-propyl *p*-bromobenzenesulfonate,[4] dehydronorbornyl *p*-bromobenzenesulfonate[5] and *i*-cholesteryl derivatives.[6] The preferred interpretation[3a] of these internal rearrangements involves formation of an ion-pair (*e.g.*, II) which gives solvolysis products or returns to the covalent condition (internal return) giving either racemized ester (I and III) or rearranged material (III). In the case of norbornyl[2] and 3-phenyl-2-butyl[3a] esters, the internal phenomenon results in a

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