pleted. Anhydrous Dowex 50 (H^+) (washed with anhydrous methanol and dried) (40 ml.) was added to the reaction mixture and stirred vigorously until complete disappearance of the nitronate precipitates was observed (2 hr.). The resin was filtered and washed with 80 ml. of anhydrous ethanol. The filtrate and washings were combined and hydrogenated with 40 g. (wet wt.) of activated alcoholic Raney nickel at an initial pressure of 3 atm. The uptake of hydrogen ceased within 2 hr. The catalyst was filtered and the filtrate was diluted to 2 l. with deionized water. The solution (T.O.D. of 330,000 units) was passed through a column of Dowex 50 × 8 (H^+) (50–100 mesh) (2.2 × 28 cm.). The column was washed with 500 ml. of water; 99,000 T.O.D. units were unabsorbed on the column and were eluted with water. The column was then eluted with 0.02 *N* HCl. The first 3.6 l. was discarded. The next 5.3 l. of acid eluted fraction 1 which contained 88,000 T.O.D. units and the last 2 l. (fraction 2) contained 89,000 T.O.D. units. The over-all recovery of T.O.D. units from the column was 90%.

Fraction 1 was evaporated under reduced pressure at about 40° to a syrup. The syrup was dissolved in a minimum amount of hot methanol. To the solution was added an equal volume of ethanol. On cooling to room temperature, precipitation occurred. The semisolid was collected by decantation and again dissolved in a minimum amount of hot methanol and a few drops of ethanol. The solution was kept standing for 2 days at 0–5°. The precipitated solid was filtered and crystallized from methanol to yield 302 mg. of colorless needles, m.p. 234–235° eff., $[\alpha]^{23}D$ +67° (*c* 0.68, water).

Anal. Calcd. for $C_{10}H_{15}N_3O_6 \cdot HCl \cdot H_2O$: C, 36.64; H, 5.49; N, 12.82. Found: C, 36.84; H, 5.50; N, 13.05.

From the mother liquor of crystallization an additional 624 mg. of the same compound was obtained.

Electrophoretic migration (+12.1 cm., borate buffer, pH 9.2, 900 v., 8 hr.) and the optical rotation of this material were identical with those of the galacto derivative XVI.

Evaporation of fraction 2 afforded a syrup which was dissolved in a small amount of methanol. The solution was treated with a twofold volume of ethanol. The precipitate was gathered by decantation and was again dissolved in a small amount of hot methanol and treated with ethanol. This procedure was repeated once more and the mixture was kept at ~0° for several hours. Colorless needles crystallized, 276 mg., m.p. 212–214°, $[\alpha]^{23}D$ +52° (*c* 0.59, water). From the mother liquor an additional 775 mg. of crystalline material was obtained.

Anal. Calcd. for $C_{10}H_{15}N_3O_6 \cdot HCl \cdot 0.5\ H_2O$: C, 37.68; H, 5.37; N, 13.19. Found: C, 37.52; H, 5.60; N, 13.25.

Paper electrophoresis showed that the crystalline material from fraction 2 was a mixture of the gluco II and the galacto XVI derivatives. No mannosyl derivative X was detected electrophoretically in this crystalline material.

Acknowledgment.—The authors are indebted to Dr. George B. Brown for his warm and continued interest.

Synthetic Nucleosides. LXIX.[1,2] Synthesis of Some New Types of Branched-Chain Amino Sugars

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Reaction of methyl 3-benzamido-4,6-*O*-benzylidene-3-deoxy-α-D-*arabino*-hexopyranosid-2-ulose (III) with methylmagnesium iodide proceeded by a stereospecific axial attack to give methyl 3-benzamido-4,6-*O*-benzylidene-3-deoxy-2-*C*-methyl-α-D-glucopyranoside (IV) in 82% yield; since III is readily obtained from methyl α-D-glucopyranoside *via* oxidation of methyl 3-benzamido-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside (II) with the Pfitzner–Moffatt reagent, this sequence readily leads to amino sugar derivatives with a branch on a carbon not bearing the amino group. A similar Grignard reaction with methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranosid-3-ulose (VIII) proceeded by equatorial attack with formation of methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*C*-methyl-α-D-allopyranoside (X) in 65% yield; thus compounds of type X are also fairly accessable from methyl α-D-glucopyranoside *via* oxidation of methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside (IX) to VIII.

As yet, no branched-chain amino sugars have been found in nature; since many unusual amino sugars[3] and many branched-chain sugars[4] are found in antibiotics or bacterial cell walls, it does not seem unreasonable that branched-chain amino sugars will ultimately be found in nature. Even though the first structure determinations will be made with the aid of n.m.r. spectroscopy and mass spectrometry, new synthetic methods for such branched-chain amino sugars are worthy of exploration; such branched-chain amino sugars could also be converted to unusual nucleosides which might have interesting biological properties.

Two groups of investigators[5,6] have independently developed a route to sugars containing the amino and branched moieties on the same carbon by a variation of the now classical sugar dialdehyde–nitromethane route[7]; by its synthetic nature, this route is limited to branching on the carbon bearing the amino group. A new route to branched-chain amino sugars has now been developed which is complementary to the nitroalkane route[5–7] in that branching can presumably be introduced on a carbon of the sugar not bearing the amino group; this new route is the subject of this paper.

In a recent publication from this laboratory,[8] the oxidation of either methyl 3-benzamido-4,6-*O*-benzylidene-3-deoxy-α-D-glucopyranoside (I) or methyl 3-benzamido-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside (II) with phosphoric acid and dicyclohexylcarbodiimide in dimethyl sulfoxide—the Pfitzner–

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(2) Paper LXVIII: B. R. Baker and T. L. Hullar, *J. Org. Chem.*, **30**, 4053 (1965).

(3) R. W. Jeanloz and E. A. Balasz, Ed., "The Amino Sugars," Academic Press Inc., New York, N.Y., 1964.

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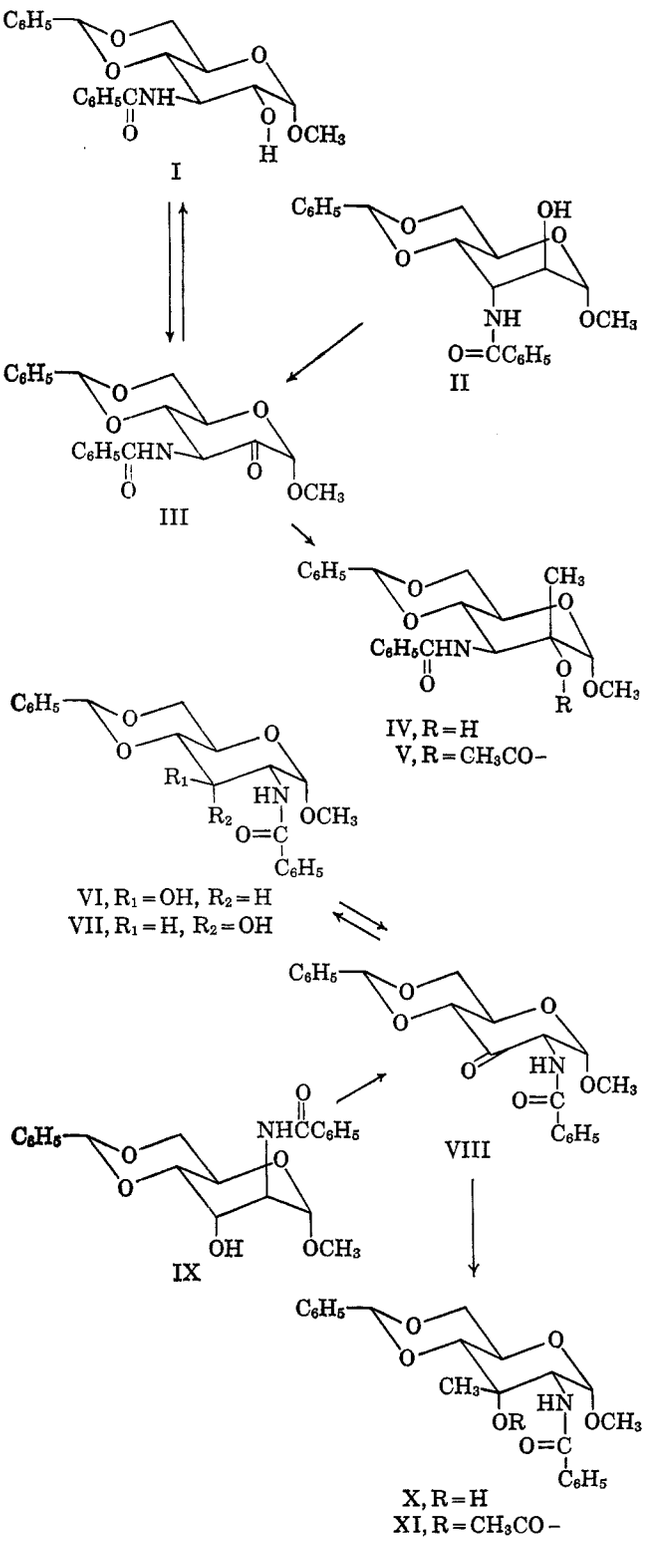
SCHEME I



Moffatt reagent[9]—gave the identical ketone, methyl 3-benzamido-4,6-*O*-benzylidene-3-deoxy-α-D-*arabino*-hexopyranosid-2-ulose (III) in 96 and 87% yields, respectively; since I and II are readily prepared from the common methyl α-D-glucopyranoside, the oxo sugar III is an easily accessible material that should be utilizable for a number of transformations. Similarly, methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranosid-3-ulose (VIII) was readily accessible from D-glucosamine *via* oxidation of VI or methyl α-D-glucopyranoside *via* oxidation of IX. Reduction of the *arabino* ketone III with sodium borohydride proceeded virtually stereospecifically by axial attack to the *gluco* configuration, I; reduction of the *ribo* ketone VIII also proceeded stereospecifically, but by equatorial attack to give the *allo* configuration, VII. (See Scheme I.)

The reaction of the ketones III and VIII with excess methylmagnesium iodide gave, in each case, a crystalline product in good yield. These products were isomeric by elemental analysis and by infrared spectra; both had retained their benzylidene and benzamido groups, had lost the ketone carbonyl, but had gained a methyl and a hydroxyl group. These reactions appeared to be strongly stereoselective. Grignard reagents[10] and sodium borohydride are known to attack ketones preferentially from the least hindered side of the molecule[12]; since sodium borohydride has been demonstrated to give axial attack of III with generation of the *gluco* configuration (I) and to give equatorial attack of VIII with generation of the *allo* configuration (VII), it can be predicted that the predominant products from the Grignard reaction on III and VIII should have structures IV and X, respectively.

Even though the structures IV and X are quite predictable, it was considered wise to find supporting evidence for these unusual structures. Since IV has *trans*-diequatorial groups at positions 2 and 3, it should not be possible to form fused ring systems such as a cyclic carbamate between these 2- and 3-functional groups easily; however, without the availability of the corresponding axial alcohol, such a negative experiment can be fraught with uncertainty. A similar argument can be advanced for X where X should form a cyclic carbamate with greater ease than the epimeric carbinol.

It should be possible to remove the *O*-benzylidene group, block the 6-hydroxyl group, and then form a cyclic carbonate between the 3- and 4-hydroxyls in the case of X; in this case it should be possible to form a cyclic carbonate with these *cis*,equatorial,axial groups; again it is dangerous to make such an assignment without comparison to the alternate 3-equatorial alcohol which would form a cyclic carbonate even easier with the *trans*-4-hydroxyl.[13] Total degradation by a combination of hydrolysis and oxidation steps would not only be long and laborious, but it would be difficult to relate the products to compounds of known stereochemistry. Specific optical rotations cannot be used since few even remotely similar compounds are known.

It has been demonstrated by Lemieux, *et al.*,[14] and

(9) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem Soc.*, **85**, 3027 (1963).

(10) The use of Grignard reagents for the synthesis of nonnitrogenous branched-chain sugars is not new; sugar epoxides have been opened with these reagents[11] and nonnitrogenous oxo sugars have been treated with a number of Grignard reagents and the resultant products have been further transformed.[11]

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(12) (a) E. L. Eliel, "The Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., New York, N. Y., 1962, p. 69; (b) J. R. Dyer, W. E. McGonigal, and K. C. Rice, *J. Am. Chem. Soc.*, **87**, 654 (1965).

(13) L. Hough, J. E. Priddle, and R. S. Theobald, *Advan. Carbohydrate Chem.*, **15**, 91 (1960).

(14) R. U. Lemieux, R. K. Kullhig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

extended by others[15] that the n.m.r. signal of the acetyl protons of a ring *O*-acetate is dependent primarily on whether the acetate is equatorial or axial and, as a first approximation, is independent of its relationship to other groups on the molecule. It should thus be possible to confirm the structures postulated for IV and X by conversion of their *O*-acetates, V and XI, since little change in the position of the acetyl protons should occur by influence of the *C*-methyl compared to the normal straight-chain carbohydrate derivative. Similar considerations led Overend, *et al.*,[5] to tentative assignments of the configuration of an *N*-acetate on a tertiary carbon. When other experimental results are added to those known[5,6] and to the present results, more exact predictions should be possible for unknown branched sugars.

As could be anticipated,[11c,16] the tertiary-hydroxyl group of IV failed to acetylate with acetic anhydride in pyridine. In contrast, acid-catalyzed acetylation of IV and X with acetic anhydride–*p*-toluenesulfonic acid[17] proceeded with remarkable speed and in good yield to V and XI, respectively. Even though highly unlikely, that rearrangement *via* a carbonium ion had not taken place was demonstrated by basic hydrolysis of the acetates V and XI back to the original alcohols IV and X, respectively.

The n.m.r. spectrum of XI showed three different methyl signals as singlets at τ 6.68, 7.89, and 8.33. The first at τ 6.68 is well characterized as due to the anomeric methoxy group.[14] The signal at τ 8.33 is assigned to the *C*-methyl protons since Baer and Rao[6] noted a C-3 methyl signal at τ 8.53. An equatorial C-5 methyl has been reported[15a] to give a signal at τ 8.76–8.84. The signal at τ 7.89 is assigned to the acetyl protons, since equatorial acetyl protons give a signal at τ 7.91–7.96 and axial acetyl protons at 7.81–7.84 on a pyranoside. Furthermore, the axial acetyl protons always give a lower τ value than equatorial acetyl protons.[14,15a] It was further noted that V, which presumably had an equatorial acetyl group, gave an acetyl proton signal at τ 8.01, the methoxyl at 6.59 and the *C*-methyl at 8.31; it follows that XI most probably has an acetyl of axial conformation and V an acetyl of equatorial conformation since V gives a higher τ value.

This route used for introduction of chain branching on amino sugars should be quite general for branching at carbons other than that carbon bearing the amino group; the feasibility is limited only by the blocking problems to make a precursor of the oxo sugar that has a single free hydroxyl group; most of these blocking problems have been solved or are solvable. Functionalization of the new branch introduced on a nonnitrogenous oxo sugar has been considerably extended by Overend and his co-workers.[11] An interesting problem that yet remains is to control the stereochemistry to give the opposite configuration of branching, starting with the oxo sugars III or VIII.

Experimental Section[18]

Methyl 3-Benzamido-4,6-*O*-benzylidene-3-deoxy-2-*C*-methyl-α-D-glucopyranoside (IV).—A suspension of 252 mg. (0.66 mmoles) of III[8b] in 20 ml. of warm tetrahydrofuran was added over a period of about 10 min. to the Grignard reagent prepared from 1.25 ml. of methyl iodide and 480 mg. of magnesium in 10 ml. of reagent ether. The mixture was refluxed with stirring for 1 hr., then the excess reagent was destroyed by the dropwise addition of excess 20% aqueous ammonium chloride with ice cooling. After the addition of water and chloroform, the lower organic layer was separated and the aqueous layer was extracted three more times with chloroform. The combined extracts were washed with water until neutral and then spin evaporated *in vacuo*. Recrystallization of the crystalline residue from ethanol–petroleum ether gave 214 mg. (82%) of white needles: m.p. 243–247° dec.; ν_{max} 3650 (OH), 3450 (NH), 1630, 1520 (amide I and II), 1120, 1100, 1090, 1075 (C–OH, C–O–C), 765, 714, 700 cm.$^{-1}$ (C_6H_5), no C=O near 1740 cm.$^{-1}$; $[\alpha]^{23}D$ −15.6 ± 1.6°. This compound on t.l.c. in chloroform–ether (1:1) showed a trace of a faster moving compound, presumably the isomeric mannopyranoside, which was not removed by recrystallization.

Anal. Calcd. for $C_{22}H_{25}NO_6$: C, 66.1; H, 6.31; N, 3.51. Found: C, 66.0; H, 6.10; N, 3.53.

Methyl 2-Benzamido-4,6-*O*-benzylidene-2-deoxy-3-*C*-methyl-α-D-allopyranoside (X).—Treatment of 800 mg. (2.08 mmoles) of VIII[8b] with the methylmagnesium iodide from 3.95 ml. of methyl iodide and 1.51 g. of magnesium for 2 hr., as described for the preparation of IV, gave a crystalline residue on evaporation of the chloroform extracts. Recrystallization from ethanol–petroleum ether gave 470 mg. (57%) of product, m.p. 196–199°. The filtrate showed at least nine components on t.l.c., but an additional 68 mg. (8%) of X could be isolated by rebenzoylation with benzoic anhydride in ethanol.[8b] Further recrystallization from ethanol–petroleum ether gave white needles, m.p. 200–202°, that were uniform on t.l.c. and had ν_{max} 3450, 3380 (OH, NH), 1640, 1530 (amide I and II), 1130, 1100, 1075 (C–O–C, C–OH), 755, 715, 700 cm.$^{-1}$ (C_6H_5), no ketone C=O near 1740 cm.$^{-1}$; $[\alpha]^{23}D$ +66.1 ± 1.3°.

Anal.: Calcd. for $C_{22}H_{25}NO_6$: C, 66.1; H, 6.31; N, 3.51. Found: C, 66.0; H, 6.08; N, 3.67.

Methyl 2-*O*-Acetyl-3-benzamido-4,6-*O*-benzylidene-3-deoxy-2-*C*-methyl-α-D-glucopyranoside (V).—A mixture of 403 mg. (1.01 mmoles) of IV, 192 mg. (1.01 mmoles) of *p*-toluenesulfonic acid, and 10 ml. of acetic anhydride was magnetically stirred at ambient temperature protected from moisture for 1 hr. Solution took place in about 15 min., then the product separated. Since only about half of the product separated at this point, the mixture was poured into excess aqueous sodium bicarbonate and stirred for 30 min. The mixture was extracted with chloroform (four 20-ml. portions). The combined extracts were washed with 5% aqueous sodium bicarbonate and then water. Spin evaporation of the chloroform solution *in vacuo* left a crystalline residue which was recrystallized from ethanol–petroleum ether; yield 286 mg. (85%) of white crystals that decomposed at 240–270°. This material on t.l.c. in chloroform–acetone (3:1) contained a trace of a slower moving spot, presumably IV. Two recrystallizations from acetone–water gave 185 mg. (42%) of white needles that were uniform on t.l.c. and had m.p. 250–275° dec.; $[\alpha]^{24}D$ +10 ± 1°; ν_{max} 3400 (NH), 1725 (ester C=O), 1640, 1520 (amide I and II), 1090, 1070 (ether C–O–C), 765, 718, 695 cm.$^{-1}$ (C_6H_5); τ 6.59 (OCH_3), 8.01 (*O*-acetyl), 8.31 (*C*-methyl).

Anal. Calcd. for $C_{24}H_{27}NO_7$: C, 65.3; H, 6.16; N, 3.17. Found: C, 65.5; H, 6.30; N, 3.31.

Deacetylation with excess methanolic sodium methoxide at room temperature for 16 hr. gave IV as shown by mixture melting point and their identical infrared spectra.

Methyl 3-*O*-Acetyl-2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*C*-methyl-α-D-allopyranoside (XI).—A mixture of 46.8 mg. (0.25

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(16) N. G. Brink, F. A. Kuehl, Jr., E. H. Flynn, and K. Folkers, *J. Am. Chem. Soc.*, **68**, 2405 (1946).

(17) Huang-Minlon, E. Wilson, N. L. Wendler, and M. Tishler, *ibid.*, **74**, 5394 (1952).

(18) Melting points were determined in capillary tubes with a Mel-Temp block and those below 230° are corrected. Infrared spectra were determined in Nujol mull with a Perkin-Elmer Model 137B spectrophotometer. N.m.r. spectra were run in deuteriochloroform with a Varian A-60 spectrophotometer using tetramethylsilane as an internal standard. Optical rotations were determined in *N,N*-dimethylformamide in a 1-dm. microtube. Thin layer chromatograms (t.l.c.) were run with Brinkmann silica gel GF_{254} and spots were detected by iodine vapor or by visual examination under ultraviolet light or both. Petroleum ether was a fraction boiling at 40–60°.

mmoles) of *p*-toluenesulfonic acid, 98 mg. (0.25 mmoles) of X, and 1.0 ml. of acetic anhydride was stirred at ambient temperature for 10 min., solution taking place in 1 min.; when processed as described for V, a syrup was obtained on evaporation of the chloroform that was crystallized with difficulty from *N,N*-dimethylformamide–water–ethanol; yield 62.5 mg. (58%), m.p. 156–159°, uniform on t.l.c. Recrystallization from aqueous ethanol gave white needles: m.p. 157–159°; $[\alpha]^{24}D$ +43 ± 2°; ν_{max} 3400 (NH), 1730 (ester C=O), 1660, 1520 (amide I and II), 1130, 1110, 1070 (ether C–O–C), 760, 722, 696 cm.$^{-1}$ (C_6H_5); τ 6.86 (OCH_3), 7.89 (*O*-acetyl), 8.33 (*C*-methyl).

Anal. Calcd. for $C_{24}H_{27}NO_7$: C, 65.3; H, 6.16; N, 3.17. Found: C, 65.4; H, 6.39; N, 3.12.

Deacetylation with excess methanolic sodium methoxide at room temperature for 20 hr. gave X, identified by mixture melting point and comparative infrared spectra.

Preparation and Some Reactions of Mono-*O*-ethylidene Derivatives of D-Galactose, Methyl α- and β-D-Galactopyranosides, and of D-Threose

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Received August 23, 1965

Mono-*O*-ethylidene derivatives of D-galactose and of methyl α- and β-D-galactopyranosides have been prepared and shown by methylation studies to be 4,6-*O*-ethylidene derivatives. Reduction of 4,6-*O*-ethylidene-D-galactose (1) gave crystalline 4,6-*O*-ethylidene-D-galactitol and condensation of 1 with acetone–zinc chloride afforded crystalline 4,6-*O*-ethylidene-1,2-*O*-isopropylidene-D-galactose. Oxidation of 1 with sodium metaperiodate gave 2,4-*O*-ethylidene-D-threose, which crystallized as a dimer.

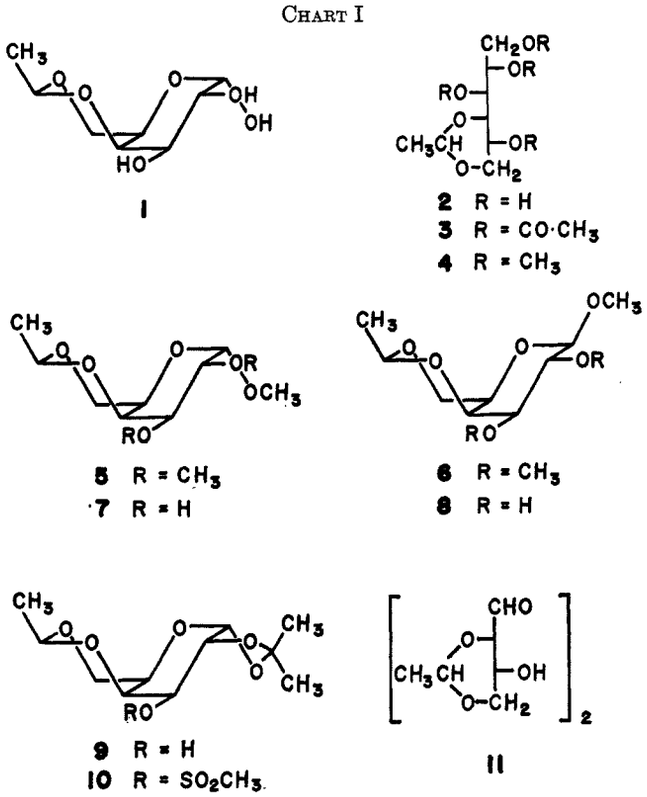
The preparation of crystalline 4,6-*O*-ethylidene-D-galactose (1) was reported several years ago[2] and this paper describes some reactions of this compound and also the preparation of 4,6-*O*-ethylidene derivatives of methyl α- and β-D-galactopyranosides.

Other workers have described 4,6-*O*-benzylidene-D-galactose[3] and the 4,6-*O*-benzylidene derivatives of methyl α-[4] and β-D-galactopyranosides[5] and of benzyl β-D-galactopyranoside.[6] The 4,6-*O*-ethylidene derivatives of glucose,[7] methyl α-[8] and β-D-glucopyranosides[7,9] and of methyl α-D-mannopyranoside[10] have also been reported.

Yields of 1 obtained from different commercial samples of D-galactose by treatment with paraldehyde–sulfuric acid under identical conditions were found to vary greatly. Experiments with samples of meshed D-galactose indicated that in addition to time, temperature, and acid concentration, particle size was a factor in the condensation. Satisfactory results were obtained by following trial condensations on paper chromatograms or by thin layer chromatography in acetone or 1-propanol.

Periodate oxidation of 1 resulted in the uptake of 2 equiv. of oxidant and the formation of 2 equiv. of formic acid. No formaldehyde was liberated by periodate oxidation at pH 8. These results indicate that the acetal group spans C-4 and C-6 of D-galactopyranose or C-5 and C-6 of D-galactofuranose. Reduction of 1 with borohydride or with hydrogen and Raney nickel gave a crystalline *O*-ethylidenegalactitol which, on periodate oxidation, consumed 2 equiv. of periodate and liberated 1 equiv. of formic acid and 1 equiv. of formaldehyde. These results eliminate the unlikely furanose structure for 1 and prove that the reduction product is 4,6-*O*-ethylidene-D-galactitol (2) (1,3-*O*-ethylidene-L-galactitol). The tetraacetate 3 and the tetramethyl ether 4 of 2 (see Chart I) were obtained crystalline.

CHART I



Methylation of 1 by the procedure of Kuhn, *et al.*,[11,12] gave two main products which were fractionated by chromatography on silica gel and shown to be the α (5) and β (6) anomers of methyl 4,6-*O*-ethylidene-2,3-

(1) This work was initiated while the author was working under the guidance of Professor J. K. N. Jones at Queen's University, Kingston, Ontario.

(2) D. H. Ball and J. K. N. Jones, *J. Chem. Soc.*, 905 (1958).

(3) E. G. Gros and V. Deulofeu, *Chem. Ind.* (London), 1502 (1962).

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(8) (a) J. Honeyman and J. W. W. Morgan, *J. Chem. Soc.*, 3660 (1955); (b) J. Honeyman and T. C. Stening, *ibid.*, 3316 (1957).

(9) (a) J. Dewar and G. Fort, *ibid.*, 492 (1944); (b) D. O'Meara and D. M. Shepherd, *ibid.*, 4232 (1955).

(10) J. Honeyman and J. W. W. Morgan, *ibid.*, 744 (1954).

(11) R. Kuhn, H. Trischmann, and I. Löw, *Angew. Chem.*, **67**, 32 (1955).

(12) Earlier attempts to methylate 1 using methyl sulfate and sodium hydroxide or silver oxide and methyl iodide alone gave complex mixtures of products (t.l.c. in ethyl acetate) owing presumably to the lability of the *O*-ethylidene group.