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SYNTHESIS OF 5-ACETAMIDO-5-DEOXY-D-XYLOPYRANOSE VIA AN OXIME*

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ABSTRACT

A useful preparative route to 5-acetamido-5-deoxy-D-xylopyranose (**1**) is described that starts from 1,2-*O*-isopropylidene-α-D-glucofuranose and proceeds via 1,2-*O*-isopropylidene-D-*xylo*-pentodialdo-1,4-furanose oxime (**4**), to produce **1** in an overall yield of about 50%. The oxime (**4**) is shown to be a mixture of the syn and anti forms, **10** and **9**, respectively. The syn form is unstable and in solution isomerizes to the more stable anti form, which is most likely in the hydrogen-bonded state **12**. The oximes were converted into acetylated derivatives. The acetate of the anti form spontaneously eliminates acetic acid to produce the cyano derivative **8**.

INTRODUCTION

5-Acetamido-5-deoxy-D-xylopyranose (**1**) is an interesting sugar having nitrogen as the ring heteroatom. It would be a useful material in numerous investigations but its yield through existing preparative procedures has varied from 4% to[1] 25%, and tedious chromatographic separation of products has been required. In exploration of an alternative, possibly simpler, route we have started with 1,2-*O*-isopropylidene-α-D-glucofuranose and have obtained **1** in an overall yield of about 50%.

Periodate oxidation of 1,2-*O*-isopropylidene-α-D-glucofuranose gave the "5-aldehyde"[2] **3**, which was converted into the oxime **4** in 80% yield. The oxime could be obtained in the same high yield whether pyridine or sodium acetate was used as catalyst, but the former method gave a product having m.p. 151–152° after one recrystallization, whereas the sodium acetate method gave a product having m.p. 139°, which needed many recrystallizations to raise the m.p. to 151–152°. The melting point increased gradually after each recrystallization, but the products all gave correct analyses for the oxime **4**. In most solvent systems, these products having

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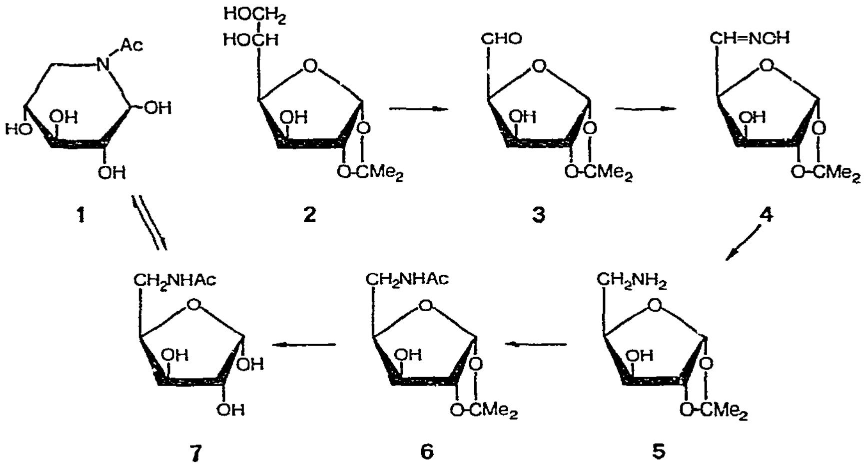
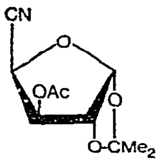
different melting points had the same R_F value and moved as a single spot on silica gel plates, but in solvent system A, two spots, close together, were observed. These observations indicated that the oxime was present in both the syn- and anti-forms, and that the difference in melting point of the products was due to their containing different proportions of the two forms.





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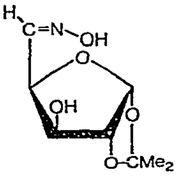

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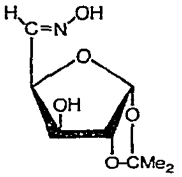

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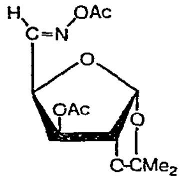

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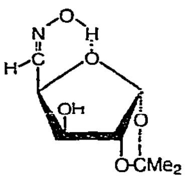

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Although the isomeric oximes could be separated on a thin-layer chromatographic plate in some irrigants, the R_F values in the best irrigant found, (system A), were so close (0.54 and 0.48) that separation, even on plates, was difficult. The oximes isomerized rapidly in solution; a solution in ethanol that gave two distinct, well separated spots immediately after dissolving the oxime, showed after 10 min only one intense spot, followed by a faint tail. Separation on thick-layer plates yielded the pure isomer having R_F 0.54, m.p. 151–152°. However, rechromatography of the second product (R_F 0.48) always produced some of the isomer having R_F 0.54. Little of the fast-moving isomer could be obtained unless the oxime mixture produced initially was rapidly separated. This indicated that isomerization to the more stable isomer (R_F 0.54) occurred at room temperature but that the isomerization did not proceed in the reverse direction, at least not at a detectable rate. Isomerization of oximes in solution has been observed before[3].

Since characterization of oximes via their acetates is a usual procedure, and since trial experiments indicated that acetylation gave products that had reasonably different chromatographic mobilities, the oxime mixture was acetylated with acetic anhydride and pyridine. After acetylation for 5 min in the cold, the mixture gave eight spots on a silica gel plate (irrigant B). This result could be explained by acetylation, in each of the two forms (syn and anti) of both or either of the hydroxyl groups on C-3 and the oxime to give six products; the other two spots were the two unreacted oximes. After refluxing the acetylation mixture for 1 h, t.l.c. with irrigant system B showed only two components, an intense spot having R_F 0.72 and another fainter spot having R_F 0.36. Separation of these acetyl derivatives on a column of silica gel gave mainly the compound having R_F 0.72, with only small amounts of the other component (R_F 0.36).

These acetates could be related to the individual oximes by acetylation of the chromatographically separated oximes. The oxime having R_F 0.54 gave the acetate having R_F 0.72, and the oxime R_F 0.48 gave the acetate R_F 0.36.

The major product of the acetylation (R_F 0.72) gave analyses for $C_{10}H_{13}NO_5$ and gave, in addition to a strong i.r. absorption for an acetate grouping, weak absorption at 2260 cm^{-1}, indicating the presence of a cyanide group. The evidence suggested that this acetate had the structure **8**, and this structure was confirmed by the n.m.r. spectrum, which showed the H-1, H-2, H-3, and H-4 signals as doublets at τ 4.00, 5.39, 4.55, and 5.03, respectively. This n.m.r. spectrum has been discussed by Pachler and Wessels[4]. The spectra indicate that acetylation of the oxime having R_F 0.54 was accompanied by loss of acetic acid to give the nitrile. This type of reaction is known to be a *trans*-elimination, and to be given by the acetates of the anti-isomers of oximes. The oxime having R_F 0.54 is thus identified as the anti-isomer (**9**), and hence the oxime having R_F 0.48 must be the syn-isomer (**10**). This latter conclusion was proved correct with the acetate of R_F 0.36 chromatographically separated. It showed no cyanide absorption and reverted on treatment with sodium hydroxide to the oxime having R_F 0.48, although a very small proportion of the oxime of R_F 0.54 was also produced. The latter, as shown above, was most probably formed by isomerization of the former oxime during the extraction and working up process. The acetate having R_F 0.36 must thus be the syn diacetate (**11**).

It can be concluded that the anti-oxime (**9**) is the stable isomer. The labile syn-form was not obtained pure, as it was always mixed with some anti-form. It was a very minor constituent when the pyridine method of acetylation was used, and was present in slightly larger proportion when the sodium acetate method was used.

The great difference in the stability of the two isomers can be attributed to the ability of the anti-isomer to form hydrogen bonds between the hydroxyl hydrogen atom of the oxime and the ring oxygen atom (structure **12**), whereas syn-isomer cannot. The i.r. spectrum clearly indicates strong intramolecular hydrogen-bonding of one hydroxyl group (3350 cm^{-1}, broad), whereas the other hydroxyl group on C-3 gives a sharp band at 3650 cm^{-1}.

Various methods of reduction of oximes to amines are known. Three types of reduction were investigated; (*i*) aluminum amalgam in water, (*ii*) catalytic reduction with palladium on charcoal, or with Raney nickel and (*iii*) lithium aluminum hydride The last method gave the amine in purest state and in highest (80%) yield. Thin-layer chromatography showed the amine to be the same as that prepared by the method of Szarek and Jones[5], although these authors did not isolate the amine. The amine **5** has previously been prepared[6] by reduction of the phenylhydrazone of the "aldehyde" **3**.

Selective acetylation[5] of the amine yielded the acetamido derivative (**6**). Removal of the isopropylidene group was first attempted by the partial hydrolysis procedure with acetic acid[5], but hydrolysis was incomplete after 1.5 h and even after 36 h at 80° some starting material was present. When, however, an aqueous solution of the acetamido derivative (**6**) was treated with Amberlite IR-120 (H^+) resin at 60°, hydrolysis of the isopropylidene groups was complete in 1 h, no decomposition was evident, and the product was obtained in 65% yield. When the alcoholic filtrate, with the isomeric acetamido derivative **7** as its main constituent, was evaporated to dryness, taken up in water and heated for 30 min with Amberlite IR-120 (H^+) resin, the equilibrium reported[5] between compounds **1** and **7** was achieved. More of compound **1** was obtained on working up this solution as before. Repeating this procedure gave a 79% yield of compound **1** which, after one recrystallization had m.p. 157–158°, and was shown to be identical with the product prepared by the method of Szarek and Jones[5].

EXPERIMENTAL

General. — All i.r. spectra were obtained with a Perkin-Elmer spectrophotometer model 237G, and the n.m.r. spectra with a Varian A-60 spectrometer. Thin-layer chromatography was effected with "Silica Gel G nach Stahl (Merck)", and the column chromatography on "Silica Gel for chromatography" by May & Baker.

All solvents used were of analytical quality. The irrigants for chromatography were: A. 1:1 (v/v) acetone–ethyl acetate; B. 5:1 (v/v) chloroform–ethyl acetate; C. butanol saturated with water; D. 5:3:2 (v/v) chloroform–ethyl acetate–ethanol.

*1,2-O-Isopropylidene-α-*D-xylo*-pentodialdo-1,4-furanose oxime* (**4**). — To a solution of 1,2-*O*-isopropylidene-D-glucofuranose[7] (**2**) (69.5 g) in water (900 ml) was added sodium metaperiodate (79 g) and the solution was kept for 4 h at 20°. The solution was concentrated at a temperature not exceeding 30°, and then further concentrated to a thick syrup on a rotary evaporator at less than 50°. The solid and syrup so obtained were well extracted with several portions of chloroform (total 350 ml). The dried (Na_2SO_4) extract was evaporated to a thick syrup (59 g) that showed essentially one spot by t.l.c. and the product was used without further purification. The syrup was dissolved in water (500 ml), sodium acetate (116 g) and hydroxylamine hydrochloride (58 g) were added, and the mixture was heated for 4 h under reflux. The solution was then concentrated to 100 ml, whereupon some oxime crystallized on cooling. After filtration of the mixture the filtrate was extracted with ethyl acetate (3 x 100 ml), and the dried (Na_2SO_4) extract was evaporated to give more oxime. The combined crops of oxime were recrystallized from ethyl acetate–petroleum ether (b.p. 65–67°) to give the oxime **4** (yield 53 g), m.p. 139°. Recrystallization from ethyl acetate gave colorless needles, m.p. 141–142°. Repeated recrystallization from ethyl acetate raised the m.p. steadily to 151–152°.

When the "aldehyde" **3** (20 g), hydroxylamine hydrochloride (20 g), ethanol (22 ml), and pyridine (120 ml) were heated under reflux for 1.5 h and the solvent evaporated, a thick syrup was obtained. This was dissolved in water (40 ml) and extracted with ethyl acetate (3 x 75 ml). The dried (Na_2SO_4) extract was evaporated to give a thick syrup, which soon crystallized to the colorless oxime (24.1 g) m.p. 149–151°. Recrystallization from a mixture of ethyl acetate and petroleum ether (b.p. 65–67°) yielded the oxime as colorless needles, m.p. 151–152°.

The product from the sodium acetate method after one recrystallization, m.p. 141–142°, and the product from the pyridine method after one recrystallization, m.p. 151–152° had the same R_F value in irrigant C, but had R_F 0.54 and R_F 0.48, respectively, in irrigant A, the faster-moving spot being the major product in both cases. Although the product having m.p. 151–152° showed only a small proportion of the slower-moving component and the product of m.p. 141–142° appreciable amounts, both products gave correct analyses for the oxime. Separation of the two components on thick-layer plates (irrigant A) gave *anti*-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose oxime (**9**) as colorless needles, m.p. 151–152°, which moved as a single component (silica gel, irrigant A) at R_F 0.5; ν_{max} (chloroform solution) 3578 cm (s), 3340 cm^{-1} (s) (broad). The ν_{max} (Nujol) showed only one peak, at 3400 cm^{-1} as a broad band, with weak absorptions at 3080 and 2700 cm^{-1}.

Anal. Calc.: for $C_8H_{13}NO_5$: C. 47.2; H, 6.4; N, 6.9. Found: C, 47.2; H, 6.6; N, 6.7.

The slower-moving component extracted from the silica gel, although mainly the product having R_F 0.48, was still a mixture of both components, and repeated separation on thick-layer plates did not produce the compound pure. The longer the extraction process, the more of the component having R_F 0.54 was present in the mixture.

Reduction of the oxime **4**. — *A. Catalytic hydrogenation.* A solution of the oxime **4** (1 g) in ethanol (100 ml) was added to 3 g of palladium-on-charcoal (5%) and shaken at 25° with hydrogen at 3 atm. pressure. After 12 h, t.l.c. showed that some oxime was still present, but after 22 h it was absent. Filtration of the mixture and evaporation of the ethanol yielded a thick syrup (0.83 g), which contained the amine **5** as one of the major constituents, but was mixed with three other products. The amine crystallized in the syrup, but could not be separated easily.

Use of Raney nickel as catalyst under the same conditions gave similar results.

B. Reduction with lithium aluminum hydride. To the oxime **4** (10 g) in dry tetrahydrofuran (80 ml) was slowly added, under anhydrous conditions and with stirring, lithium aluminum hydride (4.2 g) in tetrahydrofuran (150 ml). The solution was refluxed for 2 h, and the product was then carefully decomposed with water. The mixture was filtered with the aid of Celite, and the filter cake washed well with tetrahydrofuran. Removal of the solvent left a thick syrup, which crystallized to give a colorless solid (7.8 g, 84%) m.p. 99–100°. T.l.c. in irrigant D showed it to be almost pure, with a minor proportion of another faster-moving component. Recrystallization gave the pure amine **5** as colorless crystals, m.p. 105–106°; ν_{max} (Nujol) 3330 (strong), 3282 (strong), 1622 cm^{-1} (moderate to strong), and hydrogen-bonded OH stretching as a broad band from 3200–2400 cm^{-1}.

Anal. Calc.: for $C_8H_{15}NO_4$: C, 50.8; H, 7.9; N, 7.4. Found: C, 50.5; H, 7.9; N, 7.2.

*Hydrolysis of 5-acetamido-5-deoxy-1,2-O-isopropylidene-α-*D*-xylose* (**6**). — The acetamido compound **6** (10 g), prepared from the amine (**5**), by the method of Jones and Szarek[2], was dissolved in water (70 ml). Amberlite IR-120 (H^+) resin (45 ml slurry in water) was added, and the flask containing the mixture was slowly rotated in a bath at 60°. After 45 min t.l.c. showed that no more starting material was present. The mixture was filtered, the resin washed with water (100 ml), and the filtrate concentrated under diminished pressure at 50° to a thick syrup. Ethanol (30 ml) was added and again evaporated until a white, opaque froth was obtained. Ethanol (5 ml) was added until solution was barely attained, whereupon crystallization occurred. Ethanol (3 ml) was added and the mixture was filtered. The crystals were washed with cold, anhydrous ethanol (20 ml) to yield **1** (5.35 g, 65%). The alcoholic filtrate was evaporated to dryness, water (25 ml) was added, and the solution was again treated with Amberlite IR-120 (H^+) resin (10 ml slurry) for 30 min at 60° to isomerize the acetamido derivative **7** to the required product **1**. On repeating the previous procedure of working up the solution, more product **1** (0.86 g) was obtained. Repeating the procedure again gave a further (0.27 g) of **1**, giving a total yield of 6.48 g (78.5%) of compound **1** as colorless crystals, m.p. 152–153°. Heating the crystals in boiling ethanol, in which it is only sparingly soluble, filtering and washing with boiling ethanol, raised the m.p. to 157–158° and gave a product identical (chromatographically, and spectroscopically) with the compound **1** as prepared by the method of Jones and Szarek[2].

Acetylation of oxime **4**. — The oxime **4** (4.00 g), dry pyridine (12 ml), and acetic anhydride (8 ml) were mixed and shaken. After 5 min t.l.c. (irrigant *B*) showed eight spots, of which the slowest moving two spots corresponded to the unchanged oximes. Refluxing the mixture for 4 h produced a mixture of three products, a fast-moving, major component (R_F 0.72) a slower-moving, minor component R_F, 0.36, and a slower-moving, trace component.

Similar acetylation of the chromatographically separated anti-oxime (R_F 0.54 m.p. 151–152°) gave only the one acetate, R_F 0.72 after 1 h. The other oxime obtained from the chromatographic separation, which was largely the isomer having R_F 0.48

and a small proportion of the anti-oxime, gave under similar conditions of acetylation a mixture of two acetates, the major product being the slower-moving component (R_F 0.36) and a minor component (R_F 0.72).

Separation of the products from acetylation of the oximes. — The mixture of acetates was separated on a column of silica gel with irrigant B as eluting solvent.

*3-*O*-Acetyl-4-*O*-cyano-1,2-*O*-isopropylidene-α-*D-xylo*-tetrafuranose* (**8**).— The faster-moving, major component was obtained as a syrup on evaporating the solvent, and crystallized when kept for a few days. Recrystallization from water, with charcoaling, gave colorless crystals which were dried in a vacuum desiccator over paraffin wax and solid sodium hydroxide. The product moved a as single spot in all irrigants tried, and had R_F 0.72 in irrigant B. The crystals (4.0 g) had m.p. 50–52°; i.r. 3040 (moderate), 2260 (weak), 1756 (strong), 1388 (moderate to strong), 1166 (moderate), 1063 (strong), 1018 (strong), and medium peaks at 950, 900, 883, 862, 846 cm^{-1}; n.m.r.[4] (CDCl$_3$): τ 4.04 (d, 1, $J_{1,2}$ 3.6 Hz, H-1), 4.55 (basically d, 1, $J_{3;4}$ 3.4 Hz, H-3), 5.03 (bascically d, 1, H-4), 5.39 (basically d, 1, H-2), 7.84 (s, 3, Ac), 8.68 and 8.50 (each s, 3, CMe$_2$).

Anal. Calc.: for $C_{10}H_{13}NO_5$: C, 52.8; H, 5.7; N, 6.2. Found: C, 52.9; H. 5.9; N, 6.5.

*3,*N*-Di-*O*-acetyl-1,2-*O*-isopropylidene-α-*D-xylo*-pentodialdo-1,4-furanose oxime* (**11**). — The second component (R_F 0.36) was obtained as a syrup, moved as a single spot on t.l.c. and although the analysis indicated that it was compound **11** the values were not satisfactory for complete characterization.

Alkaline treatment of compounds **8** *and* **11**. — Compounds **8** and **11** were separately dissolved in the minimum of 2M sodium hydroxide with gentle warming and the solutions were saturated with carbon dioxide by addition of Dry Ice. T.l.c. (irrigant A) showed that the acetate (R_F 0.36) expected to be **11**, had reverted to the syn-oxime, R_F 0.48, but the product contained a minor proportion of the anti-oxime R_F 0.54 (most likely arising from isomerization). The product from compound **8** remained at the origin in both irrigants A and B, showing that the oxime was not regenerated. A solution of the product in chloroform gave no cyanide peak in the i.r. spectrum, which may indicate hydrolysis of the nitrile or quenching by the oxygen atoms in the molecule.

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