for authentic samples and for obtaining mixed melting points and infrared spectra for comparison of 2-acetamido-2-deoxy-4,6-di-*O*-methyl-α-D-glucopyranose and the methyl α-D-glucopyranosides of the 3,4-, 3,6- and 4,6-di-*O*-methyl derivatives.

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NEW YORK 32, N. Y.

[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY[1]]

The Acid–Base-Catalyzed Conversion of Aldohexose into 5-(Hydroxymethyl)-2-furfural[2]

M. L. MEDNICK

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Either glucose or starch, in water containing weak acids and weak bases, is converted at 150–250° into 5-(hydroxymethyl)-2-furfural (X) in maximum yields considerably higher than those obtained with acid catalysts alone. A reaction pathway is proposed involving the isomerization of glucose to fructose followed by dehydration.

The acid-catalyzed conversion of carbohydrates to 5-(hydroxymethyl)-2-furfural (HMF) has long been known to produce comparatively high yields from ketohexose but relatively insignificant yields from aldohexose.[3] In the more recent literature, Montgomery and Wiggins[4] obtained 6.7% of HMF by heating glucose in water with a hydrogen atmosphere at 162–167°. Under these same conditions, 21.6% of HMF was produced from sucrose. The highest reported yield of HMF by direct conversion of glucose of 16.6%.[5] McKibbins obtained this yield by heating a dilute aqueous sulfuric acid solution at 250° for a short time. In a similar manner, but using levulinic acid as catalyst, Garber, Cranford, and Jones obtained 31 to 38% HMF from sucrose.[6] They described the unchanged residue as mainly glucose. Haworth and Jones[7] equilibrated glucose, primarily with mannose and fructose, by pretreatment with aqueous sodium hydroxide. The solution was then neutralized with hydrochloric acid, acidified with oxalic acid, and heated. The best yield of HMF obtained was 17%. Using calcium hydroxide for pretreatment, they passed unchanged residue through two additional cycles of this system for a total yield of 28.5%.

The history of this process led us to the tentative conclusion that the fructofuranose structure (VI, Fig. 1) is a possible intermediate on the reaction route between glucose and HMF. The keto-enol isomerization is acid–base-catalyzed.[8] We, therefore, tested the hypothesis that suitable combinations of acidic and basic catalyst constituents might accelerate its formation and, accordingly, the over-all rate of glucose conversion to HMF. It was found that any chosen combination of weak acid and weak base, under suitable conditions of concentration, time, and temperature, improved maximum HMF yield over that obtained in a control experiment using phosphoric acid alone as catalyst. Table I summarizes a comparison series of such experiments conducted in the 170–190° range. All examples show improved yield over the control except those employing ammonia and hydrochloric, the strongest acid used. In this temperature range, the best yield (23%) was obtained with ammonia and phosphoric acid in such proportions as to produce an initial *p*H of approximately 4. When the process was carried out at somewhat higher temperatures (200–230°), the yield, using ammonia and phosphoric acid, fell off to 12%, and there was increased rate of humin formation. That this was probably due to reactions involving the active hydrogens of ammonia was indicated by the fact that, under similar conditions, increased yields were obtained using either trimethylamine or triethylamine and phosphoric acid (27–36%).

In addition to the factors noted, the examples

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(1) One of the laboratories of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. Article not copyrighted.

(2) Presented at the 140th National Meeting of the American Chemical Society, Chicago, Illinois, September 3–8, 1961.

(3) G. Dull, *Chemiker Ztg.*, **19**, 216 (1895); J. Kiermayer, *Chemiker Ztg.*, **19**, 1003 (1895); J. A. Middendorp, *Rec. trav. chim.*, **38**, 1 (1919); W. Alberda Van Eckenstein and J. J. Blanksma, *Ber.*, **43**, 2355 (1910); F. H. Newth, *Adv. Carbohydrate Chem.*, **6**, 83 (1951).

(4) W. R. Montgomery and L. F. Wiggins, *J. Soc. Chem. Ind. (London)*, **66**, 31 (1947).

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(6) J. D. Garber, Cranford and R. E. Jones, U. S. Patent **2,929,823**, March 22, 1960.

(7) W. N. Haworth and W. G. M. Jones, *J. Chem. Soc.*, 667 (1944).

(8) J. C. Speck, *Adv. Carbohydrate Chem.*, **13**, 79 (1958).

TABLE I

HMF YIELDS IN THE 160–190° HEATING RANGE[a]

Catalyst	Catalyst Amount, Mole	Approx. Initial *p*H	Time of Warm-up, Min.	Upper Temp. Range	Time at Upper Temp. Range	HMF, % Theory
NH_4Cl	0.1		37	180–186	18	2.9
NH_4Cl	0.01		36	158–190	24	5.8
$(NH_4)_2HPO_4$	0.008	8	35	172–182	20	10.6
$(NH_4)_2HPO_4$	0.038					
H_3PO_4	0.036	5	37	168–180	23	12.8
$(NH_4)_2HPO_4$	0.0076					
H_3PO_4	0.006	4	37	174–180	20	23.2
$(NH_4)_2HPO_4$	0.0076					
H_3PO_4	0.009	2–3	36	174–187	20	19.0
$(NH_4)_2HPO_4$	0.0076					
H_3PO_4	0.003	6–7	38	173–188	20	15.4
NaH_2PO_4	0.008	5–6	36	172–184	24	10.3
$(NH_4)_2SO_3$	0.015	4–5	35	174–190	20	13.1
$(NH_4)OAc$	(1.0 g. hydrated)	7	31	173–186	21	7.7
$(NH_4)OAc$	(1.0 g. hydrated)					
H_3PO_4	0.012	5–6	31	172–191	20	10.9
$(NH_4)_2SO_4$	0.0076		33	180–185	20	11.3
$(C_2H_5)_3N$	0.015					
H_3PO_4	0.014	5	35	176–189	20	12.4
H_3PO_4[b]	0.015		37	173–187	20	4.9

[a] Glucose (25.0 g., 0.138 mole), distilled water (100 ml.), nitrogen atmosphere. [b] Control.

TABLE II

HMF YIELDS IN THE 200–250° HEATING RANGE[a]

Catalyst	Catalyst Amount, Mole	Time of Warm-up to 200°, Min.	Upper Temp. Range	Time at Upper Temp. Range, Min.	HMF, % Theory
Pyridine	0.015		200–225	30	44.0
H_3PO_4	0.009	33			
Pyridine[b]	0.015				
H_3PO_4	0.009	36	200–226	30	44.0
Pyridine[c]	0.015				
H_3PO_4	0.009	32	200–229	30	43.7
Pyridine[d]	0.0075				
H_3PO_4	0.0045	32	200–226	30	85
Pyridine	0.030				
H_3PO_4	0.018	32	200–228	11	45
Pyridine	0.030				
H_3PO_4	0.018	33	200–228	20	46
Pyridine	0.060				
H_3PO_4	0.036	28.5	200–225	8.5	45
Pyridine	0.015				
H_3PO_4	0.009	30	200–250	14	44
Pyridine	0.030				
H_3PO_4	0.018	28	200–252	12	41
Pyridine	0.030				
H_2SO_4	0.010	38	200–228	13	35
Pyridine	0.030				
Citric acid	0.016	35	200–229	13	36
α-Picoline	0.030				
H_3PO_4	0.020	33	200–230	15	36
Collidine	0.015				
H_3PO_4	0.014	34	200–229	11	29
Pyridine	0.0061				
Nicotinic acid	0.015	39	200–228	30	33

[a] The substrate was glucose (50.0 g., 0.277 mole). The solvent was water (100 ml.) and *p*-dioxane (100 ml.), except as noted under *b*, *c*, and *d*. [b] The substrate was corn starch, 0.277 mole. [c] The substrate was sucrose, 0.138 mole. [d] The substrate was 5-(hydroxymethyl)-2-furfural, 0.138 mole. The solvent was water (50 ml.) and *p*-dioxane (50 ml.).

of Table II differ from those of Table I in that all catalyst proportions were chosen to give an initial *p*H of approximately 4.5 and the solvent system employed was 1-1. (v./v.) water–*p*-dioxane. This last usage was suggested by the work of Teunissen who found that the rates of acid-catalyzed transformation of HMF to levulinic and formic acids were greatly decreased in aqueous methanol

or ethanol.[9] Peniston also exploited this finding and reported modestly improved yields in acid-catalyzed production of HMF from sucrose by using butanol–water (1:1).[10] In the present study, dioxane and butanol were found of approximately equal value. Dioxane was chosen both because it minimized the possibility of acetal formation, and because it could be more readily flash distilled from extraction residues with less excessive heating. In this work, the aqueous-organic solvent was observed to provide some reduction in rates of both HMF hydrolysis and humin formation. The highest HMF yields (46%) were obtained with the pyridine–phosphoric acid system. It is particularly noteworthy that, under near optimal conditions with this system, experiments differing only in the use of equivalent quantities of glucose, corn starch, or sucrose produced identical HMF yields (44%) well within experimental error. A like experiment in which the carbohydrate was replaced by an equivalent quantity of HMF gave 85% recovery of HMF. This indicates that, when yield maximum is attained, under these conditions, a high proportion of pre-HMF material is still present, and significant improvement in yield should be obtainable *via* a multicycle system.

Small variations in reaction times and temperatures do not materially affect the reproducibility of these yields. The yield-time curve does not have a sharp peak but rises to a plateau region wherein, for a relatively long period, HMF formation and destruction rates are close to equality and the yield varies slowly about a maximum.

DISCUSSION

Wolfrom, Schuetz, and Cavalieri examined the transformation of glucose to HMF in water and dilute hydrochloric acid at reflux temperatures.[11] By following the course of reaction with ultraviolet spectroscopy, they observed, initially, the development of a 228-mμ absorption peak which was distinguishable from the weaker 230-mμ absorption of HMF, because the more intense 284-mμ peak of that substance was, at first, absent. The 228-mμ peak was attributed to the α,β-unsaturated aldehyde IIIa and, for this reason, the pathway II → III → IIIa → IX → X (Fig. 1) was proposed for HMF formation from glucose. Anet reported that IIIa, 3-deoxy-D-erythrohexosone, has no intense absorption in the ultraviolet.[12] The 228-mμ peak may constitute evidence for the presence of the alternative possibility IX. Anet prepared IIIa from di-D-fructose-glycine (XIa, Fig. 2); 3-deoxy-D-threohexosone (IIIb) was similarly prepared from di-D-tagatoseglycine (XIb, Fig. 2). When heated in 2*N* aqueous acetic acid at 100° for two hours, IIIa, IIIb, and fructose produced respectively, 45%, 80%, and 0.5% HMF.[12] Anet also isolated the *trans* and *cis* forms of 3,4-dideoxy-3,4-unsaturated D-hexosone (XIII, XIV) as by-products in the preparation of 3-deoxy-D-erythrohexosone. Wolfrom, Schuetz, and Cavalieri have also proposed XIV as an intermediate in the glucose to HMF transformation.[11] These compounds absorb strongly at 233 and 228 mμ, respectively. Dehydration of the *cis* isomer was very easy. In 0.03*N* acetic acid at 100°, the reaction was half completed in twelve minutes. The *trans* isomer was more stable. Under the same conditions it reacted at the same rate as 3-deoxy-D-erythrohexosone being approximately half reacted in eight hours. This suggests that IIIa dehydrates to a mixture of XIII and XIV while IIIb yields predominantly XIV.

If the lowered yield of HMF from XIII is due, in part, to diversion of XIII into side reactions not leading to HMF, and if these compounds are intermediates in the glucose to HMF sequence, then it seemed probable that higher maximum yield might be obtained from an aldohexose differing from glucose only in the C-4 configuration. Accordingly, the reaction was carried out using D-galactose. Under conditions that produced approximately 44% HMF from glucose and 85% recovery from an HMF blank, the ultraviolet assay yield of HMF from galactose was 39%.

Another variety of useful information can be derived from the present work. The identity of maximum yields found for both glucose and corn starch, using the pyridine–phosphoric acid catalyst system, showed that, under the conditions of this experiment, hydrolysis of the α-glucosidic linkage in starch and, therefore presumably also in sucrose (I), is not over-all rate determining for HMF production. With this point established, the identical maximum yields for glucose and sucrose under the same conditions then indicate that glucose and fructose converge, *via* a series of relatively fast reactions, to a common intermediate whose next reaction step is relatively slow and over-all rate determining for the formation of HMF. The maximum yield of HMF obtainable is a function of this single rate and the rates for the subsequent reactions of HMF. The common intermediate cannot be III. Its formation would require isomerization of fructose to the open chain form of mannose or glucose and, if this were the case, then in the long known acid-catalyzed reaction, formation of HMF from fructose would be slower than or equal in rate to its formation from glucose. Haworth and Jones have shown that when sucrose is heated in water at 145° with oxalic acid catalysis

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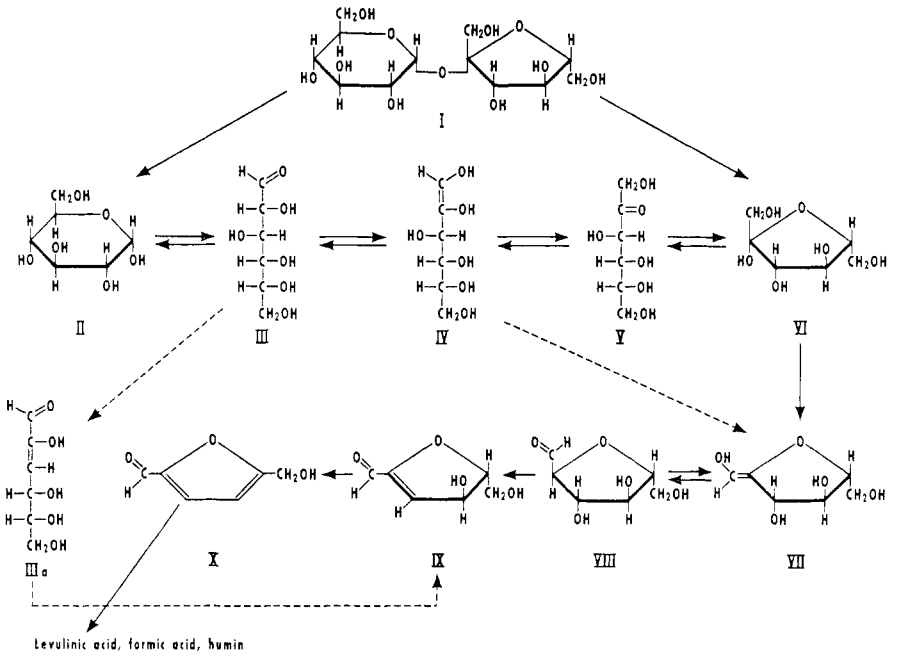
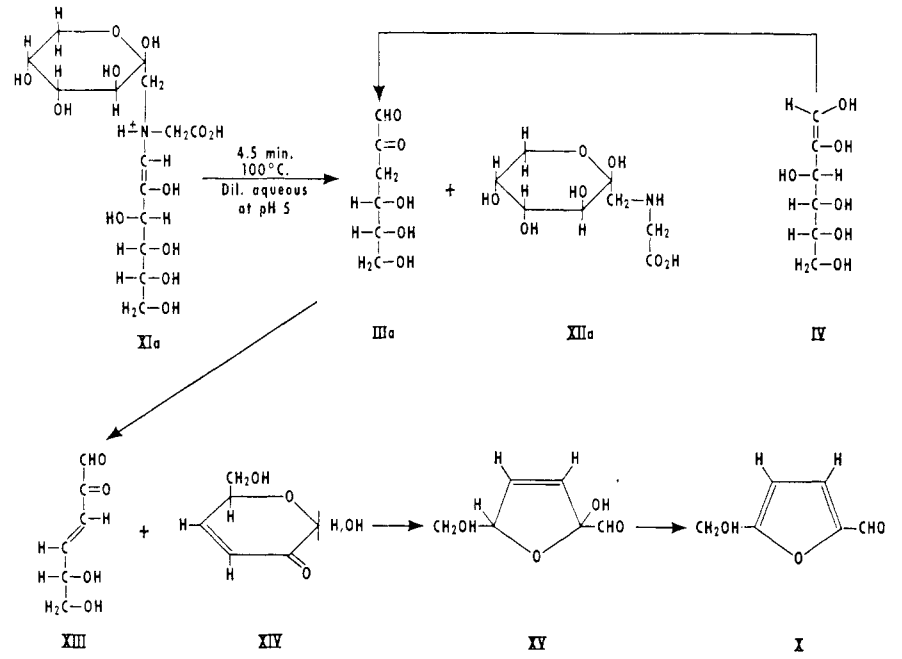


Figure 1



IIIb, IVb, XIb, XIIIb have the opposite configuration at carbon 4

Figure 2

until most of the fructose moiety is reacted, the glucose part remains essentially unchanged.[7]

A similar argument can be used against the pathway II → III → IV → VII → VIII → IX → X (Fig. 1) suggested by Haworth and Jones.[7] Their proposal would require either that IV be the common intermediate or that two distinct mechanisms obtain for HMF formation from glucose or fructose. If the latter were the case, then compound VII would be the common intermediate. It appears hardly likely, as would then be necessary, that the dehydration VIII → IX would be slower than both the first dehydration of fructose (VI → VII) and the cyclizing dehydration (IV → VII), which do not involve the activating effect of the enolizable proton or the driving force contributed by the conjugated unsaturated system developed in IX. The former case, with modification, cannot be ruled out. The work of Anet on the syntheses and reactions of 3-desoxyhexosones and 3,4-dideoxy-

3,4-unsaturated D-hexosones provides support for the pathway IV → IIIa → XIV → XV → X (Fig. 2). The production of IIIa, however, has not yet been demonstrated to be a major or exclusive step in the transformations of aldose and ketose to HMF. The work of Bonner, Bourne, and Ruszkiewicz also sheds some light on this point. They found that heating sucrose in dry dimethylformamide at 100° with a catalytic amount of iodine, rapidly produced a high yield of HMF originating solely from the fructose moiety.[13] Glucose remained unchanged. These are conditions under which the rates of keto-enol transformations will certainly be minimal relative to the more usual conditions of these reactions, and the finding provides additional evidence for a possible reaction pathway of fructose to HMF without passage through any such form as IV.

Assuming the reaction pathway VI → VII → VIII → IX → X, then the reaction step IX → HMF is not likely to be over-all rate determining. In the data of Wolfrom, Schuetz, and Cavalieri, the 228-mμ absorption, possibly IX, is essentially swamped in the weaker 230-mμ-peak of HMF when the total transformation of glucose to HMF, as computed from the 284-mμ peak, is still only a small fraction of 1%.[11] If one reasonably assumes for this substance a molecular extinction coefficient on the order of 5000–15,000, this shows that it does not pile up in the system but is rapidly dehydrated to HMF. A considerable body of chemical experience leads one to expect a very rapid dehydration of the β-hydroxyaldehyde (VIII) under the conditions used here. The best probability, then, for the over-all rate-determining reaction in this pathway would be the first dehydration step of fructose itself (VI → VII).

In summation, when this reaction is carried on in water or aqueous acid, the rate of HMF production from glucose is considerably lowered while that from fructose remains high. In acid-base media more favorable to keto-enol isomerization the rates from glucose and fructose become equal. This indicates that glucose and fructose converge to a common intermediate. In media less favorable for keto-enolization the transformation of glucose to this intermediate is over-all rate determining for HMF production. With suitable acid-base catalysis, the next reaction step of the common intermediate becomes over-all rate determining. The findings of Wolfrom, Schuetz, and Cavalieri[11] and of Anet[12] indicate that the intermediate is the enediol IV. Some possibility remains, however, that it may be the furanose form of fructose (VI).

EXPERIMENTAL

Experiments of Table I. Glucose (Bacto-Dextrose,[14] Difco certified, 25.0 g., 0.138 mole) and the respective catalysts were dissolved in water (tap distilled, 100 ml.) in a 1-l. steel bomb equipped with a Pyrex glass liner. Air was displaced with nitrogen. The bomb was heated as shown in Table I, held within the temperature range indicated, then rapidly cooled in a water bath. The total reaction mixture was stirred with ethyl acetate (125 ml.) and vacuum filtered to remove insoluble humin. The filtrate phases were separated, and the aqueous phase was extracted with two more 125-ml. portions of ethyl acetate. The organic extracts were combined, dried over anhydrous sodium sulfate, and filtered. The solvent was flash distilled at aspirator pressure using a rotating vacuum evaporator in a water bath at approximately 70°. The residue of amber liquid was weighed. A weighed sample was immediately diluted with water in a volumetric flask and analyzed by ultraviolet spectroscopy for HMF content using the 284 mμ peak ϵ_{max} 16,800.[15] All the analyses were performed on a Beckman DU spectrophotometer.

Examination of the total ultraviolet spectrum relative to that of pure HMF indicated little contamination of the crude material by the probable ultraviolet absorbing materials, with the possible exception that small amounts of 5,5′-di(5-formylfurfuryl) oxide cannot be excluded. The residues were completely soluble in small amounts of cold water, except for traces of dark humin material indicating that any contamination with this substance was small. The analytical procedure was therefore considered adequate for comparing yields in this exploration. To prepare pure HMF, pooled crudes from a number of experiments were distilled at 1 mm. or less. The distillate, which completely crystallized on cooling to approximately 0°, was recrystallized from anhydrous ether or ether–petroleum ether. HMF so prepared had m.p. 31–32° (uncorr.) after vacuum drying over phosphorus pentoxide (lit. 30–31°, 31–32°).

Anal. Calcd. for $C_6H_6O_3$: C, 57.2; H, 4.8. Found: C, 57.1, 57.3; H, 4.8, 4.9.

It was assayed as 101% by the ultraviolet absorption method using ϵ_{284}^{max} 16,800. This pure material did not display the high degree of instability previously reported. After 3 months in a refrigerator with intermittent warming to room temperature and exposure to air and light, it was still colorless, but the melting point had lowered to 12–25°. This decline was partly due to water absorption for when the material was again dried *in vacuo* over phosphorus pentoxide, the melting point rose to 29–32° (uncorr.), and the sample was assayed as 97.0% by the spectrophotometric method.

Experiments of Table II. Glucose (50.0 g., 0.277 mole) and the respective catalysts were dissolved in water (100 ml., tap distilled) and *p*-dioxane (100 ml., peroxide-free redistilled) in a 1-l. Pyrex-lined bomb. Air was displaced with nitrogen. The bomb was heated as shown in Table II, held within the temperature range indicated (mostly within the upper third of the range), then rapidly cooled in a water bath. The reaction mixture was stirred with 250 ml. of ethyl acetate and vacuum filtered. The filtrate phases were separated, and the aqueous phase was extracted with two more 250-ml. portions of ethyl acetate. The organic extracts were combined, dried over anhydrous sodium sulfate, then worked up and analyzed as already described.

For the experiments using corn starch, sucrose, and HMF, the following materials and amounts were used: Sucrose (Difco saccharose, B-176, 2.0% H_2O, 48.2 g., 0.138 mole). Starch (Globe corn starch, ZE15 3001, dried to 1.1% water

(13) T. G. Bonner, E. J. Bourne, and M. Ruszkiewicz, *J. Chem. Soc.*, 787 (1960).

(14) The mention of firm names or trade products does not imply that they are endorsed or recommended by the U. S. Department of Agriculture over other firms or similar products not mentioned.

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and assumed otherwise pure, 0.277 equiv., 46.4 g.). HMF (prepared by vacuum distillation of pooled residues and one crystallization from ethyl ether, refrigerated 2 months, ultraviolet assay 97.8%, 0.138 mole, 18.0 g.). The HMF blank was carried out with one half the amount of each component used in the other experiments of this series.

PEORIA, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY]

5-*O*-Methyl-D-ribose and 5-*O*-Methyl-D-ribitol

EMIL B. RAUCH AND DAVID LIPKIN

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Using the well characterized, crystalline benzyl β-D-ribofuranoside as the starting compound, an unequivocal synthesis of 5-*O*-methyl-D-ribose was developed. This compound was obtained as a sirup only, but it was chromatographically and electrophoretically pure. It was converted to its crystalline benzylphenylhydrazone. 5-*O*-Methyl-D-ribitol(1-*O*-methyl-L-ribitol) was prepared from the methylated ribose by reduction with sodium borohydride. Although the ribitol itself could not be crystallized, it was found that it forms a surprisingly stable crystalline adduct with one mole of methyl trifluoroacetate. A convenient new technique is described for isolating a polyol from solutions containing borate.

An important reference compound for structural studies in nucleic acid chemistry is 5-*O*-methyl-D-ribose (I).[1-6] Although several methods of obtaining this compound have been described,[1,2,4,7,8] the principal method of preparation of I which has been used by various investigators is the method of Levene and Stiller.[2,9-11] There no longer is any doubt about the preponderant product being I, but the synthesis is hardly unequivocal. Furthermore, it leads in actuality to a rather complex mixture of methylated riboses,[2,10,12] and chromatography has been introduced at some stage or other in order to obtain a pure product.

Using the well characterized, crystalline benzyl β-D-ribofuranoside (II) of Ness *et al.*[13] as the starting compound, an unequivocal synthesis of 5-*O*-methyl-D-ribose was developed. As the first step, II was converted to benzyl 2:3-*O*-isopropylidene-β-D-ribofuranoside (III). Only anhydrous copper sulfate was used as a catalyst[14] in this step, in order to avoid the possibility of ring migration[10,15,16] during the acetonation. Methylation of III and removal of the blocking groups from the resulting benzyl 2:3-*O*-isopropylidene-5-*O*-methyl-β-D-ribofuranoside (IV) gave the desired I, in reasonable over-all yield and free of contamination.

Although I was well characterized by means of physical properties and the preparation of crystalline derivatives, I was obtained only as a sirup. It was converted by reduction with sodium borohydride[17] to 5-*O*-methyl-D-ribitol (1-*O*-methyl-L-ribitol, Va), another reference compound of interest.[1] The polyol was isolated as 5-*O*-methyl-D-ribitol 1,2,3,4-tetrakis(trifluoroacetate) (VI), and the ester then was converted by methanolysis to Va. Even though Va could not be crystallized, it was obtained as the crystalline methyl trifluoroacetate adduct (Vb). It also was converted to the crystalline 1,2,3,4-tetrabenzoate.

EXPERIMENTAL[18]

Melting points and boiling points are uncorrected. All evaporations of solvents were carried out at room temperature *in vacuo* using a rotating evaporator (Rinco Instrument Co., Greenville, Ill.)

The R_f values reported were obtained by ascending chromatography using Whatman No. 1 paper. The solvent systems used, which were all made up on a volume basis, were: 1-butanol–water, 86:14 (solvent A); 1-butanol–saturated aqueous boric acid, 85:15 (solvent B)[19]; collidine saturated

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