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Note

Preparation of some carbohydrate pyrazolines by cycloaddition of diazomethane to nitroalkenic sugars*,†

HANS H. BAER AND IAN GILRON
Department of Chemistry, University of Ottawa, Ottawa, Ontario, K1N 9B4 (Canada)

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Among the pioneering achievements carbohydrate research owes to H. O. L. Fischer is the inception and early development of the chemistry of nitro sugars[1]. Commencing[2] in 1944 and continuing[3,4] until his death in 1960. Fischer and his associates provided the cornerstones for the important methodologies[5] of sugar-chain extension by nitroalkane addition, the introduction of nitrogenous functionality into sugars and cyclitols by way of dialdehyde cyclization, and the use of nitro carbohydrates as eminently versatile intermediates for many synthetic purposes. One prominent aspect of nitro sugar chemistry, exemplifying its preparative versatility, is the ease with which nitroalkenic sugar derivatives undergo useful addition reactions, especially[5] of the nucleophilic (Michael) type. Carbohydrate nitroalkenes can also serve as acceptors in 1,3-dipolar cycloadditions, although fewer examples have been reported. Thus, a number of 2,3-dideoxy-3-nitrohex-2-enopyranosides underwent dipolar addition with alkali azides[6] and with diazomethane[7], leading to the annellation of triazole and pyrazoline rings, respectively, to the pyranosidic structure. Nitrogen extrusion from the pyrazolino derivatives (*e.g.* **8**) so obtained, afforded[7] pyranoid 2-*C*-methyl and 2,3-*C*-methylene 3-nitro glycosides, and our interest in this subject was recently rekindled when we studied[8] different methods for the preparation of nitrocyclopropano carbohydrates from terminal *C*-nitro alditols. We therefore decided to examine the addition of diazomethane to carbohydrates possessing a terminal nitroalkene grouping.

3-*O*-Acetyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*xylo*-hex-5-enofuranose[9] (**1**) in ether reacted instantly with ethereal diazomethane at room temperature, and rapidly even at temperatures as low as −60°. However, the reaction appeared to be quite complex, as more than 1 mol. equiv. of the reagent was consumed and several product spots occurred in t.l.c. When the amount of diazo-

*Dedicated to the memory of Hermann O. L. Fischer.
†Reactions of Nitro Sugars, part XLV. For part XLIV see ref. 8.

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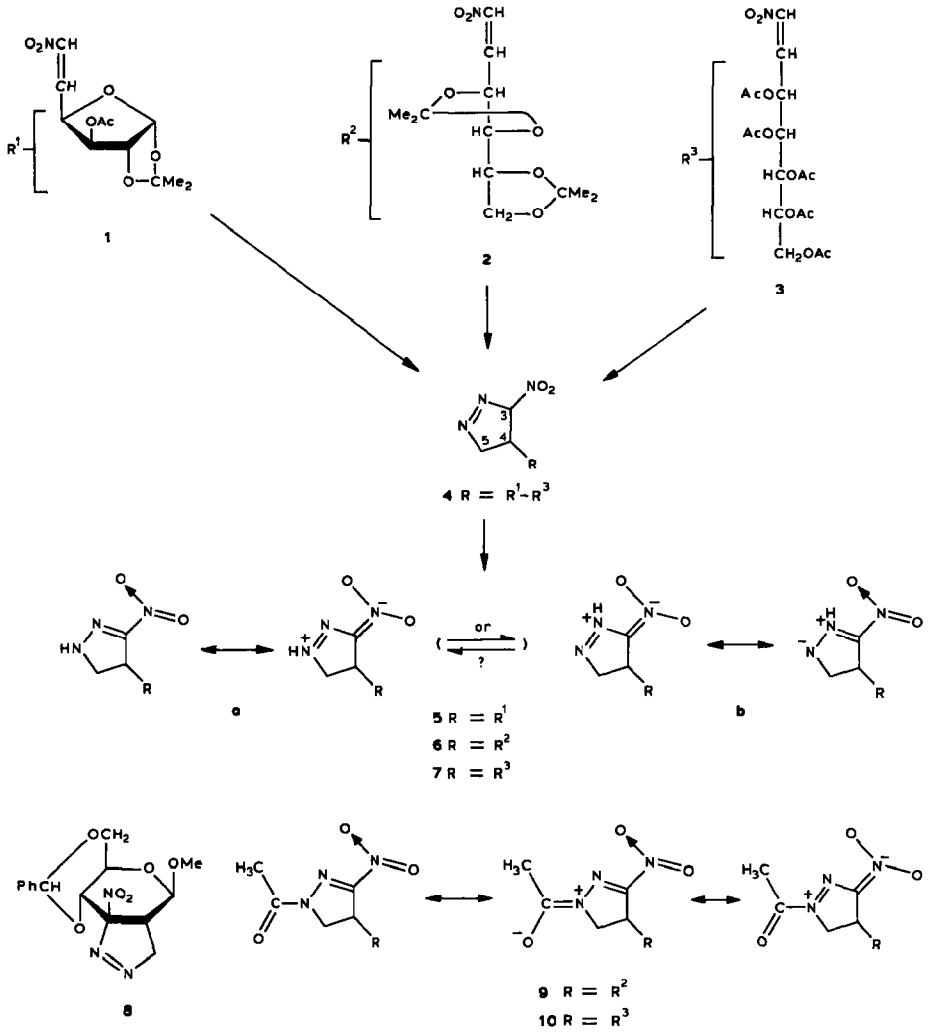

methane added at −15° was limited to 1 mol. equiv., the t.l.c. pattern was qualitatively similar except for the presence of a spot due to unconsumed **1**. 1,2-Dideoxy-3,4:5,6-di-*O*-isopropylidene-1-nitro-D-*arabino*-hex-1-enitol[10] (**2**) and 3,4,5,6,7-penta-*O*-acetyl-1,2-dideoxy-1-nitro-D-*manno*-hept-1-enitol[11] (**3**) showed analogous behavior. In some experiments, dark, resinous products of decomposition or polymerization were observed. Nevertheless, all three of the substrates furnished moderate yields (17, 54, and 29%, respectively) of identifiable products which crystallized from the reaction mixtures without resort to chromatography. These products were established by spectral and microanalytical data to be 4-substituted 3-nitropyrazolines. In the case of **2**, two isomeric products were isolated by fractional crystallization in comparable amounts (combined yield, 54%). They differed strongly in optical rotation, but their i.r. and ^{1}H-n.m.r. spectra conformed to the

same general patterns although they displayed significant differences in details.

There was one conspicuous difference immediately evident between the fused-ring, 1-pyrazolino derivatives (*e.g.*, **8**) previously described[7], and the new products. Whereas the former were colorless (λ_{max} ~325 nm), the latter absorb visible light, being yellow both in the crystalline state and in solution. The absence of ^{1}H-n.m.r. signals attributable to nitromethine protons ruled out the general structure **4** for the isolated products, although such 1-pyrazolines doubtless were the primary products of the diazomethane addition. In the infrared, compounds of type **8** show a *strong* band at 1560 cm^{-1} for the asymmetric stretching mode of the nitro group, with a shoulder at 1540–1535 cm^{-1} presumably due to N=N vibrations, and N–H bands are absent[7]. By contrast, the new compounds exhibit a sharp N–H band at 3360–3310 cm^{-1}, and absorptions in the 1555–1530 cm^{-1} region are of low intensity*. We therefore suggest the constitutions **5–7**; either one of the resonance-stabilized structures **a** and **b** could apply, or both may perhaps exist in tautomeric equilibrium. The two isomeric products (**6**) obtained from **2** are most likely epimers with respect to C-4 of the pyrazoline ring, resulting from nonstereoselective cycloaddition. (Naturally, the isolation of single epimers in modest yields, as in the cases of **5** and **7**, does not imply higher selectivity.) The configuration at C-4 is as yet unknown for all of the products.

In the ^{1}H-n.m.r. spectra of **5**, **6** (both epimers), and **7** the signals for the carbohydrate protons were for the most part well separated, and unambiguously assignable with the aid of the homonuclear shift correlation technique. The methine proton at C-4 of the heterocycle was found to be strongly deshielded in every case (δ 3.9–4.1). Whereas the neighboring, heterocyclic methylene protons in **5** had shifts sufficiently different to permit first-order analysis, this was not so for **6** and **7**, where the CH_2CH signals were unresolvable multiplets. However, treatment of **6** and **7** with acetic anhydride in methanol at room temperature readily effected *N*-acetylation, after which those signals showed enhanced separation and gave recognizable ABM patterns; changes in the shifts of the protons belonging to the carbohydrate moieties were minor. Although the *N*-acetyl derivatives, obtained as chromatographically homogeneous, yellow oils, were characterized by spectral parameters only, it is assumed that they can be represented as **9** and **10**.

EXPERIMENTAL

General methods. — Diazomethane in diethyl ether was generated from *N*-methyl-*N*-nitrosourea, and its concentration estimated by reaction with benzoic acid. Thin-layer chromatography on precoated silica gel plates was performed with

*Attempts were made to isolate intermediates corresponding to **4** from mother liquors, or by performing diazomethane additions at lower temperatures, but these efforts failed to provide chromatographically and spectroscopically homogeneous products. Some impure materials isolated did show i.r. spectra compatible with the structure **4**, however.

1:1 (v/v) ethyl acetate–hexane. Optical rotations were measured at ~25° in a Perkin–Elmer model 241 polarimeter. Infrared data were recorded for Nujol mulls with a Perkin–Elmer model 783 spectrometer. All ^{1}H-n.m.r. data are from 300-MHz spectra obtained with $CDCl_3$ solutions. Chemical shifts, referenced to tetramethylsilane, were measured from the $CHCl_3$ lock signal at δ 7.24. Signal assignments were aided by homonuclear shift correlation experiments. In the listings of data, unprimed positional indicators refer to protons in the carbohydrate unit, and primed ones to pyrazoline ring-protons.

*3-O-Acetyl-1,2-O-isopropylidene-4-C-(3-nitro-2-pyrazolin-4-yl)-α-*D*-xylo-tetrofuranose* (**5**)*. — Diazomethane (1 mmol) in ether (6 mL) was added dropwise to a cooled (−15°) solution of compound[9] **1** (273 mg, 1 mmol). T.l.c. then indicated some unreacted **1** (R_F 0.9) and two spots (R_F 0.3–0.6) representing at least two products. During storage overnight at −18° the yellow solution deposited **5** (R_F 0.3) as yellow needles (54 mg, 17%), m.p. 167–169° (dec.), $[\alpha]_D$ +145°, $[\alpha]_{578}$ +156°, $[\alpha]_{546}$ +197°, $[\alpha]_{436}$ +84°, $[\alpha]_{365}$ ~+2° (*c* 1.6, chloroform); i.r.: ν_{max} 3360 (NH), 1735 (OAc), and 1530 cm^{-1} (weak); ^{1}H-n.m.r.: δ 5.88 (d, $J_{1,2}$ 3.8 Hz, H-1), 5.18 (d, $J_{3,4}$ 3.0 Hz, H-3), 4.79 (~t, width 7.3 Hz, H-4), 4.51 (d, $J_{1,2}$ 3.8 Hz, H-2), 4.31 (dd, $J_{4',5'a}$ 8.0, $J_{5'a,5'b}$ 11.1 Hz, H-5'a), 4.04 (dd, $J_{5'a,5'b}$ 11.1, $J_{4',5'b}$ 12.6 Hz, H-5'b), 3.91 (septet, $J_{4,4'}$ 4.3, $J_{4',5'a}$ 8.0, $J_{4',5'b}$ 12.6 Hz, H-4'), 2.10 (s, 3 H, OCOCH_3), 1.48 and 1.28 (2 s, each 3 H, CCH_3); m.s. (c.i., ether): *m/z* 316 (M^+ +1).

Anal. Calc. for $C_{12}H_{17}N_3O_7$ (315.3): C, 45.7; H, 5.4; N, 13.3. Found: C, 45.9; H, 5.5; N, 12.8.

T.l.c. of the mother liquor gave strong spots for **1** (R_F 0.9) and an unidentified product (R_F 0.6), and a weak spot for **5** (R_F 0.3). Column chromatography of the mixture on silica gel (7 g) with 1:1 ethyl acetate–hexane as the eluant resulted in poor separation. By rechromatography of the pooled eluates using 1:3 ethyl acetate–hexane, crystalline **1** was recovered; however, contrary to expectations only a few milligrams of the material having R_F 0.6 emerged, and this was followed by a substantial amount of **5**. It appears that an interconversion of products had occurred during the chromatographic operations.

Performance of diazomethane addition to **1** (273 mg) as just described, but at −60 to −50°, resulted in a t.l.c. pattern similar to that mentioned for the foregoing mother liquor: no crystallization took place. Evaporation of the solution at room temperature gave a yellow oil which showed two additional, weak spots (R_F 0.7–0.8) in t.l.c. Flash chromatography of the oil on silica gel (7 g) with 1:3 ethyl acetate–hexane produced colorless **1** (~100 mg), a yellow solid (150 mg), and **5** (40 mg). The yellow solid was not homogeneous (double spot on t.l.c., R_F 0.6). Its complex ^{1}H-n.m.r. spectrum showed substituent and ring-proton resonances that were similar to, but not identical with, those recorded for **5**, and there was extensive duplication of signals. The i.r. spectrum exhibited a sharp ester carbonyl band (1745

*For the purpose of registration, the uncharged form of tautomer **a** is named; no prejudice concerning any tautomeric or electromeric predominance is implied. The same holds for **6** and **7**.

cm^{-1}) and a *strong* NO_2 band (1550 cm^{-1}), but lacked the NH band and the weak band at 1530 cm^{-1} seen in the spectrum of **5**, from which it also differed significantly in the fingerprint region. Attempts at separating the components of this product by recrystallization and preparative t.l.c. were unsuccessful.

1,2:3,4-Di-O-isopropylidene-1-C-[(4R and 4S)-3-nitro-2-pyrazolin-4-yl]-D-arabino-tetritol (**6**). — In pilot experiments the mixing of ether solutions of **2** and CH_2N_2 in equimolar proportions resulted in rapid consumption of the latter, but incomplete reaction of the former, both at 25 and at −12°. Therefore, a solution of **2** (639 mg) in ether (30 mL) was treated at 0° with ethereal CH_2N_2 in excess of 1 equiv., the reagent being added dropwise until **2** (R_F 0.9) was no longer visible on t.l.c. The two stereoisomeric forms of the product **6**, having R_F 0.3 and 0.4, respectively, were designated as epimers I and II. Epimer I crystallized spontaneously from the solution as yellow needles (177 mg, 24%) having m.p. 165–170°, raised to 174–176° by recrystallization from ether. Concentration of the mother liquor afforded a crystalline mixture of I and II (121 mg, 16%), followed by a fraction of pure epimer II (103 mg, 14%), m.p. 125–130°.

Epimer I showed $[\alpha]_D$ +157°, $[\alpha]_{578}$ +167°, $[\alpha]_{546}$ +207°, $[\alpha]_{436}$ +628°, $[\alpha]_{365}$ −83° (!) (*c* 0.6, chloroform); i.r.: ν_{max} 3300 (sharp, NH), 1555 (weak single peak), 1500 (weak single peak), 1350, 1340, and 1300 cm^{-1} (weak but distinct bands); ^{1}H-n.m.r.: δ 4.65 (dd, lines broadened due to long range coupling, $J_{1,4'}$ 1.1, $J_{1,2}$ 8.3 Hz, H-1), 4.16–4.03 (complex m, 5 H, H-3, 4a, 4', 5'a, 5'b), 3.93 (dd, $J_{3,4b}$ 4.3, $J_{4a,4b}$ 8.3 Hz, H-4b), 3.38 (t, $J_{1,2} = J_{2,3}$ = 8.3 Hz, H-2), 1.37, and 1.32 (pairs of nearly coincident singlets, 12 H, CCH_3); m.s. (c.i., ether): *m/z* 316 ($M^+ + 1$).

Anal. Calc. for $C_{13}H_{21}N_3O_6$ (315.3): C, 49.5; H, 6.7; N, 13.3. Found: C, 49.4; H, 6.4; N, 13.3.

The ^{1}H-n.m.r. data for the *N*-acetyl derivative (**9**) obtained from epimer I were: δ 4.56 (dd, $J_{1,4'}$ 2.2, $J_{1,2}$ 8.3 Hz, H-1), 4.3–4.2 (ABM-multiplet, 3 H, H-4', 5'a, 5'b), 4.10 (m, H-4a), 4.06 (octet, H-3), 3.93 (dd, $J_{3,4b}$ 4.2, $J_{4a,4b}$ 8.3 Hz, H-4b), 3.38 (t, $J_{1,2} = J_{2,3}$ = 8.4 Hz, H-2), 2.37 (s, 3 H, $NCOCH_3$), 1.36, 1.35, 1.32, and 1.31 (4 s, 3 H each, CCH_3).

Epimer II showed $[\alpha]_D$ +70°, $[\alpha]_{578}$ +74°, $[\alpha]_{546}$ +86°, $[\alpha]_{436}$ +174°, (*c* 0.6, chloroform; strong absorption at 365 nm); i.r.: ν_{max} 3315 (sharp, NH), 1555 and 1548 (weak doublet), 1495 and 1490 (weak doublet), 1405, and 1330 cm^{-1} (weak but distinct bands), and in the fingerprint region, noticeable differences from the spectrum of epimer I. ^{1}H-n.m.r. data: δ 4.62 (ddd, $J_{1,4'}$ 2.5, $J_{1,2}$ 7.0, $J_{1,5'a}$ −1.2 Hz, H-1), 4.14 (dd, $J_{3,4a}$ 5.8, $J_{4a,4b}$ 8.2 Hz, H-4a), 4.10 (narrow m, 3 H, H-4', 5'a, 5'b), 3.89 (dt, H-3), 3.82 (dd, $J_{3,4b}$ 6.3, $J_{4a,4b}$ 8.2 Hz, H-4b), 3.72 (dd, $J_{1,2}$ 7.0, $J_{2,3}$ 8.8 Hz, H-2), 1.40, 1.34, 1.30, and 1.26 (4 s, 3 H each, CCH_3); m.s. (c.i., ether): *m/z* 316 ($M^+ + 1$).

Anal. Found: C, 49.7; H, 6.4; N, 13.1.

1,2,3,4,5-Penta-O-acetyl-1-C-(3-nitro-2-pyrazolin-4-yl)-D-manno-pentitol (**7**). — A solution of compound[11] **3** (1.132 g) in oxolane (30 mL) was treated at −5° with ethereal CH_2N_2 until most of the **3** (R_F 0.85) was consumed; a major product

spot (R_F 0.3) accompanied by trace spots (R_F 0.5–0.7) was seen in t.l.c. Evaporation of the solvent gave a yellow oil, which was dissolved in a small amount of methanol. The careful addition of water to incipient cloudiness, and subsequent cooling, produced yellow crystals of **7** (360 mg, 29%), m.p. 148–153° (dec.), increasing to 152–156° (dec.) after recrystallization, $[\alpha]_D$ +11.4°, $[\alpha]_{578}$ +9.3°, $[\alpha]_{546}$ 0°, $[\alpha]_{436}$ −280° (*c* 1.2, chloroform; strong absorption at 365 nm); i.r.: ν_{max} 3360 (sharp, NH), 1753 and 1740 (OAc), 1535 (weak), and 1340, with shoulder at 1327 cm^{-1}; m.s. (c.i., ether): *m/z* 476 ($M^+ + 1$); ^{1}H-n.m.r.: δ 5.65 (dd, $J_{2,3}$ 1.95, $J_{1,2}$ 10.3 Hz, H-2), 5.50 (d of narrow dd, indicating $J_{1,2}$ 10 Hz and $J_{1,4'} \approx -J_{1,5'a} \approx 2$ Hz, H-1), 5.39 (dd, $J_{2,3}$ 1.95, $J_{3,4}$ 9.2 Hz, H-3), 4.95 (ddd, $J_{4,5a}$ 2.8, $J_{4,5b}$ 4.7, $J_{3,4}$ 9.2 Hz, H-4), 4.17 (dd, $J_{4,5a}$ 2.8, $J_{5a,5b}$ 12.6 Hz, H-5a), 4.14–4.04 (unresolved m, 3 H, H-4′, 5′a, 5′b), 4.03 (partially obscured dd, $J_{4,5b}$ 4.7 Hz, H-5b), 2.10, 2.06, and 2.05 (s, 3 H each, 3 OCOCH_3), and 2.02 (s, 6 H, 2 OCOCH_3).

Anal. Calc. for $C_{18}H_{25}N_3O_{12}$ (475.4): C, 45.5; H, 5.3; N, 8.8. Found: C, 45.4; H, 5.2; N, 8.8.

The ^{1}H-n.m.r. spectrum of the *N*-acetyl derivative (**10**) of **7** showed essentially the same *J* values: δ 5.55 (dd, H-2), 5.43 (dd, H-1), 5.38 (dd, H-3), 4.88 (ddd, H-4), 4.43 and 4.23 (centers of 1-H and 2-H multiplets showing an ABM pattern, H-4′, 5′a, 5′b), 4.15 (dd, H-5a), 4.02 (dd, H-5b), 2.30 (s, 3 H, NCOCH_3), 2.08, 2.07, 2.03, 2.01, and 1.99 (s, 3 H each, 5 OCOCH_3).

When crystallization of **7** from its concentrated, methanolic solution was forced by strong cooling, or by the addition of too much water, lower-melting mixtures of the compound characterized above and what appeared to be an isomer were deposited. These gave twin spots in t.l.c., and complex n.m.r. spectra showing signal duplication. One such mixture was found to be strongly dextrorotatory in the range of λ 589–436 nm.

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