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DIBORANE REDUCTION OF CARBOXYL GROUPS IN CARBOHYDRATES

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ESTER and lactone groups in carbohydrate compounds may be reduced by complex metal hydrides in aqueous solution[1,2] or in dry ether-type solvents.[3,4,5] Reduction of carboxyl groups may also be effected by lithium aluminum hydride[6] and related metal hydrides, but the method is limited to carboxylic acids soluble in organic solvents which are not affected by the reducing agent.[7] Consequently it has been possible to convert a methylated acidic polysaccharide into a methylated neutral polysaccharide[4] by carrying out the reduction in tetrahydrofuran but our attempts to reduce an acylated acidic polysaccharide have failed because the ester groups are attacked first and as a result acidic polysaccharide

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[1] M. L. Wolfrom and H. B. Wood, J. Amer. Chem. Soc. 73, 2933 (1951).

[2] M. L. Wolfrom and K. Anno, J. Amer. Chem. Soc. 74, 5583 (1952).

[3] B. Lythgoe and S. Trippett, J. Chem. Soc. 1983 (1950).

[4] M. Abdel-Akher and F. Smith, Nature, London 166, 1037 (1950).

[5] F. Smith and R. Montgomery, Chemistry of Plant Gums and Mucilages, pp. 140-144. Reinhold Corp., New York (1959).

[6] R. F. Nystrom and W. G. Brown, J. Amer. Chem. Soc. 69, 2548 (1947).

[7] N. G. Gaylord, Reduction with Complex Metal Hydrides. Interscience, New York and London (1956).

material is precipitated from the reaction mixture.[8] Since diborane has been shown to reduce carboxyl groups in preference to ester groups[9] it seemed likely that this reducing agent might well be capable of reducing carboxyl groups in suitable derivatives of both simple and complex carbohydrate compounds.

We wish to report herein the successful transformation of the -COOH group to $-CH_2OH$ not only in monosaccharide acids but also in acidic polysaccharides. Our preliminary experiments indicate that diborane reduction of acidic carbohydrates is a general reaction and that the production of neutral polysaccharides from acid polysaccharides such as pectic substances, acidic hemicelluloses, plant gums and mucilages is within the scope of the reaction. The new method also opens up the possibility of producing certain sugars and their derivatives (e.g. L-gulose from alginic acid and 4-O-methyl-D-glucose from mesquite gum) by a more direct route than has hitherto been available. It is also apparent that the effect of uronic acid residues on the physical, chemical and immunological properties of polysaccharides can now be investigated.

The reductions were conducted in bis (2-methoxyethyl) ether ("diglyme")[10] solution at room temperature. Diborane was generated[11] in situ by slowly adding boron trifluoride etherate in ether-diglyme to the product obtained by mixing solutions in diglyme of the carbohydrate

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[8] F. Smith and D. Spriestersbach, unpublished.

[9] H. C. Brown and B. C. Subba Rao, J. Org. Chem. 22, 1135 (1957).

[10] H. C. Brown, E. J. Mead and B. C. Subba Rao, J. Amer. Chem. Soc. 77, 6209 (1955).

[11] H. I. Schlesinger, H. C. Brown, H. R. Hoekstra and L. R. Rapp, J. Amer. Chem. Soc. 75, 199 (1953); H. C. Brown and P. A. Tierney, Ibid. 80, 1552 (1958).

acid and of sodium borohydride.[9] Sodium borohydride and boron trifluoride were employed throughout in the molar ratio 3:4, but the quantity of reducing agent used per carboxyl group was varied.

(1) Reduction of methyl α-D-galactopyranosiduronic acid to methyl α-D-galactopyranoside. Methyl α-D-galactopyranosiduronic acid, prepared by saponifying the corresponding methyl ester (0.9 millimoles), was reduced during 3 hr. by sodium borohydride (2.6 millimoles) and boron trifluoride etherate (3.5 millimoles) in diglyme solution. The product was kept overnight, diluted with ice-water, deionized with exchange resins, and concentrated: measurement of $[\alpha]_D$ of the syrupy residue indicated 48% conversion, based upon the ester glycoside, to methyl α-D-galactopyranoside. The crystalline hydrate, m.p. 106° (undepressed by an authentic specimen), $[\alpha]_D^{21}$ + 180° (c 0.7), was obtained from a portion of the product; the remainder was hydrolyzed with acid in the usual way to give chromatographically pure D-galactose, characterized as its p-nitroaniline derivative, m.p. and mixed m.p. 215-216°.

(2) Reduction of methyl 2,3,4-tri-O-methyl-α-D-galactosiduronic acid to methyl 2,3,4-tri-O-methyl-α-D-galactoside. Methyl 2,3,4-tri-O-methyl α-D-galactopyranosiduronic acid, prepared as in (1) by saponification of its methyl ester, was reduced under the same conditions. The product, after terminating the reaction by addition of ice-water, was isolated by chloroform extraction and hydrolysed with acid to give 2,3,4-tri-O-methyl-D-galactose, $[\alpha]_D^{20}$ + 93° (c 5.6), in 56% overall yield. The sugar, which was chromatographically pure, was characterized by conversion to the aniline derivative, m.p. and mixed m.p. 168-169° after recrystallization from ethanol.

In an experiment carried out under the same conditions except that no boron trifluoride was added, no detectable reduction of the acid occurred.

(3) Conversion of galactaric acid to galactitol. Tetra-O-acetylgalactaric acid, dried thoroughly at 130° in vacuo, was reduced by the same general technique, using twice the amount of reducing agent for each carboxyl group as was employed in (1) above. The reaction mixture was then neutralized (aqueous sodium carbonate) and evaporated in vacuo to near dryness. The residue containing partially acetylated galactitol was boiled under reflux with acetic anhydride to dissociate any borate complex and to ensure complete acetylation.[12,13] Most of the residual acetic anhydride and diglyme was distilled in vacuo and the reaction mixture was poured into ice-water with stirring. The hexa-O-acetylgalactitol, recovered in 75% yield by extraction with chloroform and evaporation of solvent, had m.p. 169-171° (after recrystallization from ethanol).

(4) Reduction of mesquitic acid acetate. Similar proportions of the reducing combination to those employed in the first two experiments were used in the reduction of the acetyl derivative,[14] $[\alpha]_D^{26}$ + 68° (c 1.2, $CHCl_3$), of mesquitic acid from mesquite (Prosopis juliflora D.C.) gum, the product being recovered by neutralization with ice-cold alkali followed by chloroform extraction. The partially-acetylated polymer, $[\alpha]_D^{25}$ + 70° (c 2.6, $CHCl_3$), obtained from the dried chloroform extract, gave (paper chromatography) upon hydrolysis with dilute acid

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[12] M. Abdel-Akher, J. K. Hamilton and F. Smith, J. Amer. Chem. Soc. 73, 4691 (1951).

[13] H. Klosterman and F. Smith, J. Amer. Chem. Soc. 74, 5336 (1952).

[14] J. F. Carson and W. D. Maclay, J. Amer. Chem. Soc. 68, 1015 (1946).

arabinose, galactose, 4-O-methylglucose (from reduced 4-O-methyl-D-glucuronic acid residues) and a small proportion of 4-O-methyl-D-glucuronic acid.

In order to improve the conversion of acid to neutral groupings, a second experiment was conducted using five times the relative quantity of reducing agents. Worked up as before, the polysaccharide (partly de-acetylated) appeared in the aqueous layer, which was evaporated to dryness *in vacuo*. The residue was warmed with 0.1 N-sodium hydroxide to complete the de-acetylation process, and the polysaccharide was purified by repeated precipitation from aqueous solution with ethanol-ether mixtures, by dialysis, and by treatment with ion-exchange resins. Reduced mesquitic acid, $[\alpha]_D^{20}$ + 70° (*c* 1.36, aqueous alkali), equiv., 10,000 (approx.) (by titration with 0.02 N-sodium hydroxide using phenolphthalein as indicator), was recovered in excellent yield. The equiv. represents a reduction of nearly 90% of the original carboxyl groups to primary alcohol. Acid hydrolysis of a small portion of the product gave a mixture of the sugars arabinose, galactose, and 4-O-methylglucose. Only traces of uronic acid, together with unidentified reducing substances which may be artefacts, were detectable by paper chromatography.

On graded hydrolysis with 0.01 N-sulfuric acid at 100° for 14 hr. the reduced mesquitic acid yielded 30% of its weight of arabinose but little or no other reducing sugar was generated. The residue was fully hydrolyzed by heating at 95° for 8 hr. with N-sulfuric acid. From the neutralized (barium carbonate) hydrolysate, 4-O-methyl-D-glucose, $[\alpha]_D^{20}$ + 69° (*c* 1.45, MeOH), was separated by cellulose column chromatography and characterized as its phenylosazone, m.p. and mixed m.p. 158-159°,

$[\alpha]_D^{21}$ - 22° → 0° (equil.) (c 0.9, EtOH). The 4-O-methyl-D-glucose constituted 8% of the weight of reduced mesquitic acid hydrolysate. Assuming that the equiv. of mesquitic acid is 1300, this yield represents a recovery of 4-O-methyl-D-glucose of approx. 60%.

(5) Reduction of pectic acid acetate.[15] The acetylated derivative of pectic acid (prepared from citrus pectin), when reduced under the conditions used in the first mesquitic acid experiment and re-acetylated, yielded a chloroform-soluble acetylated galactose polymer which on acid hydrolysis gave galactose and only traces of galacturonic acid (paper chromatographic analysis).

(6) Reduction of alginic acid propionate. Since alginic acid[16] acetate was not sufficiently soluble in diglyme, a dipropionate, $[\alpha]_D^{20}$ -150° (c 1.0, pyridine), was prepared,[14] and reduced under the conditions used in the second mesquitic acid experiment. The reaction mixture was dialyzed and concentrated, and after saponification and several precipitations from aqueous solution with ethanol-ether, a polysaccharide was recovered which had equiv., 1000 and $[\alpha]_D^{20}$ - 86° (c 0.8, aqueous alkali). The equiv. represents 82% conversion of carboxyl groups to primary alcohol. Paper chromatographic and ionophoretic examination of the acid hydrolysate showed the presence of mannose, with smaller amounts of gulose.[17] Unreduced mannuronic acid was also detected as well as traces of glucose and pentoses, possibly arabinose and xylose.

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[15] Cf. G. O. Aspinall and A. Cañas-Rodriguez, J. Chem. Soc. 4020 (1958).

[16] Kindly supplied by Kelco Company, San Diego, California, courtesy Dr. A. Miller.

[17] F. G. Fischer and H. Dörfel, Z. physiol. Chem. **302**, 186 (1955).

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