by automatic potentiometric titrations of weighted samples against standard solutions of sodium hydroxide. Titrations were performed on an Amel 235 instrument, using a motorized buret (Model 232–233). Each percentage value is the average of at least ten titrations and the estimated error is ±0.1%. Two different normal solutions of HCl were used for the standardization of normal solutions of NaOH.

Kinetic Measurements. Separate solutions of aromatic compounds (with and without added AcOH) and nitric acid in the appropriate concentration of sulfuric acid were prepared and thermostated at 25 °C. Equal volumes of solutions of both reagents were rapidly mixed by syringes in a thermostated silica cell and the changes of absorbance with time, at selected wavelengths, were obtained on Perkin-Elmer EPS-3T and CGA PM5 spectrophotometers. Because of the limited solubilities of aromatic compounds in sulfuric acid, preliminary experiments were carried out using aromatic solutions in acid solutions kept for different times before use. The rates were independent of time. By using nitric acid concentrations at least ten times those of the substrates, good linear pseudo-first-order kinetic plots were obtained and $k_{2(obsd)}$ values were calculated from the stoichiometric concentration of nitric acid. Guggenheim's method was used in a few cases. Second-order rate constants for the nitration at 25 °C of the substrates are given in Table I.

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Registry No.—Benzene, 71-43-2; fluorobenzene, 462-06-6; chlorobenzene, 108-90-7; bromobenzene, 108-86-1; iodobenzene, 591-50-4; nitric acid, 7697-37-2; sulfuric acid, 7664-93-9.

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m-Nitrophenyl D-Glucose and D-Galactose Ethers via Alkoxide Displacement of a *m*-Nitro Group

Frederick L. Weitl,*[1] Milos Sovak, and Debra Keil

Department of Radiology S-004, School of Medicine, University of California, San Diego, La Jolla, California 92093

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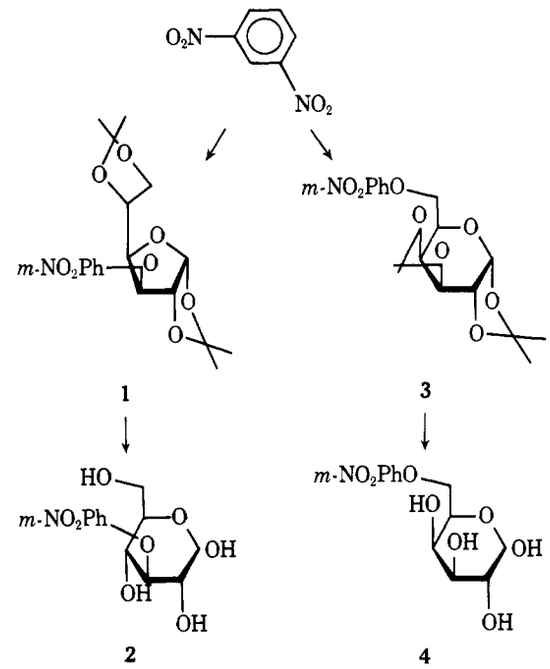
Our interest in the design and synthesis of carbohydrate derivatives[2a,b] as compounds with possible application as radiocontrast agents[3] brought our attention to the feasibility of *m*-nitrophenyl sugar ether synthesis. The unusual hydrolytic stability of benzyl sugar ethers,[4] e.g., relative to glucosides, suggests high relative stability for phenyl sugar ethers.

For design reasons, precursors to benzene based radiocontrast agents must have a meta orientation of substituents.[3] Yet only *p*-nitrophenyl[5] and 2,4-dinitrophenyl[6] sugar ethers were heretofore reported. However, a recent report of the synthesis of *m*-nitroanisole by methoxide displacement of a nitro group from *m*-dinitrobenzene[7] suggested the parallel reaction with a sugar alkoxide. We wish to report the synthesis of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*m*-nitrophenyl)-D-glucofuranose (1) and 1,2:3,4-di-*O*-iospropylidene-6-*O*-(*m*-nitrophenyl)-D-galactopyranose (3) by this route. The corresponding nonsubstituted compounds 2 and 4 were also prepared (Scheme I).

Scheme I



Since benzylation of carbohydrates using a strong base in dry, aprotic media (e.g., benzylbromide/DMF/NaH[8]) proceeds with isomeric integrity, and since the use of diisopropylidene sugars precludes any isomeric products based upon the position of phenylation, it was anticipated that *m*-nitro phenylation (*m*-dinitrobenzene/HMPA/NaH) would not involve significant amounts of isomerization. This contention was borne out by the relatively high yields of isomerically pure products 1 (82%) and 3 (62%). Both crude products 1 and 3, after decolorization on alumina columns, were readily crystallizable from cyclohexane/petroleum ether to give sharp melting points, 119–121 and 109–111 °C, respectively. Removal of the isopropylidene groups from 1 and 3 (H_2O/*p*-dioxane/H_2SO_4) was accomplished in high yields as monitored by TLC, but isolated yields were 50 and 26%, respectively, suggesting anomeric mixtures.[9]

We anticipate that this work may engender interest in pharmacophysiological investigation of meta-substituted sugar ethers as relatively stable sugar derivatives, since product 2 exhibited no apparent hydrolysis[10] (monitored by TLC) at pH 7.4 after 48 h at 75 °C in a 1% aqueous solution. Compound 4 was not sufficiently H_2O soluble to test for hydrolytic stability.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus in open capillaries and are uncorrected. Infrared spectra (KBr) were recorded on a Beckman Acculab 4 instrument. NMR spectra were recorded on a Varian EM 360 instrument using tetramethylsilane as internal reference. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Thin layer chromatograms (TLC) were performed on silica gel 60F-254 (E. Merck, Darmstadt, Germany) precoated glass plates, developed with THF (93 mL)/C_6H_{12} (7 mL)/H_2O (5 mL), and visualized with UV and/or 40% aqueous H_2SO_4 at 110 °C. Column (30 mm o.d. × 35 cm) chromatography was accomplished on aluminum oxide, activated, basic, CAMAG (Ventron, Beverly, Mass.). Reagents were obtained from the following sources: 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose from Pfanstiehl Labo-

ratories, Inc., Waukegan, Ill.; 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose from Aldrich Chemical Co., Inc., Milwaukee, Wis.; *m*-dinitrobenzene from Fisher Scientific Co., Fair Lawn, N.J. Hexamethylphosphoramide (HMPA) was a product of Aldrich Chemical Co. and was stored before use over molecular sieves, 8–12 mesh, activated, type 4A.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-(*m*-nitrophenyl)-D-Glucofuranose (1). Into a three-necked, 250-mL round-bottom flask equipped with N_2 inlet and outlet and magnetic bar stirring were charged HMPA (75 mL) and 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (28.6 g, 110 mmol). Next NaH (50% in oil), 5.5 g (115 mmol), was added over a 1-h period in 1.0–1.5-g portions. When the evolution of H_2 was nearly complete, *m*-dinitrobenzene (16.8 g, 100 mmol) was added at once. An exothermic reaction ensued but soon subsided and the reaction mixture was allowed to cool and stir at room temperature overnight. Next, the reaction mixture was slowly poured into 1.5 L of vigorously stirred water. Subsequently, most of the water layer was decanted and then the crude product collected by filtration. The solid was dissolved in CCl_4 (250 mL), then washed well with H_2O. The CCl_4 layer was evaporated to residue, then eluted from an alumina column with initially CCl_4 and finally $CHCl_3$. Those fractions resulting in a light yellow oil were crystallized by dissolution in cyclohexane, then addition of 30–60 °C petroleum ether (PE) with scratching. The light yellow solid was filtered, washed with PE, and dried in a forced air oven at 100 °C to obtain the title compound, **1**, 31.1 g (82%): mp 119–122 °C; α^{23}_D −38° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.3–1.6 [m, 12 H, $(CH_3)_2C$], 4.0–4.9 [m, 6 H, H-(2–6)], 5.97 (d, 1 H, H-1, $J_{1,2}$ = 4 Hz), 7.2–8.0 (m, 4 H, aromatic); IR 1520, 1370, 1340 cm^{-1} (–NO_2).

Anal. Calcd for $C_{18}H_{23}NO_8$: C, 56.69; H, 6.08; N, 3.67. Found: C, 56.89; H, 6.41; N, 3.44.

1,2:3,4-Di-*O*-isopropylidene-6-*O*-(*m*-nitrophenyl)-D-galactopyranose (3). Using the same procedure as for **1**, HMPA (70 mL), 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (25.0 g, 96 mmol), NaH (50% in oil, 4.8 g, 100 mmol), and *m*-dinitrobenzene (14.5 g, 86 mmol) were combined to react, with stirring under N_2. The initial evolution of heat soon subsided and the reaction mixture was stirred for 44 h at room temperature before workup. The reaction mixture was partitioned between 1 L of H_2O and 300 mL of CCl_4. The CCl_4 layer was then washed well with H_2O before concentrating for elution from an alumina column with CCl_4 and then $CHCl_3$. Those fractions which gave a light yellow oil were crystallized from cyclohexane/PE at room temperature with scratching to obtain the title compound **3**, 20.3 g (62%): mp 109–111 °C; α^{23}_D −106° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.4–1.6 [m, 12 H, $(CH_3)_2C$], 4.2–4.9 [m, 6 H, H-(2–6)], 5.63 (d, 1 H, H-1, $J_{1,2}$ = 5 Hz), 7.3–8.0 (m, 4 H, aromatic); IR 1540, 1370, 1340 cm^{-1} (–NO_2).

Anal. Calcd for $C_{18}H_{23}NO_8$: C, 56.69; H, 6.08; N, 3.67. Found: C, 57.07; H, 6.14; N, 3.67.

3-*O*-(*m*-Nitrophenyl)-D-glucopyranose (2). The following ingredients were combined and heated at reflux overnight: *p*-dioxane (20 mL), H_2O (15 mL), concentrated H_2SO_4 (4 drops), compound **1** (7.6 g, 20 mmol). TLC showed the absence of protected sugar derivative **1**. The reaction mixture was evaporated to residue, dissolved in minimum hot H_2O, and cooled with stirring overnight to crystallize. The off-white solid was collected by filtration, then recrystallized from MeOH/Et_2O/PE. The nearly white solid was filtered, washed with PE, and dried in a forced air oven at 100 °C to obtain pure title compound **2**, 3.0 g (50%): mp 142–144 °C; α^{23}_D 40° (*c* 1.0, MeOH); ^{1}H NMR (Me_2SO) showed the absence of isopropylidene groups.

Anal. Calcd for $C_{12}H_{15}NO_8$: C, 47.91; H, 5.01; N, 4.64. Found: C, 48.37; H, 5.40; N, 4.67.

6-*O*-(*m*-Nitrophenyl)-D-galactopyranose (4). Using precisely the same procedure as for **2**, compound **3** (7.6 g, 20 mmol) was deprotected to give a crude product which was dissolved in boiling MeOH by the addition of minimum H_2O. The addition of Et_2O and cooling overnight at ice temperature gave nearly white, crystalline title compound **4**, 1.6 g (26%): mp 203–206 °C; α^{23}_D 33° [*c* 1.0, THF/H_2O (1:1 v/v)]; ^{1}H NMR (Me_2SO) showed the absence of isopropylidene groups.

Anal. Calcd for $C_{12}H_{15}NO_8$: C, 47.91; H, 5.01; N, 4.64. Found: C, 47.91; H, 5.17; N, 4.57.

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Registry No.—**1**, 62263-57-4; **2**, 62263-58-5; **3**, 62263-59-6; **4**, 62263-60-9; 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose, 582-52-5; *m*-dinitrobenzene, 99-65-0; 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose, 4064-06-6.

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Synthesis of 2*H*-Pyrido[1,2-*b*]-*as*-triazines Using Azirines Generated by Modified Neber Reactions

Akikazu Kakehi,* Suketaka Ito, Takashi Manabe, Toshiaki Maeda, and Kazuhiko Imai

Department of Industrial Chemistry, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380, Japan

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In earlier studies[1,2] we have shown that pyridinium *N*-imines reacted smoothly with 2-phenylazirine to afford the corresponding 3-phenyl-1,9a-dihydro-2*H*-pyrido[1,2-*b*]-*as*-triazine derivatives and that this reaction has a high synthetic value in virtue of the wide variability of pyridinium *N*-imines. So far as isolated azirines are used, however, further extension of this reaction must be limited to a large extent by the problems in an azirine synthesis. For example, Hassner's procedure[3,4] is one of the most convenient methods for the preparation of azirine derivatives at present, but not applicable to the cases in which appropriate olefins are not available. On the other hand, if azirines without isolation can be used in the reactions with pyridinium *N*-imines, many routes to azirine may serve for the preparation of dihydropyridotriazines. Among these types of azirine formations, Neber[5,6] and related reactions[7–9] are especially important because of the ready availability of the ketonic precursors. This paper deals with the reactions of pyridinium *N*-imines with various azirines generated in situ by modified Neber reactions and the extended syntheses of the corresponding 1,9a-dihydro-2*H*-pyrido[1,2-*b*]-*as*-triazines.

We examined at first the possibility for the preparation of dihydropyridotriazines by the reactions involving oxime *O*-tosylates as an azirine precursor, but found that these reactions have only a low synthetic value for lack of reproducibility and for the instability and the low yields of oxime *O*-tosylates. These problems were, however, solved by replacing oxime *O*-tosylates with dimethylhydrazone methiodides.

The reactions of 1-aminopyridinium salts or quinolinium *N*-imine dimer with dimethylhydrazone methiodides of several aryl alkyl ketones were carried out in tetrahydrofuran in the presence of potassium *tert*-butoxide with stirring at room temperature or on heating at the reflux temperature. For example, the reactions of the salts **1–4** with acetophenone, *p*-methyl-, *p*-chloroacetophenone, and 2-acetonaphthone dimethylhydrazone methiodides, **5**, **10**, **13**, and **16**, proceeded smoothly at room temperature to give the corresponding 3-aryldihydropyridotriazines **6–9**, **11**, **12**, **14**, **15**, **17**, and **18** in