(3 H, multiplet, olefinic protons), 6.23 (3 H, singlet, CO_2CH_3), 7.68 (2 H, doublet, J = 7.0 cps), and at 7.95 (3 H, broad singlet, CH_3) (Figure 2). The spectrum of fraction 6 differed from that of fraction 5 only in the presence of additional minor peaks. Fraction 7 appeared to be devoid of olefinic protons.

The nmr solution containing the material from fraction 5 was filtered through charcoal, concentrated, passed through a 7 × 50 mm column of Woelm basic alumina with methylene chloride, and concentrated to give 109 mg of a clear straw-colored liquid: $n^{25}D$ 1.5344; ultraviolet absorption (MeOH) at 284 mμ (ϵ 6.17 × 10^3) and 215 (1.53 × 10^4).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.40; H, 7.35.

The cycloheptatriene from fraction 4 above (190 mg), dimethyl acetylenedicarboxylate (200 mg; Eastman), and 10 ml of *p*-xylene were heated at 140° for 11 hr. Removal of the xylene at reduced pressure (bp 80–82° at 94 mm) left a liquid which was distilled at 0.6 mm with the bath temperature raised slowly to a maximum of 200°. Analysis of the distillate by nmr spectroscopy revealed nearly complete recovery of unchanged reactants. The residue after distillation amounted to about 30 mg.

Reaction of methyl diazoacetate (2.5 ml) and toluene (25 ml) as before produced 2.5 g of the cycloheptatriene mixture upon distillation of the solvent at a maximum bath temperature of 110°. The crude material (1.0 g) was placed on a 1 × 25 cm column of Woelm basic alumina packed in carbon tetrachloride. Elution with 125 ml of carbon tetrachloride followed by 125 ml of methylene chloride gave 0.8 g of a straw-colored liquid. From the nmr spectrum (Figure 1) it was apparent that the major constituent of this mixture was identical with that isolated in fraction 5 above; additional signals appeared in the aromatic, methoxy, and aliphatic regions.

Carbomethoxy-*t*-butylcycloheptatrienes.—Methyl diazoacetate (4 ml) and *t*-butylbenzene (40 ml) were heated at 150° for 1 hr. The solvent was vacuum distilled at 108° (100 mm) and the residue was flash distilled at 90–95° (1 mm). Redistillation gave 2 g of material having bp 88–89° (1 mm). A 0.6-g sample of the crude mixture was chromatographed on a 1 × 15 mm column of Woelm basic alumina packed in hexane. After elution with 30 ml of hexane to remove residual *t*-butylbenzene, five hexane fractions were cut (a total of 165 ml), followed by one fraction (250 ml) eluted by benzene, chloroform, and methanol in succession. Fractions 1–5 appeared (nmr) to be mixtures of two cycloheptatrienes. The major isomer (Figure 3) had peaks at τ 2.48 (1 H, broad doublet, J = 6 cps), 3.3–4.7 (3 H, multiplet, olefinic protons), 6.23 (3 H, singlet, CO_2CH_3), 7.72 (2 H, doublet, J = 7.2 cps), and at 8.83 (9 H, singlet, $C(CH_3)_3$).

Registry No.—**1** (R = Me), 7264-18-8; **2** (R = Me), 14194-58-2; **4** (X = 2-Me), 14194-59-3; **4** (X = 3-Me), 14194-60-6; **4** (X = 4-Me), 14194-61-7; **4** (X = 3-Bu-*t*), 14194-62-8; **4** (X = 4-Bu-*t*), 14320-33-3; **5**, 14194-63-9; **6**, 14194-64-0; **9**, 14194-65-1; **10**, 14194-66-2; **12**, 14194-67-3; **13**, 14194-68-4; toluene, 108-88-3; *t*-butylbenzene, 98-06-6.

Behavior of Ketene toward α-Methoxy Hemiacetal Halides Related to Tetrahydropyran and to Carbohydrates

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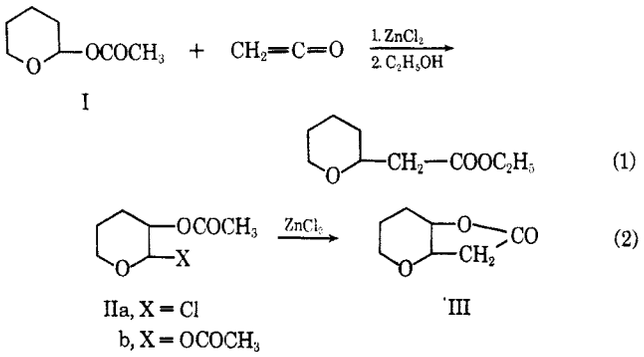
Received April 20, 1967

A 3-methoxyl substituent in tetrahydropyran-2-yl chloride inhibits reactivity of the halogen toward ketene and zinc chloride more than does a 3-acetoxyl group. Both give rise to a γ-lactone. A trace of γ-lactone results also from interaction of ketene ($ZnCl_2$) with tetra-*O*-methyl-D-glucopyranosyl bromide. Related structures in the tetrahydropyran series which showed negative response with ketene are discussed and alternate syntheses of many of them are included.

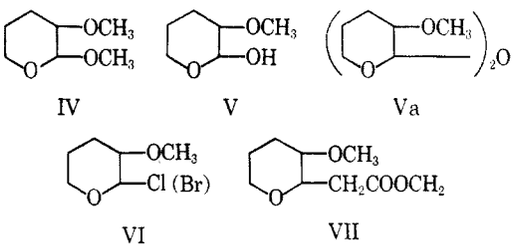
Tetrahydropyran-2-yl acetate, tetrahydropyran-2,3-diol diacetate, and 3-acetoxytetrahydropyran-2-yl chloride have been shown to react at the acylal function or the chloride position with ketene[2] in the presence of zinc chloride. The yield of ester from I was 70% (eq 1), that of lactone III from IIa was 43%, and



from IIb only a trace (eq 2). Thus, the 3-acetoxyl group lessens the reactivity at position 2. This lessening effect was magnified by having several acetoxyl groups in the molecule, for 2,3,4-tri-*O*-acetyl-α-D-xylosyl chloride yielded no lactone when treated with ketene and zinc chloride.

The present paper takes up the related question of the effect of a methoxyl group at position 3 on the reactivity of substituents at position 2. Several compounds related to 3-methoxytetrahydropyran were synthesized, and methyl ethers of carbohydrate analogs were included.

The hemiacetal hydroxyl of tetrahydropyran-2,3-diol[3] was methylated by refluxing with methanol (HCl) after which the alcoholic hydroxyl, as the anion, was converted to ether IV by reaction with methyl



iodide. Then the 2-methoxyl was removed by acid hydrolysis, yielding V. Compound V was obtained

(1) Sugar Research Foundation Fellow, 1961–1963.

(2) C. D. Hurd and R. D. Kimbrough, Jr., *J. Am. Chem. Soc.*, **82**, 1373 (1960); **83**, 236 (1961).

(3) C. D. Hurd and C. D. Kelso, *ibid.*, **70**, 1484 (1948); C. D. Hurd, J. Moffat, and L. Rosnati, *ibid.*, **77**, 2793 (1955).

also from 2,2′-oxybis(tetrahydropyran-3-yl) diacetate[3] by saponification, methylation to Va, and hydrolysis of the aldal linkage. The acetate of V was converted to hemiacetal halide VI by reaction with hydrogen chloride (in ether) or hydrogen bromide (in Ac_2O, AcOH).

If VI behaved toward ketene ($ZnCl_2$) as I or II did, one would expect the product to be either ester VII (*via* methanol) or lactone III. None of VII was found, but there was evidence for a fair amount of III because of the infrared absorption at 5.6 μ. No VII or III was observed by similar treatment of IV (an acetal) with ketene and zinc chloride although simple acetals[2] are known to react. Also, the acetate of V (an acylal) failed to produce VII or III with ketene. Obviously, the methoxyl at position 3 interferes with this reaction.

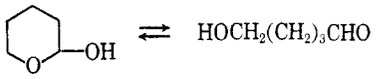
Synthesis of compound VII and related substances was undertaken to have reference compounds at hand. These steps were preceded by syntheses of related compounds having no substituent at position 3.

Tetrahydropyran-2-ylmalonic ester, prepared[4,5] by base-catalyzed condensation of tetrahydropyran-2-ol and malonic ester, was converted by Zelinski[4] into tetrahydropyran-2-acetic acid (VIII) by acid hydrolysis that involved decarboxylation. We found that VIII could be obtained more simply by direct refluxing of a solution of malonic acid and tetrahydropyran-2-ol in piperidine and pyridine, followed by treatment with hydrochloric acid. (Here, the tetrahydropyran-2-yl

$$(C_5H_9O)OH \rightarrow (C_5H_9O)CH(COOH)_2 \rightarrow \underset{\text{VIII}}{(C_5H_9O)CH_2COOH}$$

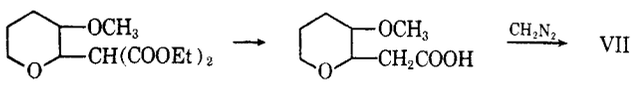
radical is shown as (C_5H_9O)–.) We obtained the methyl ester of VIII in good yield by refluxing ethyl (tetrahydropyran-2-yl)acetoacetate[6] with methanol containing sodium methoxide.

Tetrahydropyran-2-ol is an equilibrium mixture of cyclic and acyclic isomers.



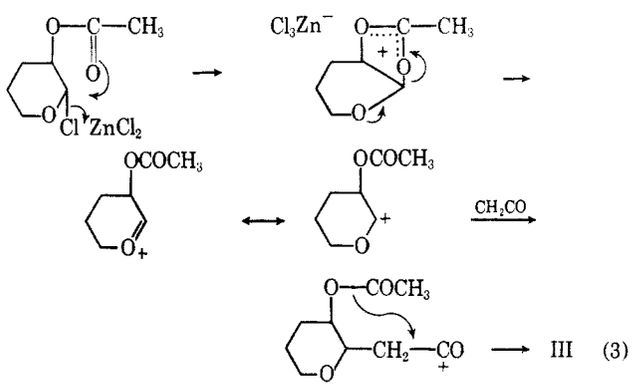
Acid VIII was synthesized also from a derivative of the acyclic form, namely, 5-acetoxypentanal, $CH_3COOCH_2(CH_2)_3CHO$, by reaction with malonic ester and pyridine. The acetoxypentanal was made from its ethyl mercaptal. A related mercaptal, synthesized in this study, is 5-(tetrahydropyran-2-yloxy)pentanal ethyl mercaptal, $(C_5H_9O)O(CH_2)_4CH(SC_2H_5)_2$.

Methoxy compound V was condensed with ethyl malonate in the presence of piperidine. Ethyl (3-methoxytetrahydropyran-2-yl)malonate was formed. From it were prepared 3-methoxytetrahydropyran-2-acetic acid and its methyl ester VII. These were

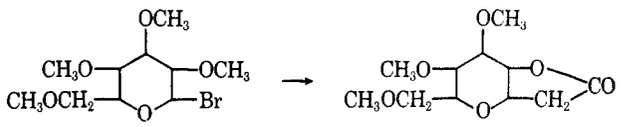


probably *threo,erythro* isomers since the substituted acetic acid, though analyzing well, melted over a 14° range, and since its methyl ester (VII) by vapor phase chromatography showed two peaks with an area ratio of 1:2.8. Vpc of the various fractions obtained by reaction of VI with ketene showed no peaks of VII when compared with this authentic specimen. As stated above, lactone III was found and in substantial amounts as judged by the intensity of the infrared peak at 5.6 μ, but it was not isolated as such.

It is evident, therefore, that the methoxyl group adjoining the hemiacetal function greatly lessens the reactivity of the latter. Since isolable yields of pure III were obtained from IIa but not from VI, the inhibitory effect of OCH_3 in these experiments would appear to be greater than that of $OCOCH_3$. It seems reasonable to assume that VI and also the acetoxy analogs of Hurd and Kimbrough[2] are *threo,erythro* mixtures. Both the 3-methoxy and 3-acetoxy substituents should, by their inductive effects, exert a restraining influence against ionization of chlorine at position 2; but that part of the acetoxy compound which is of *threo* structure may help it to ionize by neighboring group participation (eq 3). Any neighboring group participation involving the 3-methoxy group of VI would certainly be of much less magnitude. Hence, it is reasonable to find much less γ-lactone from VI than from the 3-acetoxy analog.



Methyl ethers of carbohydrates were studied to compare the effect of additional methoxyls on the tetrahydropyran system. Tetra-*O*-methyl-D-glucopyranosyl bromide was synthesized and treated with ketene and zinc chloride. A trace of γ-lactone in the product was detectable by infrared absorption at 5.57 μ, but the quantity was much lower than the yield of lactone from VI.



Tetra-*O*-methyl-D-glucopyranosyl acetate, similarly treated with ketene ($ZnCl_2$) followed by methanol, yielded no γ-lactone. Instead, the major product was methyl tetra-*O*-methyl-D-glucopyranoside in a β:α ratio of 1.35.

These new compounds related to tetra-*O*-methyl-D-glucose were synthesized: tetra-*O*-methyl-D-glucopyranosyl propionate and tetrahydropyran-2-yl tetra-*O*-methyl-D-glucopyranoside. Both compounds were distillable at reduced pressure. The latter was made by addition of tetra-*O*-methyl-D-glucopyranose to dihydropyran, initiated by a little hydrochloric acid.

(4) J. G. Schudel and R. Rice, U. S. Patent 2,522,966 (1950); *Chem. Abstr.* **45**, 6223 (1951); R. P. Zelinski, N. Peterson, and H. Wallner, *J. Am. Chem. Soc.*, **74**, 1504 (1952).

(5) J. Colonge, J. Dreux, and M. Coblentz, *Compt. Rend.*, **250**, 3202 (1960).

(6) R. Anliker, A. S. Lindsey, D. Nettleton, and R. Turner, *J. Am. Chem. Soc.*, **79**, 220 (1957).

The former was made by heating a mixture of tetra-*O*-methyl-D-glucopyranose, propionic anhydride, and sodium propionate. The calculated specific rotation for the α-D-glucosyl and β-D-glucosyl isomers are 101 and 32.5°, respectively, using Hudson's rule of isorotation. The observed value, 49.1°, points to an α,β mixture in the liquid product.

Experimental Section

Combustion analyses were performed by Hilda Beck.

Tetrahydropyran-2-acetic Acid (VIII).—A mixture of 25 g of tetrahydropyran-2-ol,[7] bp 50–52° (1–2 mm), 32 g of malonic acid, 29 g of pyridine, 4 cc of piperidine, and 5 cc of 95% ethanol was refluxed for 22 hr, then was made alkaline with 20% sodium hydroxide, diluted with water, and ether extracted until free of pyridine odor. The solution was acidified (concentrated HCl) and ether extracted several times. The ether extracts were dried (Na_2SO_4), evaporated and distilled under reduced pressure to yield 9 g of VIII, bp 90–100° (0.4 mm), which crystallized on cooling. To the undistilled residue was added 5 cc of concentrated hydrochloric acid and 50 cc of water. The mixture was refluxed for 3 hr and the solution was concentrated at 95° (20 mm). The residue was distilled, bp 94–98° (0.3 mm), yielding an additional 4.9 g of VIII. The two crops of solidified VIII, mp 52–54°, represent a 41% yield. After crystallization from hexane the melting point was 56° (lit.[2] 55–56°).

(Tetrahydropyran-2-yl)malononitrile, $(C_5H_9O)CH(CN)_2$.—To 25 g of tetrahydropyran-2-ol dissolved in 200 cc of benzene was added 17 g of malononitrile (bp 69° at 0.8 mm) and 5 g of Amberlite IRA-400 (acetate form). The suspension was heated under reflux for 18 hr, then was cooled, filtered, and distilled *in vacuo*. Four grams of unused nitrile was collected at 69–71° (0.4 mm), then 6 g (20%) of product at 108–121° (1 mm). The latter was redistilled at 90–93° (0.04 mm). Ammonia was evolved from a portion of it on alkaline hydrolysis.

Anal. Calcd for $C_8H_{10}N_2O$: N, 18.65. Found: N, 18.95.

Methyl Tetrahydropyran-2-acetate.—To 20 g of ethyl α-tetrahydropyran-2-yl)acetoacetate,[6] dissolved in 50 cc of absolute methanol, was added 450 cc of methanol in which 2 g of sodium was dissolved. The solution was refluxed for 9 hr during which time 100 cc of a fraction, bp 56–64°, was removed. The solution was cooled, neutralized with glacial acetic acid and evaporated, and the residue was dissolved in ether. After filtration, 10.5 g (71%) of a liquid distilling at 55–52° (0.1–0.04 mm) was obtained from the filtrate. The distillate gave no color with ferric chloride solution.

The same compound was made from I and ketene ($ZnCl_2$), following directions[2] given for the ethyl ester but substituting reagent methanol for ethanol.

The methyl esters from both sources gave identical vpc spectra, taken on a 4-m Carbowax 20M column (15% Carbowax on 30–60 mesh Chromosorb P)[8] with 12 psi of helium and a flow rate of 75 cc/min at 175°.

Anal. Calcd for $C_5H_{14}O_3$: C, 60.73; H, 8.91. Found: C, 61.13; H, 8.68.

5-Acetoxypentanal Ethyl Mercaptal.—A 50-g sample of 5-hydroxypentanal ethyl mercaptal[9] was dissolved in 145 cc of pyridine and 102 g of acetic acid. The mixture was kept at 20–25° for 60 hr, then was poured on ice and extracted with ether. The extract was washed with dilute sulfuric acid, saturated sodium carbonate solution, and saturated sodium chloride solution, then was dried, filtered, evaporated, and distilled to yield 45 g (75%) of an oil, bp 113–124° (0.1 mm). On redistillation it boiled at 107–110° (0.07 mm), $n^{20}D$ 1.4956. It gave a positive hydroxamic acid test. Its infrared spectrum showed no hydroxyl band.

Anal. Calcd for $C_{11}H_{22}O_2S_2$: C, 52.75; H, 8.85. Found: C, 52.53; H, 8.93.

Tetrahydropyran-2-acetic Acid from 5-Acetoxypentanal Ethyl Mercaptal.—This mercaptal (40 g) was converted to 5-acetoxypentanal (17 g), bp 71–72° (0.4 mm), using aqueous acetone, cadmium carbonate, and mercuric chloride using the conventional techniques.[9] To 14.4 g of this aldehyde and 48 g of ethyl malonate, cooled to 0°, was added a mixture of 10 cc of ethanol, 4 cc of piperidine, and three drops of glacial acetic acid. After 18 hr at 25° and 8 hr at 100° the mixture was diluted with ether, washed (with dilute acetic acid, saturated sodium carbonate solution, and water), then was dried (Na_2SO_4), evaporated, and distilled. Eighteen grams of ethyl malonate was removed at 45–46° (0.1 mm). The residue was refluxed for 2 hr with a solution of 20 g of potassium hydroxide in 200 cc of ethanol. Water was added, the alcohol was removed on a steam bath, and the aqueous solution was neutralized. Then 20 cc of concentrated hydrochloric acid was added and the solution was refluxed for 3 hr, cooled, extracted with ether, dried (Na_2SO_4), and evaporated. The residue was distilled, bp 119° (0.6 mm), to yield 4.43 g (31%) of tetrahydropyran-2-acetic acid. Its melting point was 56° after three recrystallizations from hexane.

5-(Tetrahydropyran-2-yloxy)pentanal Ethyl Mercaptal.—To 19 g of 5-hydroxypentanal ethyl mercaptal dissolved in 84 g of dihydropyran was added four drops of concentrated hydrochloric acid. After 3 hr at 25° the mixture was washed with saturated potassium carbonate solution and was diluted with ether. The solution was dried (Na_2SO_4), filtered, and evaporated, and the oily residue was distilled, bp 138° (0.25 mm), $n^{25}D$ 1.5054, yield 62 g or 90%.

Anal. Calcd for $C_{14}H_{28}O_2S_2$: C, 57.49; H, 9.64. Found: C, 57.33; H, 9.98.

5-(Tetrahydropyran-2-yloxy)pentanal.—To 25 g of the above mercaptal, dissolved in 20 cc of water and 200 cc of acetone, was added, with continuous stirring during 20 min, a suspension of 80 g of cadmium carbonate and 77 g of mercuric chloride in 200 cc of acetone. After 40 hr of continuous stirring the suspension was refluxed for 1 hr. When cool, it was filtered and the precipitate was washed with acetone. The filtrate was concentrated. To it was added 50 cc of water, and the solution was washed once with 50 cc of water, dried, and evaporated. To the residue was added 3 g of sodium carbonate together with 3 cc of water, and, upon stirring, an orange red precipitate separated. It was removed and washed with acetone. The acetone filtrates were dried (Na_2SO_4) and evaporated. The residue, on distillation, gave 2.8 g of liquid, bp 50–68° (0.10 mm); redistillation gave bp 64–68° (0.10 mm). The infrared spectrum, taken in carbon tetrachloride, showed absence of hydroxyl and presence of carbonyl at 5.83 μ. Analysis for carbon gave a high value but this was not improved by another fractionation.

Anal. Calcd for $C_9H_{18}O_3$: C, 64.48; H, 9.73. Found: C, 65.09; H, 9.70.

2-Methoxytetrahydropyran-3-ol.—Tetrahydropyran-2,3-diol diacetate[3] was prepared from dihydropyran. An additional helpful observation in this synthesis was made; namely, ordinary *t*-butyl alcohol can be used for the OsO_4 catalyst as well as the very pure tertiary alcohol. Any precipitated catalyst can be quickly redissolved and the catalyst regenerated by addition of a few drops of 3% hydrogen peroxide in *t*-butyl alcohol.

A solution of 75.5 g of the diacetate in 300 cc of methanol containing a trace of sodium was deacetylated in 2 hr at 25°. Solvent was removed at reduced pressure after adding a drop of glacial acetic acid. The residual diol (44 g) was dissolved in a liter of methanol containing 4% of hydrogen chloride and was refluxed for 6 hr. Then, when cool, it was neutralized with solid sodium bicarbonate, filtered, and distilled: yield, 69% of a liquid of bp 92–93° (19 mm), $n^{20}D$ 1.4540.

This substance has been reported,[10] bp 52–53° (1–2 mm), $n^{20}D$ 1.4533, starting with the diol and 1% hydrogen chloride in methanol but without mentioning yield. In view of the low reported analytical value for carbon (53.6%), it was reanalyzed.

Anal. Calcd for $C_6H_{12}O_3$: C, 54.52; H, 9.15. Found: C, 54.33; H, 8.95.

2,3-Dimethoxytetrahydropyran.—To 45 g of 2-methoxytetrahydropyran-3-ol, dissolved in 150 cc of dry benzene, was added 11 g of sodium. Care was taken to exclude moisture. After 3 hr on a steam bath, the excess sodium was removed and the benzene solution was concentrated. To the concentrate was added 43.5 cc (2 equiv) of iodomethane and the mixture was refluxed for 24 hr. Five cubic centimeters of methanol was

(7) L. E. Schniepp and H. H. Geller, *J. Am. Chem. Soc.*, **68**, 1646 (1946).
(8) M. Gee and H. G. Walker, *Anal. Chem.*, **34**, 650 (1962).
(9) C. D. Hurd and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **74**, 5324 (1952).
(10) R. V. Peterson, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 750 (1960).

added and the mixture was evaporated, dissolved in ether, filtered, and evaporated. The yield, after distillation, was 34 g (70.5%) of a liquid, bp 80–83° (29 mm), $n^{20}D$ 1.4338. The infrared spectrum (in CCl_4) showed no hydroxyl band.

Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.39; H, 9.55.

A sample of it was analyzed by vpc at 125° on the 4-m Carbowax column described above. Two peaks were resolved, suggesting a mixture of *threo,erythro* isomers. The first peak to appear constituted 63% of the mixture, or approximately a 2:1 ratio.

2,2′-Oxybis(3-methoxytetrahydropyran).—A solution of 34 g of 2,2′-oxybis(tetrahydropyran-3-yl) diacetate[8] in 200 cc of absolute methanol containing a chip of sodium was kept at 25° for 4 hr, after which the alcohol was evaporated leaving 24 g (94%) of the "disaccharide" 2,2′-oxybis(tetrahydropyran-3-ol). The latter was dissolved in 100 cc of benzene and to it was added 6 g of sodium hydride, care being taken to exclude moisture. The mixture was refluxed 6 hr. The crystalline sodium derivative separated, but, instead of filtering it off, the benzene was distilled away at reduced pressure and to the residue 74 g of methyl iodide was added. After 24 hr of refluxing the excess of methyl iodide was removed and the residue was taken up in 50 cc of methanol. The solution was filtered and evaporated. A second methylation step was carried out by dissolving the residue in 300 cc of dimethylformamide[11] and adding 51 g of silver oxide and 93 g of methyl iodide, and stirring the suspension continuously for 36 hr. The flask was cooled at the beginning as heat was evolved. Moisture was excluded. After filtration and concentration under reduced pressure, 300 cc of chloroform was added. An abundant white precipitate was obtained that turned yellow with the addition of water. It was separated and washed with chloroform. The filtrate and washings were evaporated and the residue was distilled: yield 11.6 g (43%) of an oil, bp 101–107° (0.15 mm). It boiled at 88–90° (0.02 mm) on redistillation. The yield would have been 7 g without the second methylation.

Anal. Calcd for $C_{12}H_{22}O_5$: C, 58.51; H, 9.00. Found: C, 58.36; H, 8.73.

3-Methoxytetrahydropyran-2-ol (V).—After heating a mixture of 15 g of 2,3-dimethoxytetrahydropyran and 200 cc of 0.5 *N* hydrochloric acid for 8 hr at 95°, then neutralizing ($NaHCO_3$), saturating with sodium chloride, and extracting with chloroform, the extract was dried and distilled: yield 6.2 g (49%) of an oil of bp 61–62° (0.08 mm).

The same oil was obtained in 69% yield by heating 9.9 g of 2,2′-oxybis(3-methoxytetrahydropyran) and 100 cc of 0.1 *N* hydrochloric acid for 2 hr at 95°, then processing as before.

Redistillation of the products gave bp 60° (0.05 mm). The compound gave a positive Tollens' test for aldehydes, and its infrared spectrum showed a peak at 3.00 μ (hydroxyl) and a small band at 5.77 μ (carbonyl). The low carbon analysis was not improved by redistillation of the product.

Anal. Calcd for $C_6H_{12}O_3$: C, 54.52; H, 9.15. Found: C, 53.89; H, 9.54.

3-Methoxytetrahydropyran-2-yl Acetate.—A mixture of 6 g of V, 3 g of fused sodium acetate and 100 cc of acetic anhydride was heated on a steam bath for 3 hr, then was cooled to permit addition of methanol. Volatile matter, including acetic acid, was removed at 90° and 25 mm. The residue was dissolved in anhydrous ether, filtered, evaporated, and distilled: yield 6.8 g (86%) of a liquid of bp 62–64° at 0.04–0.03 mm. It came over at 50–51° (0.03 mm) on redistillation.

Anal. Calcd for $C_8H_{14}O_4$: C, 55.15; H, 8.10. Found: C, 55.32; H, 7.97.

Ethyl (3-Methoxytetrahydropyran-2-yl)malonate.—Equimolar (0.065 mole) amounts of V and ethyl malonate were mixed with 40 cc of pyridine, 3 cc of piperidine, 10 cc of 95% ethanol, and two drops of glacial acetic acid. After 18 hr of refluxing and 10 hr at 20° most of the bases were removed at 95° (20 mm). The residue was dissolved in chloroform, washed once with dilute sulfuric acid, then with saturated sodium carbonate solution, and dried (Na_2SO_4). Solvent was removed and the residue was distilled: bp 102–115° (0.05–0.2 mm), yield 8.5 g (48%). It was redistilled at 112° (0.14 mm).

Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.20. Found: C, 57.21; H, 8.10.

(11) H. G. Walker, M. Gee, and R. M. McCready, *J. Org. Chem.*, **27**, 2100 (1962).

3-Methoxytetrahydropyran-2-acetic Acid.—To 7.6 g of ethyl (3-methoxytetrahydropyran-2-yl)malonate was added a solution of 3.5 g of potassium hydroxide in 100 cc of 95% alcohol. After refluxing the mixture for an hour the alcohol was removed under reduced pressure and the residue was dissolved in water. This was acidified (dilute HCl) and extracted with ether, and the ether extracts were evaporated. The residue was dissolved in water (4 cc), four drops of concentrated hydrochloric acid was added, and the mixture was heated on a steam bath for 30 min. Then the water and acid were distilled away. The residue was vacuum distilled to yield 1.7 g (35%) of product, bp 97–115° (0.2 mm). On redistillation, it boiled at 115° (0.15–0.10 mm). The oily distillate was dissolved in hot hexane. On cooling with Dry Ice a white solid separated that, after two recrystallizations from hexane, melted at 55–69°.

Anal. Calcd for $C_8H_{14}O_4$: C, 55.15; H, 8.10. Found: C, 55.30; H, 8.17.

Methyl 3-Methoxytetrahydropyran-2-acetate (VII).—To 0.60 g of the above acid, dissolved in 30 cc of dry ether, was added dropwise a solution of diazomethane in ether. A slight excess was added after reaching the equivalence point. After standing for 2 hr at 25° the excess of diazomethane was decomposed by adding a few drops of formic acid solution. Solid sodium bicarbonate was then added and the ethereal solution was filtered and evaporated, and the residue was distilled under reduced pressure. The boiling point was 65° at 0.06 mm, yield 0.21 g (32%).

Anal. Calcd for $C_9H_{16}O_4$: C, 57.42; H, 8.56. Found: C, 57.73; H, 8.84.

Vpc analysis at 175° on the above-described Carbowax column showed two peaks with a ratio of 2.8:1 and probably representing *threo,erythro* isomers. The more abundant was the one with the lower retention time.

Infrared Spectra.—The C–O bonds in the above compounds not only include methoxy groups which represent both ether and acetal functions but also include the tetrahydropyran ring. Here too, the C–O bonds represent cyclic ethers or acetal functions, but in one example it also includes aldal bonds (2,2′-oxybis(3-methoxytetrahydropyran)). It would be expected, therefore, that the infrared spectra (in CCl_4) would show two or three weak bands between 7.46–7.81 μ and two or three strong bands between 8.68–9.40 μ. Such were found, and for IV there were five strong bands at 8.71, 8.90, 9.00, 9.26, and 9.42 μ.

The characteristic weak band at 7.26–7.35 μ for CH_3 was in all of the spectra, but in that from IV it appeared at 7.38 μ, and in the acetate of V it was strong at 7.32 μ.

The alcoholic hydroxyl of 2-methoxytetrahydropyran-3-ol appeared in the strong nonassociated band at 2.85 μ. The more acidic hemiacetal hydroxyl of V absorbed strongly at 3.00 μ, showing hydrogen bonding.

The three acetic esters, namely, the acetate of V, 5-acetoxypentanal ethyl mercaptal, and 5-acetoxypentanal, all showed strong carbonyl peaks at 5.72, 5.77, 5.79 μ respectively, but the smaller value for the acetate of V is in keeping with the fact that it is really an acylal and not an ester. The oxidation state of an acylal is midway between that of an ester and that of an acid anhydride. Since carbonyl stretching absorptions for acid anhydrides occur at typically lower wavelengths than for esters, the present observation (5.72 lower than 5.77, 5.79) correlates well. 5-Acetoxypentanal, with an aldehyde group in its molecule, showed no splitting of the carbonyl band at 5.79 μ. 5-(Tetrahydropyran-2-yloxy)pentanal showed the expected band at 5.83 μ, but unexpectedly it was only medium in intensity.

A strong carbonyl band at 5.83 μ appeared in the spectrum of 3-methoxytetrahydropyran-2-acetic acid. A broad absorption from 2.8–4.2 μ, with a peak at 3.40 μ, shows the merging of the OH and CH bands, as expected for carboxylic acids.

Carbohydrate Derivatives.—Tetra-*O*-methyl-D-glucopyranose was made following directions of West and Holden:[12] mp 84–86°, $[\alpha]^{25}D$ 80.6 (*c* 2.9, water). Tetra-*O*-methyl-D-glucopyranosyl acetate, bp 102–104° (0.15 mm), was made from the above compound by reaction[13] with acetic anhydride and sodium acetate. The acetate was converted into sirupy tetra-*O*-methyl-D-glucopyranosyl bromide[13] by reaction with hydrogen bromide in

(12) E. West and R. F. Holden, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 800.

(13) M. L. Wolfrom and D. Husted, *J. Am. Chem. Soc.*, **59**, 2559 (1937).

acetic acid and acetic anhydride. The sirupy bromide was used promptly (below).

Tetra-*O*-methyl-D-glucopyranosyl Propionate.—Tetra-*O*-methyl-D-glucopyranose (10 g) and 6 g of freshly fused sodium propionate were dissolved in 80 cc of propionic anhydride. The mixture was heated on a steam bath for 2 hr, after which the unused anhydride was removed under reduced pressure. The sirupy residue was dissolved in ether, filtered, and distilled: bp 105–107° (0.04 mm), yield 7.2 g (57%), $[\alpha]^{29}D$ 49.15 (*c* 3.56, chloroform).

Anal. Calcd for $C_{13}H_{24}O_7$: C, 53.41; H, 8.27. Found: C, 54.00; H, 7.90.

Behavior of the Compounds toward Ketene. General Directions.—These substances failed to react when tested with ketene: IV, acetate of V, and tetra-*O*-methyl-D-glucopyranosyl acetate. In view of the nonreaction of the last compound, the corresponding glycosyl propionate was not included. Three compounds did appear to attach ketene to the aldehydic carbon, namely, VI-Cl, VI-Br, and tetra-*O*-methyl-D-glucopyranosyl bromide. Amounts taken of these three substances were 0.03–0.1 mole, dissolved in 15–100 cc of ethyl acetate to which 1–5 g of zinc chloride was added. A stream of ketene gas, made by pyrolysis of acetone, was introduced at a rate of 0.16 mole/hr until 0.4–0.8 mole had been added. Temperature was held at 0–3° during this period. Then, 400–600 cc of methanol was added. The solution was refluxed for a few hours and then was concentrated to remove methanol and ethyl acetate by heating on a steam bath under reduced pressure. The residues were dissolved in ether, washed with saturated sodium bicarbonate solution, saturated sodium chloride solution, dried, evaporated, and distilled into fractions at about 0.1 mm. Some acetoacetic ester appeared in the first cuts. It was formed either from ketene *via* diketene or from ethyl acetate *via* an acid-catalyzed Claisen condensation. Significant deviations from this procedure will be mentioned below, as well as other details.

VI Chloride.—This chloride was made *in situ* from 10 g of 3-methoxytetrahydropyran-2-yl acetate by dissolving the latter in 20 g of a 25% solution of hydrogen chloride in dry ether. After 4 days at 0° most of the solvent was removed under reduced pressure. The residue was taken up in 20 cc of ethyl acetate which contained 1 g of zinc chloride. Ketene (0.59 mole) was added to this. No methanol was used in processing the mixture. The distilled products included 5 g at 52–54.5° (0.1 mm), 0.35 g at 73–85° (0.2 mm), and a residue. The first fraction gave a red color with ferric chloride and was chiefly acetoacetic ester. It contained no γ-lactone. The second fraction absorbed strongly at 5.60 μ (γ-lactone) in the infrared but there were other carbonyl absorptions. The residue, after treatment with alcoholic potassium hydroxide, acidification, and ether extraction, yielded 0.5 g of a fraction, bp 61–65° (0.05 mm), that absorbed strongly for γ-lactone. From this fraction there was obtained 0.3 g of solid that melted at 59–66°. If pure, lactone III is known to melt at 79–80°.

VI Bromide.—This also was made *in situ* from the acetate (8 g) by dissolving it in 40 cc of 1:1 acetic anhydride and acetic acid which contained 24 g of hydrogen bromide. After 2 hr at 0°, 4 g of zinc chloride was added, then 0.77 mole of ketene. The distilled products at 0.1 mm were 10 g at 32–49°, 0.85 g at 50–61°, and 0.65 g at 61–69°. The last fraction only showed a small γ-lactone band at 5.60 μ in the infrared spectrum. The vpc analysis showed no VII in any fraction.

Tetra-*O*-methyl-D-glucopyranosyl Bromide.—The bromide taken weighed 17.4 g. After removing the methanol in processing, the residue was dissolved in chloroform, washed once with saturated sodium chloride solution, dried, and distilled (0.15 mm) yielding 1.5 g at 43–62° which gave a red color with ferric chloride, 5.25 g at 62–82° and 2.35 g at 82–88° both of which contained methyl tetra-*O*-methyl-D-glucopyranoside by vpc analysis,[8] and 1.4 g of residue whose infrared spectrum (in CCl_4) showed a strong peak at 5.57 μ (γ-lactone), with absorption also elsewhere in the carbonyl region.

Vapor phase chromatography provided a simple, effective way of recognizing the two methyl tetra-*O*-methyl-D-glucopyranosides. In our instrument at 175°, with conditions as cited above, the β isomer appeared as a peak of the chromatogram in about 36 min and the peak for the α isomer at about 48 min. In the 62–82° cut the β:α ratio was about 3:1, but this cut also showed a fraction "B" at about 102 min. The relative percentages of the three substances were 56:20:24. These three substances also appeared in the 82–88° cut but the major component was a fraction "A," absent in the previous cut, that appeared at about 92 min. Here, the relative percentages for β:α:A:B were 7.8, 15.6, 71.1, 5.5. From these percentages and the weights of the two fractions, the yields are 3.1 g of β, 1.4 g of α, 1.7 g of B, and 1.4 g of A. Substances A and B were not identified.

Registry No.—III, 5270-44-0; IV (*threo*), 14194-71-9; IV (*erythro*), 6559-03-1; V, 14194-73-1; Va, 14194-74-2; VI (chloride, *threo*), 14194-75-3; VI (chloride, *erythro*), 14194-76-4; VI (bromide, *threo*), 14194-77-5; VI (bromide, *erythro*), 14194-78-6; VII (*threo*), 14194-79-7; VII (*erythro*), 14194-80-0; VIII, 13103-40-7; (tetrahydropyran-2-yl)malononitrite, 14194-82-2; methyl tetrahydropyran-2-acetate, 13103-41-8; 5-acetoxypentanal ethyl mercaptal, 14194-84-4; 5-(tetrahydropyran-2-yloxy)pentanal ethyl mercaptal, 14194-85-5; 5-(tetrahydropyran-2-yloxy)pentanal, 14194-86-6; 2-methoxytetrahydropyran-3-ol, 14194-87-7; 3-methoxytetrahydropyran-2-yl acetate, 14194-88-8; ethyl (3-methoxytetrahydropyran-2-yl)malonate, 14194-89-9; 3-methoxytetrahydropyran-2-acetic acid (*threo*), 14194-90-2; 3-methoxytetrahydropyran-2-acetic acid (*erythro*), 14320-57-1; tetra-*O*-methyl-D-glucopyranosyl propionate (α isomer), 14194-91-3; tetra-*O*-methyl-D-glucopyranosyl propionate (β isomer), 14194-92-4; tetra-*O*-methyl-D-glucopyranosyl bromide, 14194-93-5; γ-lactone from tetra-*O*-methyl-D-glucopyranosyl bromide and ketene, 14194-94-6; methyl tetra-*O*-methyl-D-glucopyranoside (α isomer), 605-81-2; methyl tetra-*O*-methyl-D-glucopyranoside (β isomer), 3149-65-3; ketene, 463-51-4.