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SYNTHESIS OF 2-DEOXY-D-*arabino*-(6-^{13}C)HEXOSE

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ABSTRACT

2-Deoxy-D-*arabino*-[6-^{13}C]hexose (**10**), to be used to test the stability of 2-deoxy-D-*arabino*-hexose 6-phosphate in brain tissue, was prepared. 2-Deoxy-D-*arabino*-hexose was labeled at C-6 because of the large difference in chemical shift between C-6 in the free sugar and C-6 in the 6-phosphate. The synthetic scheme resembled that used for the synthesis of D-[6-^{13}C]glucose that involved the removal of C-6 from D-glucose followed by its replacement with ^{13}C. The protected derivative methyl 2-deoxy-α-D-*arabino*-hexofuranoside was prepared, using trifluoroacetic acid in methanol. This was treated with periodate, which cleaves only between C-5 and C-6, to afford an aldehyde which reacted directly with K^{13}CN to give a mixture of the D-*arabino* and L-*xylo* nitriles. The enriched nitriles were reduced with hydrogen in the presence of 5% Pd–carbon catalyst to a mixture of 6-*aldehydo* sugars. These were reduced with $NaBH_4$ to a mixture of the two labeled methyl furanosides. Acid hydrolysis followed by ion-exchange chromatography on AG-50(Ca^{2+}) resin at 65° gave **10** in an overall yield of 16% from K^{13}CN.

INTRODUCTION

Radioisotopically labeled 2-deoxy-D-*arabino*-hexose has been used in studies of brain metabolism[1]. Feasibility of these studies is based on the assumption that 2-deoxy-D-*arabino*-hexose 6-phosphate is metabolically stable. The results of recent ^{31}P-n.m.r. experiments[2] have, however, raised questions as to whether the disappearance of the sugar phosphate is faster than had been assumed from the radio tracer studies. ^{13}C-n.m.r. spectroscopy can be used as a probe of the ultimate fate of 2-deoxy-D-*arabino*-hexose (**1**) by direct observation of the metabolites. We chose to label **1** at C-6 because of the large chemical-shift difference (3 p.p.m.) between C-6 in the free sugar and C-6 in the 6-phosphate analog (see Table I).

Several methods[3–5] have recently been reported for the synthesis of **1**, but all of the schemes start with a precursor intact at C-6. To adapt these procedures for the synthesis of a 6-^{13}C derivative would involve numerous steps with the labeled material. The scheme used for the synthesis of **1** labeled with ^{11}C or ^{14}C at C-1 involved the introduction of labeled carbon *via* cyanide[6,7], but the chemistry involved is not appropriate for the synthesis of the 6-^{13}C derivative.

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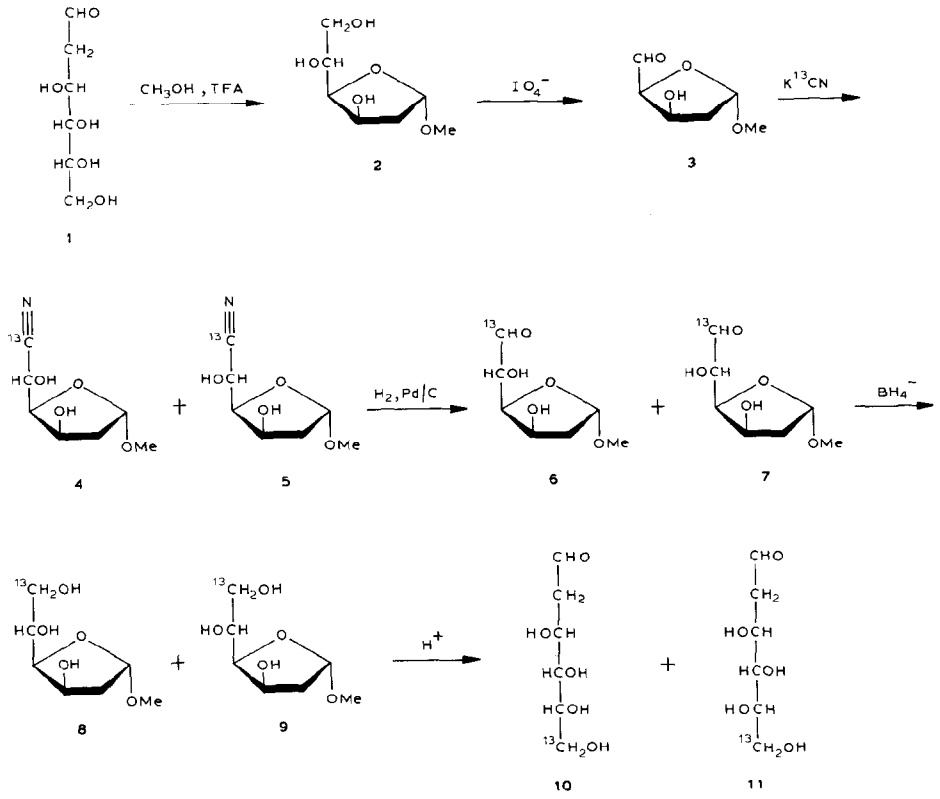
TABLE I

CHEMICAL SHIFTS[a] FOR 2-DEOXY-D-*arabino*-HEXOSE AND 2-DEOXY-L-*xylo*-HEXOSE

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*OMe*
2-Deoxy-α-D-*arabino*-hexopyranose[b]	92.4	38.4	69.1	72.3	73.1	61.9	
2-Deoxy-β-D-*arabino*-hexopyranose[b]	94.5	40.7	71.4	72.0	77.0	62.1	
2-Deoxy-α-D-*arabino*-hexofuranose	99.0	43.5	[c]	81.3	[c]	64.8	
2-Deoxy-β-D-*arabino*-hexofuranose	99.3	42.4	[c]	83.1	[c]	64.8	
Methyl 2-deoxy-α-D-*arabino*-hexopyranoside[b]	99.3	37.6	69.3	72.1	73.1	61.8	55.4
Methyl 2-deoxy-β-D-*arabino*-hexopyranoside[b]	101.7	39.2	71.5	72.2	77.1	62.2	57.6
Methyl 2-deoxy-β-D-*arabino*-hexofuranoside	106.3	41.5	71.0[d]	83.4	70.9[d]	64.9	56.0
Methyl 2-deoxy-α-D-*arabino*-hexofuranoside	106.0	42.4	71.9	81.2	70.2	64.8	56.2
Methyl 2-deoxy-β-L-*xylo*-hexofuranoside	105.3	43.1	72.0	82.2	71.8	63.9	56.2
Methyl α-D-*threo*-pentodialdo-1,4-furanoside	106.0	42.6	71.8	84.1	89.7		56.4
Methyl 2-deoxy-α-D-*arabino*-hexofuranosidurononitrile[e]	105.7	41.6	70.6	81.5	60.7	120.4	56.0
Methyl 2-deoxy-β-L-*xylo*-hexofuranosidurononitrile[e]	105.9	41.8	71.2	81.4	61.0	119.7	56.0
2-Deoxy-α-D-*arabino*-hexopyranose 6-phosphate	92.5	38.4	68.6	71.8	72.6	63.8[d]	
2-Deoxy-β-D-*arabino*-hexopyranose 6-phosphate	94.6	40.6	71.0	71.5	76.5	63.7[d]	

[a]Samples at 25°; chemical shifts are reported in p.p.m. from external tetramethylsilane. [b]Assignments are from the literature[16]. [c]These resonances were unresolved. [d]These assignments may have to be reversed. [e]This sample was at pH 4 in water containing acetic acid and D_2O (for the lock).

We have used an approach similar to that of Williams and Whaley[8], who described the synthesis of D-[6-^{13}C]glucose from unlabeled D-glucose. In their scheme, D-glucose was degraded to a 5-*aldehydo*-pentose, which reacted with potassium [^{13}C]cyanide to re-form the hexose. The synthesis of 2-deoxy-D-*arabino*-[6-^{13}C]hexose (**10**) was carried out by a similar method, in which a 5-*aldehydo*-pentose is generated from 2-deoxy-α-D-*arabino*-hexose (**1**), as shown in formulas **1–11**.



EXPERIMENTAL

Materials and methods. —Trifluoroacetic acid, 2-deoxy-D-*arabino*-hexose, D_2O, 5% Pd–$BaSO_4$, and 5% Pd–C were obtained from Sigma Chemical Co. Ion-exchange resins (AG 50 and AG 1) were obtained from Bio-Rad Laboratories, Richmond, CA. The K^{13}CN was prepared as described by Walker *et al.*[9]. Melting points were determined on a Thomas–Hoover melting-point apparatus and are uncorrected. Optical rotations were measured with a Rudolph Research Autopol III polarimeter.

^{13}C-n.m.r. spectroscopy. — Proton-decoupled, ^{13}C-n.m.r. spectra were

recorded for samples dissolved in water containing 5–10% D_2O by using a Bruker AM-200 spectrometer operated at 25°. Spectral widths of 3500 Hz were used to give a typical spectral resolution of 0.2 Hz/point. Peak integrals were determined by using the Bruker integrate routine.

*Methyl 2-deoxy-α-*D-arabino-*hexofuranoside* (**2**). — To a suspension of **1** (25 g, 152 mmol) in MeOH (500 mL) was added CF_3CO_2H (5 mL), and the mixture was stirred at room temperature. After 18 h, the solvent was evaporated *in vacuo*, and the resultant syrup was dissolved in 1,4-dioxane (50 mL) and the solvent evaporated *in vacuo*. This treatment with 1,4-dioxane was carried out twice to remove residual CF_3CO_2H; the residue was dried in a vacuum desiccator. The resultant syrup (31 g) contained a mixture of the methyl glyco-pyranosides and -furanosides, which where then separated by chromatography[10]. A solution of the syrup in the minimal volume of water was applied to a column (5 × 80 cm) of AG-1 X8 (OH^-)resin, and the sugars were eluted with water. Fractions (15 mL) were monitored by using a refractive-index detector (Waters Model 404) and were identified by ^{13}C-n.m.r. spectroscopy. The first peak (fractions 30–50) contained 1,4-dioxane, which was discarded. The leading edge of the second peak (fractions 57–60) contained primarily the α-pyranoside (2.3 g). The balance of the peak (fractions 61–84) contained the two pyranosides and the β-furanoside (total 8.1 g). The broad, third peak (fractions 85–160), which contained the α-furanoside (**2**), was evaporated to a syrup which crystallized following storage overnight in a desiccator; yield: 12.7 g, 71.3 mmol, 47%; m.p. 74–77°, $[\alpha]_D^{25}$ +111.9° (*c* 0.99, ethanol) [lit.[11] m.p. 80–81°, $[\alpha]_D^{25}$ +117.1° (*c* 0.99, ethanol)].

*Methyl α-*D-threo-*pentodialdo-1,4-furanoside* (**3**). — A solution of **2** (5 g, 28.1 mmol) in water (25 mL) at 0° was treated with an aqueous equimolar solution of $NaIO_4$ during 45 min, followed by stirring for an additional hour. After the reaction was complete, a solution of $Ba(OAc)_2$ (7.5 g) was added dropwise to precipitate $Ba(IO_3)_2$, which was removed by filtration through Celite. The cold filtrate containing **3** was used immediately for the synthesis of the labeled nitriles (**4** and **5**).

*Methyl α-*D-arabino-*hexodialdo-1,4-furanoside* (**7**) *and methyl β-*L-xylo-*hexodialdo-1,4-furanoside* (**6**). — The pH of a solution of $K^{13}CN$ (3.7 g, 56 mmol) in ice–water (25 mL) was adjusted to 7 with HOAc; the cold filtrate containing aldehyde **3** was added, and the pH was readjusted to 7.0–7.2. After ~40 min, the intensities of the ^{13}C-n.m.r. resonances due to the two desired nitriles (**4** and **5**) were no longer increasing, and the reaction was terminated by addition of glacial HOAc to pH 4. Nitrogen was bubbled through the solution for 15 min to sweep out the excess of cyanide. The nitriles (**4** and **5**) were then reduced with hydrogen in a Parr hydrogenation apparatus with the pressure maintained between 55 and 103 kPa; 5% Pd–C (2 g) was used as the catalyst. The reduction, which required several hours, was deemed complete when the nitriles could no longer be observed by ^{13}C-n.m.r. spectroscopy. The catalyst was removed by filtration through Celite, and the filtrate was treated with AG 50 (H^+) ion-exchange resin to pH 2.8, and the suspension filtered. The filtrate was evaporated to dryness *in vacuo*, followed by

the addition of water and removal by evaporation *in vacuo* three times, to remove the excess of HOAc. Five resonances were observed in the ^{13}C-n.m.r. spectrum of the dialdo sugars (**6** and **7**): free aldehydes, 205.8 p.p.m.; α and β forms of the 3,6-hemiacetals, 105.0, 102.6, 99.4, and 97.4 p.p.m.

2-Deoxy-D-arabino-[*6-^{13}C*]*hexose* (**10**) *and 2-deoxy*-L-xylo-[*6-^{13}C*]*hexose* (**11**). — The syrupy mixture of **6** and **7** was dissolved in water (50 mL), and the pH was adjusted to 7 with NaOH. $NaBH_4$ (1.06 g) was added, and the solution was kept for 3 h at room temperature; the pH was then adjusted to 6 with glacial HOAc. The pH was now lowered to 2.4 by the addition of AG 50 (H^+) resin, and the solution was evaporated to dryness *in vacuo* to remove the HOAc. The residue containing the labeled methyl glycosides was dissolved in 0.05M H_2SO_4 (100 mL), and the solution was kept for 16 h at room temperature at which time the acid was neutralized with $BaCO_3$. The precipitate of $BaSO_4$ and the excess of $BaCO_3$ were filtered through Celite, and the filtrate evaporated *in vacuo* to a syrup which was chromatographed on a column (5 × 80 cm) of AG-50 (Ca^{2+}) resin at 65°, with degassed water as the eluant. Compound **10** was eluted in fractions 47–50 (1.50 g, 9.14 mmole; 16.3% yield from K^{13}CN) and crystallized from EtOH. A mixture of **10** and **11** was eluted in fractions 51–53 (0.42 g); compound **11**, along with several impurities, was eluted in fractions 54–60 (1.14 g).

RESULTS AND DISCUSSION

The synthetic route chosen for the preparation of 2-deoxy-D-*arabino*-[6-^{13}C]hexose (**10**) is a modification of that used for the synthesis of D-[6-^{13}C]glucose described by Williams and Whaley[8]. The objective was to protect 2-deoxy-D-*arabino*-hexose so that the only site susceptible to periodate oxidation would be the bond between C-5 and C-6. With this technique, an aldehyde can be generated at C-5 which will react with $^{13}CN^-$ to form a 6-^{13}C adduct. Because 2-deoxy-D-*arabino*-hexose has no hydroxyl group on C-2, the 1,2-*O*-isopropylidene derivative used by Williams and Whaley was not a possible starting material. Therefore, methyl 2-deoxy-α-D-*arabino*-hexofuranoside (**2**), which has the desired characteristics, was chosen as the starting material for the reaction. Unfortunately, conventional techniques for synthesizing this compound preferentially produce the undesired methyl pyranoside forms instead of the methyl furanosides. Several methods have been described[11–13] for obtaining higher yields of the methyl α-furanoside; however, we found that 1% trifluoroacetic acid in methanol[9] gives the best results. The subsequent conversion of the methyl furanoside into the labeled product proceeded satisfactorily, except that the intermediate compounds exhibited properties different from those of the corresponding intermediates in the preparation of D-[6-^{13}C]glucose. As a consequence, unique reaction conditions were required for the synthesis of 2-deoxy-D-*arabino*-[6-^{13}C]hexose.

There were two possibilities for the subsequent incorporation of ^{13}C at C-6 of **1**. The first (similar to the method of Williams and Whaley[8]) was to prepare during

the cyanide condensation reaction a uronic acid derivative which could be reduced with $LiAlH_4$ to give the labeled hydroxymethyl group containing C-6. An alternative procedure (similar to the method of Serianni *et al.*[14] for carbohydrates labeled at C-1) was the preparation of a nitrile (stabilized at pH 4 with acetic acid) in the condensation reaction, followed by reduction with hydrogen to give an aldehyde, and with borohydride to give the desired primary alcohol. For the cyanide condensation reaction with 2-deoxy-D-*arabino*-hexose, we observed several unidentified resonances in the ^{13}C-n.m.r. spectrum when the pH was increased above 7.5. This suggested that extensive side-reactions could be expected if the uronic acid approach were used; therefore, the route *via* the stabilized nitrile was chosen.

Three steps in the synthesis of 2-deoxy-D-*arabino*-[6-^{13}C]hexose (**10**) were satisfactory. (*1*) The synthesis of the methyl furanosides was accomplished in good yield from **1**; (*2*) the desired methyl furanoside was readily separated and crystallized; and (*3*) the D-*threo* isomer was the predominant species during the nitrile formation. Unfortunately, major problems were encountered at each of the other steps, requiring reaction conditions different from those used for the synthesis of D-[6-^{13}C]glucose.

The first problem was finding a technique for preparing methyl 2-deoxy-α-D-*arabino*-hexofuranoside (**2**). We used anhydrous methanol containing 1% of trifluoroacetic acid, a new technique that we have used for the synthesis of other methyl glycofuranosides[9]. For the synthesis of furanosides, this method is vastly superior to the more traditional techniques[11-13] that employ such dilute mineral acids as anhydrous HCl which yield much higher ratios of the methyl pyranosides. After 18 h at room temperature, the reaction mixture derived from 2-deoxy-D-*arabino*-hexose was found by ^{13}C-n.m.r. spectroscopy to consist of 67% of methyl furanosides, 33% of methyl pyranosides, and 2.9% of residual free sugar (see Fig. 1). The desired α-furanoside **2** was purified by chromatography on AG-1 X8 (OH^-) resin, using the technique described by Austin *et al.*[10]. The overall yield of **2** was

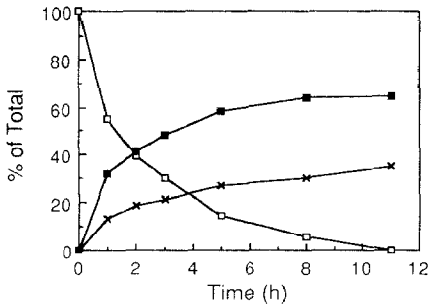


Fig. 1. The synthesis of methyl 2-deoxy-D-glycosides from 2-deoxy-D-*arabino*-hexose (**1**), methanol, and trifluoroacetic acid. Dry **1** (1.25 g) was dissolved in dry methanol (25 mL), trifluoroacetic acid (0.25 mL) was added, and the solution was kept at room temperature. ^{13}C-n.m.r. spectra were recorded at the specified intervals, and the ratio of sugars calculated from the signal intensities. Free sugar (□), furanosides (■), and pyranosides (×).

47% and the overall recovery of the methyl glycosides was 85%. The β-furanoside could also be used in the synthesis, although we have not found conditions suitable for its purification.

To determine that the material was indeed the α-furanoside, our product was found to have the same melting point and specific rotation as described by Bhat and Zorbach[11]. In addition, the ^{1}H-n.m.r.-spectral and specific rotation data were compared with those described by Angyal[15] for other methyl aldofuranosides. Angyal[15] found that all of the methyl α-D-aldofuranosides that the examined were dextrorotatory, which is consistent with the large positive rotation found for **2**. The proton $^3J_{1,2}$ values found for **2** (the α anomer) were 3.8 and 5.5 Hz, which are close to the 4.4 and 4.2 Hz found by Angyal[15] for the analogous methyl α-D-gluco- and β-L-manno-furanosides, respectively. Alternatively, the proton $^3J_{1,2}$ values found for the β anomer of **2** were 1.0 and 5.4 Hz, which are close to the 0 and 4.5 Hz found by Angyal[15] for the analogous methyl β-D-gluco- and α-L-manno-furanosides, respectively.

The second problem was purification of the 5-*aldehydo* compound (**3**). Compound **3** was prepared at 0° with no excess of periodate, and the iodate precipitated as the insoluble barium salt, but we were unable to remove the formaldehyde which is formed from C-6. Although **3** was formed in excellent yield (as determined by ^{13}C-n.m.r. spectroscopy), all attempts to purify the product and remove the formaldehyde resulted in a multitude of by-products. In one experiment, the solution was lyophilized after precipitating barium iodate; the resulting residue was found by ^{13}C-n.m.r. spectroscopy to contain at least four compounds. Subsequently, we carried out a ^{13}C-n.m.r. DEPT experiment, which distinguishes between methylene carbon atoms (such as those in formaldehyde) and methine carbon atoms (such as sugar carbon atoms other than C-2). The results demonstrated that the formaldehyde had not been removed, and further suggested that a complex had been formed between the formaldehyde and the sugar. In another experiment, an attempt was made to chromatograph the aldehyde (**3**), but this resulted in a water-insoluble product which presumably consisted of a polymer of the sugar.

There are several problems when the 5-*aldehydo* sugar (**3**) is not purified following the periodate reaction. One minor problem is that an impurity that inhibits the hydrogenation then remains. The major problem, however, is that the formaldehyde consumes [^{13}C]cyanide, resulting in the formation of 50 atom % [^{13}C]ethylene glycol, which appears as a by-product in subsequent reactions. Fortunately, this material is readily separated on the final column. However, the additional cyanide required also leads to a decrease in the final yield from a possible 32 to 16%. Another problem is that unreacted methyl 2-deoxy-α-D-*arabino*-hexose (**2**) is carried through the entire series of reactions and leads to a dilution of the label from 99+ atom % to the 93% enrichment observed in the product. Unfortunately, we have not been able to purify the 5-*aldehydo* compound (**3**), which is surprising considering the excellent stability of the analogous compound derived from 1,2-*O*-isopropylidene-α-D-glucofuranose[8].

Because of the low stability of the 5-*aldehydo* compound (**3**), the cold solution was used immediately for the formation of the nitriles. The reaction with $K^{13}CN$ was much more sensitive to alkaline conditions than expected, and so the pH was kept below 7.2, and the reaction was carried out at 0°. The 40-min reaction time allowed us to monitor the reaction by ^{13}C-n.m.r. spectroscopy. We found the nitriles to be stable at this pH and temperature during this reaction time.

Our attempts to reduce the nitriles (**4** and **5**) using palladium-on-barium sulfate as the catalyst[14] were unsuccessful. In order to determine whether the reduction was inhibited by some component in the reaction mixture, we mixed the nitriles (**4** and **5**) with nitriles derived from arabinose, and we found that none of the nitriles were reduced. In a control experiment employing only the nitriles derived from L-arabinose, the reduction proceeded well. It is possible that residual iodate acts as an inhibitor; however, it is difficult to remove final traces without causing degradation of the aldehyde **3**. As a consequence, we reduced the nitriles (**4** and **5**) with palladium-on-carbon as the catalyst although completing the reduction usually required several hours. Furthermore, if the reduction was not carried out at hydrogen pressures below 138 kPa, we obtained excessive amounts of the amines rather than the desired reducing sugars. The mixture (**6** + **7**) derived from the hydrogen reduction of **4** and **5** was shown by ^{13}C-n.m.r. spectroscopy to contain three forms of the labeled dialdo sugars: two (α and β) 3,6-hemiacetal derivatives each of **6** and **7** in which ^{13}C-6 forms a 5-membered ring with C-3, and a free aldehyde which may represent both **6** and **7**.

As expected, the borohydride reduction proceeded satisfactorily, to yield the two labeled isomeric methyl furanosides **8** and **9**. These two compounds are not

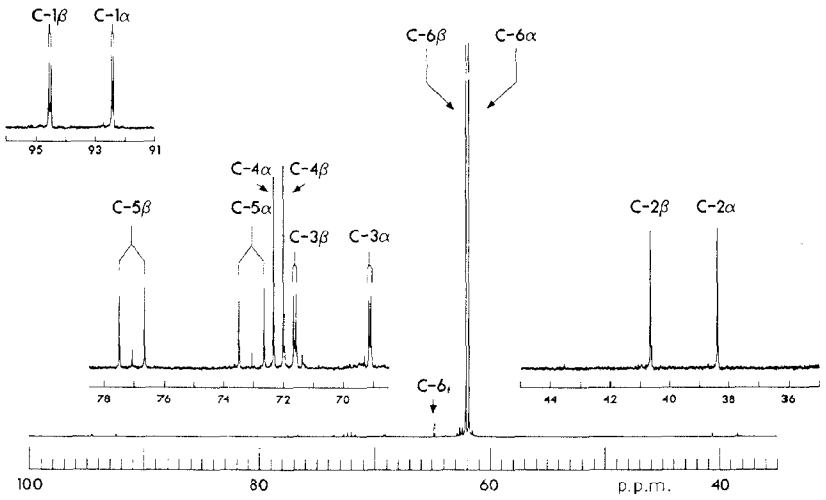


Fig. 2. The ^{13}C-n.m.r. spectrum of 2-deoxy-D-*arabino*-[6-^{13}C]hexose, showing expanded regions of the unenriched carbon atoms. The signal labeled C-6_f represents carbon-6 for the α- and β-furanoses. All of the other labels designate carbon atoms of the α- and β-pyranoses.

TABLE II

^{13}C–^{13}C COUPLING CONSTANTS FOR 2-DEOXY SUGAR DERIVATIVES

Compound	*Coupling constant*[a]			
	$^{1}J_{5,6}$	$^{3}J_{1,6}$	$^{3}J_{3,6}$	$^{2}J_{4,6}$
2-Deoxy-α-D-*arabino*-[6-^{13}C]hexopyranose	43.3	3.3	3.5	[b]
2-Deoxy-β-D-*arabino*-[6-^{13}C]hexopyranose	43.3	4.1	4.2	[b]
Methyl 2-deoxy-α-D-*arabino*-[6-^{13}C]hexofuranoside	41.0	[b]	[b]	[b]
Methyl 2-deoxy-β-L-*xylo*-[6-^{13}C]hexofuranoside	40.5	[b]	[b]	2.9[d]
Methyl 2-deoxy-α-D-*arabino*-[6-^{13}C]hexofuranosidurononitrile[c]	62.2	[b]	1.8[d]	1.8[d]
Methyl 2-deoxy-β-L-*xylo*-[6-^{13}C]hexofuranosidurononitrile[c]	62.2	[b]	1.2[d]	1.8[d]

[a]Coupling constants are in Hz. [b]Coupling not observed. [c]This sample was at pH 4 in water containing acetic acid and D_2O for the lock. [d]This value of the coupling is approximate due to insufficient resolution.

well separated on AG-1 (OH^-) or AG-50 (Ba^{2+} or Ca^{2+}) resins. Therefore, the mixture was hydrolyzed with dilute sulfuric acid, and the desired 2-deoxy-D-*arabino*-[6-^{13}C]hexose (**10**) separated on a column of AG-50 (Ca^{2+}) resin at 65°. The ^{13}C-n.m.r. spectrum of this compound is shown in Fig. 2. 2-Deoxy-L-*xylo*-[6-^{13}C]hexose (**11**), however, could not be well separated from several unidentified by-products, and, for this reason, a ^{13}C-n.m.r. spectrum and a yield are not included.

The ^{13}C-n.m.r. chemical shifts for the 2-deoxy sugars are given in Table I, and the observed ^{13}C–^{13}C coupling constants are given in Table II. In no case did the observed couplings suggest assignments different from those in the literature. The furanose forms of 2-deoxy-D-*arabino*-hexose had not been observed by earlier workers, either by ^{13}C-n.m.r. (ref. 16) or by ^{1}H-n.m.r. spectroscopy[17]. We observed the two pyranose forms in nearly equal amounts, and the two furanose forms, α:β in the ratio of 7:3. The furanose forms are present at only 1.5% of the level of the pyranoses.

ACKNOWLEDGMENTS

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