DIAZO DERIVATIVES OF SUGARS. SYNTHESIS OF METHYL 2-DEOXY-2-DIAZO-D-*arabino*-HEXONATE, ITS BEHAVIOR ON PHOTOLYSIS AND THERMOLYSIS, AND CONVERSION INTO A PYRAZOLE DERIVATIVE*

D. HORTON AND KERSTIN D. PHILIPS
Department of Chemistry, The Ohio State University, Columbus, Ohio 43210 (U. S. A.)
(Received September 16th, 1971; accepted for publication, October 21st, 1971)

ABSTRACT

The action of nitrous acid on methyl 2-amino-2-deoxy-D-gluconate hydrochloride (**5**) and acetylation of the product gives methyl 3,4,5,6-tetra-*O*-acetyl-2-deoxy-2-diazo-D-*arabino*-hexonate (**6**); 4,6-*O*-benzylidene analogs of the methyl (**4**) and ethyl (**3**) esters are similarly prepared. Photolysis of the diazo sugar **6** in isopropyl alcohol gives mainly methyl 3,4,5,6-tetra-*O*-acetyl-2-deoxy-D-*arabino*-hexonate (**13**) and a small proportion of methyl 4,5,6-tri-*O*-acetyl-2,3-dideoxy-*trans*-D-*erythro*-hex-2-enoate (**14**), whereas photolysis of **6** in methanol gave a *cis,trans* mixture of methyl 3,4,5,6-tetra-*O*-acetyl-2-deoxy-D-*erythro*-hex-2-enoate (**10**); the same mixture (**10**) of enol acetates was obtained by thermolysis of **6**. The diazo sugar **6** underwent cycloaddition with phenylacetylene to give a crystalline (*R* or *S*)-3-(D-*arabino*-tetraacetoxybutyl)-3-methoxycarbonyl-5-phenyl-3*H*-pyrazole (**9**) in 85% yield.

INTRODUCTION

This report[1] has developed out of an interest in the amino sugars that began[2] in the laboratories of Professor M. Stacey in the University of Birmingham, since which time the literature on these sugars has burgeoned to a remarkable degree[3]. Not only are these compounds of interest as constituents of many antibiotics and macromolecules of living tissues, but they have also intrigued the synthetic organic chemist by the diversity of their reactions stemming from their multiple functionality, and they have been exploited as starting materials for synthesis of other molecules of biogical importance.

Diazo derivatives of sugars were investigated extensively[4] by the late Professor M. L. Wolfrom at The Ohio State University, who used the diazomethyl ketones ($RCOCHN_2$) obtained from acetylated aldonyl chlorides and diazomethane as the key step in a useful synthesis of higher ketoses[5]. Non-terminal, diazo derivatives of sugars, stable enough to be sublimed unchanged, were prepared in this laboratory[6]

*Dedicated to Professor M. Stacey, C. B. E., F. R. S., in honour of his 65th birthday.

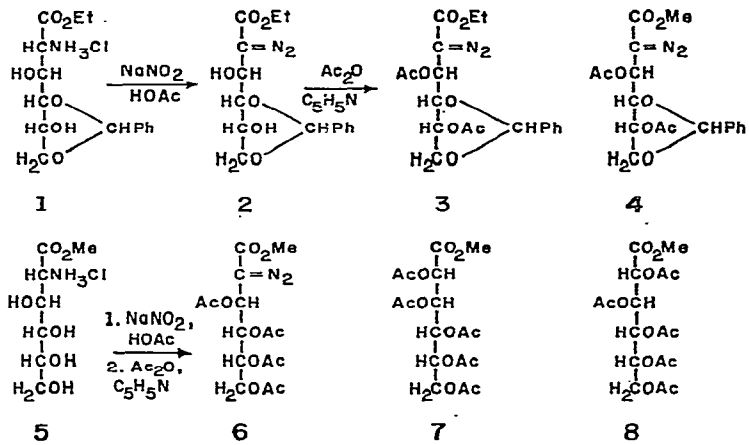
from keto sugars by the Bamford–Stevens[7] route, and their synthetic potential as precursors of modified nucleosides as potential carcinolytes has been noted[6]. However, the first example of a stable diazo derivative of a sugar was recorded by Levene[8] who found that, although 2,5-anhydro derivatives resulted when 2-amino-2-deoxyaldoses or their aldonic acids reacted with nitrous acid (with stereochemical consequences that still invite debate)[3,8–10], cautious treatment with nitrous acid of the benzylidene acetal of ethyl 2-amino-2-deoxy-D-gluconate did not give a nitrogen-free product but gave[11] a solid whose nitrogen content suggested that it was the 2-diazo derivative. Curtius[12] had earlier shown the formation of ethyl diazoacetate by action of nitrous acid on glycine ethyl ester; in contrast, the free amino acids underwent loss of the nitrogenous substituent at once. Levene showed that his diazo derivative underwent hydrolysis to give 2,5-anhydroglucaric acid in low yield, and that hydrogen bromide in ether led to loss of nitrogen and incorporation of the elements of hydrogen bromide. Reduction of the diazo derivative with aluminium amalgam in isopropyl alcohol gave a mixture of a 2-deoxy and a 2-amino-2-deoxy derivative[14]. Levene proposed that the compound was ethyl 5,6-*O*-benzylidene-2-deoxy-2-diazo-D-*arabino*-hexonate. It is now known that stable diazo derivatives can be formed from amines by the action of nitrous acid when a strongly electronegative group, such as RC=O[15], SO_3H[16], CF_3[17], or C≡N[18], is situated adjacent to the amino group.

As part of a general study in sugar systems of reactions that are of potential value in synthesis of compounds of biological interest, we have examined in more detail the diazo sugars obtainable from amino sugar derivatives by the action of nitrous acid, and have established that Levene's product is ethyl 4,6-*O*-benzylidene-2-deoxy-2-diazo-D-*arabino*-hexonate. The behavior of these systems on thermolysis and photolysis has been examined, and the formation of a pyrazole having a sugar chain attached, by 1,3-dipolar cycloaddition of phenylacetylene, has been demonstrated. Similar cycloadditions, leading to 1,2,3-triazoles having a sugar residue at C-4, have been performed in this laboratory[19] by treating sugar derivatives having chain-terminal ethynyl groups with azides. Such reactions are of interest since they provide potential access to the *C*-nucleoside type of structure, as in the formycins[20], showdomycin[21], and pyrazomycin[22]; these derivatives and their analogs are of high current interest as antitumor agents. A synthesis of formycin itself has recently been achieved[23] in which the key step was the 1,3-dipolar cycloaddition of an acetylene derivative to a terminal diazo derivative of 2,5-anhydro-D-ribose. The present approach gives *C*-substituted heterocycles having acyclic sugar chains; since conditions for cyclization of such chains to give oxolanes have been examined in detail with respect to stereochemical control of cyclization[24,25], an alternative route to structural variants of the *C*-furanosyl substituted heterocyclic skeleton is available.

DISCUSSION

When ethyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-gluconate hydrochloride[11] (1) was treated with nitrous acid by a modification of the procedure of Levene[11,12],

there was obtained a yellow, crystalline solid in 78% yield that gave satisfactory elemental analyses for the formula $C_{15}H_{18}N_2O_6$ and had the same specific rotation as that recorded by Levene. The i.r. spectrum of the product showed a strong absorption at 4.76 μm characteristic of the diazo group. A gas was evolved when the compound melted, and t.l.c. of the product after melting indicated that decomposition had occurred. The product was formulated as ethyl 4,6-*O*-benzylidene-2-deoxy-2-diazo-D-*arabino*-hexonate (**2**) rather than the 5,6-*O*-benzylidene structure proposed by Levene[11], since the starting material (**1**), assumed by Levene to be the 5,6-acetal, was later shown[26] to be the 4,6-acetal.



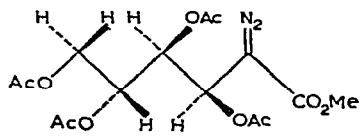
Acetylation of the diazo derivative **2** with acetic anhydride–pyridine gave the 3,5-diacetate **3**, in 92% yield. The mass spectrum of this product showed the $M^+ - N_2$ fragment at *m/e* 378, and the compound decomposed with loss of nitrogen at its melting point. Its n.m.r. spectrum (see Experimental) was entirely concordant with the structure assigned; the low-field positions of the H-3 and H-5 signals and the observed spin-couplings confirmed that a 1,3-dioxane ring was present (4,6-acetal) and not a 1,3-dioxolane ring (5,6-acetal). The crystalline methyl ester analog (**4**) of **3** was similarly prepared and likewise characterized by analysis, and by i.r., n.m.r., and mass spectrometry.

The reactions of the diazo derivative **2** with hydrogen bromide, hydrogen chloride, and aqueous acetic have been reported by Levene[12].

2-Amino-2-deoxy-D-gluconic acid[27] was converted in 94% yield into the hydrochloride (**5**) of the methyl ester by the action of methanolic hydrogen chloride. Cautious treatment of the ester **5** with nitrous acid, followed by acetylation of the product with acetic anhydride–pyridine, gave methyl 3,4,5,6-tetra-*O*-acetyl-2-deoxy-2-diazo-D-*arabino*-hexonate (**6**) as a yellow, crystalline solid in yields of 30–50%. Evidently, the non-acetylated diazo derivative reacts to some extent with the aqueous acetic acid medium in which it is formed, by loss of nitrogen and incorporation of the elements of water, as evidenced by the isolation from the acetylated product of small

proportions of methyl 2,3,4,5,6-penta-*O*-acetyl-D-gluconate (**8**, ~5%) and the D-*manno* analog (**7**, ~3%). For the hydrolysis of the diazo ester **2**, Levene reported[12] isolation of a D-gluconate derivative but not the *manno* isomer.

The peracetylated diazo ester **6** showed the characteristic diazo-group absorption at 4.70 μm in the i.r., and showed strong u.v. absorption at 242 nm. Its mass spectrum showed the anticipated $M^+ - N_2$ ion at *m/e* 360 and its n.m.r. spectrum gave spin-couplings in agreement with the molecule's adopting a planar, zigzag arrangement (**6a**) as the favored conformation; the $J_{3,4}$ and $J_{4,5}$ couplings of 4.5 and 7.4 Hz,

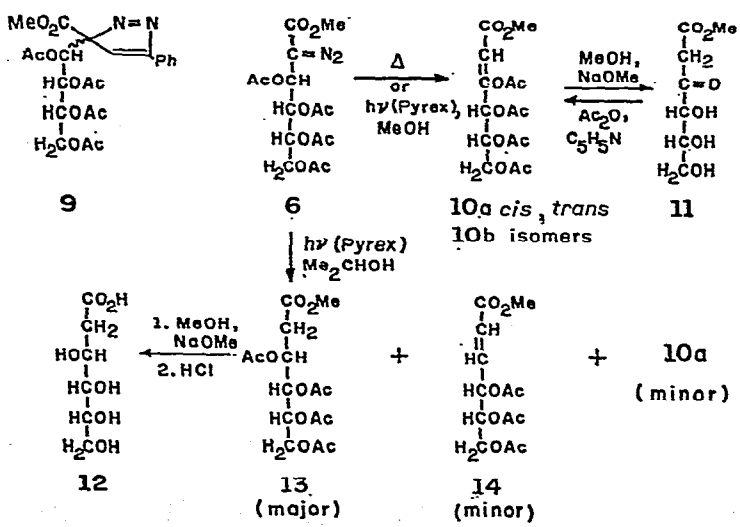


6a

respectively, indicate that H-3 and H-4 are preponderantly gauche and that H-4 and H-5 are preponderantly antiparallel, as observed for related acyclic derivatives of sugars[28].

Although the diazo ester **6** reacts rapidly with aqueous acetic acid, it is stable toward glacial acetic acid at room temperature.

Thermolysis of the diazo ester **6** for 6–8 h at 100–110° gave a 4:1 mixture of two products formulated as the isomeric enol acetates **10a** and **10b** resulting from loss of nitrogen and migration of H-3 to C-2. The n.m.r. spectrum of the mixture showed two singlets [at τ 4.04 for **10a** ($J_{2,4} < 1$ Hz) and τ 3.98 for **10b**, ratio 4:1] in the region for vinyl protons, and the i.r. absorption at 5.95 μm was indicative of an enol ester. Column chromatography gave the preponderant isomer as an analytically pure syrup in 52% yield; its mass spectrum showed the molecular ion (*m/e* 360) and an ion (*m/e*



318) corresponding to loss of ketene, presumably to give a 2-deoxy-3-keto derivative. The broadened singlet at τ 4.04 observed for the vinyl proton in the pure isomer confirmed that the product was that of hydrogen migration to C-2; had acetyl-group migration to C-2 occurred, the vinyl proton would have given a larger doublet signal through vicinal coupling with H-4. Specific *cis,trans* isomeric assignments were not made for the two isomers.

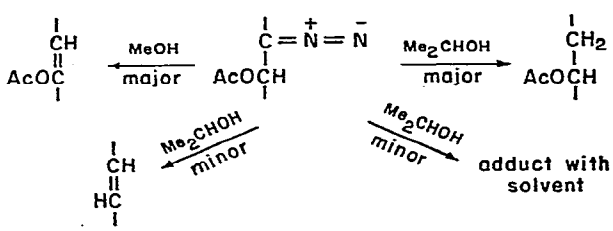
Catalytic deacetylation of **10a** (or of the mixture of **10a** and **10b**) with subsequent reacetylation without neutralization gave back the same mixture of enol acetates **10a**+**10b**, together with other products probably resulting from the furanoid forms of the 2-deoxy-3-hexulosonate **11**. The deoxyketo ester **11** has apparently not been described, and the ease with which it gives the enol acetate is noteworthy.

Photolysis of the diazo ester **6** in isopropyl alcohol with light from a mercury arc filtered through Pyrex glass gave the expected methyl 3,4,5,6-tetra-*O*-acetyl-2-deoxy-D-*arabino*-hexonate (**13**) in 61% yield; the sequence **5**→**6**→**13** provides a method for net conversion of an amino sugar derivative into a deoxy sugar that may be of use in structural modifications of antibiotics. The deoxy ester **13** showed a two-proton doublet at τ 7.42 in its n.m.r. spectrum, assigned to the methylene group having protons essentially equivalent. The ester **13** was characterized by conversion into the free acid **12**, that was compared directly with its known[29] enantiomorph.

Minor side-products from the photolysis of **6** in isopropyl alcohol included the enol acetates **10a**+**10b**, evidently formed by migration of hydrogen from C-3, together with methyl 4,5,6-tri-*O*-acetyl-2,3-dideoxy-*trans*-D-*erythro*-hex-2-enoate (**14**), and a product resulting from incorporation of a molecule of solvent. The unsaturated ester **14** was obtained as a syrup that gave an acceptable analysis, a molecular-ion peak (*m/e* 302) in its mass spectrum, and an n.m.r. spectrum (see Experimental) that was fully in accord with the structure assigned; the $J_{2,3}$ coupling was 15.7 Hz. The other minor component was not characterized, but its n.m.r. spectrum showed the presence of *C*-methyl groups (τ 8.62 and 8.73) evidently resulting from incorporation of solvent.

The course of photolytic decomposition of **6** was altered when methanol was used as the solvent, and the enol acetates **10a**+**10b** were the principal products from the reaction; this variant thus provides potential access to a vicinal deoxyketo system from a vicinal amino alcohol precursor.

The reactions[30] involved in the various photochemical conversions described are summarized in Scheme I.



Scheme I. Photochemical decomposition pathways observed for the diazo ester **6**.

The diazo derivative **6** readily underwent cycloaddition with an excess of phenylacetylene at 50° to give a single, crystalline product, the pyrazole **9**. The stereoselectivity of this addition is somewhat surprising as there are four possible isomers. That the 5-phenylpyrazole is formed, rather than the 4-phenyl derivative, would be expected on the basis of steric and electronic considerations[31]. The configuration about C-3 of the pyrazole moiety appears to be either *R* or *S* and not a mixture. The vinylic proton gives rise to a sharp singlet in the n.m.r. spectrum, and the m.p. and $[\alpha]_D$ remained constant upon recrystallization several times.

The high-resolution mass spectrum of **9** showed two fragments, at *m/e* 103 ($PhC{\equiv}N^{+}$) and 104 ($PhC^{+}{=}NH$), that would be expected from the 5-phenyl derivative rather than the 4-phenyl isomer. Most of the fragments of high mass number corresponded to fragmentation of the carbohydrate side-chain with retention of the intact pyrazole nucleus.

Further studies are in progress on the cyclization of the side chain in derivatives such as **9** to establish a route to analogs of the furanosyl *C*-nucleosides.

EXPERIMENTAL

General methods. — Unless otherwise stated, solutions were evaporated under diminished pressure at room temperature. Melting points were determined with a Thomas–Hoover "Unimelt" apparatus and are uncorrected. I.r. and u.v. spectra were measured with a Perkin–Elmer Model 137 spectrophotometer and a Cary Model 14 recording spectrophotometer, respectively. N.m.r. spectra were determined, by using Varian A-60-A and HA-100 instruments, in chloroform-*d* with tetramethylsilane as the internal standard. Optical rotations were measured with a Perkin–Elmer Model 141 recording polarimeter. Mass spectra were obtained with an AEI MS-902 double focusing, high-resolution spectrometer at an ionization potential of 70 eV, an accelerating potential of 8 kV, and a source temperature of 250°. The mass spectrum of **9**, recorded on an AEI MS-9 spectrometer operated at an ionizing potential of 70 eV and an accelerating potential of 8 kV and a source temperature of 200°, was digitized and data were reduced by programs developed by Battelle Memorial Institute on a Control Data 6400 computer. Microanalyses were performed by W. N. Rond of this laboratory. X-ray powder diffraction data give interplanar spacings in Å for CuKα radiation (camera diameter = 114.59 mm). Relative intensities were estimated visually: m, moderate; s, strong; v, very; w, weak. The three strongest lines are numbered (1, strongest). T.l.c. was performed with 0.25-mm layers of Silica Gel G (E. Merck, Darmstadt, Germany), activated at 120°, as the adsorbent and sulfuric acid as the indicator. Column chromatography was performed with Silica Gel (7734, Merck) as the adsorbent with 1 g of mixture to be separated per 100 g of adsorbent. The petroleum ether employed was the fraction boiling 30–60°.

Ethyl 4,6-O-benzylidene-2-deoxy-2-diazo-D-arabino-*hexonate*[11,13] (**2**). — A modification of the procedure of Levene[11,13] was used. Sodium nitrite (13.8 g) was added to a solution of ethyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-gluconate hydro-

chloride[11] (**1**, 17.4 g, 0.05 mole) in water (250 ml) at 0°. Acetic acid (8.6 ml) was added dropwise while the temperature of the reaction mixture was maintained at 0° by means of an ice–salt bath. The formation of insoluble material was observed immediately. After 40 min, the mixture was extracted with dichloromethane (4 × 100 ml), and the combined extracts were evaporated to a pale-yellow powder that was recrystallized from ether to give **2** (12.6 g, 78%), m.p. 119–119.5°, $[\alpha]_D^{22}$ −49.7° (*c* 1.03, dichloromethane); lit.[13] $[\alpha]_D$ −50°; R_F 0.30 (3:1 dichloromethane–ether); λ_{max}^{KBr} 3.05, 3.45, 4.76 (C=N_2), 5.95 μm (CO_2Et); X-ray powder diffraction data: 14.36 vs (1), 9.93 vw, 8.54 w, 7.40 s (3), 5.69 m, 5.43 w, 4.52 m, 4.13 m, 3.88 s (2).

Anal. Calc. for $C_{15}H_{18}N_2O_6$: C, 55.89; H, 5.63; N, 8.69. Found: C, 55.83; H, 5.47; N, 8.46.

*Ethyl 3,5-di-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-diazo-*D*-arabino-hexonate* (**3**). — Acetylation of **2** (3.2 g, 10 mmoles) with pyridine (10 ml) and acetic anhydride (5 ml) for 8 h at ~25° gave the diacetate **3**; yield 3.7 g (92%). Recrystallized from ether, it has m.p. 90.5–91°, $[\alpha]_D^{23}$ −21.2° (*c* 1.8, dichloromethane); R_F 0.95 (3:1 dichloromethane–ether); λ_{max}^{KBr} 2.90, 3.35, 4.68 (C=N_2), 5.66 (OAc), 5.82 μm (CO_2Et); *m/e* 378 ($M^+ - N_2$); X-ray powder diffraction data: 8.66 s (1), 7.32 s (3), 6.43 vw, 5.76 w, 5.01 vw, 4.63 vw, 4.40 vw, 3.93 m, 3.84 s (2), 3.68 vw, 3.39 w, 3.19 vw.

Anal. Calc. for $C_{19}H_{22}N_2O_8$: C, 56.15; H, 5.46; N, 6.89. Found: C, 56.20; H, 5.47; N, 6.66.

*Methyl 3,5-di-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-diazo-*D*-arabino-hexonate* (**4**) — A sample of **4**, prepared as described for the ethyl ester **3**, had m.p. 139–140°, $[\alpha]_D^{22}$ −49° (*c* 1.2, dichloromethane); R_F 0.85 (3:1 dichloromethane–ether); λ_{max}^{KBr} 2.91, 3.38, 4.69 (C=N_2), 5.66 (OAc), 5.83 μm (CO_2Me); n.m.r. data: τ 2.52 (s, 5H, Ph), 3.97 (d, $J_{3,4}$ 2.1 Hz, H-3), 4.64 (s, PhC*H*), 5.03 (sextet, H-5), 5.60 (q, $J_{5,6}$ 5.4 Hz, $J_{6,6'}$ 10.2 Hz, H-6), 5.87 (q, $J_{4,5}$ 12.0 Hz, H-4), 6.24 (s, 3H, OMe), 6.48 (t, $J_{5,6'}$ 11.4 Hz, H-6), 7.96, 8.02 (s, 3H, OAc); *m/e* 364 ($M^+ - N_2$).

Anal. Calc. for $C_{18}H_{20}N_2O_8$: C, 55.10; H, 5.14; N, 7.14. Found: C, 55.26; H, 5.09; N, 7.06.

*Methyl 2-amino-2-deoxy-*D*-gluconate hydrochloride* (**5**). — A slurry of 2-amino-2-deoxy-D-gluconic acid[27] (20 g, 0.1 mole) in dry methanol (150 ml) was saturated with hydrogen chloride. The solution, which became hot, was shaken vigorously for ~5 min, and the pale-yellow solution was concentrated to a volume ~50 ml on a rotary evaporator. Dry methanol was evaporated from the concentrated solution several times to remove the excess hydrogen chloride, and the white crystals that resulted were filtered off, washed with 1:1 ether–methanol, and dried in a vacuum desiccator over sodium hydroxide; yield 23 g (94%), m.p. 133.5–134°, $[\alpha]_D^{20}$ −12° (*c* 2, water), R_F 0.80 (methanol); λ_{max}^{KBr} 3.05 (OH), 3.40 (NH_3^+), 5.72 μm (C=O); X-ray powder diffraction data: 10.46 s (2,2), 8.04 s (2,2), 5.24 w, 4.60 s (3), 4.00 w, 3.69 vs (1), 3.17 w, 2.86 w, 2.67 m.

Anal. Calc. for $C_7H_{16}ClNO_6$: C, 34.22; H, 6.57; Cl, 14.43; N, 5.70. Found: C, 34.06; H, 6.80; Cl, 14.50; N, 5.80.

*Methyl 3,4,5,6-tetra-*O*-acetyl-2-deoxy-2-diazo-*D*-arabino-hexonate* (**6**). — To a

solution of methyl 2-amino-2-deoxy-D-gluconate hydrochloride (**5**, 12.2 g, 0.05 mole) in water (150 ml) at 0° was added sodium nitrite (3.8 g) in several portions. The temperature of the solution was kept at 0° by means of an ice–salt bath while glacial acetic acid (8.6 ml) in water (5 ml) was added dropwise. The reaction mixture was kept for 5 h at 0° and then allowed to warm to room temperature. The solution was purged with nitrogen for 30 min and then freeze-dried. The solid residue was treated with pyridine (30 ml) and acetic anhydride (15 ml), and the mixture then cooled to 0° and refrigerated overnight. The mixture was poured into ice–water (200 ml) and after 15 min the product was extracted with dichloromethane (4 × 100 ml). The combined extracts were dried ($MgSO_4$) and evaporated to a thick, dark-red syrup (16 g). T.l.c. (3:1 dichloromethane–ether) indicated the presence of at least five components (R_F 0.75, 0.65, 0.60, 0.20, 0.00). Column chromatography (9:1 dichloromethane–ether) of 3 g of syrup gave 1.2 g (33%) of **6** as a yellow syrup that crystallized from methanol–ether as pale-yellow needles, m.p. 63.5–64° (evolution of gas), $[\alpha]_D^{25}$ +8.2° (*c* 2.1, dichloromethane); R_F 0.75; λ_{max}^{KBr} 3.35, 4.70 (C=N_2), 5.62 (OAc), 5.82 μm (CO_2Me); λ_{max}^{MeOH} 242 nm (ε 10,620); n.m.r. data: τ 4.11 (d, $J_{3,4}$ 4.5 Hz, H-3), 4.47 (q, $J_{4,5}$ 7.4 Hz, H-4), 4.80 (sextet, H-5), 4.72 (q, $J_{5,6}$ 3.5 Hz, $J_{6,6'}$ 12.6 Hz, H-6), 5.85 (q, $J_{5,6'}$ 5.3 Hz, H-6'); the chemical shifts of H-6 and H-6', and $J_{5,6}$ and $J_{5,6'}$ were obtained by ABX analysis; *m/e* 360 ($M^+ - N_2$); X-ray powder diffraction data: 9.20 m, 7.66 w, 6.95 m, 6.35 vs (1), 5.68 w, 5.47 w, 4.99 s (3,3), 4.41 s (3,3), 4.19 vw, 3.93 w, 3.79 w, 3.62 vw, 3.45 s (2), 3.04 m.

Anal. Calc. for $C_{15}H_{20}N_2O_{10}$: C, 46.39; H, 5.19; N, 7.22. Found: C, 46.25; H, 5.10; N, 7.10.

The next two components (R_F 0.65 and 0.60) were eluted as a mixture, but by rechromatography with 1:1 ether–petroleum ether as the eluent, the two components were readily separated to give 120 mg (~3%) of methyl 2,3,4,5,6-penta-*O*-acetyl-D-mannonate (**7**), m.p. 78.5–79°, $[\alpha]_D^{20}$ +20.5° (*c* 1.0, dichloromethane), R_F 0.50 (3:1 ether–petroleum ether), identical with an authentic sample of methyl 2,3,4,5,6-penta-*O*-acetyl-L-mannonate[32] by mixed m.p., X-ray powder photograph, and absolute value of $[\alpha]_D$; lit.[32] m.p. 79–80°, $[\alpha]_D^{27}$ −19° (*c* 3.3, chloroform).

The fraction (205 mg, ~5%) having R_F 0.45 (3:1 ether–petroleum ether) was identified as the known methyl 2,3,4,5,6-penta-*O*-acetyl-D-gluconate (**8**), m.p. 123.5–124°, $[\alpha]_D^{21}$ +10.3° (*c* 1.4, dichloromethane); lit.[33] m.p. 124°, $[\alpha]_D$ +9.2° (chloroform).

The component (40 mg) having R_F 0.20 (3:1 dichloromethane–ether) was shown to be methyl 2-acetamido-3,4,5,6-tetra-*O*-acetyl-2-deoxy-D-gluconate, m.p. 113.5–114° (from methanol–ether), $[\alpha]_D^{23}$ −16.6° (*c* 1.0, dichloromethane), resulting from acetylation of unreacted starting material; λ_{max}^{KBr} 2.90, 3.32, 5.69, 5.88 μm; X-ray powder diffraction data: 11.33 m, 8.47 vw, 7.82 s (2,2), 7.28 w, 6.69 s (2,2), 5.85 vw, 5.37 vs (1), 4.69 s (3), 4.43 m, 4.26 w, 3.90 m, 3.74 w, 3.63 m, 3.46 m, 3.36 w, 3.22 vw, 3.07 m.

Anal. Calc. for $C_{17}H_{25}NO_{11}$: C, 48.68; H, 6.01; N, 3.34. Found: C, 48.95; H, 6.17; N, 3.45.

The diazo derivative **6** could be crystallized directly from the acetylated syrup

(30–50% from **5**) if the material was first chromatographed through a short column containing silica gel to remove a dark red, syrupy side-product having R_F 0.0. Crystallization was best effected from methanol–ether at low temperatures.

*Thermolytic conversion of methyl 3,4,5,6-tetra-*O*-acetyl-2-deoxy-2-diazo-*D-arabino-*hexonate* (**6**) *into* cis,trans-*methyl 3,4,5,6-tetra-*O*-*acetyl-2-deoxy-*D-erythro-*hex-2-enoate* (**10**). — The diazo ester **6** (1.0 g, 2.6 mmoles) in a Pyrex test-tube was heated in an oil bath under a nitrogen atmosphere for 6–8 h at 100–110° to give a colorless syrup that by t.l.c. showed two spots, R_F 0.75 and 0.70 (3:1 ether–petroleum ether), in an approximate ratio of 4:1. Separation by chromatography on silica gel (9:1 dichloromethane–ether) gave the major, faster-migrating product, methyl 3,4,5,6-tetra-*O*-acetyl-2-deoxy-D-*erythro*-hex-2-enoate (**10a**) as a colorless syrup (483 mg, 52%), $[\alpha]_D^{25}$ +22.9° (*c* 1.1, dichloromethane); λ_{max}^{film} 3.38, 5.69, 5.95 μm (C=C); n.m.r. data: τ 4.04 (broadened s, $J_{2,4} < 1$ Hz, H-2), 4.41 (broadened d, $J_{4,5}$ 6.5 Hz), 4.66 (m, H-5), 5.68 (t, H-6,6'), 6.31 (s, 3H, OMe), 7.73, 7.90, 7.95 (s, 3H, OAc); *m/e* 360 (M^+), 318 ($M^+ - CH_2{=}C{=}O$).

Anal. Calc. for $C_{15}H_{20}O_{10}$: C, 50.00; H, 5.60. Found: C, 50.32; H, 5.63.

The minor product could not be isolated pure but was considered to be the isomeric enol acetate (**10b**), since the mass spectrum of the mixture of **10a** and **10b** was identical with that of **10a**, and the n.m.r. spectrum of the mixture was very much like that of **10a** except for the presence of an additional singlet for the vinyl proton of **10b** at τ 3.98. No observable change in the H-4 signal was noted, indicating the absence of a proton at C-3. The elemental analysis for the mixture indicated an empirical formula of $C_{15}H_{20}O_{10}$.

*Attempted preparation of methyl 4,5,6-tri-*O*-acetyl-2-deoxy-*D-erythro-*3-hexulosonate.* — The mixture of enol acetates **10a**+**10b** (100 mg) or pure **10a** was treated with 10 ml of 10 mM methanolic sodium methoxide and the mixture was kept for 6 h at room temperature. The methanol was removed by evaporation, and the syrup was immediately treated with pyridine (4 ml) and acetic anhydride (2 ml). After 12 h at room temperature, the reagents were removed first by evaporation and then by evaporation of toluene from the residue. The pale-yellow syrup showed four spots (R_F 0.75, 0.70, 0.55, 0.30) by t.l.c. (3:1 ether–petroleum ether). The fastest-moving component (36 mg), R_F 0.75, was isolated by column chromatography (9:1 dichloromethane–ether) and was identical with **10a** by t.l.c. and n.m.r. spectrum. No attempt was made to isolate the three minor products.

*Photolysis of methyl 3,4,5,6-tetra-*O*-acetyl-2-deoxy-2-diazo-*D-arabino-*hexonate* (**6**). — A solution of the diazo ester **6** (1.0 g, 2.6 mmoles) in reagent-grade 2-propanol (190 ml) was irradiated under nitrogen through a Pyrex filter with light from a mercury arc[34]. The yellow solution became colorless as the irradiation proceeded, and after ~3 h, the product no longer showed i.r. absorption at 4.70 μm. The solution was evaporated to a syrup that by t.l.c. (3:1 dichloromethane–ether) showed three spots having R_F 0.80, 0.75, and 0.65. Column chromatography on silica gel (9:1 dichloromethane–ether) gave four products. The fastest-moving component (R_F 0.80, 12 mg) was not characterized, but the n.m.r. spectrum of this colorless, syrupy product

indicated that it was a product of solvent incorporation, since signals (τ 8.73 and 8.62) characteristic of *C*-methyl groups were present.

Two products having R_F 0.75 (t.l.c.) were isolated. The component (45 mg, 6%) first eluted from the column was identified as methyl 4,5,6-tri-*O*-acetyl-2,3-dideoxy-*trans*-D-*erythro*-hex-2-enoate (**14**), a colorless syrup, $[\alpha]_D^{22}$ +13.6° (*c* 1.1, dichloromethane); λ_{max}^{film} 3.38, 5.68 (OAc), 5.98 μm (C=C); n.m.r. data: τ 3.12 (q, $J_{2,3}$ 15.7 Hz, $J_{3,4}$ 5.4 Hz, H-3), 3.94 (q, $J_{2,4}$ 1.3 Hz, H-2), 4.33 (m, $J_{4,5}$ ~10 Hz), 4.74 (m, H-5), 5.76 (m, H-6,6'), 6.25 (s, 3H, OMe), 7.90, 7.93, 7.96 (s, 3H, OAc); *m/e* 303 ($M^+ + 1$), 302 (M^+).

Anal. Calc. for $C_{13}H_{18}O_8$: C, 51.65; H, 6.00. Found: C, 51.41; H, 5.88.

The third component to be eluted (R_F 0.75, 63 mg, 7%) was identical with the enol acetate **10a** by i.r. and n.m.r. spectra and by specific rotation.

The major component (569 mg, 61%), R_F 0.65, was methyl 3,4,5,6-tetra-*O*-acetyl-2-deoxy-D-*arabino*-hexonate (**13**), obtained as a colorless, waxy solid, m.p. 55–56° (from methanol–ether), $[\alpha]_D^{20}$ +28.6° (*c* 1.0, dichloromethane); λ_{max}^{KBr} 2.80, 3.35, 5.76 μm (OAc); n.m.r. data: τ 4.25–4.98 (overlapping multiplets, 3H, H-3,4,5), 5.74 (m, H-6,6'), 6.28 (s, 3H, OMe), 7.42 (d, $J_{2,3}$ 7.0 Hz, H-2,2'), 7.83, 7.90 (s, 3H, OAc), 7.92 (s, 6H OAc); *m/e* 363 ($M^+ + 1$); X-ray powder diffraction data: 9.76 vw, 8.66 s (2), 6.80 w, 6.46 s (1,1), 6.08 w, 5.79 w, 4.86 w, 4.62 m, 4.44 m, 4.15 m, 3.92 w, 3.71 s (1,1).

Anal. Calc. for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12. Found: C, 50.00; H, 6.18.

Treatment of **13** (200 mg) with 10mM sodium methoxide for 6 h at room temperature gave, after neutralization with Amberlite IR-120 (H^+) resin, filtration, and evaporation, syrupy methyl 2-deoxy-D-*arabino*-hexonate which was hydrolyzed by heating for 30 min on a steam bath with M hydrochloric acid (15 ml). Evaporation of the aqueous solution and crystallization from ethanol, according to the procedure of Corbett[29], gave 2-deoxy-D-*arabino*-hexonic acid (**12**), m.p. 144°, $[\alpha]_D^{20}$ +4.3° (*c* 2, water) [lit.[29] m.p. 145°, $[\alpha]_D^{18}$ +5° (water)], identical with an authentic sample by X-ray powder photograph and mixed m.p.; X-ray powder diffraction data: 6.12 m, 4.81 m, 4.35 w, 4.15 s (1), 3.87 m, 3.62 m, 3.26 s (2,2), 3.12 s (2,2), 2.50 s (3), 2.39 w.

Irradiation of **6** in methanol and examination of the reaction mixture by n.m.r. spectroscopy and by t.l.c. indicated that the enol acetate **10a** was the preponderant product. The 2-deoxy derivative was not observed.

*3-(*D-arabino-*Tetraacetoxybutyl)-3-methoxycarbonyl-5-phenyl-3*H*-pyrazole* (**9**). — A mixture of **6** (388 mg, 1.0 mole) and phenylacetylene (153 mg, 1.5 mmoles) was heated for 3 h at 50° to give a colorless syrup that showed only one product by t.l.c. (R_F 0.50, 3:1 ether–petroleum ether). The syrup was crystallized and the product recrystallized from methanol–water to give **9** (419 mg, 85%) as colorless needles, m.p. 133–135.5°, $[\alpha]_D^{26}$ −22° (*c* 0.95, methanol); λ_{max}^{KBr} 2.84, 3.31, 5.63, 6.31 μm; λ_{max}^{MeOH} 262 (ε 19,900), 280 sh (ε 8,490), 287 nm sh (ε 4,365); n.m.r. data: τ 2.16 (m, Ph), 2.58 (m, Ph), 3.17 (d, $J_{3,4}$ 2.3 Hz, H-3), 3.30 (s, HC=C), 4.17 (q, $J_{4,5}$ 9.3, H-4), 4.54 (m, H-5), 5.68 (m, H-6,6'), 5.81 (s, 3H, OMe), 7.73, 7.79, 7.88, 8.02 (s, 3H, OAc); *m/e* 492 ($M^+ + 2$), 491 ($M^+ + 1$), 490 (M^+), 104.0500 ($PhC^+{=}NH$), 103.0427 ($PhC{\equiv}N^+$);

X-ray powder diffraction data: 12.89 w, 10.27 m, 8.42 s (3), 7.86 s (1), 6.51 w, 6.15 m, 5.81 w, 5.52 m, 5.23 w, 4.83 s (2).

Anal. Calc. for $C_{23}H_{26}N_2O_{10}$: C, 56.32; H, 5.34; N, 5.71. Found: C. 56.62; H, 5.64; N, 5.58.

Repeated recrystallization of **9** gave samples having the same m.p. and $[\alpha]_D$, indicating that the product was a single isomer.

ACKNOWLEDGMENTS

This work was supported, in part, by Grant No. GM-11976-08 from the National Institute of General Medicine, National Institutes of Health, U. S. Public Health Service (The Ohio State University Research Foundation Project 1820). The authors thank Dr. R. L. Foltz and C. R. Weisenberger for recording the mass spectra employed in this study.

REFERENCES

1 For a preliminary report, see D. HORTON AND KERSTIN D. PHILIPS, *Abstr. Papers Amer. Chem. Soc. Meeting*, 161 (1971) CARB 5.
2 D. HORTON, Ph. D. Thesis, University of Birmingham, England, 1957.
3 D. HORTON, *Monosaccharide Amino Sugars*, in R. W. JEANLOZ (Ed.), *The Amino Sugars*, Vol. IA, Academic Press, New York, 1969, pp. 3–211.
4 M. L. WOLFROM, D. I. WEISBLAT, W. H. ZOPHY, AND S. W. WAISBROT, *J. Amer. Chem. Soc.*, 63 (1941) 201.
5 M. L. WOLFROM, Acyclic Derivatives, in W. PIGMAN AND D. HORTON (Eds.), *The Carbohydrates, Chemistry and Biochemistry*, Vol. IA, Academic Press, New York, 1972, Chap. 10.
6 D. HORTON AND E. K. JUST, *Chem. Commun.*, (1969) 1116.
7 W. R. BAMFORD AND T. S. STEVENS, *J. Chem. Soc.*, (1952) 4735.
8 P. A. LEVENE, *Hexosamines and Mucoproteins*, Longmans Green, London, 1925.
9 J. DEFAYE, *Advan. Carbohyd. Chem. Biochem.*, 25 (1970) 181.
10 J. DEFAYE, T. NAKAMURA, D. HORTON, AND K. D. PHILIPS, *Carbohyd. Res.*, 16 (1971) 133.
11 P. A. LEVENE AND F. B. LAFORGE, *J. Biol. Chem.*, 21 (1915) 345.
12 T. CURTIUS, *Ber.*, 16 (1883) 2230.
13 P. A. LEVENE, *J. Biol. Chem.*, 53 (1922) 449.
14 P. A. LEVENE, *J. Biol. Chem.*, 54 (1922) 809.
15 A. ANGELI, *Ber.*, 26 (1893) 1715.
16 H. VON PECHMANN AND P. MANCK, *Ber.*, 28 (1895) 2374.
17 H. GILMAN AND R. G. JONES, *J. Amer. Chem. Soc.*, 65 (1943) 1458.
18 R. BRESLOW AND C. YUAN, *J. Amer. Chem. Soc.*, 80 (1958) 5991.
19 H. EL KHADEM, D. HORTON, AND M. H. MESHREKI, *Carbohyd. Res.*, 16 (1971) 409.
20 R. K. ROBINS, L. B. TOWNSEND, F. CASSIDY, J. F. GERSTER, A. F. LEWIS, AND R. L. MILLER, *J. Heterocycl. Chem.*, 3 (1966) 110.
21 K. R. DARNALL, L. B. TOWNSEND, AND R. K. ROBINS, *Proc. Nat. Acad. Sci., U. S. A.*, 57 (1967) 548; Y. NAKAGAWA, H. KANŌ, Y. TSUKUDA, AND H. KOYAMA, *Tetrahedron Lett.*, (1967) 4105.
22 R. H. WILLIAMS, K. GERZON, M. HOEHN, M. GORMAN, AND D. C. DELONG, *Abstr. Papers Amer. Chem. Soc. Meeting*, 158 (1969) MICR 38.
23 E. M. ACTON, K. J. RYAN, D. W. HENRY, AND L. GOODMAN, *Chem. Commun.*, (1971) 986.
24 J. DEFAYE AND D. HORTON, *Carbohyd. Res.*, 14 (1970) 128.
25 J. DEFAYE, D. HORTON, AND M. MUESSER, *Carbohyd. Res.*, 20 (1971) 305.
26 P. KARRER AND J. MAYER, *Helv. Chim. Acta*, 20 (1937) 407; D. B. HOPE AND P. W. KENT, *J. Chem. Soc.*, (1955) 1831.
27 H. PRINGSHEIM AND G. RUSCHMANN, *Ber.*, 48 (1915) 680; M. L. WOLFROM AND M. J. CRON, *J. Amer. Chem. Soc.*, 74 (1952) 1715.

28 D. HORTON AND M. J. MILLER, *J. Org. Chem.*, 30 (1965) 2457; D. HORTON AND J. D. WANDER, *Carbohyd. Res.*, 10 (1969) 279; 15 (1970) 271; J. DEFAYE, D. GAGNAIRE, D. HORTON, AND M. MUESSER, *ibid.*, 21 (1972) 407.
29 W. M. CORBETT, *Methods Carbohyd. Chem.*, 2 (1963) 18.
30 F. WEYGAND, W. S. SCHWENKE, AND H. J. BESTMANN, *Angew. Chem.*, 70 (1958) 506; S. HAUPTMANN AND K. HIRSCHBERG, *J. Prakt. Chem.*, 34 (1966) 262.
31 R. HUISGEN, *Angew. Chem. Int. Ed. Engl.*, 2 (1963) 565, 633.
32 M. L. WOLFROM AND H. B. WOOD, *J. Amer. Chem. Soc.*, 73 (1951) 730.
33 G. B. ROBBINS AND F. W. UPSON, *J. Amer. Chem. Soc.*, 62 (1940) 1074.
34 D. HORTON AND J. S. JEWELL, *J. Org. Chem.*, 31 (1966) 509.