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

Lithium Aluminum Hydride Reduction of 3,4,5,6-Di-*O*-isopropylidene-D-gluconamide and Di-*O*-isopropylidene-galactaramide[1]

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3,4,5,6-Di-*O*-isopropylidene-D-gluconamide, prepared from D-glucono-δ-lactone, and di-*O*-isopropylidenegalactaramide are reduced by lithium aluminum hydride to 1-amino-1-deoxy-3,4,5,6-di-*O*-isopropylidene-D-glucitol (hydrochloride) and 1,6-diamino-1,6-dideoxydi-*O*-isopropylidene-galactitol (dihydrochloride), respectively. The latter substance was converted to the *N*,*N*-ditosyl derivative and hydrolyzed to 1,6-diamino-1,6-dideoxy-galactitol dihydrochloride.

The reaction of amides to amines using ethereal solutions of lithium aluminum hydride is an established procedure outside the carbohydrate field.[2] The application of this reagent to certain aldonamides is here described.

D-Glucono-δ-lactone was condensed with acetone in the presence of sulfuric acid to give both di-*O*-isopropylidene- and tri-*O*-isopropylidene-D-gluconic acid. The preparation of these two compounds, in low yield, from calcium D-gluconate has been reported,[3] the former compound having been shown to be substituted on C-3, C-4, C-5 and C-6. The present method of synthesis of these substances is superior to that of Haworth and associates. In this study the di-*O*-isopropylidene-D-gluconic acid was esterified by means of diazomethane, and the resulting sirupy methyl ester, which was not isolated, was treated with ammonia in methanol to give the hitherto unreported 3,4,5,6-di-*O*-isopropylidene-D-gluconamide. This same compound was more readily obtained by the action of methanolic ammonia on tri-*O*-isopropylidene-D-gluconic acid. Reduction of the amide by lithium aluminum hydride in ether gave the amine, which was isolated in 58% yield as 1-amino-1-deoxy-3,4,5,6-di-*O*-isopropylidene-D-glucitol hydrochloride (1-amino-1-deoxy-3,4,5,6-di-*O*-isopropylidene-sorbitol hydrochloride).

Diethyl di-*O*-isopropylidene-galactarate[4] is readily converted to di-*O*-isopropylidene-galactaramide (hitherto unreported) by ammonia in methanol. In spite of the fact that the diamide is apparently insoluble in ether, it reacts smoothly with an ethereal solution of lithium aluminum hydride. 1,6-Diamino-1,6-dideoxydi-*O*-isopropylidene-galactitol dihydrochloride (1,6-diamino-1,6-dideoxy-di-*O*-isopropylidene-dulcitol dihydrochloride) was obtained in 45% yield by adding the theoretical amount of hydrogen chloride in ethanol to an ethereal solution of the reaction product. The dihydrochloride decomposed above 220° without melting, hence the di-*N*-*p*-toluenesulfonyl derivative, m.p. 210°, was prepared for reference purposes. On one occasion dry hydrogen chloride was bubbled through the solution of the reaction product in ether, in an attempt to isolate the dihydrochloride. The solid obtained was found, upon purification, to be 1,6-diamino-1,6-dideoxygalactitol dihydrochloride, showing that deacetonation had occurred.

Experimental

3,4,5,6-Di-*O*-isopropylidene- and Tri-*O*-isopropylidene-D-gluconic Acid.—D-Glucono-δ-lactone (50 g.) was stirred with acetone (500 ml.) containing concentrated sulfuric acid (5 ml.) until the solid dissolved (about 2 hr.), and the solution was kept at room temperature overnight. It was then shaken with powdered, anhydrous potassium carbonate until its yellow color faded, and it was immediately filtered. Evaporation of the filtrate gave a sirup which was extracted repeatedly with boiling hexane.[5] The combined extracts were evaporated to a crystalline solid (26 g.) which was washed with water, dried and recrystallized from hexane as tri-*O*-isopropylidene-D-gluconic acid, yield 20.5 g., m.p. 109°,[6] $[\alpha]^{32}_{\mathrm{D}}$ +34° (*c* 2.2, chloroform), $[\alpha]^{23}_{\mathrm{D}}$ +31.5° (*c* 1.8, ethanol) (recorded[3] m.p. 111° and $[\alpha]_{\mathrm{D}}$ +31° in ethanol).

Anal. Calcd. for $C_{15}H_{24}O_7$: C, 57.00; H, 7.70. Found: C, 57.00; H, 7.76.

The sirup which remained after the boiling hexane extraction was dissolved in ether. The solution was filtered from a small amount of a deliquescent solid (not identified), and then concentrated. Crystals of 3,4,5,6-di-*O*-isopropylidene-D-gluconic acid, yield 11 g., m.p. 155° (slight dec. at 145°), separated from the cooled solution, which after two recrystallizations from ether–hexane had m.p. 157–158° (slight dec. at 145°), $[\alpha]^{24}_{\mathrm{D}}$ +13° (*c* 2, ethanol) (recorded[3] m.p. 154° and $[\alpha]_{\mathrm{D}}$ +11° in ethanol).

Anal. Calcd. for $C_{12}H_{20}O_7$: C, 52.19; H, 7.25. Found: C, 52.29; H, 7.35.

When tri-*O*-isopropylidene-D-gluconic acid was the only product required from the reaction, it was most readily isolated by shaking the neutralized, evaporated reaction mixture with water. The crystalline tri-*O*-isopropylidene compound remained undissolved.

3,4,5,6-Di-*O*-isopropylidene-D-gluconamide. (a) **From 3,4,5,6-Di-*O*-isopropylidene-D-gluconic Acid.**—An ice-cold solution of diazomethane[7] (0.7 g.) in ether (25 ml.) was added to a solution of di-*O*-isopropylidene-D-gluconic acid (3 g.) in ether (30 ml.) at 0°. The yellow color of the diazomethane disappeared, and an ethereal solution of diazomethane of like concentration, was added dropwise until the color persisted. After keeping the solution at 0° for a few minutes, excess diazomethane was decomposed by the dropwise addition of an ethereal solution of acetic acid. The solution was diluted with ether, washed with sodium bicarbonate solution, dried (anhydrous sodium sulfate) and evaporated to a sirup which did not crystallize. A solution of the sirup in methanol (20 ml.) at 0° was saturated with ammonia; after 6 hours at 0° the solution was allowed to warm slowly to room temperature. Evaporation gave a gel-like residue, which crystallized when shaken with ether, yield 1 g. The product was recrystallized from ether containing a small amount of ethanol as 3,4,5,6-di-*O*-isopropylidene-D-gluconamide, m.p. 151–152°, $[\alpha]^{20}_{\mathrm{D}}$ +31° (*c* 1.4, chloroform), $[\alpha]^{20}_{\mathrm{D}}$ +32° (*c* 1.1, water, unchanged after 7 days). The

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(2) V. M. Mićović and M. L. Mihailović, *J. Org. Chem.*, **18**, 1190 (1953); W. G. Brown in "Organic Reactions," R. Adams, ed., John Wiley and Sons, Inc., New York, N. Y., 1951, Vol. VI, p. 469.

(3) W. N. Haworth, E. L. Hirst and K. A. Chamberlain, *J. Chem. Soc.*, 795 (1937).

(4) J. W. W. Morgan and M. L. Wolfrom, THIS JOURNAL, **78**, 1897 (1956).

(5) "Skellysolve B," b.p. 65–69°.

(6) Melting points are uncorrected.

(7) F. Arndt, *Org. Syntheses*, **15**, 3 (1935). The simplified method of preparation was used.

substance was soluble in water, sparingly so in chloroform and in ethanol, and was insoluble in hexane and in ether.

Anal. Calcd. for $C_{12}H_{21}O_6N$: C, 52.36; H, 7.64; N, 5.09. Found: C, 52.55; H, 7.48; N, 5.18.

(b) **From Tri-*O*-isopropylidene-D-gluconic Acid.**—A solution of tri-*O*-isopropylidene-D-gluconic acid (20.5 g.) in methanol (200 ml.) was nearly saturated with ammonia at 0° and maintained for 20 hr. at that temperature. Evaporation of the reaction mixture gave a residue which was shaken with ether (50 ml.). The insoluble part (8.5 g.) was collected and recrystallized from ether–ethanol as stout needles of 3,4,5,6-di-*O*-isopropylidene-D-gluconamide, yield 6.2 g., m.p. (and mixed m.p.) 151–152°. The ether solution was evaporated to a solid (9 g.) which was triturated with hexane (50 ml.). The insoluble part, recrystallized from ether–ethanol, gave more of the above compound, yield 3.3 g., m.p. 150–151°.

1-Amino-1-deoxy-3,4,5,6-di-*O*-isopropylidene-D-glucitol Hydrochloride.—A solution of lithium aluminum hydride (all apparatus used for the preparation and reactions of this reagent was dried for several hours at 100°) in ether (35 ml., 5% w./v.) was diluted with ether (150 ml.). 3,4,5,6-Di-*O*-isopropylidene-D-gluconamide (5 g.) was added in portions to the stirred solution, which effervesced at each addition. When all of the solid had been added, the stirred suspension was boiled under reflux for 5 hr. Ethanol was added dropwise to decompose excess hydride, and the solution, diluted with ether, was shaken with 10% aqueous sodium hydroxide. The ethereal layer was separated from the aqueous layer, which was extracted once more with ether. The combined extracts were dried (anhydrous sodium sulfate) and evaporated to a basic sirup which did not crystallize. A solution of this sirup in ether was titrated with ethanolic hydrogen chloride (0.57 *N*) until the solution was neutral (16.4 ml. required). No precipitate formed and the solution was evaporated to a sirup which crystallized on standing. The solid was triturated with hexane, from which it was filtered, yield 3.15 g., 58%. Recrystallization from ether–methanol gave silky needles of 1-amino-1-deoxy-3,4,5,6-di-*O*-isopropylidene-D-glucitol hydrochloride, m.p. 132–133°, $[\alpha]^{21}D$ +9° (*c* 1.6, ethanol). The substance was soluble in water, ethanol and chloroform but was insoluble in hexane and in ether.

Anal. Calcd. for $C_{12}H_{24}O_5NCl$: C, 48.41; H, 8.06; N, 4.71. Found: C, 48.47; H, 7.99; N, 4.75; chlorine, present.

Di-*O*-isopropylidene-galactaramide.—Methanol (300 ml.) was nearly saturated at 0° with ammonia gas. Diethyl di-*O*-isopropylidenegalactarate[4] (30 g.) was then added to the stirred solution, into which ammonia gas was passed for 1 hr. longer. Stirring was continued for 3 hr. more and then the ammonia was allowed to escape overnight. Concomitantly with this the product crystallized, yield 22.5 g. This was recrystallized from 95% ethanol as di-*O*-isopropylidene-galactaramide, m.p. 229–230°. The substance was sparingly soluble in water and ethanol, and was insoluble in chloroform, ether and hexane.

Anal. Calcd. for $C_{12}H_{20}O_6N_2$: C, 50.00; H, 6.95; N, 9.72. Found: C, 49.85; H, 6.96; N, 9.55.

1,6-Diamino-1,6-dideoxy-di-*O*-isopropylidene-galactitol Dihydrochloride.—A solution of lithium aluminum hydride in ether (100 ml., 5% w./v.) was diluted with ether (300 ml.) and di-*O*-isopropylidene-galactaramide (10 g.) was added in portions, with stirring. When effervescence had ceased, the solution was boiled under reflux for 5 hr. An ethereal solution of the product was obtained in the manner described above for 1-amino-1-deoxy-3,4,5,6-di-*O*-isopropylidene-D-glucitol. To this solution, ethanolic hydrogen chloride (0.57 *N*, 40 ml.) was added dropwise with stirring, and a fine microcrystalline precipitate of the dihydrochloride appeared, yield 4.47 g. This was filtered from the solution, to which ethanolic hydrogen chloride was added dropwise until a turbidity was no longer produced (10 ml. required). A further 0.7 g. of solid was obtained making the total yield 5.17 g., 45%. Pure 1,6-diamino-1,6-dideoxy-di-*O*-isopropylidene-galactitol dihydrochloride, obtained by dissolving the crude solid in ethanol and precipitating with ether, decomposed slowly above 200° without melting. The substance was soluble in water and ethanol but was insoluble in chloroform, hexane and ether.

Anal. Calcd. for $C_{12}H_{26}O_4N_2Cl_2$: C, 43.25; H, 7.81; N, 8.40. Found: C, 43.25; H, 7.84; N, 8.50; Cl, present.

1,6-Diamino-1,6-dideoxy-di-*O*-isopropylidene-N,N′-di-*p*-toluenesulfonyl-galactitol.—A solution of *p*-toluenesulfonyl chloride (2 g.) in pyridine (5 ml.) was added to a suspension of the above dihydrochloride (1.2 g.) in pyridine (5 ml.) and the mixture was kept at room temperature for 17 hr. On decomposing the mixture with cold water, a solid was obtained which was recrystallized from ethanol–acetone as 1,6-diamino-1,6-dideoxy-di-*O*-isopropylidene-*N*,*N*′-di-*p*-toluenesulfonyl-galactitol, yield 1.4 g., m.p. 210–211°. The substance was soluble in chloroform and acetone but was insoluble in water and the other common organic solvents.

Anal. Calcd. for $C_{26}H_{36}O_8N_2S_2$: C, 54.96; H, 6.34; N, 4.94; S, 11.26. Found: C, 55.17; H, 6.54; N, 5.03; S, 11.31.

1,6-Diamino-1,6-dideoxy-galactitol Dihydrochloride.—The reduction of di-*O*-isopropylidene-galactaramide (5 g.) was carried out as described above. Dry hydrogen chloride was bubbled into the ethereal solution of the reaction products, and a solid precipitated. This was collected on the filter, washed with ether, then ethanol and dried under reduced pressure over potash. The solid (2.84 g.) was recrystallized from aqueous alcohol as fine needles of 1,6-diamino-1,6-dideoxy-galactitol dihydrochloride, yield 0.55 g. The compound decomposed above 220° without melting, and after acidification gave a negative iodoform test. The substance was soluble in water and was insoluble in the common organic solvents.

Anal. Calcd. for $C_6H_{18}O_4N_2Cl_2$: C, 28.45; H, 7.12; N, 11.07. Found: C, 28.52; H, 7.17; N, 11.11; Cl, present.

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