eluate at reduced pressure and the residue was recrystallized three times from 95% ethanol to give material with a constant m.p. of 123.7–124.4°. After sublimation, this material melted at 127.0–128.0° with a change in appearance at 123.8°; recrystallization of this sublimate from 95% ethanol gave material melting at 123.8–124.4°.

Anal. Calcd. for $C_7H_7ClN_2O_3$: C, 41.50; H, 3.48; N, 13.83. Found: C, 41.43; H, 3.49; N, 14.05.

2-Chloro-4-nitroanisole.—From 0.40 g. (0.0020 mole) of 2-chloro-3-methoxy-6-nitroaniline, 8 ml. of glacial acetic acid, 0.17 g. (0.0025 mole) of sodium nitrite, 1.5 ml. of concentrated sulfuric acid, and 2.5 ml. (0.024 mole) of 50% aqueous hypophosphorous acid there was obtained 0.27 g. (73%) of 2-chloro-4-nitroanisole, m.p. 93.8–94.6° (lit.[18] m.p. 95°). This material was shown by infrared spectral comparison and a mixture melting point determination to be identical with an authentic sample of 2-chloro-4-nitroanisole, m.p. 93.6–94.9°, that was prepared[19] by methylation of 2-chloro-4-nitrophenol.

Proton N.m.r. Spectra.—Proton n.m.r. spectra were obtained at 60 Mc. in deoxygenated deuteriochloroform solution (except where noted) with tetramethylsilane as an internal standard using a Varian Associates A-60 spectrometer. The spectrum of each of the compounds exhibited an AB quartet attributed to the two aromatic protons that were present in each case; the chemical shifts in parts per million downfield from tetramethylsilane and the coupling constants in cycles per second for these aromatic protons are given in Table I.

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(18) F. Reverdin, *Ber.*, **29**, 2595 (1896); F. Reverdin and F. Eckhard, *ibid.*, **32**, 2622 (1899); A. F. Holleman and W. J. DeMooy, *Rec. trav. chim.*, **35**, 14 (1916).

(19) This preparation was carried out by Dr. Suzanne P. Varimbi.

Substitution of the Exocyclic Secondary Hydroxyl Group by an Amino Group in a D-Glucofuranose Structure[1]

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A route to the synthesis of 5-amino-5-deoxy derivatives of D-glucose is provided by double inversion at the exocyclic asymmetric carbon atom, C-5, in a D-glucofuranose structure. Both inversions involve nucleophilic displacement on carbon atom C-5.

3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-tolylsulfonyl-6-*O*-triphenylmethyl-α-D-glucofuranose[2] can be converted, by selective hydrolysis and subsequent acetylation, to crystalline 6-*O*-acetyl-3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose in a yield of 56%. Exposure of this acetyl derivative to base gives 5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-idofuranose (I). Reaction of I with sodium benzoxide produces 3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-β-L-idofuranose (II), which on tosylation gives 3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-β-L-idofuranose (III). Hydrazinolysis of the latter compound affords 3,6-di-*O*-benzyl-5-deoxy-5-hydrazino-1,2-*O*-isopropylidene-α-D-glucofuranose (IV) and this on catalytic hydrogenolysis produces crystalline 5-amino-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (V).

N-Acetylation, followed by mild methanolysis of V, similar to conditions employed by Jones and Szarek,[3] gives a product suggested to be methyl 5-acetamido-5-deoxy-α,β-D-glucoside. Since formic acid is not detected when the N-acetylated D-glucosides are subjected to periodate oxidation, it is concluded that a piperidine sugar derivative is not present.

Experimental conditions would suggest that the uncharacterized product is probably 5-acetamido-5-deoxy-α,β-D-glucofuranoside (VI).

Experimental

Analytical Methods.—Chromatographic identification of sugar derivatives was made at 25° on Whatman No. 1 filter paper, developed in irrigants (A) 1-butanol–ethanol–water (40:11:19, v./v.) or (B) ethyl acetate–pyridine–water (10:4:3, v./v.). Spray indicators employed were (C) potassium permanganate–periodate and (D) iodine vapor. Purity of crystalline products were determined by thin layer chromatography on 25 × 75 mm. silica gel G[4] coated microscope slides irrigated with (G) 1-butanol saturated with water or (H) chloroform–acetone (1:1, v./v.). Plates were sprayed with a dilute ethanolic solution containing 5% sulfuric acid and charred at 110° until permanent spots were visible. A calibrated Fisher-Johns apparatus was used for melting point determinations. Evaporations were done at reduced pressure.

6-*O*-Acetyl-3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose.—Ninety grams of 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-6-*O*-triphenylmethyl-α-D-glucofuranose[2] were dissolved in 800 ml. of an ice-cold solution of anhydrous acetone which contained 36 g. of dry hydrogen chloride per liter. This mixture was kept for 10 min. at 0°, then for an additional 1.5 hr. at 20° and slowly neutralized with solid sodium bicarbonate. On filtration and concentration, a colorless sirup was obtained. The product was dissolved in 100 ml. of chloroform and the organic extract was washed with two 25-ml. portions of water, dried over anhydrous magnesium sulfate, filtered, and evaporated to a sirup. Acetylation of this material in a mixture of pyridine and acetic anhydride gave a product which crystallized from a mixture of benzene and petroleum ether (b.p. 40–60°) and which was identified as 6-*O*-acetyl-3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose; yield 36 g. (the yield from the 6-*O*-trityl derivative was 56%), m.p. 132°, $[\alpha]^{25}D$ −4.8° (c 2.1, chloroform).

Anal. Calcd. for $C_{25}H_{30}O_9S$ (506.49): C, 59.28; H, 5.97; S, 6.33. Found: C, 59.54; H, 6.04; S, 6.24.

5,6-Anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-idofuranose (I).—A 30-g. portion of the acetyl derivative described above was dissolved in 60 ml. of alcohol-free chloroform. The mixture was cooled to 15° and 30 ml. of absolute methanol containing 3 g. (2.3 mole) of sodium were added. The solution was stirred for 2 hr. at −15° and then for an additional 12 hr. at 0°. After the addition of a saturated solution of potassium bicarbonate, the mixture was evaporated at 5° to remove methanol. The residue was extracted four times with 60-ml. portions of chloroform and the latter extracts were combined, washed with water, dried over anhydrous magnesium sulfate, and evaporated to

(1) Journal Paper No. 2306 of the Purdue University Agricultural Experiment Station.

(2) R. E. Gramera, R. M. Bruce, S. Hirase, and R. L. Whistler, *J. Org. Chem.*, **28**, 1401 (1963).

(3) J. K. N. Jones and W. A. Szarek, *Can. J. Chem.*, **41**, 636 (1963).

(4) Brinkman Instruments Inc., Great Neck, Long Island, N. Y.

a thick sirup. The anhydro derivative I, when examined by thin layer chromatography, showed that it was sufficiently pure to be used for subsequent reactions; yield 16.5 g., $[\alpha]^{25}D$ −70.5° (*c* 2.6, chloroform).

3,6-Di-*O*-benzyl-1,2-*O*-isopropylidene-β-L-idofuranose (II).—To 200 ml. of a cooled, stirred solution of benzyl alcohol, containing 1.7 g. of sodium, was added 15 g. of sirupy I. The mixture was held for 3 days at 25° during which darkening occurred. It was then slowly neutralized with a chilled dilute solution of sulfuric acid. Sodium sulfate was removed by filtration and washed with two 10-ml. portions of benzyl alcohol. The combined washings and filtrate were extracted with two 25-ml. portions of water and dried over anhydrous magnesium sulfate. After filtration, the excess benzyl alcohol was removed by distillation at 95° and 0.05 mm. pressure. The dark-colored, sirupy product which remained was dissolved in methanol containing activated charcoal. This solution was refluxed for 10 min., and filtered through a fine fritted-glass funnel. The filtrate was evaporated to approximately 25 ml. and water was added to the point of incipient turbidity, whereupon compound II slowly crystallized from solution; yield 15.6 g. (76%). It was recrystallized from methanol–water and had m.p. 89–90°, $[\alpha]^{25}D$ −44.0° (*c* 1.7, chloroform).

Anal. Calcd. for $C_{23}H_{28}O_6$ (400.45): C, 68.98; H, 7.04. Found: C, 69.10; H, 6.94.

3,6-Di-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-β-L-idofuranose (III).—A solution containing 2.6 g. of compound II, dissolved in 8 ml. of pyridine, was cooled to 10° and 10 ml. of alcohol-free chloroform containing 3.5 g. of tosyl chloride (*p*-toluenesulfonyl chloride) was added. After the reaction was kept for three days at 37°, it was cooled to 0° and 2 ml. of water were added to hydrolyze excess tosyl chloride. After 20 min., the solution was poured into 100 ml. of ice in water and 20 ml. of chloroform was added. The aqueous layer was drawn off, extracted twice with chloroform, and the combined organic extracts were washed free of pyridine with several portions of cold dilute solution of hydrochloric acid. The chloroform solution was then washed with a dilute solution of sodium bicarbonate and water and dried over anhydrous magnesium sulfate. After filtration and evaporation, compound III was crystallized from a benzene–petroleum ether (b.p. 40–60°) mixture, yielding 3.55 g., m.p. 75–76°, $[\alpha]^{25}D$ −15.3° (*c* 1.51, chloroform).

Anal. Calcd. for $C_{30}H_{34}O_8S$ (554.63): C, 64.96; H, 6.17; S, 5.78. Found: C, 64.74; H, 5.90; S, 5.82.

3,6-Di-*O*-benzyl-5-deoxy-5-hydrazino-1,2-*O*-isopropylidene-α-D-glucofuranose (IV).—A 3-g. portion of compound III was added to a stirred solution of 25 ml. of absolute 1-butanol and the mixture was heated to 95°. On addition of 30 ml. of anhydrous hydrazine, the solution remained homogenous. The mixture was gently refluxed at 117–119° for 24 hr. It was then cooled to 25° and extracted five successive times with 20-ml. portions of diethyl ether. The ether extracts were combined and washed successively with two 10-ml. portions of 50% potassium hydroxide solution and two 10-ml. portions of water, and then dried over anhydrous potassium carbonate. After filtration and evaporation of the solution, the hydrazino derivative was obtained as a colorless sirup; yield 1.86 g.

5-Amino-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (V).—The sirupy hydrazino derivative IV (1.5 g.) was dissolved in 25 ml. of absolute ethanol containing 15 g. of freshly prepared Raney nickel. This mixture was stirred for 10 hr. at 60° and filtered; the hydrogenolysis repeated with another fresh portion of Raney nickel. After filtration, the solution was evaporated and 1.13 g. of clear sirupy product was obtained. Quantitative conversion of the hydrazino group to an amino group was evidenced by negative tests[5,6] for the presence of hydrazino group activity. Since reductive debenzylation was incomplete a further reduction was employed. A 1-g. portion of the first Raney nickel reduction was dissolved in 25 ml. of absolute ethanol containing 10 g. of 5% palladium on carbon. The mixture was subjected to hydrogen at 50 p.s.i. pressure in a Parr shaker for 3 days at 25°. Filtration and evaporation of the product gave a sirup which was dissolved in chloroform and extracted three successive times with water. The combined water extracts were evaporated under reduced pressure to a sirup which slowly crystallized on standing to give 263 mg. of compound V, m.p. 86°, R_f 0.78 in irrigant A and 0.80 in irrigant B, $[\alpha]^{25}D$ −12.2 (*c* 0.58 water).

Anal. Calcd. for $C_9H_{17}NO_5$ (219.23): C, 49.30; H, 7.81; N, 6.39. Found: C, 48.93; H, 7.51; N, 6.46.

***N*-Acetylation and Glycosidation of Compound V.**—A 200-mg. portion of compound V was dissolved in 1 ml. of water containing 0.22 ml. of acetic anhydride. This solution was heated to 30° for 0.5 hr. and then evaporated to a sirup under reduced pressure. The sirupy product (220 mg.) was treated with 10 ml. of 0.8 *N* methanolic hydrogen chloride at 25° until constant optical rotation of the solution was obtained in 46 hr. The reaction mixture was neutralized with silver carbonate, filtered, and concentrated under reduced pressure to a thin sirup. The sirupy glycoside was dissolved in 5 ml. of water, treated with hydrogen sulfide to remove excess silver ions, filtered, concentrated to a sirup (152 mg.), and subjected to periodate oxidation. After the excess periodate was destroyed with ethylene glycol, an aliquot of the solution was adjusted to pH 2.0 with potassium hydrogen sulfate and steam distilled.[7,8] Formic acid was not detected in the distillate.

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(5) F. Feigl, V. Anger, and O. Frehden, *Mikrochemie*, **15**, 184 (1934).
(6) F. Feigl, V. Anger, and R. Zappert, *ibid.*, **15**, 190 (1934).
(7) D. J. Bell, A. Palmer, and T. Johns, *J. Chem. Soc.*, 1536 (1949).
(8) R. Markham, *Biochem J.*, **36**, 790 (1942).