Carbohydrate Research
Elsevier Publishing Company, Amsterdam
Printed in Belgium

2-DEOXY SUGARS

PART XV. THE FOUR ISOMERIC METHYL GLYCOSIDES OF 2-DEOXY-D-*ribo*-HEXOSE*

CLARITA C. BHAT, K. VENKATRAMANA BHAT, AND W. WERNER ZORBACH

Division of Bio-Organic Chemistry, Gulf South Research Institute, P. O. Box 1177, New Iberia, Louisiana 70560 (U. S. A.)

(Received November 1st, 1968)

ABSTRACT

Brief treatment of 2-deoxy-D-*ribo*-hexose in methanol with a small proportion of hydrogen chloride resulted in a 100-% yield of crystalline methyl 2-deoxy-α,β-D-*ribo*-hexofuranoside in an anomeric ratio of 1:1, fractional recrystallization of which resulted in partial separation of the α-D anomer. The furanoside mixture was converted into its tris-*p*-nitrobenzoate, and, thence, into crystalline 2-deoxy-3,5,6-tri-*O*-*p*-nitrobenzoyl-D-*ribo*-hexosyl bromide. The new halide underwent methanolysis to yield mainly methyl 2-deoxy-β-D-*ribo*-hexofuranoside. Methanolysis of 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*ribo*-hexosyl bromide, followed by deacylation, gave the hitherto-unknown methyl 2-deoxy-β-D-*ribo*-hexopyranoside. Controlled hydrolysis of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside with acid gave crystalline methyl 2-deoxy-α-D-*ribo*-hexopyranoside, hitherto reported as a syrup.

INTRODUCTION

Nucleosides that contain 2-deoxy-β-D-*ribo*-hexofuranose as the carbohydrate residue are unknown, and, because of their very close structural relationship to the natural, "2-deoxy-D-ribofuranosyl" (2-deoxy-D-*erythro*-pentofuranosyl) nucleosides, their preparation for evaluation as potential anticancer compounds is warranted. A direct (and general) method was envisaged, involving, as a key intermediate, a suitably protected and reasonably stable tri-*O*-acylglycofuranosyl halide of 2-deoxy-D-*ribo*-hexose. This paper reports the preparation of crystalline 2-deoxy-3,5,6-tri-*O*-*p*-nitrobenzoyl-D-*ribo*-hexosyl bromide, constituting an extension, to the furanoid forms of 2-deoxyhexoses, of our original discovery[1] that *p*-nitrobenzoic esters of 2-deoxy sugars lead to stable, crystalline per-*O*-acyl-2-deoxyglycosyl halides having utility in the direct synthesis of biologically important glycosides[2].

As an outgrowth of this study, all of the four isomeric methyl glycosides of 2-deoxy-D-*ribo*-hexose have been prepared, and isolated in crystalline form.

*Presented before the Division of Carbohydrate Chemistry, American Chemical Society, 156th National Meeting, Atlantic City, N. J., September 10th, 1968.

RESULTS AND DISCUSSION

We have recently shown[3] that the direct methyl glycosidation of 2-deoxy-D-*arabino*-hexose* results in a 30–35% yield of methyl 2-deoxy-α-D-*arabino*-hexofuranoside. Although this procedure was of value in the preparation of some pyrimidine nucleosides containing 2-deoxy-β-D-*arabino*-hexofuranose as the carbohydrate residue[3b,c], the isolation of the furanoside from the glycosidation mixture was troublesome, requiring chromatographic procedures. For 2-deoxy-D-*ribo*-hexose (**1**), an alternative procedure, developed by Pacsu and Green[4], and involving demercaptalation of a dialkyl dithioacetal of **1** in an alcohol (methanol) was investigated, with a view to obtaining furanoside(s) in yields greater than that reported for 2-deoxy-D-*arabino*-hexose. The demercaptalation reaction has added advantages, in that the reaction is irreversible and there is no anomerization or conversion into pyranosides.

Treatment of 2-deoxy-D-*ribo*-hexose[5] (**1**) with α-toluenethiol gave the dibenzyl dithioacetal (**2**), and demercaptalation of **2** in methanol, with mercuric oxide and mercuric chloride, gave *ca.* 30-% yield of a crystalline compound, the composition of which agreed with that calculated for a methyl glycoside. The new glycoside (**3**) melted in a narrow range, and was homogeneous on paper and thin-layer chromato-

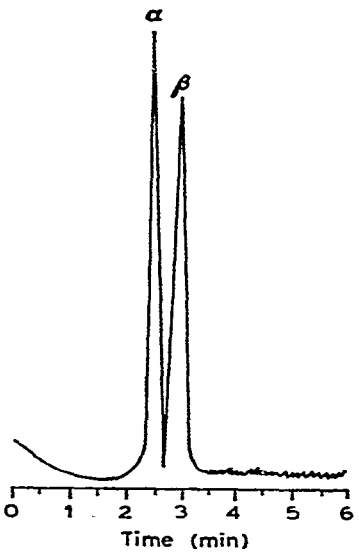


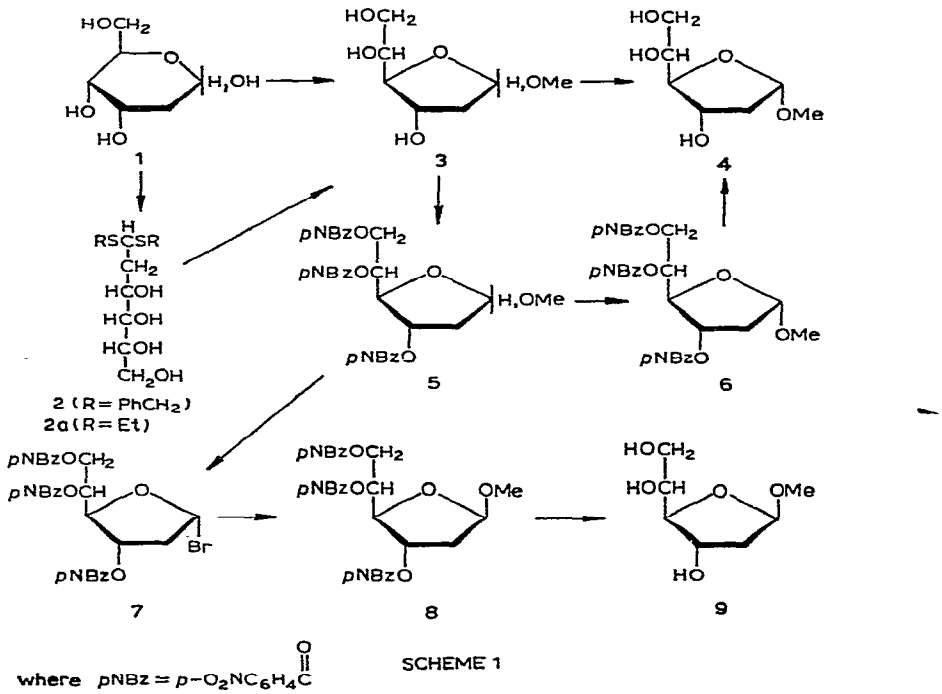
Fig. 1. G.l.c. of anomeric mixture of methyl 2-deoxy-D-*ribo*-hexofuranosides as the per(trimethylsilyl)-ated derivative.

grams, irrespective of the solvent system employed. A 60-MHz n.m.r. spectrum showed a septuplet centered at τ 5.01 for the anomeric proton(s), suggestive of a 1:1

*Similar treatment of 2-deoxy-D-*lyxo*-hexose gives only small proportions (5–10%) of furanosides, regardless of the time interval (S. J. Sexton, K. V. Bhat, and W. W. Zorbach, unpublished results).

molecular compound of the anomers of methyl 2-deoxy-D-*ribo*-hexofuranoside (**3**). The components of **3** were, nevertheless, readily separable (as their trimethylsilylated derivatives) on g.l.c. (see Fig. 1), giving peaks of approximately equal area. Both anomers were subsequently secured in pure form, and chromatographed separately, disclosing that the α-D and β-D forms have retention times of 2.5 and 3.0 min, respectively.

In order to improve the yield of furanoside by the foregoing procedure, the diethyl dithioacetal (**2a**) of **1** was prepared; when this was demercaptalated in methanol, crystalline furanoside (**3**) was readily obtained, but no improvement in the yield was noted. Considering the ease with which **3** separated, it occurred to us that the methyl glycosidation of the unsubstituted hexose (**1**) would be simpler to execute, despite the possibility that relatively low yields of furanoside (**3**) might be obtained.



SCHEME 1

2-Deoxy-D-*ribo*-hexose (**1**) was added to rapidly stirred methanol containing 0.2% of hydrogen chloride, and the reaction was followed polarimetrically. When the rotation reached a minimum (30 min), the reaction was stopped by the addition of an excess of silver carbonate. On processing the reaction mixture, a 55-% yield of product was obtained, which was identical in all respects with the furanoside (**3**) obtained through the demercaptalation procedure. Another, similar study was made, in which the reaction was stopped at different time-intervals; the results are given in Table I. The most striking feature is the yield obtained after 6 min, and, when the reaction was stopped at this point by the addition of an excess of silver carbonate,

a syrup was obtained that crystallized spontaneously to give pure methyl 2-deoxy-α,β-D-*ribo*-hexofuranoside[6] (3). At other time-intervals, the syrups obtained were (to a greater or lesser degree) impure, and it was necessary to recrystallize the products to obtain 3 relatively free from impurities.

TABLE I

METHYL GLYCOSIDATION OF 2-DEOXY-D-*ribo*-HEXOSE IN 0.2% METHANOLIC HYDROGEN CHLORIDE. OPTICAL ROTATION AND YIELD[a] OF FURANOSIDE 3 AS A FUNCTION OF TIME

Time, in min	$[\alpha]_D$, *degrees*	*Yield, %*
0	+58	0
3	+51	65
5	+45	70
6	+44	100
30	+36[b]	55
24 h	+61	15

[a]Based on recovery of crystalline material. [b]Minimum rotation.

With regard to the results shown in Table I, it is significant to note that maximum formation of furanoside does *not* occur at the point of minimum rotation, and it may be that 2-deoxy-D-*ribo*-hexose (1) is a special case, in that the furanoside (3) formed after elapse of any time-interval is, most likely, always a 1:1 anomeric mixture. Accordingly, any marked rotatory contribution provided by one anomer is offset by the other, in which event the rotatory contributions of any pyranosides present become manifest. Thus, in the present instance, a balance has been effected, as evidenced by the relatively slight change in rotation (in either direction) over a 24-h period. Also striking is the fact that the furanoside 3 is isolable (albeit in lower yield) after elapse of 24 h, a time-period after which, for other sugars, it is generally considered that most, if not all, of the furanosides has been converted into pyranosides. During the early stages of the reaction, a single spot, only*, could be observed on thin-layer chromatograms; however, after 24 h, another, slower-moving spot (*ca.* 20%) appeared, and this was subsequently identified (by comparison of R_F values) as the α-D-pyranoside (14).

Methyl 2-deoxy-D-*ribo*-hexofuranoside (3), having an ethylene glycol side-chain, should consume one mole of periodate per mole, and yield one mole of formaldehyde. Accordingly, 3 was oxidized with periodate (see Table II), and the liberated formaldehyde was estimated with chromotropic acid, giving values approaching 100% (the same as that for methyl 2-deoxy-α-D-*arabino*-hexofuranoside[3], used as a control). Similar treatment of the anomeric pyranosides (12 and 14) gave values close to zero, as expected. A second oxidation of 3 was performed, and, without isolation of the

*It was later discovered that the β-D-pyranoside co-chromatographs with 3 on paper or thin-layer sheets, irrespective of the solvent system used.

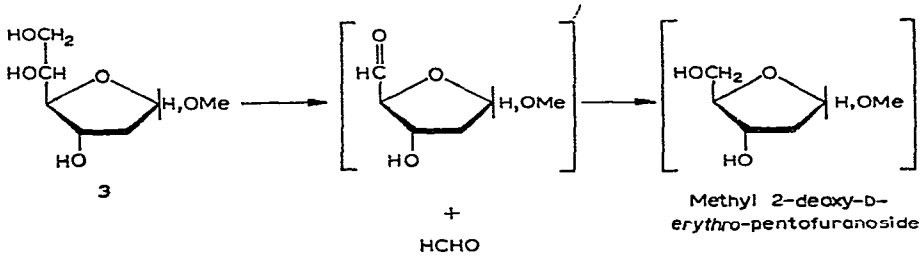
TABLE II

PERIODATE OXIDATION OF METHYL GLYCOSIDES OF 2-DEOXY-D-*ribo*-HEXOSE

Methyl glycoside of	*Conc., in μmole/ml*	*Conc. formaldehyde, in μmole/ml*	*Formaldehyde produced (%)*
2-Deoxy-α,β-D-*ribo*-hexofuranose (3)	0.25	0.22	88
2-Deoxy-α-D-*arabino*-hexofuranose[3] (control)	0.28	0.24	86
2-Deoxy-α-D-*ribo*-hexopyranose (14)	0.29	0.06[a]	0
β anomer (12)	0.23	0.04[a]	0
α-D-Glucopyranose (control)	0.52	0.03[a]	0

[a]The reading is spurious and has been disregarded.

carbohydrate product, the reaction mixture was treated with sodium borohydride. Chromatography of the latter reaction mixture revealed a single component, having an R_F value the same as that for authentic methyl 2-deoxy-D-*erythro*-pentofuranoside[8].



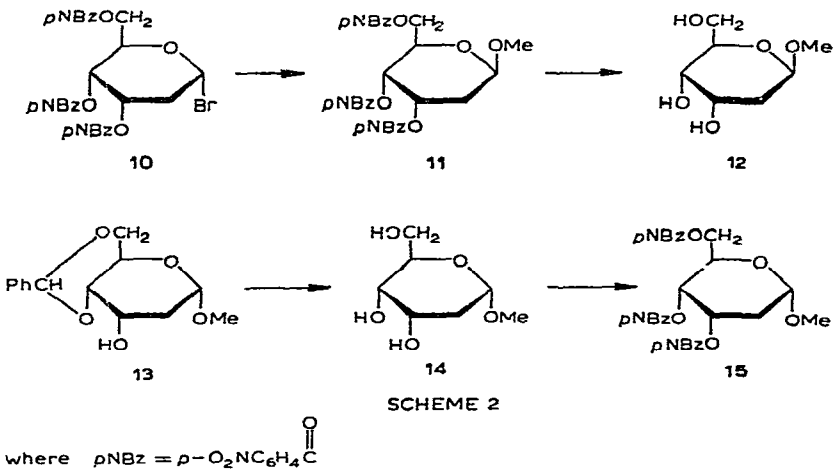
Although it appeared unlikely that the furanoside mixture (3) (behaving as a 1:1 molecular compound) could be resolved by fractional recrystallization, a partial (5%) resolution was obtained from different solvents employed in sequence. This procedure led to the isolation of pure methyl 2-deoxy-α-D-*ribo*-hexofuranoside (4). When 3 was *p*-nitrobenzoylated, the tris-*p*-nitrobenzoate (5) was obtained as an anomeric mixture, partial fractional recrystallization of which was accomplished (more readily, however, than with 3), resulting in an anomerically pure furanoside (6) having the α-D configuration, as shown by its conversion into 4 when the nitrobenzoyl groups were removed by saponification. The *p*-nitrobenzoylated furanoside (5) reacted readily with hydrogen bromide in dichloromethane to yield crystalline 2-deoxy-3,5,6-tri-*O*-*p*-nitrobenzoyl-D-*ribo*-hexosyl bromide* (7), and it is of interest that methyl 2-deoxy-3,5,6-tri-*O*-*p*-nitrobenzoyl-α-D-*arabino*-hexoside[3a,b] (C-3 epimer of the α-D anomer of 5), when treated under essentially the same conditions as given for 5, was completely unreactive. With the latter, because of the orientation of the *p*-nitrobenzoyloxy group on C-3 (on the same side of the ring as the side chain),

*The conversion of compound 3 into halide 7, *via* 5, was the subject of a preliminary communication [C. C. Bhat, K. V. Bhat, and W. W. Zorbach, *Carbohyd. Res.*, 8 (1968) 368].

there is, probably, extensive shielding about the anomeric center, whereas, with **5**, this effect would be minimized considerably.

The new halide (**7**) is very reactive, and attempts to recrystallize it resulted in decomposition. In subsequent glycosidation studies, crystalline **7** was dissolved immediately in dry dichloromethane, and the solution was added rapidly to methanol containing suspended silver carbonate, to give mainly methyl 2-deoxy-3,5,6-tri-*O*-*p*-nitrobenzoyl-β-D-*ribo*-hexoside (**8**). The crude glycoside **8** was deacylated in methanol with methoxide ion, affording a crystalline product which, by g.l.c., was shown to consist of 85% of the β-D-furanoside (**9**) and 15% of the α-D-furanoside (**4**); the β-D anomer (**9**) was readily secured in pure form by fractional recrystallization. Because of its large, positive specific rotation (+120°) and because it undergoes solvolysis (under conditions that generally lead to inverted products) to give mainly the β-D-furanoside (**8**), the halide (**7**) probably has the α-D configuration. This conclusion is, however, difficult to accept, as the bromine atom on C-1 and the *p*-nitrobenzoyloxy group on C-3 would then be on the same side of the ring, resulting in considerable conformational instability. If, indeed, **7** does have the α-D configuration, this situation could account, not only for the extreme reactivity of **7**, but also for its rapid anomerization in solution, as suggested by the formation of some α-D-furanoside during the methanolysis of **7**.

To demonstrate further that **3** does, in fact, possess the furanoid structure, unequivocal syntheses of both anomers of methyl 2-deoxy-D-*ribo*-hexopyranoside were executed (see Scheme 2). 2-Deoxy-D-*ribo*-hexose (**1**) was converted into the



SCHEME 2

where pNBz = p-$O_2NC_6H_4C(=O)$

known 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*ribo*-hexosyl bromide[5,9] (**10**), which underwent replacement, by inversion at the anomeric center, to give methyl 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-β-D-*ribo*-hexoside (**11**). Deacylation of the protected glycoside (**11**) yielded crystalline methyl 2-deoxy-β-D-*ribo*-hexopyranoside (**12**). In a separate experiment, methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside[5] (**13**) was heated briefly with dilute acetic acid, to afford a syrup which, by t.l.c.,

was shown to consist of approximately 90% of the desired methyl 2-deoxy-α-D-*ribo*-hexopyranoside (**14**) and 10% of 2-deoxy-D-*ribo*-hexose (**1**). A resolution of the mixture was obtained by column chromatography, and, thus purified, the syrupy **14** crystallized on storage in a desiccator; it had $[\alpha]_D$ +183°. The α-D-pyranoside (**14**) was originally reported[10] as a syrup, having $[\alpha]_D$ +143°, a value that suggests that their preparation, like ours, was contamined with 2-deoxy-D-*ribo*-hexose ($[\alpha]_D$ +58°). Treatment of **14** with *p*-nitrobenzoyl chloride in pyridine gave the hitherto-unreported tris-*p*-nitrobenzoate (**15**).

With all of the four isomeric methyl glycosides of 2-deoxy-D-*ribo*-hexose now available in pure, crystalline form, it was of interest to record their n.m.r. spectra and examine the regions of the anomeric protons (see Fig. 2). As expected, the anomeric proton of the α-D-pyranoside (**14**) appeared as a triplet, centered at τ 5.31 (J 3 Hz) and, for the β-D anomer (**12**), appeared as a quadruplet at τ 5.38 ($J_{1,2}$ 9 Hz; $J_{1,2'}$ 3 Hz). The signals for the anomeric protons of both furanosides (**4** and **9**) appeared at lower fields than those of the pyranosides; that for the α-D-furanoside (**4**) is a quadruplet, centered at τ 5.05 ($J_{1,2}$ 2 Hz; $J_{1,2'}$ 3.5 Hz), and that for the β-D anomer (**9**), a triplet at τ 4.97 (J 4 Hz). The septuplet centered at τ 5.01, for the furanoside mixture (**3**), contains the signals for the α- and β-D-furanosides, and each is clearly distinguishable.

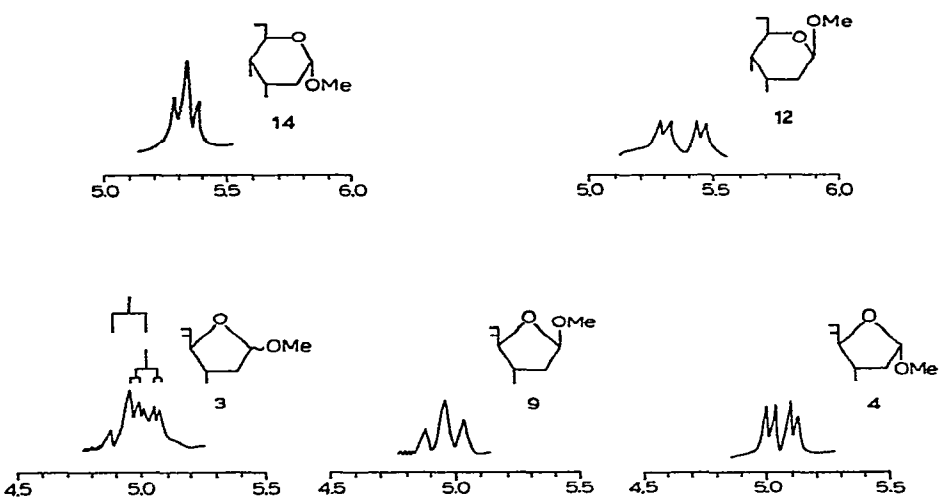
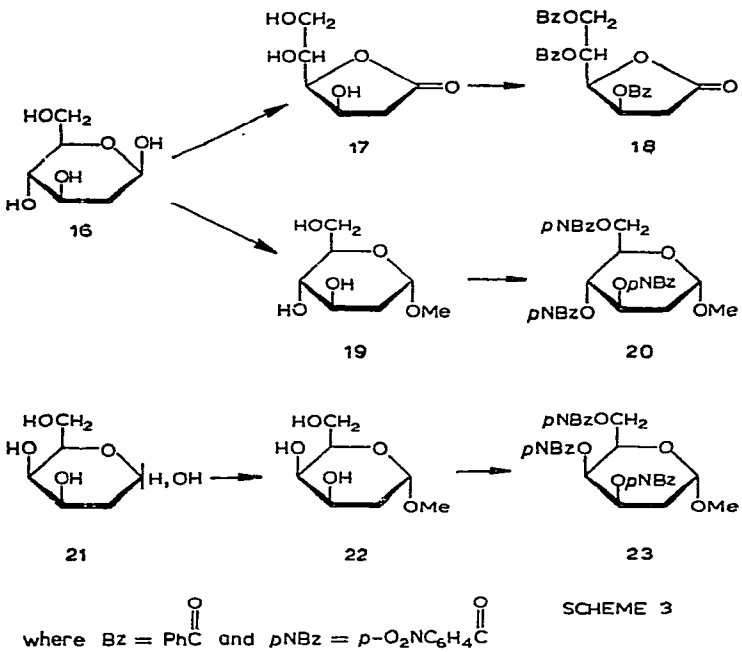


Fig. 2. N.m.r. spectra (anomeric protons) at 60 MHz of the isomeric methyl glycosides of 2-deoxy-D-*ribo*-hexose (in τ values).

Final confirmation of the furanoid structure of **3** was furnished by an unequivocal synthesis, developed by Kohn *et al.*[11], involving, as the key step, the reduction of 3,5,6-tri-*O*-benzoyl-2-deoxy-D-*ribo*-hexono-1,4-lactone[12] with disiamylborane [bis-(3-methyl-2-butyl)borane]. Much difficulty was encountered in this reduction, in which, as disclosed by t.l.c., an array of products was formed. In order to conserve the costly lactone, pilot studies were performed on 3,5,6-tri-*O*-benzoyl-2-deoxy-D-

arabino-hexono-1,4-lactone (**18**), prepared by converting 2-deoxy-D-*arabino*-hexose (**16**) into the corresponding 1,4-lactone[13] (**17**) followed by benzoylation (see Scheme 3), which afforded the lactone (**18**); this required storage in a refrigerator for three months in order to obtain it in crystalline form.

The reduction of **18** was likewise unsuccessful, and it was subsequently learned that the commercial disiamylborane used was of inferior quality*. Accordingly, the reagent was freshly prepared and, without consideration of further exploratory studies with **18**, the following synthesis was performed, in which none of the intermediates were isolated or characterized: 3,5,6-tri-*O*-benzoyl-2-deoxy-D-*ribo*-hexono-1,4-lactone[12] → 3,5,6-tri-*O*-benzoyl-2-deoxy-D-*ribo*-hexose → 3,5,6-tri-*O*-benzoyl-2-deoxy-1-*O*-*p*-nitrobenzoyl-D-*ribo*-hexose → 3,5,6-tri-*O*-benzoyl-2-deoxy-D-*ribo*-hexosyl bromide** → methyl 3,5,6-tri-*O*-benzoyl-2-deoxy-D-*ribo*-hexoside → methyl 2-deoxy-D-*ribo*-hexofuranoside. T.l.c. of the syrupy product revealed a major component (furanoside) and a minor component, identified as 2-deoxy-D-*ribo*-hexose (**1**). G.l.c. of the per(trimethylsilyl)ated mixture gave a major peak having a retention time of 3.0 min (see Fig. 1); the major component of the mixture is, therefore, methyl 2-deoxy-β-D-*ribo*-hexofuranoside (**9**).



SCHEME 3

where Bz = PhC(=O) and pNBz = p-O2NC6H4C(=O)

As a result of the work thus far described, anomeric pairs are now available for three of the four possible methyl 2-deoxyaldohexopyranosides. Save for two isomers, the corresponding *p*-nitrobenzoic esters are also available; the missing

*Personal communication from Dr. Paul Kohn.

**This conversion, and its application to nucleoside synthesis, is the subject of a forthcoming paper by P. Kohn and co-workers.

nitrobenzoylated pyranosides (**20** and **23**) were, therefore, prepared as shown in Scheme 3. Treatment of a methanol solution of 2-deoxy-D-*arabino*-hexose (**16**) with hydrogen chloride resulted in a mixture of the anomers of methyl 2-deoxy-D-*arabino*-hexopyranoside[14], from which, by fractional recrystallization, the α-D anomer (**19**) was secured in pure form*. *p*-Nitrobenzoylation of **19** resulted in the desired tris-*p*-nitrobenzoate (**20**). The methyl glycosidation of 2-deoxy-D-*lyxo*-hexose (**21**) resulted in a 70-% yield of crystalline methyl 2-deoxy-α-D-*lyxo*-hexopyranoside (**22**), considerably in excess of that originally reported[15] for this reaction, and *p*-nitrobenzoylation of **22** gave the crystalline, high-melting *p*-nitrobenzoic ester **23**.

In Table III are shown the molecular rotations of some methyl 2-deoxy-D-hexosides (furanoid and pyranoid) and their *p*-nitrobenzoates, where available. Molecular rotational differences (2A values) for anomeric pairs have been calculated; and, for the four pairs of unsubstituted glycosides shown in Table III, the values

TABLE III

MOLECULAR ROTATIONS OF SOME METHYL 2-DEOXY-D-ALDOHEXOSIDES AND THEIR *p*-NITROBENZOATES

Methyl glycoside of	[*M*]	Δ[*M*]
2-Deoxy-α-D-*arabino*-hexopyranose[14] (**19**)	+ 24,410	31,929
β anomer[14,17]	− 7,519	
2-Deoxy-α-D-*lyxo*-hexopyranose[a] (**22**)	+ 29,192	37,522
β anomer[12]	− 8,330	
2-Deoxy-α-D-*ribo*-hexopyranose[a] (**14**)	+ 32,611	36,175
β anomer[a] (**12**)	− 3,564	
2-Deoxy-α-D-*arabino*-hexofuranose[3]	+ 20,867	
2-Deoxy-α-D-*ribo*-hexofuranose[a] (**4**)	+ 26,017	34,214
β anomer[a] (**9**)	− 8,197	
2-Deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*arabino*-hexose[a] (**20**)	− 1,312	21,018
β anomer[17]	− 22,330	
2-Deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*lyxo*-hexose[a] (**23**)	+ 10,360	32,985
β anomer[12]	− 22,625	
2-Deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*ribo*-hexose[a] (**15**)	+141,250	44,375
β anomer[a] (**11**)	+ 96,875	
2-Deoxy-3,5,6-tri-*O*-*p*-nitrobenzoyl-α-D-*arabino*-hexose[3a,b]	− 76,438	156,438
2-Deoxy-3,5,6-tri-*O*-*p*-nitrobenzoyl-α-D-*ribo*-hexose[a] (**6**)	+ 80,000	

[a]This paper.

given fall well within the range for other aldose pairs[16]. For the corresponding nitrobenzoylated derivatives, however, the differences for the three anomeric pairs shown are more widely divergent, suggesting that the bulky, electronegative *p*-nitrobenzoyloxy groups increase the dissymmetry about the carbon atoms to which they are attached, resulting in anomalous Δ[M] values. The last two compounds listed in Table III constitute a pair of furanoid, C-3 epimers, having the same configuration at the anomeric center. The molecular rotational difference for these two is exceedingly

*The authors thank Dr. Gerhard Pietsch for this preparation.

large, and is particularly striking when compared with $\Delta[M] = 5150$ for the corresponding, unsubstituted furanosides. Accordingly, the two *p*-nitrobenzoylated furanosides must have highly strained structures, with much distortion of the already strained, furanoid rings, and it would be of considerable moment to have X-ray crystallographic analyses made of the two compounds.

EXPERIMENTAL

All melting points were determined with a Kofler hot-stage, optical rotations were measured with a Rudolph Model 80 polarimeter, i.r. spectra were recorded with a Perkin–Elmer Model 457 spectrophotometer, nuclear magnetic resonance (n.m.r.) spectra were recorded with a Varian Model A-60 spectrometer, g.l.c. was performed on a Micro-Tek Model 220 instrument having a dual flame detector (column packing: 2% SE-52 on Chromosorb W), and optical absorbances at 570 nm were measured with a Coleman Junior Model 6C spectrophotometer (for the estimation of formaldehyde in the periodate-oxidation studies).

Samples for t.l.c. were spotted on plates of Kiesel-Gel DF-5 (ultraviolet indicating), and developed with one of the following solvents: *A* (upper phase of 10:6:5:3 ethyl acetate–methanol–water–heptane), *B* (upper phase of 10:6:5:3 ethyl acetate–ethyl-alcohol–water–2,2,4-trimethylpentane), and *C* (upper phase of 9:6:3:1 butyl alcohol–acetic acid–ether–water). Alkaline potassium permanganate spray was used to visibilize the spots.

Samples for paper chromatography were spotted on strips of Whatman No. 1 paper, and developed with one of the following solvents: *D* (upper phase of water-saturated 9:1 butyl alcohol–toluene) and *E* (upper phase of 10:6:1:4 ethyl acetate–isobutyl alcohol–toluene–water). Carbohydrate derivatives were detected by spraying with 1% of boric acid in a solution of 1% of hydrogen chloride in 90% aqueous methanol[18].

2-Deoxy-D-ribo-*hexose dibenzyl dithioacetal* (**2**). — To 184 mg (1.12 mmoles) of 2-deoxy-D-*ribo*-hexose[5] (**1**) at 0° were added, with stirring, 0.5 ml (4 mmoles) of α-toluenethiol and 0.4 ml of concentrated hydrochloric acid. The mixture was stirred for 10 min at 0°, some crushed ice and ice–water were added, and stirring was continued for 5 min. The thick suspension was filtered, and the residue was thoroughly washed with water, and then with pentane to remove the excess of α-toluenethiol. The crystalline product was dissolved in tetrahydrofuran, the solution was dried with sodium sulfate, and the suspension filtered. The filtrate was evaporated to dryness under diminished pressure at 35°, and the resulting syrup was dissolved in tetrahydrofuran. Addition of ether resulted in the separation of 280 mg (70%) of **2**, m.p. 146.5–149°, $[\alpha]_D^{25}$ +55.5° (*c* 0.72, tetrahydrofuran).

Anal. Calc. for $C_{20}H_{26}O_4S_2$: C, 60.87; H, 6.64; S, 16.25. Found: C, 60.78; H, 6.64; S, 16.42.

2-Deoxy-D-ribo-*hexose diethyl dithioacetal* (**2a**). — To 200 mg (1.22 mmoles) of **1** at 0° were added, with stirring, 3 ml of ethanethiol and 0.4 ml of concentrated hydrochloric acid. The mixture was stirred for 30 min at 0°, and then poured, with

efficient stirring, into 100 ml of ice–water containing 1 ml of 3M sodium hydroxide (to neutralize the acid). The resulting solution was evaporated to dryness under diminished pressure at 45°, the residue was thoroughly extracted with tetrahydrofuran, and the extracts were combined, treated with Darco G-60 decolorizing carbon, and filtered, and the filtrate evaporated to a syrup. The product was crystallized from tetrahydrofuran–ether, to give 100 mg (30%) of **2a**, m.p. 93–96°, $[\alpha]_D^{25}$ +0.11° (*c* 0.92, tetrahydrofuran).

Anal. Calc. for $C_{10}H_{22}O_4S_2$: C, 44.41; H, 8.20; S, 23.72. Found: C, 44.67; H, 8.36; S, 23.87.

*Methyl 2-deoxy-α,β-*D-ribo-*hexofuranoside* (**3**). — (a) *From the dithioacetal* (**2** *or* **2a**). — To a stirred solution of 500 μmoles of either **2** or **2a** in 3 ml of anhydrous methanol were added 280 mg of mercuric chloride, 143 mg of freshly prepared, yellow mercuric oxide, and 50 mg of finely divided Drierite. The mixture was stirred for 1 h at room temperature, and filtered with the aid of a little Celite 545. To the filtrate was added 0.2 ml of pyridine, the mixture was kept in a refrigerator overnight, and the pyridine–mercuric chloride complex was removed by filtration. The filtrate was further purified by stirring it with Rexyn 300 (H^+, OH^-) ion-exchange resin* and filtering the suspension; the clear filtrate was evaporated *in vacuo* at 40° to a syrup, which partially crystallized on storage overnight in a desiccator containing phosphorus pentaoxide. Recrystallization from tetrahydrofuran–ether gave furanoside **3**, m.p. 93–95°, $[\alpha]_D^{25}$ +39.2° (*c* 0.473, methanol). Yields of crystalline **3** varied from 30–34%.

Anal. Calc. for $C_7H_{14}O_5$: C, 47.19; H, 7.92. Found: C, 46.98; H, 7.79.

(b) *From the methyl glycosidation of 2-deoxy-*D-ribo-*hexose*[6] (**1**). — To 60 ml of a 0.2% solution of hydrogen chloride in methanol was added 1.0 g (6.1 mmoles) of finely powdered 2-deoxy-D-*ribo*-hexose (**1**), and the reaction mixture was stirred at room temperature for 6 min. An excess (6 g) of silver carbonate was quickly added, and stirring was continued for 15 min, after which, the suspension was filtered through a bed of decolorizing carbon. Evaporation of the filtrate gave a syrup that crystallized rapidly, the product (1.08 g) having m.p. 93–95°. It was homogeneous on paper chromatograms with solvent *D* (R_F 0.47) and with solvent *E* (R_F 0.27); in each case, the R_F value was identical with that of the methyl 2-deoxy-α,β-D-*ribo*-hexofuranoside (**3**) obtained in the preceding preparation. Recrystallization from tetrahydrofuran–pentane gave 910 mg (85%), with no change in m.p.; the total yield of pure **3** was, therefore, 100%.

*Methyl 2-deoxy-α-*D-ribo-*hexofuranoside* (**4**). — Methyl 2-deoxy-α,β-D-*ribo*-hexofuranoside (1.9 g), prepared as described in the preceding experiment, was recrystallized once from tetrahydrofuran–ether, twice from ethyl alcohol–ether–pentane, and three times from ethyl acetate, to give 100 mg (5%) of **4**, m.p. 115–119°, $[\alpha]_D^{25}$ +146° (*c* 0.582, methanol). The trimethylsilylated derivative of **4** appeared, on g.l.c., as a single peak having a retention time of 2.5 min (see Fig. 1).

*Fisher Scientific Co.

*Methyl 2-deoxy-3,5,6-tri-O-*p*-nitrobenzoyl-α,β-*D*-ribo-hexoside* (**5**) *and the pure α-*D* anomer* (**6**). — To a stirred suspension of 425 mg (2.4 mmoles) of *p*-nitrobenzoyl chloride in 6 ml of anhydrous pyridine at 0° was added 100 mg (560 μmoles) of the furanoside (**3**). Stirring was continued for 1 h at 0° and for 1 h at room temperature. The mixture was kept in a refrigerator for 3 days, and then stirred for 1 h at room temperature; 10 ml of saturated, aqueous sodium hydrogen carbonate was now carefully added. The resulting mixture was poured, with stirring, into 200 ml of ice–water, stirring was continued for 1.5 h, and the product that separated was filtered off by suction and washed several times with water. After being dried in a vacuum desiccator containing phosphorus pentaoxide, the solid was crystallized from acetone–ether–pentane to give 200 mg (57%) of **5**, m.p. 137–147°.

Fractional recrystallization of the anomeric mixture (**5**) from tetrahydrofuran–ether–pentane yielded 70 mg (20%) of pure methyl 2-deoxy-3,5,6-tri-*O*-*p*-nitrobenzoyl-α-D-*ribo*-hexoside (**6**), m.p. 152–154°, $[\alpha]_D^{25}$ +128° (*c* 0.456, acetone).

Anal. Calc. for $C_{28}H_{23}N_3O_{14}$: C, 53.72; H, 3.71; N, 6.72. Found: C, 53.96; H, 3.81; N, 6.69.

Conversion of **6** *into the α-*D*-furanoside* (**4**). — A suspension of 50 mg (80 μmoles) of **6** in 5 ml of 20 mM methanolic sodium methoxide was stirred for 24 h at room temperature. The solvent was evaporated off at 40° under diminished pressure, and the residue was suspended in 5 ml of water. The suspension was washed with three 5-ml portions of ether, the aqueous layer was stirred for 7 min with a small portion of Rexyn 300 (H^+, OH^-) ion-exchange resin, the suspension was filtered, and the clear filtrate was evaporated to dryness under diminished pressure at 50°. The resulting syrup was dried by co-evaporation with absolute ethyl alcohol; it was then dissolved in a small volume of absolute ethyl alcohol, and ether–pentane was added to incipient turbidity; yield of **4**, 10 mg (70%), m.p. 115–119°. It was homogeneous by g.l.c. of its tris(trimethylsilyl) ether, which had a retention time of 2.5 min (see Fig. 1).

*2-Deoxy-3,5,6-tri-*O*-*p*-nitrobenzoyl-α-*D*-ribo-hexosyl bromide* (**7**). — To 105 mg (170 μmoles) of the tris-*p*-nitrobenzoate (**5**) was added 3.5 ml of a saturated solution of hydrogen bromide in dichloromethane. The solution was kept for 12 min at room temperature under rigorous exclusion of moisture; it was concentrated to half its volume by evaporation under diminished pressure (25°), and diluted with ether, and pentane was added to incipient turbidity. The solution was refrigerated for 2 h, and the resulting crystals were filtered off, and washed with dry ether, to give 85 mg (79%) of the bromide **7**, m.p. 93–95° (dec. 135°), $[\alpha]_D^{25}$ +120° (*c* 0.489, dichloromethane). The halide gave a strong, positive Beilstein test.

*Methyl 2-deoxy-β-*D*-ribo-hexofuranoside* (**9**). — A solution of 500 mg (740 μmoles) of the halide **7** in 15 ml of dry dichloromethane was added to a stirred suspension of 2 g of silver carbonate in 70 ml of anhydrous methanol. The mixture was stirred for 2 h, and filtered, and the silver salts were washed with hot dichloromethane. The filtrate and washing were combined and evaporated under diminished pressure to give 270 mg of the *p*-nitrobenzoylated furanoside (**8**) as syrupy material, which could not be brought to a satisfactory crystalline state. Without further processing,

the crude **8** was treated with 20 ml of 20 mM methanolic sodium methoxide, the mixture was stirred for 24 h at room temperature, and the solvent was evaporated off under diminished pressure at 40°. The residue was suspended in 15 ml of water, the suspension was washed with three 10-ml portions of ether, and the aqueous layer was stirred for 7 min with a small portion of Rexyn 300 (H^+, OH^-) ion-exchange resin. The resin was filtered off, and the filtrate was evaporated to dryness at 45° to afford a syrup that crystallized spontaneously; yield 50 mg (37% based on **7**). The product, as shown by g.l.c. of its per(trimethylsilyl) ether, consisted of 85% of the β-D anomer (**9**) and 15% of the α-D anomer (**4**). Fractional recrystallization, first from tetrahydrofuran–ether–pentane, and then from ethyl acetate, gave pure β-D-furanoside (**9**), m.p. 117–122°, $[\alpha]_D^{25}$ −46° (*c* 0.20, methanol). The product, thus purified, gave a single peak on g.l.c. of its per(trimethylsilyl) ether, which had a retention time of 3.0 min (see Fig. 1); consequently, an elementary analysis was not performed.

Methyl 2-deoxy-3,4,6-tri-O-p-*nitrobenzoyl-β*-D-ribo-*hexoside* (**11**). — A solution of 1.87 g (2.78 mmoles) of 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*ribo*-hexosyl bromide[5,9] (**10**) in 20 ml of dry dichloromethane was added to a stirred suspension of 2 g of silver carbonate in 100 ml of absolute methanol. The mixture was stirred for 2 h, and filtered, and the silver salts were washed with hot dichloromethane. The filtrate and washings were combined, and evaporated to dryness under diminished pressure, and the residue was twice recrystallized from acetone–pentane to give 700 mg (40%) of pure **11**, m.p. 209–211°, $[\alpha]_D^{25}$ +155° (*c* 0.619, acetone).

Anal. Calc. for $C_{28}H_{23}N_3O_{14}$: C, 53.72 H, 3.71; N, 6.72. Found: C, 53.93; H, 3.76; N, 6.53.

Methyl 2-deoxy-β-D-ribo-*hexopyranoside* (**12**). — A suspension of 645 mg (1.04 mmoles) of **11** in 25 ml of 20 mM methanolic sodium methoxide was stirred for 24 h at room temperature. The solvent was removed under diminished pressure at 40°, and the residue was suspended in 40 ml of water. The suspension was washed with three 15-ml portions of ether, and the aqueous layer was stirred for 7 min with 3 g of Rexyn 300 (H^+, OH^-) ion-exchange resin. The resin was filtered off, the filtrate was evaporated to dryness under diminished pressure at 50°, and the resulting syrup was dried once by co-evaporation with absolute ethyl alcohol, whereupon it crystallized spontaneously. The product was recrystallized from tetrahydrofuran–pentane to give 110 mg (60%) of methyl 2-deoxy-β-D-*ribo*-hexopyranoside (**12**), m.p. 99–100.5°, $[\alpha]_D^{25}$ −20° (*c* 0.52, methanol).

Anal. Calc. for $C_7H_{14}O_5$: C, 47.19; H, 7.92. Found: C, 47.30; H, 8.09.

Methyl 2-deoxy-α-D-ribo-*hexopyranoside*[10] (**14**). — A suspension of 2.6 g (10 mmoles) of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside[5] (**13**) in 150 ml of 0.1M acetic acid was stirred for 24 min at 80°. The acid was neutralized with 3M sodium hydroxide, the solution was washed with three 50-ml portions of chloroform, and the aqueous layer was stirred for 10 min with 25 g of Rexyn 300 (H^+, OH^-) ion-exchange resin. The suspension was filtered, and the filtrate was evaporated to a syrup, which was chromatographed on a column (4 × 40 cm) of

cellulose powder by elution with solvent *D*. Collection of fractions (3 ml each) was begun when the effluent gave a faint, positive reaction with a boric acid reagent[18], and the product (**14**) was recovered as a syrup from the first 136 tubes. It was homogeneous on paper chromatograms (solvent *D*), and had R_F 0.38; yield, 1.0 g (55%). On storage of the syrup for several days in a desiccator containing phosphorus pentaoxide, the product crystallized, and recrystallization from tetrahydrofuran–ether afforded pure **14** as slightly hygroscopic needles, m.p. 97–99.5°, $[\alpha]_D^{25}$ +183° (*c* 0.521, methanol).

Anal. Calc. for $C_7H_{14}O_5$: C, 47.19; H, 7.92. Found: C, 47.16; H, 8.13.

Methyl 2-deoxy-3,4,6-tri-O-p-*nitrobenzoyl*-α-D-ribo-*hexoside* (**15**). — To 259 mg (1.45 mmoles) of the α-D-pyranoside (**14**) in 10 ml of anhydrous pyridine at 0° was added, with stirring, 1.1 g (6.1 mmoles) of *p*-nitrobenzoyl chloride. Stirring was continued for 1 h at 0° and for 1 h at room temperature, and the mixture was kept in a refrigerator for 3 days. It was then stirred for 1 h at room temperature, and 15 ml of saturated, aqueous sodium hydrogen carbonate was then carefully added. The mixture was poured, with stirring, into 300 ml of ice–water, stirring was continued for 1.5 h, and the product that separated was filtered off, and washed well with water. The solid was dried in a vacuum desiccator (phosphorus pentaoxide) and then recrystallized three times from tetrahydrofuran–ether, to yield 450 mg (50%) of **15**, m.p. 136–140°, $[\alpha]_D^{25}$ +226° (*c* 0.48, acetone).

Anal. Calc. for $C_{28}H_{23}N_3O_{14}$: C, 53.72; H, 3.71; N, 6.72. Found: C, 53.55; H, 3.56; N, 6.58.

3,5,6-Tri-O-*benzoyl-2-deoxy*-D-arabino-*hexono-1,4-lactone* (**18**). — To 488 mg (3.0 mmoles) of 2-deoxy-D-*arabino*-hexono-1,4-lactone[13] (**17**) in 4 ml of dry pyridine at 0° was added dropwise 2.2 ml (20 mmoles) of benzoyl chloride. The mixture was stirred for 1 h at room temperature, and then kept in a refrigerator for 3 days. The excess of benzoyl chloride was decomposed by careful addition of an excess of saturated, aqueous sodium hydrogen carbonate, and the mixture was poured, with stirring, into 200 ml of ice–water. The gummy solid that separated was filtered off, washed with water, and dissolved in acetone. The solution was decolorized with Darco G-60 decolorizing carbon, the suspension was filtered, and the filtrate was evaporated under diminished pressure to a clear syrup which was homogeneous on t.l.c. (R_F 0.79) with solvent *B*. The syrup was dissolved in ethyl alcohol, and the solution was kept in a refrigerator for three months, after which time, the product crystallized slowly. The crude product (1 g) was recrystallized three times from tetrahydrofuran–pentane to give 400 mg (36%) of analytically pure **18**, m.p. 73–78°, $[\alpha]_D^{25}$ −128° (*c* 0.975, acetone); ν_{max}^{KBr} 1799 (γ-lactone) and 1730 cm^{-1} (benzoate carbonyl).

Anal. Calc. for $C_{27}H_{22}O_8$: C, 68.35; H, 4.67. Found: C, 68.51; H, 4.77.

Methyl 2-deoxy-3,4,6-tri-O-p-*nitrobenzoyl*-α-D-arabino-*hexoside* (**20**). — To a stirred suspension of 3.9 g (21 mmoles) of *p*-nitrobenzoyl chloride in 30 ml of anhydrous pyridine at 0° was added 990 mg (5.6 mmoles) of methyl 2-deoxy-α-D-*arabino*-hexopyranoside[14] (**19**). Stirring was continued for 1 h at 0° and for 1 h at

room temperature, and the mixture was kept in a refrigerator for 3 days. It was then stirred for 1 h at room temperature, and 25 ml of satured, aqueous sodium hydrogen carbonate was carefully added. The resulting mixture was poured, with stirring, into 500 ml of ice–water. Stirring was continued for 1 h, and the product that separated was filtered off, and washed several times with water. The solid was dried in a vacuum desiccator (phosphorus pentaoxide), and recrystallized from acetone–ether to afford 1.4 g (40%) of **20**, containing one molecule of acetone of crystallization per molecule, m.p. 100–110°, $[\alpha]_D^{25}$ −2.1° (*c* 0.725, acetone). After being dried for 2 days at 110°/0.1 torr, the product* (**20**) melted at 150°.

Anal. Calc. $C_{28}H_{23}N_3O_{14}\cdot C_3H_6O$: C, 54.50; H, 4.25; N, 6.15. Found: C, 55.11; H, 4.19; N, 6.44. Calc. for $C_{28}H_{23}N_3O_{14}$: C, 53.72; H, 3.71; N, 6.72. Found: C, 53.80; H, 3.61; N, 6.71.

*Methyl 2-deoxy-α-*D-lyxo-*hexopyranoside* (**22**). — A solution of 410 mg (2.5 mmoles) of 2-deoxy-D-*lyxo*-hexose** (**21**) in 10 ml of 2.5% methanolic hydrogen chloride was kept for 48 h at room temperature. An excess (1.5 g) of silver carbonate was added, the suspension was stirred for 10 min, and filtered through a bed of Darco G-60 decolorizing carbon, and the filtrate was evaporated to dryness under diminished pressure at 40°. The resulting syrup was crystallized from ethyl acetate–pentane, and two recrystallizations from the same solvent mixture gave 310 mg (70%) of pure **22**, m.p. 115–116°, $[\alpha]_D^{24}$ +164° (lit.[15] m.p. 112–113°, $[\alpha]_D$ +170°).

*Methyl 2-deoxy-3,4,6-tri-*O-p-*nitrobenzoyl-α-*D-lyxo-*hexoside* (**23**). — To a mixture of 12 ml of dry pyridine and 1.113 g (6 mmoles) of *p*-nitrobenzoyl chloride was added 267 mg (1.5 mmoles) of **22**, and the mixture was stirred for 1 h at 0°. It was kept in a refrigerator for 48 h, and then stirred for 1 h at room temperature, and the excess of the acid chloride was decomposed by stirring the mixture with 6 ml of saturated, aqueous sodium hydrogen carbonate. The resulting suspension was poured, with efficient stirring, into 200 ml of ice–water, and stirring was continued until all of the ice had melted. The precipitate was filtered off, dried in air, and then in a vacuum desiccator (phosphorus pentaoxide), and recrystallized from dichloromethane–ether, to afford 750 mg (80%) of **23**, m.p. 178–179°, $[\alpha]_D^{24}$ +58.2° (*c* 1.048, dichloromethane).

Anal. Calc. for $C_{28}H_{23}N_3O_{14}$: C, 53.72; H, 3.71; N, 6.72. Found: C, 53.50; H, 3.50; N, 6.93.

Periodate oxidation studies[7]. — To a weighed amount (50–100 μmoles) of the compound to be oxidized, in 0.5 ml of water, were added 2 ml of 0.3M periodic acid and 2 ml of M sodium hydrogen carbonate. The mixture was kept for 1 h at room temperature, and then 15 ml of 0.5M sulfuric acid and 5 ml of M sodium arsenite were added. The mixture was gently agitated until the iodine that was liberated on adding the sodium arsenite had disappeared, and it was then diluted with water,

*Attempts to recrystallize desolvated **20** from acetone–ether resulted in solvated material, m.p. 100–110°.

**Aldrich Chemical Co., Inc., Milwaukee, Wisconsin.

so that the concentration of formaldehyde was less than 600 nmoles per ml. One ml of the diluted solution was mixed with 10 ml of chromotropic acid reagent* in a test tube. The test tube was stoppered, heated for 30 min in a boiling-water bath, and cooled; the absorbance of the sample was measured against that of a blank, at 570 nm.

Standard formaldehyde solutions were prepared from samples of pure D-glucose (U. S. National Bureau of Standards) by following the procedure described above.

Methyl 2-deoxy-D-erythro-*pentofuranoside.* — To 7 mg (39 μmoles) of methyl 2-deoxy-D-*ribo*-hexofuranoside (3) in 0.5 ml of water were added 2 ml of 0.3M periodic acid and 2 ml of M sodium hydrogen carbonate. The mixture was kept for 1 h at room temperature, 20 mg of sodium borohydride was added, and the mixture was shaken gently for a few min. The excess of sodium borohydride was neutralized with 0.1M sulfuric acid, and the solution was examined by t.l.c. with solvent *A*, revealing a single component having an R_F value (0.23) identical with that of authentic methyl 2-deoxy-D-*erythro*-pentofuranoside[8].

ACKNOWLEDGMENTS

The authors thank Messrs. V. W. Tripp and G. J. Boudreaux, Southern Regional Research Service, U. S. Department of Agriculture, New Orleans, Louisiana, for the n.m.r. spectra, and Mr. Ralph Wheeler and Dr. Eleanor E. Storrs, Gulf South Research Institute, for their assistance with the gas–liquid chromatography.

REFERENCES

1 W. W. ZORBACH AND T. A. PAYNE, JR., *J. Amer. Chem. Soc.*, 80 (1958) 5564.
2 W. W. ZORBACH AND T. A. PAYNE, JR., *J. Amer. Chem. Soc.*, 81 (1959) 1519; 82 (1960) 4979.
3 K. V. BHAT AND W. W. ZORBACH, *Carbohyd. Res.*, (a) 1 (1965) 93; (b) 6 (1968) 63; (c) K. V. BHAT, in W. W. ZORBACH AND R. S. TIPSON (Eds.), *Synthetic Procedures in Nucleic Acid Chemistry*, Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1968, pp. 304–308.
4 E. PACSU AND J. W. GREEN, *J. Amer. Chem. Soc.*, 58 (1936) 1823.
5 K. V. BHAT AND W. W. ZORBACH, in Ref. 3 (c), pp. 309–312.
6 C. C. BHAT, K. V. BHAT, AND W. W. ZORBACH, *Chem. Commun.*, (1968) 808.
7 J. C. SPECK, *Methods Carbohyd. Chem.*, 1 (1962) 441.
8 R. E. DERIAZ, W. G. OVEREND, M. STACEY, AND L. F. WIGGINS, *J. Chem. Soc.*, (1949) 2836.
9 W. W. ZORBACH AND W. BÜHLER, *Ann.*, 670 (1963) 116.
10 T. REICHSTEIN, R. W. JEANLOZ, AND D. A. PRINS, *Helv. Chim. Acta*, 29 (1946) 371.
11 P. KOHN, R. H. SAMARITANO, AND L. M. LERNER, *J. Amer. Chem. Soc.*, 87 (1965) 5475; *J. Org. Chem.*, 31 (1966) 1563.
12 W. W. ZORBACH, C. C. BHAT, AND K. V. BHAT, *Advan. Chem. Ser.*, 74 (1968) 1.
13 I. W. HUGHES, W. G. OVEREND, AND M. STACEY, *J. Chem. Soc.*, (1949) 2846.
14 M. BERGMANN, H. SCHOTTE, AND W. LESCHINSKY, *Ber.*, 55 (1922) 158; 56 (1923) 1052.
15 W. G. OVEREND, F. SHAFIZADEH, AND M. STACEY, *J. Chem. Soc.*, (1950) 671.
16 W. PIGMAN, in W. PIGMAN (Ed.), *The Carbohydrates*, Academic Press Inc., New York, N. Y., 1957, pp. 72–74.
17 W. W. ZORBACH AND G. PIETSCH, *Ann.*, 655 (1962) 26.
18 M. PÖHM AND R. WEISER, *Naturwissenschaften*, 43 (1956) 582.

*The reagent was prepared by dissolving 1 g of chromotropic acid (4,5-dihydroxy-2,7-naphthalenedisulfonic acid) in 100 ml of water and adding sufficient 12.5M sulfuric acid to bring the total volume to 500 ml.