CCA-771

547.457:542.941.7
Original Scientific Paper

Catalytic Hydrogenation of Some 2-Acetamidoaldose Derivatives*

N. Pravdić, B. Židovec, I. Franjić, and H. G. Fletcher, Jr.

Department of Organic Chemistry and Biochemistry, »Ruđer Bošković« Institute, 41000 Zagreb, Croatia, Yugoslavia and National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare, Bethesda, Md. 20014, U. S. A.

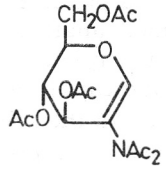
Received November 22, 1972

In earlier work, the double bond in aldohexopyranose derivatives with the grouping $C{=}CNAc_2$ was shown to be resistant to catalytic reduction. Further examples of this phenomenon are now described. Thus, compounds IV, V, and VI were found to be unaltered by hydrogen in the presence of a palladium catalyst. However, 1,4,6-tri-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranose (VII) and its D-*threo* isomer VIII undergo allylic hydrogenolysis of the C-1 acetoxy group with migration of the double bond to the C-1—C-2 position to give IX and X, respectively. The acetamido group does not inhibit the reduction of adjacent double bonds; 2-acetamido-1,4,6-tri-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranose (XIII) and 2-acetamido-4,6-di-*O*-acetyl-1-*O*-benzoyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranose (XV) are reduced to the same 2-acetamido-4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-*arabino* (or D-*ribo*)-hexitol (XIV) and 2-acetamido-1,4,6-tri-*O*-acetyl-2,3-dideoxy-β-D-*arabino* (or D-*ribo*)-hexopyranose (XX).

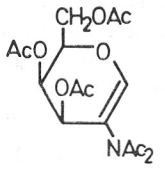
Some mechanistic features of these reactions are pointed out. The pattern of selectivity shown in the hydrogenation is discussed and a rationalization of the observed facts is offered.

INTRODUCTION

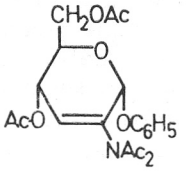
In the course of earlier studies of 2-acetamidoglycal derivatives, it was observed that fully acetylated structures, bearing an *N*-acetylacetamido group at C-2, appeared to be wholly immune to the action of hydrogen and palladium catalysts. Thus, attempts to reduce the double bond in 3,4,6-tri-O-acetyl-2-(*N*-acetylacetamido)-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol[1] (I) and in its D-*lyxo* stereoisomer[2] II through hydrogenation in acetic acid solution with palladium black as a catalyst were completely unsuccessful, the substrates being recovered unchanged.



I



II



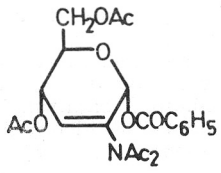
III

* Supported by a P. L. 480 grant from the National Institutes of Health, Bethesda, Maryland, U. S. A., Agreement No. 02-010-1.

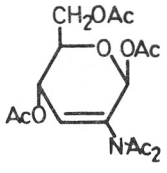
Later it was found[3] that phenyl 4,6-di-*O*-acetyl-2-(*N*-acetylacetamido)-2,3--dideoxy-α-D-*erythro*-hex-2-enopyranoside (III) could be reduced to the corresponding cyclohexyl glycoside in acetic acid solution through the action of hydrogen and a platinum catalyst, the double bond in the pyranose ring being unaffected. Further 2-acetamidoaldose derivatives, with a double bond at C-2—C-3, have been synthesized[3,4] and the behavior of some of these with hydrogen in the presence of various catalysts will now be described.

RESULTS

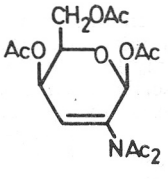
4,6-Di-*O*-acetyl-2-(*N*-acetylacetamido)-1-*O*-benzoyl-2,3-dideoxy-α-D-*erythro*--hex-2-enopyranose[3] (IV), 1,4,6-tri-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy--β-D-*erythro*-hex-2-enopyranose[4] (V), and 1,4,6-tri-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy-β-D-*threo*-hex-2-enopyranose[4] (VI) were individually subjected to the action of hydrogen and a palladium catalyst;



IV



V



VI

the three compounds (IV, V, and VI) were subsequently recovered in yields of 82, 80, and 95%, respectively, and thus their behavior is consistent with that of those investigated earlier. In sharp contrast, 1,4,6-tri-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranose[3] (VII) and the corresponding α-D-*threo* derivative[4] VIII were found to consume 2—3 molar equivalents of hydrogen when shaken in acetic acid or methanol solution in the presence of palladium black or palladium-on-carbon catalyst. In both cases the products which formed were syrupy but their NMR spectra clearly showed the presence of two *N*-acetyl groups and two *O*-acetyl groups whilst the elemental composition of each corresponded to $C_{14}H_{19}NO_7$. These data indicated that hydrogenolysis of one acetoxy group had occurred but that the double bond, doubtless »protected« by the presence of the 2-(*N*-acetylacetamido) group, remained.

The hydrogenolysis of allylic ester groups in non-nitrogenous unsaturated aldopyranose derivatives has been observed by several investigators[5–7]. The reaction is more effectively catalyzed by platinum than by palladium[6] and may involve reductive elimination of acetoxy groups from C-1, C-2, C-3, or C-4[6,7]. With both VII and VIII, hydrogenation in the presence of a palladium catalyst gave but a single product, the formation of which seemed unaffected by the nature of the catalyst or the solvent used; furthermore, the products from the two unsaturated sugar derivatives were not identical, indicating that simple hydrogenolysis of the C-4 acetoxy group was not involved. We then synthesized 4,6-di-*O*-acetyl-2-(*N*-acetylacetamido)-1,5-anhydro-2,3-dideoxy-D-*erythro*-hex--2-enitol (XII), the product that would be expected had the hydrogenolysis of VII involved only the acetoxy group at C-1. Compound VII was treated with thiophenol in boiling benzene containing 2% of hydrogen chloride[3] to yield

phenyl 4,6-di-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy-1-thio-α-D-*erythro*--hex-2-enopyranoside (XI). Although this product was obtained as a rather unstable syrup, its NMR spectrum indicated the α-D anomeric configuration and suggested that the compound exists in the H_5^0 conformation. The thioglycoside was reductively desulfurized with Raney nickel under mild conditions to give 4,6-di-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy-D-*erythro*-hex-2-enitol (XII) which was isolated in crystalline form. Its physical constants, chromatographic mobility and NMR spectrum (Table I) readily distinguished XII from the isomeric product derived by the hydrogenolysis of VII.

TABLE I

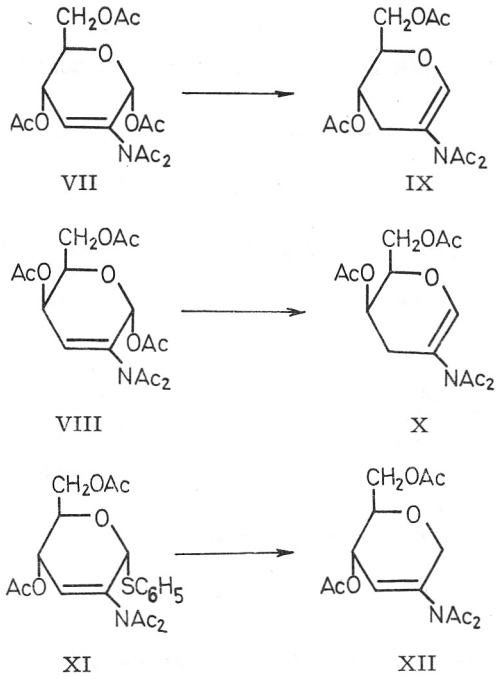
Assignments in the NMR Spectra[a] *of Isomeric Compounds IX, X, and XII*

No.	Chemical shifts (τ values) and coupling constants (Hz)					
	H-1	H-4	H-5, 2H-6	H-3e	NAc[b]	OAc
IX	3.47 $J_{1,3e}$ 1.8	4.80 $J_{3a,4}$ 10.8 $J_{3e,4}$ 5.6	5.50—5.80	7.33 $J_{3a,3e}$ 17.0 $J_{1,3e}$ 1.8 $J_{3e,4}$ 5.6	7.64 (7H)	7.92 (6H)
X	3.44 $J_{1,3e}$ 2.1	4.78 $J_{3a,4}$ 3.0 $J_{3e,4}$ 4.8	5.73	7.24 $J_{3a,3e}$ 17.5 $J_{1,3e}$ 2.1 $J_{3e,4}$ 4.8	7.66 (7H)	7.90, 7.93
		H-4	2H-1, H-5, 2H-6		NAc	OAc
XII		4.78	5.60—6.20		7.67 (6H)	7.93, 7.97

[a] Spectra were taken at 100 MHz. [b] The H-3a proton was among the acetyl signals.

With simple hydrogenolysis of an acetoxy group excluded, the possibility of concomitant shift of the double bond was next considered. The 100 MHz NMR spectrum of the compound obtained from the α-D-*erythro* isomer, VII, showed signals from the two geminal protons at high field where they merged partially with the *N*-acetyl resonances. The chemical shift tended to indicate that the protons were not attached to a carbon bonded to oxygen; where there is such bonding the signals fall at lower field[2,7–10], approximately τ 5—6, since the most important direct shielding effect in the carbohydrates is that of the ring oxygen[11]. However, geminal protons bonded at C-2, C-3, or C-4 are usually found[8,10,12–15] at τ values higher than 7. In the spectrum of our compound, one of the geminal protons is found as an octet centered at τ 7.33 with coupling constants of 1.8, 5.6, and 17.0 Hz. Irradiation of this signal caused the low-field one-proton signal at τ 3.47 to collapse to a singlet and the multiplet centered at τ 4.80 to collapse to a triplet. The low-field signal at 3.47 is assigned to H-1

with a long-range coupling of 1.8 Hz which has been removed through irradiation of the octet at 7.33. Irradiation of the H-1 signal caused the octet to collapse to a quartet. These NMR spectral data are consistent with structure IX, 4,6-di-*O*-acetyl-2-(*N*-acetylacetamido)-1,5-anhydro-2,3-dideoxy-D-*erythro*--hex-1-enitol.The signal assignments and coupling constants are presented in Table I. The magnitude of the $H_{3a,3e}$ coupling constant is fully acceptable as the large geminal coupling constant is attributed to the effect of an sp^2 hybridized carbon acting across an sp^3 carbon atom[16] and, for six-membered unsaturated cyclic systems, it amounts to —17.0 to —19.0 Hz[17].

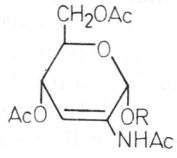


The product derived from the α-D-*threo* derivative VIII, showed a very similar NMR spectrum and we therefore ascribe to it structure X, 4,6-di-*O*-acetyl-2-(*N*-acetylacetamido)-1,5-anhydro-2,3-dideoxy-D-*threo*-hex-1-enitol. Spin decoupling allowed estimation of the coupling constants which are given in Table I. In passing, it may be noted that the spectrum of X shows both H-6 protons, together with H-5, appearing as a sharp singlet at τ 5.73; the H-4 signal is, therefore, simplified to a pair of doublets showing only the coupling with both of the vicinal H-3 protons. This indicates that $J_{4,5}$ is practically zero which is in agreement with the observation[18] that this coupling constant in galactosides is usually abnormally small.

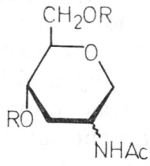
Leaving, temporarily, compounds containing the *N*-acetylacetamido group, we turned our attention to the reduction of unsaturated aldohexopyranose derivatives with an acetamido function at C-2. In various solvents and in the presence of various catalysts 2-acetamido-1,4,6-tri-*O*-acetyl-2,3-dideoxy-α-D-

-*erythro*-hex-2-enopyranose[4] (XIII) invariably absorbed more than one mole equivalent of hydrogen to give, as a major product, a saturated compound which was isolated in amorphous but chromatographically homogeneous form. Its elemental composition and NMR spectrum identified it as a 2-acetamido--4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxyhexitol with the D-*erythro* configuration at C-4—C-5 (XIV). The same substance was also prepared through the following sequence of reactions: VII → IX → unstable 2-acetamido derivative of IX → XIV, proving that the acetoxy group lost from XIII was at C-1. Furthermore, hydrogenation of 2-acetamido-4,6-di-*O*-acetyl-1-*O*-benzoyl-2,3-dideoxy--α-D-*erythro*-hex-2-enopyranose[4] (XV) under the conditions used for XIII also gave, through loss of the benzoyloxy group at C-1, the same product (XIV).

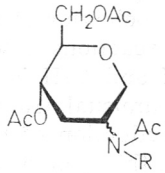
As the NMR spectra of di-*N*-acyl aminosugar derivatives are often more readily interpretable than those of the corresponding mono-*N*-acyl aminosugars[2,19], two such derivatives, XVI and XVII, were prepared from XIV; however, the ring methylene groups in these compounds rendered their spectra so complex that elucidation of the steric situation at C-2 appeared impossible. De-*O*-acetylation of XIV gave XVIII; in methyl sulfoxide-d_6 solution, the NMR spectrum of this substance shows an *N*-acetyl signal at τ 8.15. Such a value is within the range found to be characteristic of axially bonded acetamido groups in various inosamine derivatives in this solvent[20]. In water, XVIII has a specific rotation of $[\alpha]_D$ + 21.2° and 1,5-anhydro-2,3-dideoxy-D-*erythro*--hexitol[7,21] has $[\alpha]_D$ + 53°. If acetamido derivatives conform to the isorotation rule which was found to be valid for the epimeric 1,5-anhydroglycitols[22], XVIII has the D-*arabino* configuration. A third point in support of the D-*arabino* configuration is that axially oriented acetamido groups are normally a feature of the main product when unsaturated acetamido sugars are reduced catalytically[1,2]. Nevertheless, it should be emphasized that we do not regard the full configuration of compounds XIV and XVI—XVIII as established.



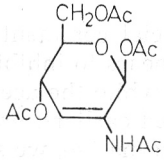
XIII R=Ac
XV R=COC_6H_5



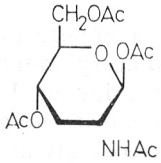
XIV R=Ac
XVIII R=H



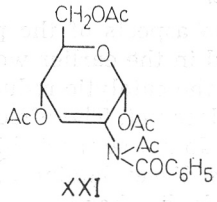
XVI R=Ac
XVII R=COC_6H_5



XIX



XX



XXI

The anomer of XIII, 2-acetamido-1,4,6-tri-*O*-acetyl-2,3-dideoxy-β-D-*erythro*--hex-2-enopyranose[4] (XIX), was found, on hydrogenation, to consume only one mole equivalent of hydrogen. The NMR spectrum of the product clearly showed the presence of three *O*-acetyl groups and of one *N*-acetyl group; the elemental analysis corresponded to $C_{14}H_{21}NO_8$, and the mass spectrum revealed a molecular ion of 331. On these pieces of evidence, the saturated compound is assigned the structure 2-acetamido-1,4,6-tri-*O*-acetyl-2,3-dideoxy-β-D-*arabino*(*or* D-*ribo*)-hexopyranose(XX). Evidence for the configuration at C-2 was not obtained. In passing, certain features of the mass spectrum of XX seem worthy of note. The spectrum is characterized by the presence of fragments initially formed through elimination of acetic acid or of the C-5 substituent (see Experimental for details). Essentially the same type of fragmentation has been observed in the mass spectrum of 2-acetamido-4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-*arabino*(or D-*ribo*)-hexitol (XIV). However, the mass spectrum of XX included ions produced by the loss of the substituent from C-1[23], *e. g. m/e* 288 (M — CH_3CO) and *m/e* 273 [M — (OAc-1)], and others formed through subsequent degradation of these fragments. Although the ion *m/e* 273 might actually originate from *m/e* 288 through the loss of 15 (CH_3), it appears more plausible that it is a rearranged ion formed directly from the molecular ion through the cleavage of the C-1 acetoxy group with preliminary binding of one of its hydrogens to the ring oxygen.

In the course of the present work, 1,4,6-tri-*O*-acetyl-2-(*N*-acetylbenzamido)--2,3-dideoxy-α-D-*erythro*-hex-2-enopyranose (XXI) was synthesized through the benzoylation of XIII. This di-*N*-acyl derivative, which also adopts the H_5^0 conformation in chloroform solution, was hydrogenated. The product, obtained in 95% yield, was identified as XIV; no information regarding the sequence of steps in this transformation was obtained.

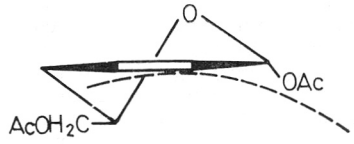
DISCUSSION

Allylic hydrogenolysis is, of course, a well-known phenomenon[24] and, in view of the behavior of non-nitrogenous unsaturated sugar derivatives[6,7] cited earlier, the reactions noted here are not unexpected. However, the hydrogenolysis of VII and VIII is accompanied by a shift of the double bond. Such an apparently unusual transformation was found by Dauben and Hance[25] in an attempted reduction of the sesquiterpene lactone ψ-santonin; as these authors pointed out, this type of double bond migration may be masked in many allylic hydrogenolyses, owing to the fact that it is generally followed by saturation of the double bond. Indeed, this is almost certainly what occurred in the reduction of XIII and XV to XIV. Examples of a related type of double bond migration have recently been noted [26,27] in the transformation of 2,3-unsaturated methyl pyranosides into 3-deoxyglycals through the action of lithium aluminum hydride.

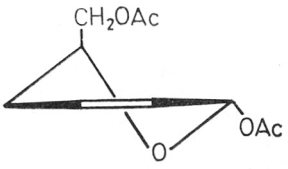
Two aspects of the present work appear to merit special comment. First, as noted in the earlier work[1-3], the diacetylamino group appears to inhibit completely the catalytic reduction of a contiguous double bond while the acetamido group does not. The effect may be a steric one as susggested earlier[3]; however, models do not support this view convincingly and, as an alternative, we suggest that the diacetylamino group may simply be providing resonance deactivation of the double bond.

Second, we wish to draw attention to the steric aspects of these hydrogenolyses. With the exception of compound IV, the findings present a remarkably consistent picture: the β-D esters, V and VI are not attacked and reduction of the double bond only is found with the β-D ester XIX. On the other hand, the α-D esters, VII, VIII, XIII, and XV, underwent hydrogenolysis.

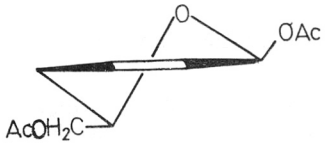
The conformation of 2,3-unsaturated derivatives of some 2-acetamido-2--deoxyaldohexopyranoses has been discussed in the preceding paper[4] and it has been suggested that the α-D esters, VII and VIII, adopt the H_5^0 conformation while the β-D esters, V, VI, and XIX, most probably assume a conformation which is not far from H_5^0 . These conclusions were originally reached on the basis of NMR spectra measured in deuterochloroform. Glacial acetic acid was used as a solvent in the hydrogenation experiments but the NMR spectra of VII and VIII in deuteroacetic acid also show them to be in the H_5^0 conformation. However, the free energy barrier between the H_0^5 and H_5^0 conformations of any of these C-2—C-3 unsaturated derivatives is likely to be such that a significant population of both conformers would be expected in solution. Thus, if hydrogenolysis depended wholly on conformation, one would expect to observe differing rates of hydrogenolysis. Instead, we find what appear to be clear-cut »go« or »no-go« situations. The reactions do not go in the absence of hydrogen and it is reasonable to assume that an essential feature is the approach of the double bond *and* the allylic oxygen at C-1 to the catalyst surface which carries the hydrogen necessary for the reaction. In order for reaction to take place, the molecule must be capable of existing in a conformation which will permit the requisite approach. Let us now consider the two most important conformations of each of the two D anomers (the substituents at C-2 and C-4 have been omitted for clarity). It will be seen than an α-D anomer in the H_5^0



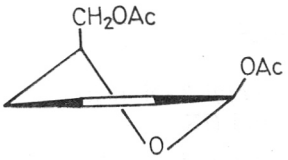
α-D, H_5^0



α-D, H_0^5



β-D, H_5^0



β-D, H_0^5

conformation permits the necessary approach of the catalyst surface from the lower side as depicted; its companion, the α-D, H_0^5 is hindered from approach above by the axial acetoxymethyl group and below by the lone pairs of the ring

oxygen. With the β-D anomers the H_5^0 conformation would have to be approached from the upper side and here the lone pairs of the oxygen stand in the way; in the β-D, H_0^5 form the lone pairs of the oxygen on one side and the axial acetoxymethyl on the other hinder a productive collision. In studying the reduction of allylic lactones, Dauben and his coworkers noted a case in which an isomer with the lactone oxygen in an axial position underwent hydrogenolysis while the corresponding equatorial isomer did not; they suggested[28] that the axial oxygen may be a prerequisite for such hydrogenolyses. The view we have taken in the present case, being associated with the greater leaving properties of *quasi*-axial allylic ester groups, appears to be in harmony with that of Dauben and his coworkers.

The reason for the failure of compound IV to undergo hydrogenolysis (while its very close relative, XV, did) remains unexplained. We do not know the energy change involved in the adsorption of an α-D, H_5^0 form on a catalyst surface; the operation may be very sensitive to steric factors which are not as yet apparent to us.

Aside from the work of Dauben already cited, we find only one other observation in the literature which may bear on the question of steric dependence of allylic hydrogenolysis. Ferrier, Overend, and Sankey[29] found that 1-*O*-acetyl-2,4,6-tri-*O*-benzoyl-3-deoxy-β-D-*erythro*-hex-2-enopyranose could not be hydrogenated under conditions which were successful with the corresponding α-D anomer; the reaction shown by the latter anomer was not, however, allylic hydrogenolysis but simple reduction of the double bond.

In conclusion, we wish to emphasize that our understanding of the factors governing the behavior of these unsaturated esters is as yet highly deficient and that the rationalizations presented here can only be regarded as tentative and speculative.

EXPERIMENTAL

Melting points are uncorrected. Specific rotations were measured at 20—23° in chloroform unless otherwise stated. Thin layer chromatography was conducted on silica gel G (E. Merck) using the solvent system specified on microscope slides and 5 × 20 cm plates; 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). A Hewlett-Packard No. 700 instrument, equipped with a thermal conductivity detector, was used for GLC; the column employed (0.25 in × 6 ft) was filled with 10% SE 52 on Chromosorb W. Infrared spectra were recorded on a Perkin-Elmer Model 137 instrument. The NMR spectra were obtained in chloroform-*d* (unless otherwise stated) solutions using Varian A-60*A* and JEOL JNM-4-H-100 spectrometers and tetramethylsilane as an internal standard. Mass spectra were measured on a Varian CH-7 spectrometer at 70 eV applying the direct insertion probe technique.

4,6-Di-O-acetyl-2-(N-acetylacetamido)-1,5-anhydro-2,3-dideoxy-D-erythro--hex-1-enitol (IX)

a) To a solution of 1,4,6-tri-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranose[3] ($[\alpha]_D$ + 22.8°, VII, 400 mg) in glacial acetic acid (30 ml) palladium black catalyst (200 mg) was added and the suspension was stirred with hydrogen until absorption of the gas ceased (24 hours). Examination by TLC in ether showed the presence of a single component (brown spot) migrating almost at the same rate as the starting material (gray spot). The catalyst was removed by filtration and the solution was concentrated *in vacuo* (40° bath), the residual syrup was dried in a dessicator over sodium hydroxide. It was then chromatographed on a column of silica gel (45 g) using ether as eluent. A homogeneous product was obtained (288mg, 85%)

in the form of a colorless syrup showing $[\alpha]_D$ + 99.5° (*c* 1.00). Prior to analysis the substance was rechromatographed on silica gel using the same solvent and was dried in high *vacuo* at 40°: 250 mg, $[\alpha]_D$ + 102.5° (*c* 0.88).

Anal. $C_{14}H_{19}NO_7$ (313.31) calc'd.: C 53.67; H 6.11; N 4.47%
found: C 53.38; H 6.21; N 4.46%

The same product was obtained when catalytic hydrogenation was performed in the presence of palladium-on-carbon catalyst (10% Pd).

b) To a solution of 1,4,6-tri-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy-D-*erythro*-hex-2-enopyranose (mixture of anomers, $[\alpha]_D$ + 140°, 517 mg) in glacial acetic acid (30 ml) palladium black catalyst (250 mg) was added and the suspension was stirred with hydrogen for 24 hours. The catalyst was filtered off and the solution was concentrated to a syrup which was treated with ether to give semicrystalline material. The solvent was evaporated and the residue, when thoroughly dry, was treated again with anhydrous ether (2 ml). It was kept in a refrigerator for 2 hours, the crystals were filtered and washed with ether: 105 mg.

The mother liquor and washings were concentrated to a syrup (382 mg) which was dissolved in chloroform (0.5 ml) and chromatographed on a column of silica gel (55 g) prepacked in ether. Ether was used for elution and the eluate was collected in 5-ml portions. Fractions 12—14 contained a syrup (113 mg); its chromatographic behavior and infrared spectrum identified it as *4,6-di-O-acetyl-2-(N-acetylacetamido)-1,5-anhydro-2,3-dideoxy*-D-erythro-*hex-1-enitol* (IX). Fractions 15—19 contained a mixture (186 mg.) which was treated with ether and kept at — 18° to yield the second crop of the crystalline material, 26 mg; total yield 131 mg, 25%. Infrared spectrum, optical rotation, m. p., and m. m. p. identified the compound as *1,4,6-tri*-O-*acetyl-2-(N-acetylacetamido)-2,3-dideoxy*-β-D-erythro-*hex-2-enopyranose*[4] (V).

From the ethereal mother liquor after rechromatography a second portion of IX was obtained increasing the total yield on 200 mg, 46%.

4-6-Di-O-*acetyl-2-(N-acetylacetamido)-1,5-anhydro-2,3-dideoxy*-D-threo-*hex-1-enitol* (X)

To a solution of 1,4,6-tri-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy-α-D-*threo*-hex-2-enopyranose[4] (VIII, 250 mg) in glacial acetic acid (20 ml) palladium black (125 mg) was added and the suspension was stirred with hydrogen overnight. The catalyst was removed by filtration, the solution was concentrated *in vacuo*, and the residue was chromatographed on a column of silica gel (30 g) using ether. The product was obtained (165 mg, 78%) in the form of a colorless syrup showing $[\alpha]_D$ + 34.6° (*c* 0.93). Prior to analysis the substance was rechromatographed on silica gel using the same solvent, and was dried in high *vacuo* at 40°: 149 mg, $[\alpha]_D$ + 39.6° (*c* 0.83).

Anal. $C_{14}H_{19}NO_7$ (313.31) calc'd.: C 53.67; H 6.11; N 4.47%
found: C 53.38; H 6.31; N 4.27%

Phenyl 4,6-di-O-*acetyl-2-(N-acetylacetamido)-2,3-dideoxy-1-thio*-α-D-erythro-*hex-2-enopyranoside* (XI)

A solution of VII (371 mg) and thiophenol (0.2 ml) in anhydrous benzene (75 ml) containing 2% of hydrogen chloride (w/w) was boiled under reflux for 20 hours. The progress of the reaction was followed by thin layer chromatography in ether: two new spots moving faster than the starting material were detectable. The solution was concentrated *in vacuo*, the residue was dissolved in chloroform (40 ml), and then washed with 1 *M* sodium hydroxyde and water. The extract was dried and concentrated to give a syrup which was chromatographed on a column of silica gel (55 g) using ether for elution and collecting the eluate in 5-ml fractions.

Fractions 20—25 contained the title compound in the form of a syrup, 95 mg, 22%. Prior to analysis it was rechromatographed using the same solvent: colorless syrup, $[\alpha]_D$ + 149.5° (*c* 1.10). Infrared absorption at 1710 and 1740 cm^{-1} (OAc and NAc). NMR signals at τ 2.50—2.80 (aromatic, 5H), 4.10 (doublet, $J_{3\,4}$ 2.0 Hz, H-3), 4.19 (singlet, H-1), 4.54 (quartet, $J_{4\,5} \sim 9$ Hz, H-4), 5.50—6.10 (multiplet, 3H), 7.61 (NAc, 6H), and 7.96 (OAc, 6H).

Anal. $C_{20}H_{23}NO_7S$ (421.48) calc'd.: C 56.99; H 5.50; N 3.32; S 7.61%
found: C 57.09; H 5.75; N 3.20; S 7.60%

*4,6-Di-O-acetyl-2-(N-acetylacetamido)-1,5-anhydro-2,3-dideoxy-*D-erythro-*-hex-2-enitol* (XII)

A solution of XI (200 mg) in 96% ethanol (20 ml) was treated with Raney nickel (*ca.* 2 ml) and the suspension was occasionally stirred and kept at room temperature for 15 minutes, the reaction being monitored by TLC in ether. The suspension was filtered through a layer of Celite and the catalyst was thoroughly washed with ethanol. The combined filtrate was concentrated to a thick syrup, which was chromatographed on a column of silica gel (20 g) using ether and collecting 2-ml fractions. Fractions 12—16 yielded XI (16 mg), fractions 19—29 contained homogeneous product which after evaporation partially crystallized (90 mg, 60%). The semicrystalline material was triturated with anhydrous ether (2 ml) and the crystals were removed by filtration: m. p. 85—86°, $[\alpha]_D$ + 78.4° (*c* 1.00).

Infrared absorption (KBr) 1720 and 1760 cm^{-1} (OAc and NAc).

Anal. $C_{14}H_{19}NO_7$ (313.31) calc'd.: C 53.67; H 6.11; N 4.47%
found: C 53.42; H 6.02; N 4.57%

*2-Acetamido-4,6-di-O-acetyl-1,5-anhydro-2,3-dideoxy-*D-arabino(*or-*D-ribo)-*-hexitol* (XIV)

*a) from 2-Acetamido-1,4,6-tri-O-acetyl-2,3-α-*D-erythro-*hex-2-enopyranose*[4] (XIII). — To a solution of XIII (300 mg) in glacial acetic acid (15 ml) was added palladium black (150 mg) and the suspension was stirred with hydrogen for 24 hours, *ca.* 3 molar equivalents of hydrogen being absorbed during this period. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to a yellowish syrup which was chromatographed on a column of silica gel (30 g) using ether-benzene-methanol (5 : 5 : 1, v/v). Fractions containing homogeneous material were pooled and concentrated to yield unstable foam, 215 mg, 87%. It was twice rechromatographed from the same solvent mixture, and for analysis the middle fractions were filtered, evaporated and dried in high *vacuo:* colorless syrup, $[\alpha]_D$ + 17.5° (*c* 1.00). A sample dissolved in dioxane was homogeneous on GLC.

NMR signals at τ 2.82 (broad doublet, NH), 5.08 (sextet, H-4), 7.93, 7.98, and 8.01 (NAc and OAc, 9H).

Anal. $C_{12}H_{19}NO_6$ (273.29) calc'd.: C 52.74; H 7.01; N 5.12; Ac 47.20%
found: C 52.48; H 7.30; N 4.94; Ac 46.91%

Catalytic hydrogenation performed in ethyl acetate with palladium-on-carbon or with palladium-on-barium sulfate afforded the same product.

*b) from IX through the unstable 2-Acetamido-4,6-di-O-acetyl-1,5-anhydro-2,3-dideoxy-*D-erythro-*hex-1-enitol.* — A solution of IX (330 mg) in dioxane was treated with saturated aqueous ammonium acetate solution following the procedure for *N*-acetyl removal[4]. The crude 2-acetamido-4,6-di-O-acetyl-1,5-anhydro-2,3-dideoxy-D-*erythro*-hex-1-enitol (340 mg), which gave a positive fluoresceine test for unsaturation and was unstable on storage, was immediately dissolved in glacial acetic acid (15 ml) and stirred with hydrogen in the presence of palladium black (150 mg). It was worked up as described above, chromatographed and rechromatographed using the same solvent mixture, yielding the product in the form of a syrup, 162 mg, 56%, $[\alpha]_D$ + 15.7° (*c* 1.00). Its chromatographic behaviour (TLC and GLC) and NMR spectrum were indistinguishable from those of a sample prepared under *a*).

*c) from 2-Acetamido-4,6-di-O-acetyl-1-O-benzoyl-2,3-dideoxy-α-*D-erythro-*hex-2-enopyranose*[4] (XV). — A solution of XV (184 mg) in glacial acetic acid (10 ml) in the presence of palladium black (90 mg) was stirred with hydrogen overnight. The mixture was worked up as described above, the crude product was chromatographed on a column of silica gel (25 g) prepacked in ether. Using ether for elution, the first component was obtained; 48 mg, 83% of a crystalline material, which was further purified by sublimation. The infrared spectrum and mixed m. p. identified it as benzoic acid.

The second component was eluted with ether-benzene-methanol (5 : 5 : 1) as a syrup, 99 mg, 77%. Its NMR spectrum and chromatographic behavior (TLC and GLC) identified it as XIV.

d) from 1,4,6-Tri-O-acetyl-2-(N-acetylbenzamido)-2,3-dideoxy-α-D-erythro-hex--2-enopyranose (XXI). — To a solution of XXI (250 mg) in glacial acetic acid (15 ml) was added palladium black (125 mg) and the suspension was stirred with hydrogen overnight. Examination of the solution by TLC in ether showed the absence of the starting compound. The crude product was worked up and chromatographed on a column of silica gel (35 g) using ether-benzene-methanol (5 : 5 : 1) as eluent. The chromatographically homogeneous (TLC and GLC) product was a colorless syrup: 150 mg, 95%, $[\alpha]_D$ + 18.3° (*c* 0.59). Its infrared spectrum and chromatographic behavior identified it as *2-acetamido-4,6-di-O-acetyl-1,5-anhydro-2,3-dideoxy-D-arabino(or D-ribo)-hexitol* (XIV).

The highest peak in the mass spectrum of the compound was *m/e* 273. In addition, the spectrum included signals at *m/e* 200 (M — CH_2OAc), *m/e* 140 (200 — AcOH), and *m/e* 98 (140 — ketene). A second pathway of fragmentation was initiated by the loss of acetic acid, *m/e* 213 (M — AcOH), *m/e* 153 (213 — AcOH), and *m/e* 94 (153 — —CH_3CONH_2). Two fragments *m/e* 114 and *m/e* 85 which are characteristic for acetamido sugars[30] were also present in the spectrum.

4,6-Di-O-acetyl-2-(N-acetylacetamido)-1,5-anhydro-2,3-dideoxy-D-arabino(or D-ribo)-hexitol (XVI)

A solution of XIV (640 mg) in isopropenyl acetate (12 ml) containing *p*-toluenesulfonic acid monohydrate (80 mg) was boiled under reflux for 30 minutes; the progress of the reaction being followed by TLC in ether. The solvent was evaporated *in vacuo* and the dark residue was separated on a column of silica gel (60 g) using ether as eluent and collecting the eluate in 6-ml fractions. Fractions 26—40 contained *4,6-di--O-acetyl-2-(N-acetylacetamido)-1,5-anhydro-2,3-dideoxy-D-arabino(or D-ribo)-hexitol* (364 mg, 49%). The second component which was eluted with ether-methanol (4 : 1) was found to be unreacted XIV (104 mg, 16%). The product was rechromatographed on silica gel using the same solvent; prior to analysis, the syrup was dried in high *vacuo* at 40°: $[\alpha]_D$ + 23.6° (*c* 1.03).

Infrared absorption at 1740 and 1700 cm^{-1} (OAc and NAc). The NMR spectrum of the substance showed peaks at τ 4.88 (unresolved, 1H), 5.3—6.5 (multiplet, 6H), 6.9—7.4 (1H), 7.62 (NAc, 6H), and 7.88 (OAc, 6H).

Anal. $C_{14}H_{21}NO_7$ (315.33) calc'd.: C 53.33; H 6.71; N 4.44%
found: C 53.42; H 6.50; N 4.73%

A sample of XVI on storage at room temperature partially lost one *N*-acetyl group, giving XIV.

4,6-Di-O-acetyl-(N-acetylbenzamido)-1,5-anhydro-2,3-dideoxy-D-arabino(or D-ribo)-hexitol (XVII)

Into a solution of XIV (580 mg) in anhydrous pyridine (5 ml) precooled to —12° was added benzoyl chloride (0.8 ml) and the mixture was stored in a refrigerator for 5 days. It was then poured into ice-water, extracted with chloroform, the extract being successively washed with 2 *M* hydrochloric acid, saturated sodium bicarbonate solution, and water, and dried with sodium sulfate. Removal of the solvent *in vacuo* left an oily residue (630 mg) which was chromatographed on a column of silica gel (60 g) using ether. Fractions containing homogeneous material were concentrated to give XVII (433 mg, 54%) in the form of a colorless syrup which was twice rechromatographed on silica gel with the same solvent prior to analysis: $[\alpha]_D$ + 31.7° (*c* 1.04). NMR signals at τ 2.1—2.5 (aromatic, 5H), 4.9—6.5 (multiplets, 7H), 7.0—7.5 (1H), 7.97-and 8.04 (OAc and NAc, 9H).

Anal. $C_{19}H_{23}NO_7$ (377.40) calc'd.: C 60.47; H 6.14; N 3.71%
found: C 60.73; H 6.38; N 3.98%

2-Acetamido-1,5-anhydro-2,3-dideoxy-D-arabino(*or* D-ribo)-*hexitol* (XVIII)

A solution of XIV (335 mg) in absolute methanol (10 ml) containing sodium methoxide was kept at room temperature for 2 hours; Dowex 50—X8 (H^+) was then added and the suspension was stirred. After filtration, the filtrate was evaporated *in vacuo*. The crude crystalline product (205 mg, 88%, m. p. 143—146°) was crystallized from isopropyl alcohol: m. p. 146—147°, $[\alpha]_D$ + 21.2° (*c* 1.04, H_2O). Infrared absorption (KBr) at 3500 (OH), 3300 (NH), 1630 and 1560 cm^{-1} (amide I and II). NMR signals (methyl sulfoxide-d_6) at τ 2.1 (doublet, NH) and 8.15 (NAc).

Anal. $C_8H_{15}NO_4$ (189.22) calc'd.: C 50.78; H 7.99; N 7.40%
found: C 50.93; H 8.01; N 7.28%

Catalytic Reduction of 2-Acetamido-1,4,6-tri-O-*acetyl-2,3-dideoxy*-β-D-erythro-*hex-2-enopyranose*[4] (XIX)

To a solution of XIX (150 mg) in glacial acetic acid (8 ml) palladium catalyst (75 mg) was added and the suspension was stirred with hydrogen until absorption of the gas ceased (6 hours). The catalyst was filtered off, the filtrate was concentrated *in vacuo* and the residue was chromatographed on a column of silica gel (20 g) using ether-methanol (9 : 1) to give 147 mg, 97% of the product, in the form of a stable colorless foam. The substance was rechromatographed on silica gel using ether-acetone-benzene (10 : 5 : 1) and then again with ether-methanol (9 : 1); *2-acetamido-1,4,6-tri-O-acetyl-2,3-dideoxy*-β-D-arabino(*or* D-ribo)-*hexopyranose* (XX) was thus obtained as a solidified hygroscopic mass, m. p. 75—77°, $[\alpha]_D$ + 6.4° (*c* 0.98).

IR absorption spectrum (KBr) at 3350 (NH), 1750 (OAc), 1670 and 1540 cm^{-1} (amide I and II). NMR signals at τ 3.50 (broad doublet, NH), 7.91, 7.96, 8.01, and 8.05 (NAc and OAc).

The mass spectrum of the compound showed signals at *m/e* 331 (parent peak), *m/e* 288 (M — CH_3CO), *m/e* 273 [M — (OAc-1)], *m/e* 231 (273 — ketene) and *m/e* 129 [231 — (AcOH + ketene)]. The pathway which started by the loss of acetic acid: *m/e* 211 (M — 2 AcOH), *m/e* 169 (211 — ketene), and *m/e* 110 (169 — CH_3CONH_2), or *m/e* 127 (169 — ketene). The second pathway of fragmentation included signals at *m/e* 198 [M — (CH_2OAc + AcOH)], *m/e* 139 (198 — CH_3CONH_2), and *m/e* 97 (139 — ketene).

For analysis the sample was dried thoroughly in high *vacuo*.

Anal. $C_{14}H_{21}NO_8$ (331.33) calc'd.: C 50.75; H 6.39; N 4.23%
found: C 50.42; H 6.37; N 4.38%

1,4,6-Tri-O-*acetyl-2-(*N-*acetylbenzamido)-2,3-dideoxy*-α-D-erythro-*hex-2-enopyranose* (XXI)

2-Acetamido-1,4,6-tri-O-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranose (XIII, 720 mg) was dissolved in anhydrous pyridine (7 ml) and the solution, cooled to — 12°, was treated with freshly distilled benzoyl chloride (0.9 ml). The mixture was stored in a refrigerator for 9 days, then was poured into ice-water and the product was extracted with chloroform. The combined extracts were washed with 2 M hydrochloric acid, saturated sodium bicarbonate solution, and water. After removal of moisture and solvent, the crude product was separated on a column of silica gel (70 g) using ether for elution. Fractions containing homogeneous material were collected to give the product (506 mg, 54%) in the form of white foam. Crystallized from ethanol: m. p. 99—100°, $[\alpha]_D$ — 8.9° (*c* 1.10).

NMR signals at τ 2.1—2.6 (aromatic, 5H), 3.43 (singlet, H-1), 4.00 (doublet, $J_{3,4}$ 2.0 Hz, H-3), 4.50 (quartet, $J_{3,4}$ 2.0 Hz, $J_{4,5}$ ~ 9Hz, H-4), 7.70, 7.90, 7.92, and 7.98 (NAc and OAc, 12H).

Anal. $C_{21}H_{23}NO_9$ (433.32) calc'd.: C 58.20; H 5.35; N 3.23%
found: C 58.27; H 5.55; N 3.26%

When the benzoylation was carried out at room temperature, the product was obtained as the mixture of anomers.

Acknowledgments. The authors thank Mrs. S. Babić for her skilful technical assistance, to Dr. O. Hadžija for microanalyses, and to Mrs. L. Tomić for 60 MHz NMR spectra. Decoupling experiments at 100 MHz were carried out at the Chemical Institute, Ljubljana by Mr. R. Smerkolj. We are indebted to Dr. D. Stefanović for recording the mass spectra and for very helpful discussions.

REFERENCES

1. N. Pravdić and H. G. Fletcher, Jr., *J. Org. Chem.* **32** (1967) 1806.
2. N. Pravdić and H. G. Fletcher, Jr., *Croat. Chem. Acta* **41** (1969) 125.
3. N. Pravdić, B. Židovec, and H. G. Fletcher, Jr., *Croat. Chem. Acta* **42** (1970) 523.
4. N. Pravdić, B. Židovec, and H. G. Fletcher, Jr., *Croat. Chem. Acta* **45** (1973) 333.
5. R. J. Ferrier and G. H. Sankey, *J. Chem. Soc* (C) (1966) 2339.
6. G. R. Gray and R. Barker, *J. Org. Chem.* **32** (1967) 2764.
7. R. U. Lemieux and J. C. Martin, *Carbohyd. Res.* **13** (1970) 139.
8. R. J. Cushley, J. F. Coddington, and J. J. Fox, *Carbohyd. Res.* **5** (1967) 31.
9. B. Coxon, H. J. Jennings, and K. A. McLauchlan, *Tetrahedron* **23** (1967) 2395.
10. L. D. Hall and J. F. Manville, in *Advances in Chemistry Series*, Vol. 74, *Deoxy Sugars* (R. F. Gould, Editor), American Chemical Society, Washington, D. C., 1968, p. 228.
11. L. D. Hall, *Advances Carbohyd. Chem.* **19** (1964) 51.
12. F. Sweet and R. K. Brown, *Can. J. Chem.* **46** (1968) 2289.
13. K. Bock and C. Pedersen, *Acta Chem. Scand.* **25** (1971) 1021.
14. P. J. Beynon, P. M. Collins, and W. G. Overend, *J. Chem. Soc* (C) (1969) 272.
15. S. Hanessian and N. R. Plessas, *J. Org. Chem.* **34** (1969) 2163.
16. S. Sternhell, *Quart. Rev.* **23** (1969) 236.
17. R. C. Cookson, T. A. Crabb, J. J. Frankel, and J. Hudec, *Tetrahedron Suppl.* **7** (1966) 355.
18. Y. Ali, L. Hough, and A. C. Richardson, *Carbohyd. Res.* **14** (1970) 181.
19. T. D. Inch, J. R. Plimmer, and H. G. Fletcher, Jr., *J. Org. Chem.* **31** (1968) 1825.
20. F. W. Lichtenthaler and P. Emig, *Carbohyd. Res.* **7** (1968) 121.
21. R. U. Lemieux, A. A. Pavia, J. C. Martin, and K. A. Watanabe, *Can. J. Chem.* **47** (1969) 4427.
22. H. G. Fletcher, Jr., and C. S. Hudson, *J. Am. Chem. Soc.* **71** (1949) 3682.
23. K. Bieman, D. C. DeJongh, and H. K. Schnoes, *J. Am. Chem. Soc* **85** (1963) 1763.
24. P. N. Rylander, *Catalytic Hydrogenation over Platinum Metals*, Academic Press, New York, 1967, p. 438.
25. W. G. Dauben and P. D. Hance, *J. Am Chem. Soc.* **77** (1955) 2451.
26. B. Fraser-Reid and B. Radatus, *J. Am. Chem. Soc.* **92** (1970) 6661.
27. O. Achmatowicz, Jr. and B. Szechner, *Tetrahedron Lett.* (1972) 1205.
28. W. G. Dauben, W. K. Hayes, J. S. Schwarz, and J. W. McFarland, *J. Am. Chem.. Soc.* **82** (1960) 2232.
29. R. J. Ferrier, W. G. Overend, and G. H. Sankey, *J. Chem. Soc.* (1965) 2830.
30. K. Heyns and H. Scharmann, *Ann.* **667** (1963) 183.

IZVOD

Katalitičko hidriranje nekih nezasićenih 2-acetamidoaldoza

N. Pravdić, B. Židovec, I. Franjić i H. G. Fletcher, Jr.

Nezasićene heksopiranoze koje imaju 2-(*N*-acetilacetamido) grupu, a dvostruki vez u položaju C-1 — C-2, ili C-2 — C-3, pokazale su se potpuno rezistentnima na katalitičko hidriranje. Tako npr. β-anomeri V i VI ostaju tokom hidriranja nepromijenjeni. Nasuprot tome, odgovarajući α-anomeri VII i VIII, hidrogenolizom gube C-1 acetoksi

grupu te uz migraciju dvostrukog veza prelaze u 4,6-di-*O*-acetil-2-(*N*-acetilacetamido)--1,5-anhidro-2,3-dideoksi-D-*eritro*-heksen-1-itol (IX), odnosno *treo* spoj X.

Prisutnost 2-acetamido grupe ne inhibira susjedni dvostruki vez. Dok β-derivat XIX zasićenjem dvostrukog veza daje spoj XX, 1-*O*-acil-α-anomeri XIII i XV, osim zasićenja dvostrukog veza podliježu hidrogenolizi C-1 acil supstituenta, te daju isti produkt XIV.

Struktura produkata određena je analizom NMR spektara. Diskutiran je mehanizam ovih reakcija, uzimajući u obzir stereokemijske faktore koji dovode do ovako različitog ponašanja.

INSTITUT »RUĐER BOŠKOVIĆ«
41000 ZAGREB
I
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD., U. S. A.

Primljeno 22. studenoga 1972.