conformation which could be expected to exhibit all the observed vicinal and long-range proton spin-coupling interactions.[18]

Registry No.—γ-Metasantonin (5), 17335-57-8.

(18) The authors wish to thank Dr. J. B. DeRoos for several of the spin-decoupling data.

Reaction of 3,4-Dihydro-2*H*-pyran with Methyl α-D-Glucopyranoside[1]

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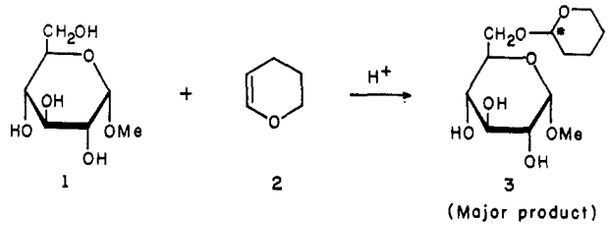
Received May 13, 1968

The use of 3,4-dihydro-2*H*-pyran[2] (2) as a hydroxyl blocking group in various synthetic reactions is well established.[3] It has been determined[4] that 3,4-dihydro-2*H*-pyran reacts unselectively with axial and equatorial hydroxyl groups in partially acetylated *myo*-inositol derivatives. In an attempt to determine how selectively alkyl vinyl ethers might react with an array of hydroxyl groups, methyl α-D-glucopyranoside was shown to form methyl 6-*O*-(1-alkoxyethyl)-α-D-glucopyranoside preferentially. The product was then readily convertible into methyl 4,6-*O*-ethylidene-α-D-glucopyranoside.[5] It was thought that this latter process should not occur with a cyclic vinyl ether such as 3,4-dihydro-2*H*-pyran and thus this reagent might be preferred for such a preferential or selective reaction.

Equimolar quantities of methyl α-D-glucopyranoside (1) and 3,4-dihydro-2*H*-pyran (2) were brought into reaction, in *N*,*N*-dimethylformamide solution and under catalysis by *p*-toluenesulfonic acid, for different reaction periods. The products obtained were fully methylated and the acetal group was later removed from them by mild acid hydrolysis. Identification of the resulting methyl ethers of methyl α-D-glucopyranoside or D-glucose indicated the location of the acetal attachment. From these data it was determined that the reaction of 3,4-dihydro-2*H*-pyran with methyl α-D-glucopyranoside gave rise to a mixture of tri- and di-*O*-methyl-D-glucose. Conversion of these into the corresponding methyl glucosides allowed their separation and isolation by preparative vapor phase chromatography. The ratio of tri- to di-*O*-methyl glycoside was 5:1. The separated tri-*O*-methyl glycoside fraction liberated a tri-*O*-methyl-D-glucose having optical rotatory, chromatographic, and electrophoretic properties identical with an authentic sample of 2,3,4-tri-*O*-methyl-D-glucose.

In another experiment, the crude reaction product resulting from the reaction of equimolar amounts of 3,4-dihydro-2*H*-pyran with methyl α-D-glucopyranoside was fractionated by thin layer chromatography. The major component, obtained in a yield of 58% of the crude reaction product, was identified as methyl 6-*O*-tetrahydro-2*H*-pyran-2-yl-α-D-glucopyranoside on the basis of the following observations. On methylation and subsequent hydrolysis, the above compound gave 2,3,4-tri-*O*-methyl-D-glucose identified by conversion into the known crystalline *N*-phenyl-2,3,4-tri-*O*-methyl-β-D-glucopyranosylamine; this major component is chromatographically identical with a compound obtained from methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside by its reaction with 3,4-dihydro-2*H*-pyran followed by deacetylation. In some experiments a portion (25%) of the syrupy reaction product crystallized. The low yield of crystals was probably due to the syrup being a mixture of diastereoisomers since the acetal carbon (see 3) is asymmetric. It is accordingly established that the cyclic 3,4-dihydro-2*H*-pyran and the acyclic vinyl ethers used previously[5] react preferentially with the C-6 hydroxyl group of methyl α-D-glucopyranoside. In the case of the acyclic vinyl ethers, the acetal formed then readily reacts further with an available hydroxyl group to give an ethylidene cyclic acetal. With 3,4-dihydro-2*H*-pyran, however, some distribution of the acetal group takes place (Table I) instead of any further reaction of the *O*-tetrahydro-2*H*-pyran-2-yl group. Reaction of 3,4-dihydro-2*H*-pyran with methyl α-D-glucopyranoside is, therefore, not as selective as is the tritylation reaction.[6]



Experimental Section[7]

Reaction of Methyl α-D-Glucopyranoside with 1 Molar Equiv of 3,4-Dihydro-2*H*-pyran.—Methyl α-D-glucopyranoside (1, 15 g) was dispersed in dry *N*,*N*-dimethylformamide (30 ml) over Drierite (calcium sulfate as soluble anhydrite, 2 g). 3,4-Dihydro-2*H*-pyran (2, 6.5 g) was added, followed by a catalytic quantity

(1) Supported by Grant No. 12-14-100-7652(71) (The Ohio State Research Foundation Project 1856) from the U. S. Department of Agriculture Northern Regional Research Laboratory, Peoria, Ill. The opinions expressed in this article are those of the authors and not necessarily those of the supporting agency.

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(7) Paper chromatography was effected on Whatman No. 1 paper in the solvent systems 1-butanol–ethanol–water (4:1:5 v/v, solvent A), 1-butanone–1% ammonium hydroxide (10:1, v/v, solvent B) with indication by *p*-anisidine hydrochloride solution [L. Hough, J. K. N. Jones, and W. H. Wadman, *J. Chem. Soc.*, 1702 (1950)] or with silver nitrate and alkali [W. E. Trevelyan, D. P. Procter, and J. S. Harrison, *Nature*, **166**, 444 (1950)]. Solutions were concentrated under reduced pressure. Melting points were determined in a Thomas–Hoover capillary melting point apparatus. Infrared spectra were obtained with a Perkin-Elmer Infracord infrared spectrometer. Ascending thin layer chromatography was effected on 0.25–1.25 mm layers of silica gel G (E. Merck, Darmstadt, Germany), activated at 110°, using the solvent systems benzene–ethanol–water–10 *N* ammonium hydroxide (200:47:15:1 v/v, solvent C) and chloroform–acetone (1:1 v/v, solvent D) with indication by iodine vapor (preparative) or sulfuric acid. Vapor phase chromatography was effected with a Beckman GC 2A gas chromatograph containing a thermal conductivity detector with helium as the carrier gas. Microanalytical determinations were made by W. N. Rond. X-Ray powder diffraction data, interplanar spacing, Å, Cu Kα radiation, λ 1.539 Å, Ni filter, camera diameter 114.6 mm, photographic recording, are expressed as relative intensities, estimated visually: vs, very strong; s, strong; m, medium; w, weak; vw, very weak. Parenthetical numerals indicate the order of the most intense lines; 1, most intense.

TABLE I

REACTION OF METHYL α-D-GLUCOPYRANOSIDE WITH 1 MOLAR EQUIV OF 3,4-DIHYDRO-2H-PYRAN

Reaction time[a]	Glycoside converted, %	Methylated methyl α-D-glucopyranoside, yield[b]	D-Glucose ether
30 min	16	95	2,3,4-Tri-O-methyl Di-O-methyl
4 hr[c]	27		2,3,4-Tri-O-methyl (58%)[d]
4 days[c]	88	94	2,3,4-Tri-O-methyl[e] Di-O-methyl[c]

[a] Ambient temperature. [b] Calculated on the basis of the material methylated. [c] See Experimental Section. [d] Yield as per cent of the acetal mixture. [e] 5:1 ratio by gas–liquid partition chromatography.

of *p*-toluenesulfonic acid (80 mg). The reaction mixture was stirred for 4 days at ambient temperatures. Unchanged methyl α-D-glucopyranoside was removed by filtration; sodium hydrogen carbonate (100 mg) and water (2.0 ml) were added to the filtrate, which was concentrated to a syrup. The addition of diethyl ether precipitated unchanged methyl α-D-glucopyranoside. The filtrate was concentrated to a syrup to yield 18.9 g. Tlc (two ascents, solvent C) showed one major component present. Data obtained at other reaction times are shown in Table I.

Methylation of the Reaction Product.—A portion of the above syrup (15 g) was dissolved in methyl iodide (100 ml), and silver oxide (25 g) was added. The mixture was shaken overnight at room temperature (or alternatively refluxed overnight), filtered, and concentrated. The methylation procedure was repeated (4–5 times) until ir analysis of the syrup showed the hydroxyl peak to be negligible.

Hydrolysis and Analysis of the Methylated Product.—A portion (5 g) of the above methylated syrup was hydrolyzed with 2 *N* sulfuric acid for 4 hr under reflux. Paper chromatographic examination (solvent A or B) of the neutralized (barium carbonate) hydrolyzate indicated a mixture of tetra-, tri-, and di-*O*-methylglucose. The hydrolyzate (3 g) was converted into the corresponding methyl glycosides by treatment with 3% methanolic hydrogen chloride under reflux. After neutralization (silver carbonate) and filtration, the solution was concentrated and dissolved in chloroform (*c* 40). The glycosides (0.5 ml chloroform solution, 200-mg sample) were separated[8] by vpc at 225° on a 3.66 m (12 ft) preparative column of 10% neopentyl glycol succinate on acid-washed Chromosorb W, 60–100 mesh, at a helium flow of 60 ml per min. The methyl glycosides were collected in a cooling chamber on elution from the gas chromatograph and weighed on a microbalance. The ratio of tri- to di-*O*-methyl glucoside was 5:1 (total return 75%). Hydrolysis (2 *N* sulfuric acid, 4 hr reflux) of the tri-*O*-methylglucosidic fraction liberated a tri-*O*-methyl-D-glucose, identified as 2,3,4-tri-*O*-methyl-D-glucose, $[\alpha]^{22}D$ +71° (*c* 1.0, acetone) (lit.[9] $[\alpha]^{22}D$ +70.5°). The syrup showed R_{glpc} values 0.87 (solvent A, lit.[10] R_{glpc} 0.85) and 0.73 (solvent B), identical with those shown by an authentic specimen.[11] Electrophoresis in borate buffer, pH 10, for 5 hr at 600 V showed the sugar to have M_{glpc} 0 (lit.[12] M_{glpc} 0) as did the authentic specimen.

The di-*O*-methyl-D-glucose fraction was not investigated. The tetra-*O*-methyl-D-glucose fraction was negligible in amount.

Prepartion of Methyl 6-*O*-Tetrahydro-2*H*-pyran-2-yl-α-D-glucopyranoside (3).—Methyl α-D-glucopyranoside (10 g) was dissolved in dry *N*,*N*-dimethylformamide (250 ml). To this solution was added 3,4-dihydro-2*H*-pyran (5.0 g, 1:1.1 molar ratio) and *p*-toluenesulfonic acid (0.1 g). The mixture was stirred in a closed flask for 3 hr at room temperature. The acid was neutralized with aqueous ammonia. The syrup obtained on removal of *N*,*N*-dimethylformamide, under reduced pressure, was thoroughly mixed with chloroform and unchanged methyl α-D-glucopyranoside separated. The chloroform solution was concentrated to a syrup (3.8 g) which showed one major spot along with several minor spots by tlc (solvent D). The major reaction product was isolated as a syrup by preparative tlc to yield 2.2 g. A portion (25%) of this syrup (probably a mixture of diastereoisomers) crystallized with difficulty from ethyl acetate: mp 170°; $[\alpha]^{20}D$ +40° (*c* 1.0, chloroform); X-ray powder diffraction data 13.81 s (**3**), 7.29 m, 6.75 m, 6.13 w, 5.62 vs (1), 5.27 vs (2), 4.54 s, 4.09 m, 3.97 m, 3.74 m, 3.47 w, 3.28 vw, 3.19 w, 3.03 s, 2.89 w, 2.83 w, 2.69 w, 2.50 m, 2.43 w, 2.35 w, 2.29 w.

Anal. Calcd for $C_{12}H_{22}O_7$: C, 51.79; H, 7.91. Found: C, 52.10; H, 7.72.

Conversion of Methyl 6-*O*-Tetrahydro-2*H*-pyran-2-yl-α-D-glucopyranoside into *N*-Phenyl-2,3,4-tri-*O*-methyl-β-D-glucopyranosylamine.—Methyl 6-*O*-tetrahydro-2*H*-pyran-2-yl-α-D-glucopyranoside (**3**, syrup, 2 g) was dissolved in methyl iodide (10 ml), and silver oxide (10 g) was added. The mixture was shaken for 24 hr at room temperature (or alternatively refluxed for the same time), filtered, and concentrated to a syrup. The methylation procedure was repeated (two–three times) until the resulting syrup showed no hydroxyl absorption in its ir spectrum. The methylated product was hydrolyzed with 1 *N* sulfuric acid for 10 hr under reflux. The evaporation of the neutralized (barium carbonate) solution afforded a syrup (1.8 g) which was homogeneous by paper chromatography (solvent A). A portion (200 mg) of the above syrup was dissolved in methanol (10 ml) followed by the addition of freshly distilled aniline (100 mg) and refluxed for 3 hr. On evaporation the product crystallized and was recrystallized from methanol to yield 150 mg, mp 145–146° undepressed on admixture with authentic[13] 2,3,4-tri-*O*-methyl-*N*-phenyl-β-D-glucopyranosylamine. The X-ray powder diffraction data[14] were identical with those of a known specimen, $[\alpha]^{20}D$ −100° (*c* 1.0, ethanol) (lit.[15] $[\alpha]^{20}D$ −103°).

Preparation of Methyl 6-*O*-Tetrahydro-2*H*-pyran-2-yl-α-D-glucopyranoside from Methyl 2,3,4-Tri-*O*-acetyl-α-D-glucopyranoside.—Methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside[16] (200 mg) was dissolved in diethyl ether (10 ml) to which *p*-toluenesulfonic acid (10 mg) and 3,4-dihydro-2*H*-pyran (0.5 ml, 1:1 molar ratio) were added. The mixture was stirred for 30 min, and the completion of the reaction was indicated by tlc (solvent D). After being neutralized with sodium carbonate and filtered, the filtrate was concentrated to a syrup and dried. This syrup (210 mg) was dissolved in anhydrous methanol (10 ml) to which was added 0.5 *N* sodium methoxide solution (1 ml). The mixture was kept at room temperature for 45 min with occasional shaking. After being treated with Amberlite 1R-120 (H^+), the methanolic solution was concentrated to a syrup which was chromatographically (thin layer, solvent D) identical with that of the major reaction product obtained by reacting methyl α-D-glucopyranoside with 3,4-dihydro-2*H*-pyran as described above.

Registry No.—**1**, 3411-23-2; **2**, 110-87-2; **3**, 17448-06-5.

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The Synthesis of 5-Phenyl-3-(substituted anilino)-2(5H)-furanones in Aqueous Solution

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Received May 14, 1968

Condensation of substituted benzylidenepyruvic acids with substituted anilines in refluxing ethanol has been established to yield the corresponding 5-phenyl-