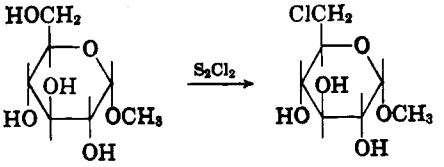
copyranoside from methyl α-D-glucopyranoside. Their procedure probably discouraged further investigation of chlorinated hexoses for it not only resulted in a low yield, but also involved successively, tritylation with trityl chloride, acetylation with acetic anhydride, chlorination with phosphorus pentachloride, and hydrolysis with barium hydroxide. In contrast, a convenient procedure has been devised, namely, reaction of methyl α-D-glucopyranoside with sulfur monochloride (S_2Cl_2) and separation of the reaction products on a Darco G-60–Celite 535[4] column. This improved procedure results in a 30–35% yield of methyl 6-chloro-6-deoxy-α-D-glucopyranoside.



When sulfur monochloride is mixed with methyl α-D-glucopyranoside in N,N-dimethylformamide, a slightly exothermic reaction occurs accompanied by the separation of sulfur. After the destruction of unreacted sulfur monochloride with water and removal of the sulfur by filtration, the filtrate is rapidly adjusted with sodium carbonate to pH 8. Following its concentration to a convenient volume, the solution is applied to a Darco G-60–Celite 535 column.[5]

Surprisingly, the chlorinated glucoside is strongly held on the Darco G-60; after elution with water to remove inorganic salts and with 5% ethanol to remove methyl α-D-glucopyranoside,[6] at least 12% ethanol is required to elute the chloroglucoside. The yield of purified methyl 6-chloro-6-deoxy-α-D-glucopyranoside, m.p. 110–112°, is 30–35%.

Experimental

Methyl 6-Chloro-6-deoxy-α-D-glucopyranoside.—To a solution of methyl α-D-glucopyranoside (10 g., m.p. 164–166°) in N,N-dimethylformamide (250 ml., reagent grade used directly from the bottle) was added in one portion sulfur monochloride (15 ml., Eastman Kodak practical grade). Immediately, a canary yellow milkiness developed and the solution warmed slightly. The stoppered flask was cooled in flowing tap water for 0.5 hr. and allowed to stand at room temperature overnight (*ca.* 17 hr.) during which time the milkiness was replaced by crystalline sulfur. Water was then added with cooling in tap water as follows:

Water, ml.	2	2	2	44	50	50
Time, min.	0	35	45	60	105	115

After standing at room temperature for 0.5 hr., the solution was filtered through a small pad of Celite 535 to remove sulfur; the filtrate was diluted with 750 ml. of water and adjusted to pH 8 (paper) with solid sodium carbonate. This solution was concentrated under vacuum (bath temperature <65°) to approximately 750 ml. and, after filtration to remove a trace of insoluble material, placed on a Darco G-60–Celite 535 column (6 × 34 cm., 1-l. bed volume). The column was eluted with 4 l. of water, 4 l. of 5% ethanol, and finally 4 l. of 12% ethanol. The final eluate was collected separately and concentrated on a steam bath to give 4.57 g. of an oil that crystallized on standing (2–4 hr.). To eliminate the majority of contaminating Celite, the crystalline solid was dissolved in boiling absolute ethanol (*ca.* 20 ml.) and filtered while hot. After concentrating the filtrate to dryness at room temperature, a crystalline solid resulted containing a trace of Celite; this trace was easily removed by dissolving the crystals in boiling absolute ethanol (*ca.* 10 ml.), adding slowly ethyl acetate (*ca.* 50 ml.) to the boiling solution until a light tan floc separated, and then filtering the hot solution. From this filtrate, concentrated at room temperature, separated crystalline[7] methyl 6-chloro-6-deoxy-α-D-glucopyranoside, 3.50 g. (32%), m.p. 110–112°. An analytical sample was prepared by recrystallization twice from ethanol–ethyl acetate, m.p. 111.2–112.0°, $[\alpha]^{25}D$ +141° (*c* 0.658, H_2O) (lit.[2] m.p. 110–112°, $[\alpha]^{21}D$ +139°).

Anal. Calcd. for $C_7H_{13}ClO_5$: C, 39.54; H, 6.16; Cl, 16.67. Found: C, 39.75; H, 6.10; Cl, 16.31.

Linear horizontal chromatography[8] revealed only one spot with an R_f of 0.61 (methyl α-D-glucopyranoside R_f 0.29) when the $AgNO_3$–NaOH dipping reagent of Smith was used.[9]

(4) The mention of trade products does not imply that they are endorsed by the Department of Agriculture over similar but unmentioned products.

(5) R. L. Whistler and J. N. BeMiller, *Methods Carbohydrate Chem.*, **1**, 42 (1962).

(6) W. J. Whelan and K. Morgan, *Chem. Ind.* (London), 78 (1954).

(7) Occasionally an oil separates that readily crystallizes.

(8) Paper was S and S 2043b; solvent was *n*-BuOH–*i*-PrOH–H_2O, 3:1:1 (v./v.). For horizontal technique refer to R. G. Strobel and J. Holme, *Cereal Chem.*, **40**, 361 (1963).

(9) I. Smith, "Chromatographic Techniques," Interscience Publishers, Inc., New York, N. Y., 1958, p. 169.

Synthesis of D-*lyxo*-Hexulose (D-Tagatose) and 1-Deoxy-D-*lyxo*-hexulose[1]

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In continuation of our work on the general method for the preparation of ketoses from the acetylated sugar acids with one less carbon atom,[3] we report herein the application of this method to the synthesis of D-*lyxo*-hexulose (D-tagatose) and 1-deoxy-D-*lyxo*-hexulose (1-deoxy-D-tagatose). D-Tagatose has been synthesized: by the action of potassium hydroxide on D-galactose,[4] by the pyridine-catalyzed epimerization of D-galactose,[5-9] by oxidation of D-talitol with *Acetobacter suboxydans*,[7] and by a series of reactions from D-galacturonic acid.[10] D-Tagatose has been obtained in crystalline condition as a hydrolytic product from a gum exudate of the tropical tree *Sterculia setigera*[11] and has been reported to be present in the lichens *Rocella linearis* and *Rocella fucoformis*.[12] The chemistry of D-tagatose has been reviewed.[13]

(1) Paper No. 22 in the series entitled "The Action of Diazomethane upon Acyclic Sugar Derivatives"; previous communication: M. L. Wolfrom and R. B. Bennett, *J. Org. Chem.*, **30**, 458 (1965); preliminary communication: Abstracts of Papers, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964, p. 15C.

(2) Charles F. Kettering Foundation Fellow, 1963; Goodyear Foundation Fellow, 1963–1964.

(3) M. L. Wolfrom, R. L. Brown, and E. F. Evans, *J. Am. Chem. Soc.*, **65**, 1021 (1943), and other papers of the series (see ref. 1).

(4) C. A. Lobry de Bruyn and W. Alberda van Ekenstein, *Rec. trav. chim.*, **16**, 265 (1897).

(5) T. Reichstein and W. Bosshard, *Helv. Chim. Acta*, **17**, 753 (1934).

(6) Y. Khouvine, G. Arragon, and Y. Tomoda, *Bull. soc. chim. France*, [5] **6**, 354 (1939).

(7) E. L. Totton and H. A. Lardy, *J. Am. Chem. Soc.*, **71**, 3076 (1949).

(8) S. Adachi, *Tohoku J. Agr. Res.*, **8**, 33 (1957).

(9) J. K. N. Jones and R. A. Wall, *Can. J. Chem.*, **38**, 2290 (1960).

(10) P. A. J. Gorin, J. K. N. Jones, and W. W. Reid, *ibid.*, **33**, 1116 (1955).

(11) E. L. Hirst, L. Hough, and J. K. N. Jones, *Nature*, **163**, 177 (1949); *J. Chem. Soc.*, 3145 (1949).

(12) B. Lindberg, *Acta Chem. Scand.*, **9**, 917 (1955).

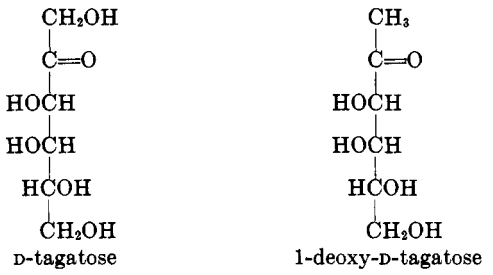
(13) J. V. Karabinos, *Advan. Carbohydrate Chem.*, **7**, 99 (1952).

The starting point for our synthesis was D-lyxono-1,4-lactone.[14] The lactone was converted to D-lyxonamide[15] with liquid ammonia.[16] The amide was found by us to be hydrolytically unstable at room temperature (see Figure 1). The initial rotation remained constant for more than 40 hr. after which the rotation changed slowly until reaching its final value (200 hr.). A similar behavior has been reported for several other aldonamides.[17] That the final product was the ammonium salt was established by isolation of the hydrolytic product and comparison with synthetic ammonium D-lyxonate.

Acetylation of D-lyxonamide in anhydrous pyridine with acetic anhydride gave sirupy 2,3,4,5-tetra-*O*-acetyl-D-lyxonamide.[15] We find that pyridine catalysis leads to a purer product than the zinc chloride catalysis previously used by Wolfrom and co-workers.[15]

The acetylated amide was converted to 2,3,4,5-tetra-*O*-acetyl-D-lyxonic acid in improved yield by a modification of the nitrous anhydride deamination procedure[18] previously used by Wolfrom and co-workers.[15] The acid was converted to 2,3,4,5-tetra-*O*-acetyl-D-lyxonyl chloride (sirup) through the action of thionyl chloride, and the acid chloride with diazomethane gave crystalline 3,4,5,6-tetra-*O*-acetyl-1-deoxy-1-diazo-D-*lyxo*-hexulose. The sirupy acid chloride was also characterized as the crystalline anilide.

Reaction of the diazomethyl ketone with glacial acetic acid yielded 1,3,4,5,6-penta-*O*-acetyl-D-*lyxo*-hexulose (sirup) which on deacetylation with barium hydroxide gave D-tagatose. Reduction of the diazomethyl ketone with hydriodic acid[19] produced 3,4,5,6-tetra-*O*-acetyl-1-deoxy-D-*lyxo*-hexulose (sirup) which on deacetylation with barium hydroxide gave crystalline 1-deoxy-D-tagatose.



Experimental[20]

Hydrolytic Instability of D-Lyxonamide.—D-Lyxono-1,4-lactone[14] was transformed to D-lyxonamide by the procedure of Wolfrom and co-workers.[15] The product was recrystallized once from absolute ethanol: m.p. 109.0–109.5°, $[\alpha]^{22}D$ −15.0° (*c* 2.0, water). These constants are in agreement with those [m.p. 110°, $[\alpha]^{20}D$ −14.4° (*c* 2.0, water)] cited by Hockett and co-workers[21]; X-ray powder diffraction data,[20] 7.67 w, 4.74 s (2), 4.52 s (1), 4.36 s (3,3), 3.80 m. 3.51 w, 3.33 s (3,3), 3.23 w, 3.10 w, 2.97 w, 2.75 m, 2.55 w, 2.45 m, 2.38 m.

Anal. Calcd. for $C_5H_{11}NO_5$: C, 36.36; H, 6.71; N, 8.48. Found: C, 36.33; H, 6.67; N, 8.80.

D-Lyxonamide (1.0000 g.) was dissolved in distilled water and the volume was adjusted to 50.0 ml. The solution was transferred to a 4-dm. glass polarimeter tube and the rotation was followed until the initial value, which remained constant for 47 hr., changed to a final constant value, −15.0° → 10.3°, 200 hr. (Figure 1).

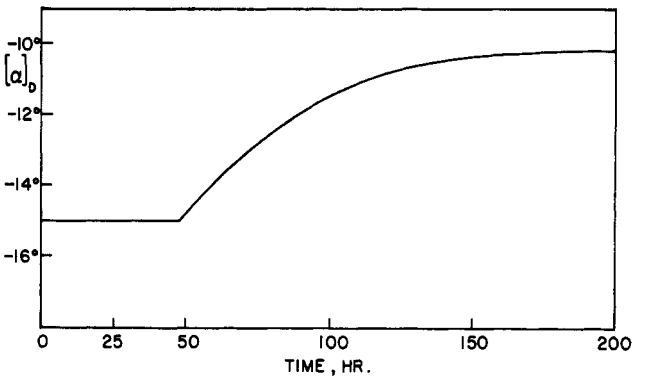


Figure 1.—Hydrolytic mutarotation of D-lyxonamide at 22° in water (*c* 2.0).

Ammonium D-Lyxonate.—D-Lyxono-1,4-lactone[14] (1.0 g.) was dissolved in water (50 ml.) and the solution was heated to boiling. Ammonium hydroxide (sp. gr. 0.900) was added until the solution was basic (pH 10). The reaction mixture was heated at 80° for 2 hr., during which time ammonium hydroxide was occasionally added to maintain basicity. The solution was cooled and evaporated under reduced pressure at 40° to give a crystalline solid (1.2 g.) which was recrystallized twice from 80% ethanol: m.p. 140–141°; $[\alpha]^{25}D$ −9.8° (*c* 2.0, water); X-ray powder diffraction data,[20] 9.56 s (3), 8.13 w, 6.53 w, 4.48 m, 4.35 m, 4.20 m, 4.05 m, 3.84 w, 3.25 s (1), 3.06 s (2), 2.61 w, 2.50 m, 2.25 w, 2.20 m, 2.04 m.

Anal. Calcd. for $C_5H_{13}NO_6$: C, 32.79; H, 7.15; N, 7.65. Found: C, 32.96; H, 7.06; N, 7.88.

Identification of Ammonium D-Lyxonate as a Hydrolytic Product of D-Lyxonamide.—The solution obtained from the hydrolytic mutarotation of D-lyxonamide as described above was evaporated to dryness under reduced pressure. The solid residue was recrystallized twice from 80% ethanol: m.p. 140–141°, $[\alpha]^{27}D$ −9.8° (*c* 2.0, water). Comparison of this compound with authentic ammonium D-lyxonate by melting point, melting point on admixture, optical rotation, and X-ray powder diffraction pattern showed them to be identical.

2,3,4,5-Tetra-*O*-acetyl-D-lyxonic Acid.—This substance was prepared in improved yield by a modification of the procedure of Wolfrom and co-workers.[15] D-Lyxonamide (10.0 g.) was mixed at 0° with dry pyridine (140 ml.) and acetic anhydride (70 ml.). After 2 hr. of stirring at 0° most of the amide had dissolved. The reaction mixture was allowed to stand overnight in a refrigerator; it was then poured into 250 g. of ice and water and stirred for 1 hr. The solution was extracted with chloroform. The extract was dried (magnesium sulfate) and evaporated under reduced pressure to a sirup. Repeated evaporation from toluene solution removed traces of pyridine; yield 20.1 g. The sirupy product

(14) A. Thompson and M. L. Wolfrom, *J. Am. Chem. Soc.*, **68**, 1509 (1946).

(15) M. L. Wolfrom, J. M. Berkebile, and A. Thompson, *ibid.*, **71**, 2360 (1949).

(16) J. W. E. Glattfeld and D. Macmillan, *ibid.*, **56**, 2481 (1934).

(17) M. L. Wolfrom, R. B. Bennett, and J. D. Crum, *ibid.*, **80**, 944 (1958).

(18) C. D. Hurd and J. C. Sowden, *ibid.*, **60**, 235 (1938).

(19) M. L. Wolfrom and R. L. Brown, *ibid.*, **65**, 1516 (1943).

(20) Paper chromatography was carried out using the descending technique with the top layer of a 4:1:5 1-butanol–ethanol–water system (solvent A), 5:5:3:1 pyridine–ethyl acetate–water–acetic acid [solvent B according to F. G. Fischer and H. J. Nebel, *Z. Physiol. Chem.*, **302**, 10 (1955)], and 6:4:3 1-butanol–pyridine–water (solvent C). Zones were located by the silver nitrate–sodium hydroxide procedure [W. E. Trevelyan, D. P. Proctor, and J. S. Harrison, *Nature*, **166**, 444 (1950)] or aniline hydrogen phthalate [S. M. Partridge, *ibid.*, **164**, 443 (1949)]. Thin layer chromatography was performed by the ascending technique on silica gel G (E. Merck, Darmstadt, Germany) activated at 100°. Zones were located by spraying the plates with 1% potassium permanganate in 10% sodium hydroxide or by heating the plates at 150° after spraying with concentrated sulfuric acid. Melting points were determined on a Hershberg-type apparatus (A. Thompson and M. L. Wolfrom in "Methods in Carbohydrate Chemistry," Vol. I, R. L. Whistler and M. L. Wolfrom, Ed., Academic Press Inc., New York, N. Y., 1962, p. 517). X-Ray powder diffraction data refer to interplanar spacing in Å. with Cu Kα radiation. Relative intensities were estimated visually: s, strong; m, medium; w, weak; v, very. The first three strongest lines are numbered (1, strongest); multiple numbers indicate approximately equal intensities. Elemental microanalyses were made by W. N. Rond.

(21) R. C. Hockett, J. B. Ames, and A. Scattergood, Abstracts of Papers 109th National Meeting of the American Chemical Society, Atlantic City, N. J., April 1946, p. 2R.

migrated as a single zone (R_f 0.58) on thin layer chromatograms with chloroform–methanol (9:1 v./v.). When zinc chloride was used as catalyst,[15] a second spot (R_f 0.74), probably the fully acetylated amide, was detected.

The above sirup, following the general deamination procedure of Hurd and Sowden,[18] was dissolved in 75 ml. of glacial acetic acid; the solution was cooled to 10° (bath temperature). Oxides of nitrogen, generated by the action of nitric acid (sp. gr. 1.35) on arsenic trioxide,[22] were bubbled into the acetic acid solution until a dark green color persisted, whereupon the flow of gas was stopped and the solution was allowed to stand at room temperature for 3 hr. This process was repeated (two or three times) until thin layer chromatography with chloroform–methanol (9:1 v./v.) showed the absence of starting material (R_f 0.58). Evaporation of the solvent under reduced pressure at 45° gave a sirup which was dissolved (three times) in toluene and concentrated under reduced pressure. On standing overnight the sirup crystallized; yield 15.9 g. (79%). Recrystallization from toluene was effected with little loss to give pure material: m.p. 114–116°; $[\alpha]^{23}D$ +18.9° (*c* 5.0, chloroform); X-ray powder diffraction data,[20] 9.00 s, 6.76 s (1), 5.94 vw, 5.08 m, 4.38 s (3), 4.08 w, 3.91 s (2), 3.53 m, 3.34 w, 3.22 m, 2.99 w, 2.92 w, 2.81 m. Wolfrom and co-workers[15] reported m.p. 113.5–115°, $[\alpha]^{23}D$ +19° (*c* 5.5, chloroform).

3,4,5,6-Tetra-*O*-acetyl-1-deoxy-1-diazo-D-*lyxo*-hexulose.—A solution of 2,3,4,5-tetra-*O*-acetyl-D-lyxonic acid (10.0 g.) in dry benzene (75 ml.) and purified[23] thionyl chloride (10 ml.) was refluxed 4 hr., cooled, and maintained at room temperature overnight. The volatile material was removed by evaporation under reduced pressure at 40°. The resultant sirup was repeatedly dissolved in dry benzene and the solvent was evaporated under reduced pressure until all of the excess thionyl chloride had been removed.

The sirupy acid chloride (10.5 g.) in dry ether (100 ml.) was slowly added to a cooled (0°), anhydrous solution of diazomethane[24] (2.5 g.) in ether (200 ml.). The solution was allowed to stand at 0° for 2 hr. and was then permitted to warm gradually to room temperature. The solution was concentrated by a stream of dry air and the sirupy residue was dissolved in 200 ml. of benzene, and 10 g. of Magnesol[25]–Celite[26] (5:1 w./w.) was added. The suspension was stirred for 30 min., filtered, and washed with 100 ml. of benzene. The filtrate and washings were evaporated to a sirup which was crystallized from ether–petroleum ether (b.p. 30–60°), yield 6.0 g., m.p. 59–60°. The mother liquors from above were concentrated under reduced pressure to a sirup (5 g.) which was dissolved in 30 ml. of benzene and chromatographed on a 74 × 270 mm. column of Magnesol[25]–Celite[26] (5:1 w./w.) using 2 l. of benzene–*t*-butyl alcohol (100:1 v./v.) as developer. An alkaline permanganate streak[27] showed a large zone near the top of the extruded column. The excised zone was eluted with acetone and the sirup obtained on solvent removal was crystallized from ether–petroleum ether (b.p. 30–60°), yield 1.0 g., m.p. 59–60°, total yield 7.0 g. (66%). Recrystallization from ether–petroleum ether (b.p. 30–60°) gave pure material: m.p. 61–62°; $[\alpha]^{20}D$ −12.5° (*c* 1.0, chloroform); X-ray powder diffraction data,[20] 9.41 m, 8.26 vw, 7.65 s (3), 5.44 s (1), 5.12 w, 4.76 m, 4.62 m, 4.39 w, 4.11 s (2), 3.82 w, 3.55 m, 3.47 m, 3.33 m.

Anal. Calcd. for $C_{14}H_{18}N_2O_9$: C, 46.93; H, 5.06; N, 7.82. Found: C, 46.74; H, 4.66; N, 7.91.

2,3,4,5-Tetra-*O*-acetyl-D-lyxonanilide.—Aniline (1 ml.) was added to a solution of sirupy 2,3,4,5-tetra-O-acetyl-D-lyxonyl chloride (0.2 g.) in ether (10 ml.). The reaction mixture was allowed to stand at room temperature for 1 hr. and then was diluted with ether (10 ml.). The ether layer was washed once with water, twice with 3 *N* hydrochloric acid, and once again with water. Concentration of the dried (magnesium sulfate) ether solution gave a sirup which was crystallized from ether–petroleum ether (b.p. 30–60°), yield 0.17 g. (74%), m.p. 102–104°. Recrystallization from the same solvent gave pure material: m.p. 103.5–104.5°, $[\alpha]^{20}D$ −11° (*c* 1.0, chloroform); X-ray powder diffraction data,[20] 8.09 s (3,3), 7.41 s (3,3), 6.38 w, 5.81 m, 5.53 s (2), 4.84 w, 4.63 m, 4.16 s (1), 3.75 m, 3.62 m, 3.49 w, 3.35 w, 3.12 w, 2.95 w.

Anal. Calcd. for $C_{19}H_{23}NO_9$: C, 55.74; H, 5.66; N, 3.42. Found: C, 55.70; H, 5.85; N, 3.62.

D-Tagatose.—A solution of 3,4,5,6-tetra-*O*-acetyl-1-deoxy-1-diazo-D-*lyxo*-hexulose (6.0 g.) in glacial acetic acid (100 ml.), to which had been added 0.02 g. of cupric acetate and a trace of powdered copper, was heated to about 80°. After the rapid evolution of gas had ceased, the reaction mixture was concentrated under reduced pressure at 40° to a sirup which was dissolved in 40 ml. of chloroform. The chloroform solution was washed three times with water, dried (magnesium sulfate), treated with carbon, and evaporated to a sirup; yield 6.5 g. The sirupy product gave a positive Pacsu[28] *keto*-acetate test.

The above sirup was cooled to 0° and deacetylated by adding a solution of barium hydroxide octahydrate (20 g.) in 200 ml. of water also at 0° and stirring for 0.5 hr. to dissolve the sirup and then 2 hr. more at 0°. The solution was saturated with carbon dioxide and the precipitated barium carbonate was removed by filtration through Celite.[26] The filtrate was decolorized with carbon and then passed through a 24 × 120 mm. column of Amberlite[29] IR-120 (H^+) resin. The resin was washed with distilled water to remove any residual sugar and the washings were combined with the eluate. The resulting solution was concentrated under reduced pressure at 40° to a sirup. Crystallization was effected by dissolving the sirup in hot methanol, adding hot absolute ethanol to turbidity, seeding, and cooling. The product was recrystallized twice from absolute ethanol–water (6:1 v./v.), yield 0.9 g., m.p. 131–133°, $[\alpha]^{22}D$ −5.0° (*c* 4.0, water); these constants are in agreement with those [m.p. 133–134°, $[\alpha]^{25}D$ −5° (*c* 1, water)] cited by Totton and Lardy[7] for D-tagatose prepared by the biochemical oxidation of D-talitol. This material migrated as a single spot on paper chromatograms and was indistinguishable from an authentic specimen in solvents A, B, and C[20]; X-ray powder diffraction data (identical with those of an authentic specimen),[20] 8.98 vw, 6.17 m, 5.89 w, 5.14 s (2), 4.41 s (1), 4.04 w, 3.61 s (3,3), 3.16 s (3,3), 3.07 w, 2.96 w, 2.88 m, 2.76 m, 2.67 w, 2.59 m, 2.53 w, 2.46 vw, 2.40 vw, 2.36 m.

The above crystallization mother liquors were subjected to phenylosazone formation; yield 0.6 g. (0.3 g. of D-tagatose or a total yield of 1.2 g. or 40%). Recrystalllization from ethanol–water yielded pure material: m.p. 185–187° dec., $[\alpha]^{23}D$ +47° (*c* 0.82, 2-methoxyethanol), in agreement with previously recorded[30] (m.p. 185–187°, $[\alpha]^{20}D$ +47° in 2-methoxyethanol) values; X-ray powder diffraction data (identical with those of a sample prepared from D-galactose),[20] 9.09 w, 8.20 w, 6.15 m, 5.51 vw, 4.81 s (3,3), 4.64 s (3,3), 4.51 s (1), 4.36 w, 4.02 m, 3.77 w, 3.45 s (2,2), 3.35 s (2,2), 3.25 w, 3.18 m, 3.03 w.

1-Deoxy-D-tagatose.—3,4,5,6-Tetra-*O*-acetyl-1-deoxy-1-diazo-D-*lyxo*-hexulose (2.0 g.), dissolved in 40 ml. of chloroform, was shaken in a separatory funnel with 8 ml. of 47% aqueous hydriodic acid. After cessation of the nitrogen evolution, water was added, and the separated chloroform layer was washed successively with water, dilute aqueous sodium thiosulfate (until free of iodine), and again with water. The dried (magnesium sulfate) chloroform solution was evaporated to s sirup; yield 1.6 g. The sirupy product migrated as a single zone (R_f 0.44) on thin layer chromatograms with benzene–ether (1:1 v./v.). This sirup has failed to crystallize and was used directly in the next step.

The above sirup (1.26 g.) was deacetylated as previously described in the synthesis of D-tagatose and the product was isolated in the same manner. The crystalline product was washed three times with acetone; yield 0.40 g. (65%). Three recrystallizations from 95% acetone gave pure material: m.p. 121–123°; $[\alpha]^{23}D$ −14° (*c* 2.0, water); X-ray powder diffraction data,[20] 8.05 vw, 6.84 s (1,1), 6.12 w, 5.48 s (2,2), 5.01 vw, 4.82 s (2,2), 4.50 s (3,3), 4.35 s (3,3), 3.99 s (1,1), 3.75 m, 3.51 m, 3.32 w, 3.16 w, 3.03 s, 2.95 m, 2.80 m, 2.72 s.

The substance reduced hot Benedict reagent and gave a positive iodoform test. It was chromatographically homogeneous in solvents A (R_f 0.40), B, and C. The n.m.r. spectrum (Varian A-60 n.m.r. spectrometer) of the above product, taken in deu-

(22) A. W. Dox, *Org. Syn.*, **4**, 27 (1925).

(23) D. L. Cottle, *J. Am. Chem. Soc.*, **68**, 1380 (1946).

(24) Th. J. DeBoer and H. J. Backer, *Org. Syn.*, **36**, 16 (1956).

(25) A synthetic magnesium silicate that had been produced by the Westvaco Chemical Division of the Food Machinery and Chemical Corp., South Charleston, W. Va.; see M. L. Wolfrom, R. M. de Lederkremer, and L. E. Anderson, *Anal. Chem.*, **35**, 1357 (1963).

(26) No. 535, Johns-Manville Co., New York, N. Y.

(27) W. H. McNeely, W. W. Binkley, and M. L. Wolfrom, *J. Am. Chem. Soc.*, **67**, 527 (1945).

(28) E. Pacsu and F. V. Rich, *ibid.*, **55**, 3018 (1933); F. B. Cramer and E. Pacsu, *ibid.*, **59**, 1467 (1937).

(29) A product of the Rohm and Haas Co., Philadelphia, Pa.

(30) N. K. Richtmyer in "Methods in Carbohydrate Chemistry," Vol. II, R. L. Whistler and M. L. Wolfrom, Ed., Academic Press Inc., New York, N. Y., 1963, p. 127.

terium oxide solution at 60 Mc.p.s. with a sodium 2,2-dimethyl-2-silapentane 5-sulfonate internal reference standard,[31] included a singlet of the proper area at τ 8.60 attributable to the terminal deoxy group. The n.m.r. spectra of other terminal deoxy sugars have been shown[32] to possess similar high-field signals.

Anal. Calcd. for $C_6H_{12}O_5$: C, 43.89; H, 7.37. Found: C, 44.15; H, 7.46.

Acknowledgment.—The authors are grateful to the late Dr. Alva Thompson and Mr. J. L. Minor of this laboratory for a supply of D-lyxono-1,4-lactone and to Mr. F. Komitsky, Jr., for obtaining and interpreting the n.m.r.

(31) G. V. D. Tiers and A. Kowalsky, Abstracts of Papers, 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April 1960, p. 17R.

(32) M. L. Wolfrom, K. Matsuda, F. Komitsky, Jr., and T. E. Whiteley, *J. Org. Chem.*, **28**, 3551 (1963).

Trifluoroacetyl as a Protecting Group for 1-Halo Sugars

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We would like to report the use of trifluoroacetyl as an effective blocking group of hydroxyl and amino substituents in the reactions of a 1-halo sugar.[2] The ease with which this group can be introduced, and, more importantly, the facility with which it can be removed, makes it a highly attractive protecting group especially for amino sugars which normally require quite vigorous conditions for N-deacylation.

Glycosidation of either cholesterol or cyclododecanol with 2-O-trifluoroacetyl-3-N-methyltrifluoroacetamido-3,4,6-trideoxyglucosyl bromide (I)[3] in 1,2-dichloroethane in the presence of mercuric cyanide[4] gave the corresponding cholesteryl and cyclododecyl glycosides II and III in good yield.

The facile removal of the trifluoroacetyl blocking group was demonstrated by converting III to its de-

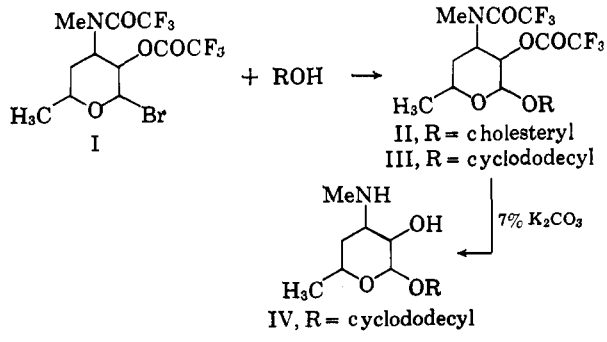
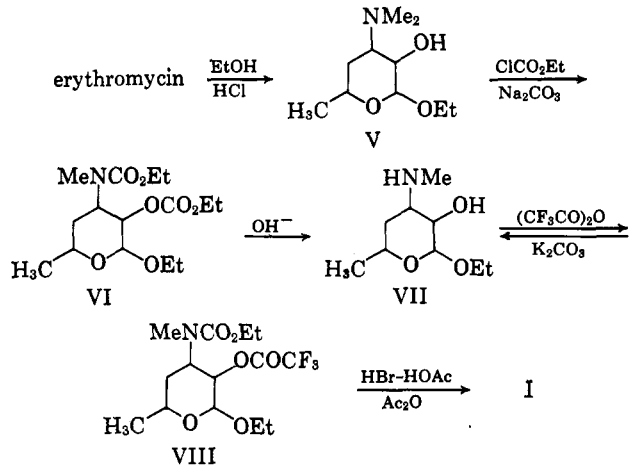


CHART I



acylated derivative IV in a 7% solution of potassium carbonate in aqueous methanol at room temperature for 4.5 hr.

The α-bromo-O,N-ditrifluoroacetylated sugar I was prepared according to the sequence outlined in Chart I. Erythromycin[5,6] was transglycosidated in refluxing ethanolic hydrogen chloride to ethyl desosaminide (V)[5] which was, in turn, converted to ethyl O,N-dicarbethoxydes-N-methyldesosaminide (VI) with ethyl chloroformate.[7] Hydrolysis to ethyl des-N-methyldesosaminide (VII) followed by trifluoroacetylation gave ethyl O,N-ditrifluoroacetyldes-N-methyldesosaminide (VIII) which was converted to I with hydrogen bromide in acetic acid. (Compound VIII could be hydrolyzed back to VII under the same conditions used to convert III to IV.)

Experimental[8]

Ethyl Desosaminide (V).—A solution of 135 g. (0.18 mole) of erythromycin[9] in 1.5–2 l. of absolute ethanol was heated under reflux for 2.5 hr. with hydrogen chloride bubbling through the solution. (The reaction mixture turned black almost immediately after refluxing began.) The ethanol was removed *in vacuo*, the black residue was dissolved in chloroform, and the chloroform solution was extracted twice with water. The combined aqueous extracts were washed with chloroform and made basic (pH *ca.* 12) with cold 10% sodium hydroxide, and the precipitated oily material was extracted into chloroform. The chloroform solution was dried and evaporated, and the orange liquid residue was distilled *in vacuo*. Ethyl desosaminide was obtained in 60% yield (22.4 g.): b.p. 73–80° (0.5 mm.), lit.[4] b.p. 65–67° (0.2 mm.); $[\alpha]^{25}D$ +116° (*c* 1.04, chloroform).

Ethyl O,N-Dicarboxydes-N-methyldesosaminide (VI).—A mixture of 1 g. (0.005 mole) of ethyl desosaminide and 2 g. of anhydrous sodium carbonate in 10 ml. (0.1 mole) of ethyl chloroformate was stirred at room temperature for 19 hr. The pale yellow reaction mixture was poured into chloroform, the chloroform solution was filtered to remove the suspended solid, and the filtrate was evaporated *in vacuo*. The evaporation was repeated twice more with fresh portions of chloroform to remove all the ethyl chloroformate. The pale yellow residue was dissolved in chloroform and the solution was washed with water, dried, and evaporated. The yellow residue was molecularly

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(2) The most commonly used protecting group is acetyl. For a comprehensive review of the preparation, properties, and reactions of 1-halo sugars, see L. J. Haynes and F. H. Newth, *Advan. Carbohydrate Chem.*, **10**, 207 (1955).

(3) Our interest in derivatives of the amino sugar desoamine derives from its being one of the more common sugar components of the macrolide antibiotics: A. B. Foster and D. Horton, *ibid.*, **14**, 213 (1959).

(4) W. W. Zorbach, G. D. Valiaveedan, and D. V. Kashelikar, *J. Org. Chem.*, **27**, 1766 (1962).

(5) E. H. Flynn, M. V. Sigal, Jr., P. F. Wiley, and K. Gerzon, *J. Am. Chem. Soc.*, **76**, 3121 (1954).

(6) P. F. Wiley, K. Gerzon, E. H. Flynn, M. V. Sigal, O. Weaver, V. C. Quarck, R. R. Chauvette, and R. Monahan, *ibid.*, **79**, 6062 (1957).

(7) This reaction parallels the reported conversion of erythromycin to O,N-dicarbethoxydes-N-methylerythromycin.[5]

(8) Melting points are corrected. Microanalyses are by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were taken as mulls in Nujol with a Perkin-Elmer Infracord spectrophotometer.

(9) We thank Abbott Laboratories for their generous gift of erythromycin.