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Allylic Displacement Reactions of a 2-Acetamido-D-glucal Derivative with Acids and Phenols*

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Fusion of 3,4,6-tri-*O*-acetyl-2-(*N*-acetylacetamido)-1,2-dideoxy--D-*arabino*-hex-1-enopyranose [I, 2-(*N*-acetylacetamido)-D-glucal triacetate] with various acids and phenols in the presence of a trace of *p*-toluenesulfonic acid causes loss of the acetoxy group at C-3, shift of the double bond to the C-2—C-3 position, and entry of an acyloxy or aryloxy group at C-1 to give esters and glycosides, respectively, of 4,6-di-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranose (compounds III, V, VI, and VII). In each case, the main product is accompanied by 1,4,6-tri-*O*--acetyl-2- (*N*-acetylacetamido) -2,3-dideoxy-α-D-*erythro*-hex-2-enopyranose (IV), a substance which is found to be readily accessible through the deliberate rearrangement of I under acidic conditions. While IV reacts with benzoic acid when boiled in benzene solution containing hydrogen chloride, I is recovered unchanged after treatment in this fashion. On the basis of these facts, a mechanism for the acid-catalyzed reaction of I with carboxylic acids and phenols is proposed.

An improved preparation of I from 2-acetamido-2-deoxy-D-mannose *via* 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-mannopyranose (II) is described.

Phenyl 4,6-di-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy-α-D--*erythro*-hex-2-enopyranoside (VI) may be reduced by catalytic hydrogenation to the corresponding cyclohexyl glycoside (VIII), the double bond remaining unaffected.

The reactions of acetylated glycals and of acetylated hydroxyglycals with alcohols[1–3], phenols[1,4], and acids[4–8] have been studied extensively. While acetylated glycals normally show simple addition reactions in the presence of an acid catalyst,** they undergo displacement reactions under neutral conditions to give 2,3-unsaturated derivatives[9]. The acetates of 2-hydroxyglycals, on the other hand, yield the products of allylic rearrangement either in the presence

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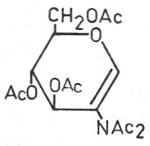
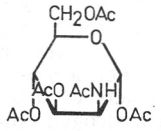
** It should be noted, however, that 3-halo-2,3-dideoxy-aldose derivatives have been isolated subsequent to the treatment of acetylated glycals with hydrogen halides; this fact seems best rationalized by assuming the intermediacy of a 2,3-unsaturated compound. [see T. Maki and S. Tejima, *Chem. Pharm. Bull.* (Tokyo) **15** (1967) 1069; K. Bock, I. Lundt, and C. Pedersen, *Acta Chem. Scand.* **23** (1969) 2083, and ref. 3 of this paper.]

or in the absence of a catalyst[5,7]. Representatives of a new class of unsaturated sugar derivative, the 2-acetamidoglycals, were recently described[10,11] and it is therefore of interest to investigate the behavior of these compounds with various nucleophiles. We shall describe here some reactions of 3,4,6-tri-*O*-acetyl-2-(*N*-acetylacetamido)-1,2-dideoxy-D-*arabino*-hex-1-enopyranose (I) with some carboxylic acids and phenols in the presence of an acidic catalyst.

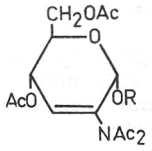
As a preliminary part of this investigation we initially turned our attention to the problem of improving the yield of I. In an earlier study[10], this substance had been made in 14% yield through treatment of 2-acetamido-2-deoxy-D-mannose with isopropenyl acetate—*p*-toluenesulfonic acid. A subsequent investigation[12] of the mechanism of the formation of I revealed 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-mannopyranose (II) to be the immediate precursor of I. We have now found that a mixture rich in II can be prepared in high yield by the acetylation of 2-acetamido-2-deoxy-D-mannose with acetic anhydride—zinc chloride. Isolation of pure II from the mixture by column chromatography on silica gel is possible but entails substantial losses as II appears to decompose in large part to 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-mannopyranose during the chromatography. However, direct treatment of the crude II with isopropenyl acetate—*p*-toluenesulfonic acid as described earlier[12] readily afforded I in a yield (based on 2-acetamido-2-deoxy-D-mannose) of 57—62%. This two-step procedure represents the most



I



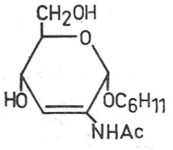
II



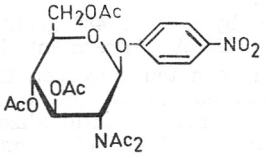
III R = $-COC_6H_5$ VI R = $-C_6H_5$

IV R = $-Ac$ VII R = $-C_6H_4-NO_2$ (p-)

V R = $-COCH_2C_6H_5$ VIII R = $-C_6H_{11}$



IX



X

convenient preparation of I and makes this unusual carbohydrate enamine comparatively accessible for further investigation.

Attention was now turned to a study of the behavior of I with benzoic and phenylacetic acids as well as with phenol and *p*-nitrophenol. For these reactions, the presence of a strong acid catalyst, *p*-toluenesulfonic acid, proved to be necessary for, without it, even benzoic acid failed to attack I. Under conditions which cause hydroxylic compounds to add to 3,4,6-tri-*O*-acetyl-D-galactal[13], fusion of I with each of the nucleophiles mentioned afforded at least four products which could be separated by repeated chromatography on columns of silica gel. The major products from each of the four fusion reactions were obtained in yields varying from 20 to 73%. The general features of the NMR spectra of these compounds included signals from two *N*-acetyl groups and two O-acetyl groups; in addition, the presence of two one-proton signals at low field, and aromatic proton signals clearly showed that the products had been formed by allylic displacement of the 3-acetoxy group and thus contained a C-2—C-3 double bond as shown in formulas III, V, VI, and VII. These products (as well as other 2,3-unsaturated compounds of this series encountered in this research) were dextrorotatory but this fact cannot safely be made the basis for the assignment of anomeric configurations owing to the rotational anomalies which have been observed with the dideoxyaldenoses[5,3]. Recourse was then had to a more detailed examination of the NMR spectra of the compounds (Table I). As an example, the spectrum of the product (III), obtained through

TABLE I

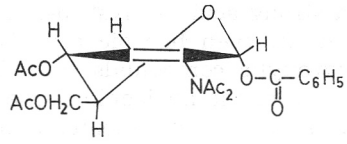
Assignments in the NMR Spectra of Acetylated 2-(N-*acetylacetamido*)-2,3-*dideoxy* D-erythro-*hex-2-enopyranose Derivatives*

No.	Chemical shifts (τ values)					Coupling consts. (Hz)	
	H-1[a]	H-3[b]	H-4[c]	NAc	OAc	$J_{3,4}$	$J_{4,5}$
III	3.33	3.89	4.41	7.60 (6H)	7.89, 8.00	2.1	9.5
IV	3.60	3.95	4.40	7.62 (6H)	7.90, 7.91	2.0	~ 8.5
V	3.56	4.00	4.50	7.81 (6H)	7.94, 8.00	2.0	~ 9
VI	4.20	3.93	4.40	7.53 (6H)	7.88, 8.04	2.0	~ 9
VII	4.10	3.88	4.40	7.51 (6H)	7.86, 8.04	2.2	~ 9
VIII	4.79	4.15	4.52	7.59 (6H)	7.90 (6H)	2.0	~ 8.5

[a] Narrow doublet, long range coupling $J_{1,4} = 1.0$ Hz, is given only for the compound III from the spectrum taken on a 100 MHz instrument; [b] doublet; [c] octet.

the fusion of I with benzoic acid, will be discussed in some detail. Here, the lowest-field signal (τ 3.33) showing a narrow splitting of 1.0 Hz, is assigned to H-1. Irradiation of H-1 deleted the smallest splitting in the octet at τ 4.41, indicating homoallylic coupling[14] between H-1 and H-4. Irradiation of H-4 changed the H-1 signal to a singlet and also caused the H-3 doublet of 2.1 Hz, centered at τ 3.89, to collapse to a singlet. The large coupling of 9.5 Hz ($J_{4,5}$) found in the H-4 octet is indicative of the *quasi*-axial—axial orientation of H-4 and H-5. The values for both $J_{3,4}$ (2.1 Hz) and $J_{4,5}$ (9.5 Hz) are fully consistent with the *H1* half-chair conformation[15] as depicted in formula XI. Couplings of similar magnitude have been observed in the NMR spectra of many 2,3-unsaturated aldose derivatives having the α-D configuration[5,7,15-19];

these exist in the *H1* conformation while the spectra of the corresponding β-D anomers[3,15,18] show them to take the *1H* conformation. The preference of of the α-D anomers for the *H1* conformation may be attributed[18] to the ano-



XI

meric effect[20] as this conformation places the C-1 substituent in these anomers in the *quasi*-axial orientation. The NMR spectral data from the other 2,3-unsaturated compounds, presented in Table I, are clearly consistent with the *H1* conformation and we therefore assign the α-D anomeric configuration to these structures. In passing, it may be noted that the compounds with an ester linkage at C-1 (III—V) give a signal for H-1 at lower field (τ 3.33—3.60) than those compounds with a glycosidic bond (VI—VIII, τ 4.10—4.79); this, of course, is the normal consequence of the difference in deshielding afforded by the two types of groups.

Column chromatography of the crude reaction mixtures from the acid-catalyzed condensation of I with each of the four nucleophiles investigated yielded a fast-running compound which although isolated in crystalline form proved to be unstable. It was obtained in such small quantity that was not characterized. More significantly, each condensation yielded a substantial quantity of a crystalline product having an elemental composition and an NMR spectrum which showed it to be an isomer of I. The general features of its NMR spectrum (Table I) closely resembled those of the main products of nucleophilic attack and the substance is, therefore, designated as 1,4,6-tri-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranose (IV). Further elution of the columns led to the isolation of several compounds which proved to be 2-acetamido derivatives, derived, presumably, through loss of one of the *N*-acetyl groups either from one of the major products or from IV.

The isolation of compound IV in these condensations leads naturally to consideration of the detailed aspects of these nucleophilic reactions. In a recent discussion of the allylic displacement of the C-3 acetoxy group of glycals, Ferrier and Prasad[2] considered an initial isomerization, followed by attack of a nucleophile at C-1, as more plausible than an alternative proposal[21] which invokes initial attack of the C-6 oxygen on C-1. If the mechanism preferred by Ferrier and Prasad is, indeed, the actual one and if the present case constitutes a valid analogy, compound IV may be an intermediate in the formation of III, V, VI, and VII. The deliberate rearrangement of I to IV, either by fusion of I with a trace of *p*-toluenesulfonic acid or through the action of acetic anhydride—zinc chloride, proved to be a simple matter. The latter combination of reagents was used by Lemieux *et al.*[22] for the analogous isomerization of 2,3,4,6-tetra-*O*-acetyl-1-deoxy-D-*arabino*-hex-1-enopyranose to 1,2,4,6-tetra-*O*-acetyl-3-deoxy-α-D-*erythro*-hex-2-enopyranose.

With IV thus readily accessible, its possible role in the conversion of I into III and into VII was investigated. Treatment of IV with benzoic acid and

with *p*-nitrophenol in the presence of *p*-toluenesulfonic acid afforded III and VII in 31 and 51% yields, respectively. Under much milder reaction conditions —boiling benzene containing 2% of hydrogen chloride — IV also reacts with benzoic acid to give III while I is recovered unchanged (in 62% yield) after exposure to these reaction conditions. These experiments are viewed as providing strong support for a mechanism analogous to that suggested for the behavior of the acetylated glycals on nucleophilic attack[2]. We may envisage I as rearranging initially to 1,4,6-tri-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy-β-D-*erythro*-hex-2-enopyranose which then isomerizes to the more stable anomer, IV; finally, the C-1 acetoxy group in IV is displaced by the nucleophile. While this (and/or some minor variation of it) may indeed represent the main pathway of the reaction, the occurrence of direct addition to the double bond as a minor concurrent reaction is not excluded. The condensation of I with *p*-nitrophenol gave a crude product containing a number of chromatographically detectable components in addition to VII and it was thought possible that a product of direct addition, such as *p*-nitrophenyl 3,4,6-tri-*O*-acetyl-2-(*N*-acetylacetamido)--2-deoxy-β-D-glucopyranoside (X) might be one of these. Compound X was therefore synthesized through the action of isopropenyl acetate—*p*-toluenesulfonic acid on the known *p*-nitrophenyl 2-acetamido-3,4,6-tri-*O*-acetyl-2--deoxy-β-D-glucopyranoside[23]; it was found, however, to be readily distinguishable chromatographically (TLC) from all of the products in the reaction mixture from the fusion of I with *p*-nitrophenol. While this experiment constitutes purely negative evidence that direct addition to the 1,2 double bond does not take place, it may be noted that protonation at C-2 is regarded as the first step in such additions to glycals[1] and that the presence of an acetoxy group or an *N*-acetylacetamido group might reasonably be expected to inhibit such a protonation.

In the course of the research described here, phenyl 4,6-di-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (VI) in glacial acetic acid solution was subjected to the action of hydrogen in the presence of a platinum catalyst. After three molar equivalents of hydrogen had been absorbed, a crystalline product was obtained in 55% yield; its infrared spectrum showed the absence of an aromatic ring while the NMR spectrum (Table I) revealed a vinyl proton, two *N*-acetyl groups, and two *O*-acetyl groups, showing that the sugar moiety had not been changed. The product is, therefore, cyclohexyl 4,6-di-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy-α--D-*erythro*-hex-2-enopyranoside (VIII); treatment of it with sodium methoxide removed the two *O*-acetyl groups and one of the *N*-acetyl groups to give cyclohexyl 2-acetamido-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (IX). While IX was levorotatory, there is no reason to believe that the α-D anomeric configuration of VIII (clearly evident from its NMR spectrum) was not retained in IX. The reduction of a phenyl glycoside to a cyclohexyl glycoside by hydrogen in the presence of noble metal catalyst has long been known[24] but the resistance of the double bond in VI to reduction under these conditions is worthy of note. It may be recalled that earlier efforts[10] to reduce I were without success and it is possible that two *N*-acyl groups in a cyclic enamine may constitute a steric barrier, effectively preventing approach of these molecules to a catalyst surface.

EXPERIMENTAL

Melting points are uncorrected. Thin layer chromatography was conducted on silica gel G (E. Merck) using the solvent system specified, the components being detected by spraying with 10% sulfuric acid and heating at 100°. Column chromatography was carried out on silica gel (0.05—0.2 mm., E. Merck). Infrared spectra were obtained in KBr disks using a Perkin-Elmer Model 137 spectrometer. Unless otherwise specified, the NMR spectra were taken in chloroform-*d* solution using a Varian A-60*A* spectrometer and tetramethylsilane as an internal standard. Specific rotations were measured at 20—23° in chloroform unless otherwise stated.

2-Acetamido-1,3,4,6-tetra-O-*acetyl-2-deoxy*-α-D-*mannopyranose* (II)

A. — A solution of 2-acetamido-2-deoxy-D-mannose monohydrate (1.0 g.) in acetic anhydride (5 ml.) containing freshly fused zinc chloride (1.0 g.) was stirred and heated at 60—65° (bath) for 24 hr. The deeply colored mixture was then poured onto crushed ice and sodium bicarbonate was added in portions until the *p*H of the solution was *ca.* 7. The product was extracted with chloroform and the combined extracts were washed successively with water, saturated sodium bicarbonate solution and water. Moisture was removed with sodium sulfate and the solution was concentrated *in vacuo* to give the product as a stable foam which was dissolved in ethanol and decolorized with charcoal. The solvent was evaporated, leaving the crude product (1.31 g., 80%); it was then chomatographed on a column of silica gel (40 g.) using benzene-ether-methanol (5 : 5 : 1, v/v) as eluent and collecting the eluate in 4-ml. portions. Fractions 20—22 contained analytically pure 2-acetamido-1,3,4,6-tetra-O-acetyl-2-deoxy-α-D-mannopyranose (211 mg., 13%) which was obtained in the form of a colorless foam: $[\alpha]_D$ + 63.9° (*c* 0.78); NMR signals were noted at τ 3.98 (doublet, 2.0 Hz, H-1), 7.83 (axial OAc)[25], 7.90, 7.93 (6H), and 8.00 (OAc and NAc). The H-1 signal for the β-D anomer[26,27] at τ 4.12 was absent.

Anal. $C_{16}H_{23}NO_{10}$ (389.37) calc'd.: C 49.36; H 5.95; N 3.60%
found: C 49.18; H 6.24; N 3.59%

Fractions 23—32 contained material (917 mg.) which was chromatographically indistinguishable from an authentic sample of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-D-mannopyranose[27].

B. — 2-Acetamido-2-deoxy-D-mannopyranose monohydrate was acetylated on a 3-g. scale with acetic anhydride in the presence of zinc chloride as described above, except that the reaction was conducted at 50—55° (bath). The crude product was obtained in the form of a stable, lightly colored foam (4.45—4.85 g., 91—99%), showing $[\alpha]_D$ in the range from + 38 to + 46°. After D_2O exchange, the NMR spectrum of the product included two low-field doublets centered at τ 3.98 and 4.12; the relative intensities of these two signals indicated that the ratio of α to β anomers was approximately 5 : 1.

3,4,6-Tri-O-*acetyl-2-*(N-*acetylacetamido*)-*1,2-dideoxy*-D-arabino-*hex-1-enopyranose* (I)

A solution of crude II (2.0 g., prepared as described in *B*, above) in isopropenyl acetate (40 ml.) containing *p*-toluenesulfonic acid monohydrate (60 mg.) was boiled under reflux for 24 hr. The solvent was evaporated *in vacuo* and the residue was chromatographed on a column of silica gel (85 g.) using ether and collecting the eluate in 10-ml. portions. Fractions 21 to 24 contained compound I, contaminated with a slightly faster-moving product (172 mg.) while fractions 25—42 yielded pure I (1.06 g., 56%) on evaporation. From other fractions an additional crop of I was obtained after recrystallization: total yield 63%. Crystallized from ethanol, the substance showed m. p. 95—96°. Its infrared and NMR spectra were identical with those of I reported in the earlier study[10].

Reaction of I with Benzoic Acid

A mixture of I (0.5 g.), benzoic acid (0.33 g.), and *p*-toluenesulfonic acid monohydrate (50 mg.) was finely powdered and then heated at 85° (bath) *in vacuo* (*ca.* 20 mm. of Hg) for 10 min. Examination of the reaction mixture by TLC (ether) showed the presence of at least four componets. The cooled mixture was dissolved

in chloroform (50 ml.) and the solution was washed with cold 1 *N* sodium hydroxide and with water. Moisture was removed with sodium sulfate and the solvent was evaporated *in vacuo,* leaving a syrupy residue, which was chromatographed on a column of silica gel (80 g.), using ether and collecting 5-ml portions of eluate. Fractions 23—26 contained a crystalline product (40 mg.) which was not identified. Fractions 27—36 were pooled and concentrated to give *4,6-di-*O*-acetyl-2-(*N*-acetylacetamido)-1-*O*-benzoyl-2,3-dideoxy-*α*-*D*-*erythro*-hex-2-enopyranose* (III, 181 mg., 31%) which was recrystallized from ethanol: m. p. 142—143°, $[\alpha]_D$ + 36.1° (*c* 1.25).

Anal. $C_{21}H_{23}NO_9$ (433.42) calc'd: C 58.20; H 5.35; N 3.23%
found: C 58.23; H 5.12; N 3.16%

The IR spectrum of the compound showed absorption at 1750 (OAC) and 1740 (NAc), 1700 (C=C), 730 and 705 $cm.^{-1}$ (aromatic).

Fractions 37—55 yielded a colorless syrup (119 mg.) which was rechromatographed using the same solvent. From ethanol solution, crystals (10 mg.) of *1,4,6-tri-*O*-acetyl-2-(*N*-acetylacetamido)-α-D-erythro-hex-2-enopyranose* (IV) were obtained: m. p. 92—93°, $[\alpha]_D$ + 22.3° (*c* 0.55). A mixed m. p. with its isomer, I, was depressed.

Anal. $C_{16}H_{21}NO_9$ (371.36) calc'd.: C 51.75; H 5.70; N 3.77%
found: C 51.83; H 5.73; N 3.99%

The infrared spectrum of the compound showed absorption at 1750 (OAc), 1725 (NAc), and 1700 $cm.^{-1}$ (C=C).

Reaction of I with Phenylacetic Acid

A finely powdered mixture of I (0.5 g.), phenylacetic acid (0.55 g.), and *p*-toluenesulfonic acid monohydrate (50 mg.) was heated *in vacuo* at 75° for 10 min. The dark product was dissolved in chloroform (50 ml.) and the solution was washed with *1N* sodium hydroxide solution and with water and then dried with sodium sulfate. The syrup obtained on removal of the solvent was chromatographed on a column of silica gel (80 g.) using ether as eluent and collecting 5-ml. portions of eluate.

Fractions 35—50 contained the major product, *4,6-di-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy-1-*O*-phenylacetyl-α-D-erythro-hex-2-enopyranose* (V), which was obtained in the form of a colorless syrup (440 mg., 73%); it was rechromatographed using the same solvent. Chromatographically homogeneous fractions were evaporated and the residue dried *in vacuo* at 40°: $[\alpha]_D$ + 15.8° (*c.* 1.26).

Anal. $C_{22}H_{25}NO_9$ (447.45) calc'd.: C 59.05; H 5.63; N 3.13%
found: C 58.77; H 5.77; N 3.23%

The compound showed infrared absorption (neat) at 1750 (OAc and NAc), 1620 (C=C), and 1510 $cm.^{-1}$ (aromatic).

Fractions 51—60 contained a mixture of IV and V (95 mg.). Fractions 61—66 contained foamy material (22 mg.); its chromatographic behavior in several solvent systems identified it as pure IV.

Reaction of I with Phenol

A mixture of I (0.5 g.), phenol (0.5 g.), and *p*-toluenesulfonic acid monohydrate (50 mg.) was heated at 100° (bath) *in vacuo* (*ca.* 20 mm. of Hg) for 5 min. Chromatography (TLC, ether) then showed the absence of the starting compound. The cooled mixture was diluted with chloroform and the solution was washed with 1 *N* sodium hydroxide and with water. The syrup obtained after drying and concentrating the solution was chromatographed on a column of silica gel (24 g.) using ether for elution and collecting 5-ml. portions of eluate. Fractions 14—16 contained *phenyl 4,6-di-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside* (VI), obtained in the form of a colorless syrup: 320 mg. (59%), $[\alpha]_D$ + 108.5° (*c* 3.40).

Anal. $C_{20}H_{23}NO_8$ (405.41) calc'd.: C 59.25; H 5.72; N 3.46%
found: C 59.00; H 5.54; N 3.65%

The infrared absorption spectrum (neat) included peaks at 1760 (OAc), 1740 (NAc), 1600 and 1500 $cm.^{-1}$ (phenyl).

When carried out at a lower temperature (85—90°) and with a mixture of I and phenol in a molar ratio of 1 : 3, the reaction gave VI in 34% yield. In addition, small quantities of unreacted I, as well as of the rearranged product IV, were isolated and chromatographically identified.

Reaction of I with p-*Nitrophenol*

A finely powdered mixture of I (2.0 g.), *p*-nitrophenol (2.0 g.), and *p*-toluenesulfonic acid monohydrate (200 mg.) was heated *in vacuo* (*ca.* 20 mm of Hg) at 90° (bath) for 10 min. The usual processing afforded a syrupy product which, on TLC in several solvent systems, was found to contain four or five components; none of these, however, corresponded to compound X, the preparation of which is described later in this paper. The mixture was chromatographed on a column of silica gel (80 g.) with ether as eluent and 8-ml. fractions of eluate being collected. Fractions 22—27 contained an unidentified product (21 mg.). Fractions 29—42 contained the major product (483 mg., 20%) which was obtained in the form of a thick syrup that could be crystallized from ethanol solution; it was identified as p-*nitrophenyl 4,6-di-*O-*acetyl-2-* (N-*acetylacetamido*) *-2,3- dideoxy-*α-D-erythro-*hex-2-enopyranoside* (VII): m. p. 124—125°, $[\alpha]_D$ + 188.5° (*c* 0.99).

Anal. $C_{20}H_{22}N_2O_{10}$ (450.41) calc'd.: C 53.33; H 4.92; N 6.22%
found: C 53.61; H 5.13; N 6.21%

The infrared spectrum of the substance showed absorption at 1750 (OAc), 1730 (NAc), 1710 (C=C), 1600 and 1500 (phenyl), 1540 and 1350 $cm.^{-1}$ (NO_2).

From fractions 43—52 a third component was isolated (162 mg., 8%) which was rechromatographed using the same solvent and then crystallized from ethanol. Its chromatographic behavior, infrared spectrum, m. p. and mixed m. p. identified it as *1,4,6-tri-*O-*acetyl-2-* (N-*acetylacetamido*) *-2,3-dideoxy-*α-D-erythro-*hex-2-enopyranose* (IV).

Fractions 53—69 contained an oil (66 mg.) with an infrared spectrum which included absorption for NH and the amide II band; it was not further investigated.

*Isomerization of I into 1,4,6-Tri-*O-*acetyl-2-(*N-*acetylacetamido)-2,3-dideoxy-*α-D-erythro-*hex-2-enopyranose* (IV)

A. With p-*toluenesulfonic acid.* — A powdered mixture of I (0.5 g.) and *p*-toluenesulfonic acid monohydrate (50 mg.) was heated at 85° for 10 min. and then freed of acid in the usual manner. The crude product, obtained after evaporation of the chloroform solution, was chromatographed on a column of silica gel (45 g.) using ether for elution. The chromatographically homogeneous product (212 mg., 42%) was crystallized from ether: m. p. 90—91°, $[\alpha]_D$ + 21.2°. The chromatographic behavior of the material, as well as its infrared and NMR spectra, identified it as 1,4,6-tri-*O*-acetyl-2- (N-acetylacetamido) -2,3-dideoxy-α-D-*erythro*-hex-2-enopyranose (IV).

B. With acetic anhydride—zinc chloride. — A mixture of I (1.0 g.) and anhydrous zinc chloride (200 mg.) was dissolved in acetic anhydride (4 ml.) and the solution was stirred at room temperature for 6 hr. The solution was then poured into ice-water and the crude product was extracted with chloroform. The extract was washed and dried in normal fashion and then concentrated to give a syrup which was chromatographed on a column of silica gel (80 g.), using ether for elution and collecting the eluate in 5-ml. portions. Fractions 34—40 contained pure IV (587 mg., 59%) which was obtained in the form of a foam; crystallized from ethanol, it had m. p. 91—92° either alone or in admixture with the analytical sample of IV.

Fractions 41—49 contained a mixture (410 mg.) which was crystallized from ethanol: 235 mg., m. p. 73—76°, $[\alpha]_D$ + 112.8° (*c* 1.12). The NMR spectrum of the material included all the signals found in the spectrum of pure IV (see Table I), together with a few additional ones. From the relative intensitites of one-proton signals it appeared that IV represented at least 60% of the mixture.

Reaction of IV with Benzoic Acid

A. — A mixture of IV (300 mg.), benzoic acid (300 mg.) and *p*-toluenesulfonic acid (30 mg.) was treated as described in the preparation of III from I. Separation

of the crude product on a column of silica gel afforded 108 mg. (31%) of crystalline 4,6-di-*O*-acetyl-2-(*N*-acetylacetamido)-1-*O*-benzoyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranose (III); recrystallized from ethanol, the substance proved to be identical by m. p., mixed m. p. and infrared spectrum with the analytical sample of III. Further elution of the column with ether led to the recovery of IV (97 mg., 32%).

B. — A solution of IV (300 mg.) and benzoic acid (200 mg.) in benzene (75 ml.) containing 2% of hydrogen chloride (w/w) was boiled under reflux for 6 hr and then concentrated *in vacuo*. The residue was dissolved in chloroform and the solution was washed with 1 *N* sodium hydroxide and with water. After removal of moisture and solvent, the crude product was separated on silica gel to give III (82 mg., 23%) and unchanged IV (21 mg., 7%). Crystallized from ethanol, the III had m. p. 139—140°, undepressed on admixture with an authentic sample.

Reaction of IV with p-*Nitrophenol*

A powdered mixture of IV (450 mg.), *p*-nitrophenol (500 mg.) and *p*-toluenesulfonic acid monohydrate (45 mg.) was heated at 90° (bath) for 10 min.; it was then worked up as described earlier. The crude product was purified on a column of silica gel to give *p*-nitrophenyl 4,6-di-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (VII) in 51% yield (275 mg.). Crystallized from ethanol, the substance had $[\alpha]_D$ + 178.8° and did not depress the m. p. of an authentic sample of VII.

*Catalytic Reduction of Phenyl 4,6-Di-O-acetyl-2-(N-acetylacetamido)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside* (VI)

To a solution of VI (840 mg.) in glacial acetic acid (20 ml.) platinum-on-carbon catalyst (400 mg., 10% Pt) was added and the suspension was shaken with hydrogen at room temperature for 2 days, 3 molar equivalents of hydrogen being absorbed during this period. The catalyst was removed by filtration and the solution was concentrated *in vacuo* (40° bath) to a colorless syrup. Examination by TLC in several solvent systems showed the presence of a single component migrating at the same rate as the starting material; however, ether—petroleum ether (b. p. 40—60) (3 : 1, v/v) revealed the presence of two components, a minor one which proved to be VI and a major one which migrated at a rate slightly greater than VI.

The syrup was chromatographed on a column of silica gel (40 g.) using ether—petroleum ether (3 : 1) as eluent and collecting 3-ml. portions of eluate. Fractions 9—12 contained a syrup which slowly crystallized (470 mg., 55%). Recrystallization from petroleum ether gave pure *cyclohexyl 4,6-di-O-acetyl-2-(N-acetylacetamido)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside* (VIII), m. p. 96—97°, $[\alpha]_D$ + 71.6° (*c* 1.00).

Anal. $C_{20}H_{29}NO_8$ (411.46) calc'd.: C 58.38; H 7.10; N 3.41%
found: C 58.66; H 7.06; N 3.41%

The infrared spectrum of the compound showed absorption at 2900 (CH), 1750 (OAc), 1730 (NAc), and 1710 $cm.^{-1}$ (C=C).

Fractions 13—14 contained a mixture (80 mg.) and from fractions 15—21 unchanged VI (105 mg., 13%) was recovered.

*Cyclohexyl 2-Acetamido-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside* (IX)

A solution of VIII (200 mg.) in absolute methanol containing sodium methoxide was stored at room temperature overnight. Dowex 50—X8 (H^+) was then added and the suspension was stirred until neutral. The resin was removed and the solution was concentrated *in vacuo* to give a syrupy residue (130 mg., 94%) which was chromatographed on a column of silica gel (22 g.) using ether—methanol (9 : 1, v/v). The product (80 mg.) was obtained in the form of a fine powder: $[\alpha]_D$ — 20.2° (*c* 1.04, H_2O).

Anal. $C_{14}H_{23}NO_5$ (285.34) calc'd.: C 58.93; H 8.12; N 4.91%
found: C 59.10; H 8.42; N 5.14%

The infrared spectrum of the compound showed absorption at 3200—3400 (OH and NH), 2850 (CH), 1650 (NAc), 1620 (C=C), and 1540 $cm.^{-1}$ (amide II). On TLC the substance gave a positive test with fluorescein-bromine.

p-Nitrophenyl 3,4,6-Tri-O-acetyl-2-(N-acetylacetamido)-2-deoxy-β-D-glucopyranoside (X)

p-Nitrophenyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranoside[23] (1.0 g.) was dissolved in isopropenyl acetate (20 ml.) containing *p*-toluenesulfonic acid monohydrate (30 mg.) and the solution was boiled under reflux for 5 hr. The solvent was removed *in vacuo* and the residue was triturated with absolute ether and then crystallized from ethanol to give 440 mg. (41%) of product. For analysis, the substance was recrystallized from isopropyl alcohol: m. p. 145—147°, $[\alpha]_D$ — 27.7° (*c* 1.05).

Anal. $C_{22}H_{26}N_2O_{12}$ (510.47) calc'd.: C 51.76; H 5.13; N 5.49%
found: C 51.90; H 5.22; N 5.67%

The infrared spectrum of the compound showed absorption at 1750 (OAc), 1680 (NAc), 1500 and 1600 (aromatic), 1580 and 1340 $cm.^{-1}$ (NO_2); the NMR spectrum included signals in the region from τ 1.80—3.00 (aromatic, 4H), 3.83 (doublet, $J_{1,2}$ 8.1 Hz, H-1), 4.08 (quartet, $J_{2,3}$ 10.0 Hz, $J_{3,4}$ 9.0 Hz, H-3), 4.82 (quartet, $J_{3,4}$ 9.0 Hz, $J_{4,5}$ 9.6 Hz, H-4), 5.70—6.10 (multiplet, 4H), 7.59 (NAc, 6H), 7.92, 7.97, and 7.99 (OAc, 9H).

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IZVOD

Alilna pregrađivanja u reakcijama 2-(*N*-acetilacetamido)-D-glukal triacetata s kiselinama i fenolima

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U reakcijama 3,4,6-tri-*O*-acetil-2-(*N*-acetilacetamido)-1,2-dideoksi-D-*arabino*-heksen-1-piranoze [I, 2-(*N*-acetilacetamido)-D-glukal triacetat] s različitim kiselinama i fenolima u prisutnosti katalitičkih količina *p*-toluensulfonske kiseline, dolazi do gubitka acetoksi skupine s C-3, do pomaka dvostrukog veza u položaj C-2—C 3 i do ulaska acil ili aril skupine na C-1. Pri tome nastaju esteri, odnosno glikozidi 4,6-di-*O*-acetil-2-(*N*-acetilacetamido)-2,3-dideoksi-α-D-*eritro*-heksen-2-piranoza (spojevi III, V, VI i VII). U svakom od ovih slučajeva uz glavni produkt nastaje i 1,4,6-tri-*O*-acetil-2-(*N*-acetilacetamido)-2,3-dideoksi-α-D-*eritro*-heksen-2-piranoza (IV). Nađeno je da se IV može također pripraviti iz I direktnom pregradnjom u kiselom mediju. U benzenskoj otopini, koja sadržava klorovodik, supstanca IV s benzoevom kiselinom daje III, dok I pod istim uvjetima uopće ne reagira. Na temelju tih činjenica predložen je mehanizam kiselo-katalizirane reakcije supstance I s karbonskim kiselinama i fenolima.

Opisana je poboljšana priprava I iz 2-acetamido-2-deoksi-D-manoze preko 2-acetamido-1,3,4,6-tetra-*O*-acetil-2-deoksi-α-D-manopiranoze (II) kao intermedijera.

Fenil 4,6-di-*O*-acetil-2-(*N*-acetilacetamido)-2,3-dideoksi-α-D-*eritro*-heksen-2-piranozid (VI) može se katalitičkom hidrogenacijom reducirati u odgovarajući cikloheksil glikozid (VIII) a da pri tome dvostruki vez ostane očuvan.

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