An Unusual Course of a Nitro Sugar Acetylation: Formation of a Crystalline Nitronic Acid – Acetic Acid Mixed Anhydride[1]

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Whereas acetylation of methyl 4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-mannopyranoside (**1**) and its β-D-*galacto* isomer **2** with acetyl chloride and triethylamine in ether furnished the expected 2-*O*-acetylated nitro glycosides, **1***a* and **2***a*, the same method applied to the α-D-*talo* isomer **3** gave the 2-*O*-acetyl derivative of the corresponding nitronic acid – acetic acid anhydride, **4**.

L'acétylation du méthyl *O*-benzylidène-4,6 déoxy-3 nitro-3 β-D-mannopyranoside (**1**) et de son isomère β-D-*galacto* **2**, par le chlorure d'acétyle et la triéthylamine dans l'éther, conduit aux produits attendus à savoir les nitro glycosides *O*-acétylés en 2, **1***a* et **2***a*. La même méthode appliquée à l'isomère α-D-*talo* **3** conduit au dérivé *O*-acétylé en 2 d'un anhydride d'acide nitronique et acétique (**4**).

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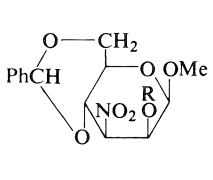
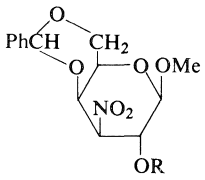
The preparation of nitro sugar acetates by standard acetylation techniques is sometimes attended with difficulties due to occurrence of dehydration or dehydroacetylation and other complications that may ensue (1). Boron trifluoride catalysis (2, 3) has proved very efficient in the acetylation of various sensitive compounds, circumventing some of the difficulties mentioned, but in one recent instance it has caused acetolysis of a trityl ether function (4). This was overcome by the use of equivalent amounts of acetyl chloride and triethylamine in ether solution at 0°. The method, which involves an intermediate generation of ketene, has now been applied to methyl 4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-mannopyranoside (**1**), -β-D-galactopyranoside (**2**), and -α-D-talopyranoside (**3**).

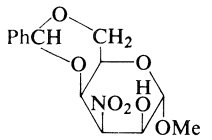
Whereas **1** and **2** gave high yields of the expected (and known) 2-acetates **1***a* and **2***a*, respectively, the taloside **3** furnished in 92% yield an abnormal product. Elemental analysis of the crystalline material (m.p. 136–137°) corresponded to $C_{18}H_{21}NO_9$, and the n.m.r. spectrum revealed that *two* acetyl groups had entered although the benzylidene acetal as well as the anomeric methoxyl group were retained. The i.r. spectrum was free from hydroxyl absorption and showed an ester carbonyl band at 1750 cm^{-1}, but it lacked the band expected for the nitro group in the 1550 cm^{-1} region. Instead, there was a sharp peak at 1800 cm^{-1} attributable to an acid anhydride structure, and an intense band occurred at 1620 cm^{-1}, in the region where nitronic acids and their esters show strong C=N absorption (5). The product exhibited high-intensity u.v. absorption (λ_{max} 242 nm, ε 8000, in methanol) in the range in which nitronic acids and their salts are known to absorb strongly (5) in contrast to nitroalkanes that have very low absorption in



1 R = H
1*a* R = Ac



2 R = H
2*a* R = Ac



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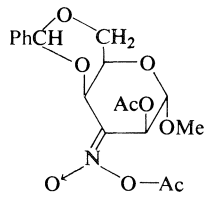

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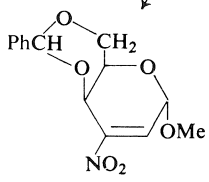

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[1]Part XXII in a series on the reactions of nitro sugars. For Part XXI see ref. 7.

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that range. Although the compound was remarkably stable in the crystalline state and could be recrystallized from ethyl acetate, it suffered loss of both acetyl groups when chromatographed on silica gel, giving in 85% yield the known methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-*threo*-hex-2-enopyranoside (**5**). This fact demonstrated that the acetylation of **3** had masked but not irreversibly altered or removed the nitro group at C-3. On the basis of all the spectroscopic and chemical evidence we allocate to the new compound the structure **4** of a mixed nitronic acid–acetic acid anhydride. Although the chemistry of nitronic esters has been investigated extensively, only a few nitronic carboxylic anhydrides have been described in the literature, and spectral data do not seem to be available (5, 6). In nitronic esters, the occurrence of geometrical isomerism has been established, and the same may be predicted for anhydrides. This matter has not yet been examined in connection with **4**, and the formula depicted is arbitrary with respect to the C=N bond geometry.

We have recently shown that nitronate formation with base occurs in **3** much more readily than it does in **1** and **2**, and the differences in nitromethylene acidity of these and a number of similar glycosides were interpreted by stereochemical considerations (7). Apparently the unusual behavior of **3** reported here is another manifestation of the special ease with which this isomer is converted into the *aci*-nitro form.

Experimental

*Methyl 2-O-Acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-β-D-mannopyranoside (**1a**)*

Triethylamine (1.93 ml, 13.8 mmol) in anhydrous ether (30 ml) was chilled in an ice water bath, and acetyl chloride (1.04 ml, 14.7 mmol) was added with magnetic stirring. A voluminous white precipitate of triethylammonium chloride occurred. After 5 min a solution of the nitro mannoside **1** (8) (206 mg, 0.66 mmol) in dry dichloromethane (4 ml) was added and the reaction mixture was stirred for 30 min at 0°. The mixture was then agitated with cold water, and after phase separation, the aqueous layer was extracted twice with ether. The combined ether solution and extract was washed three times with water, dried over sodium sulfate, and evaporated giving crystalline **1***a* (223 mg, 95%). Upon recrystallization from chloroform – petroleum ether the material (194 mg, 83%) showed m.p. 162–163°, $[\alpha]_D$ −88.7° (*c*, 0.53 in $CHCl_3$), lit. (8), m.p. 136–137° after recrystallization from aqueous ethanol; $[\alpha]_D$ not reported. Because of the melting point discrepancy the earlier acetylation procedure (8) was repeated but the product was recrystallized from chloroform – petroleum ether. The product (yield, 79%, m.p. 159–160°) was identical with that prepared by the new method according to mixed melting point, i.r. spectrum (8), and n.m.r. spectrum (100 MHz in $CDCl_3$): τ 2.6 (5-proton multiplet, phenyl), 4.13 (1-proton doublet, H-2, with $J_{2,3} = 3.5$, $J_{1,2} = 0$ Hz), 4.33 (1-proton singlet, $PhCHO_2$), 5.20 (1-proton quartet, H-3, with $J_{2,3} = 3.5$, $J_{3,4} = 10.5$ Hz), 5.48 (sharp singlet, H-1, overlapped by H-6,6′ multiplet), 6.05 (symmetrical 1-proton triplet with 10.5 Hz splitting, H-4), 6.50 (3-proton singlet, OCH_3, overlapping H-5 multiplet), 7.89 (3-proton singlet, *O*-acetyl).

*Methyl 2-O-Acetyl-4,6-O-benzylidene-3-deoxy-3-nitro-β-D-galactopyranoside (**2a**)*

The nitro galactoside **2** (8) (206 mg) was dissolved in 10 ml of dichloromethane and acetylated as described above for **1**. Upon decomposition of the reaction mixture with water, the main part of the product **2***a* (160 mg) separated as crystals which were collected, washed with cold water, and dried; m.p. 149–151°. An additional crop (43 mg, m.p. 146–148°) was obtained by work-up of the reaction mixture as described for **1**. Total yield, 87%. The i.r. spectrum was superposable with that of **2***a* prepared earlier (2).

*Methyl 2-O-Acetyl-3-(O-acetyl-aci-nitro)-4,6-O-benzylidene-3-deoxy-α-D-lyxo-hexopyranoside (**4**)*

The nitro taloside **3** (9) (103 mg, 0.33 mmol) in dichloromethane (3 ml) was treated as described above for **1** with acetylating reagent consisting of acetyl chloride (0.52 ml, 7.3 mmol) and triethylamine (0.97 ml, 6.9 mmol) in anhydrous ether (20 ml). The aforementioned work-up procedure gave 120 mg (92%) of crystals that were homogeneous on t.l.c. with carbon tetrachloride – ethyl acetate (2:3, v/v). Recrystallization from ethyl acetate gave a first crop of **4** (29 mg, m.p. 136–137°), and a second crop (83.5 mg, m.p. 132–135°) upon addition of petroleum ether to the mother liquor. For i.r. and u.v. data, see discussion. The n.m.r. data (100 MHz, in $CDCl_3$): τ 2.5–2.7 (5-proton multiplet, phenyl), 4.35 (overlapping signals with 2-proton intensity, H-2 and $PhCHO_2$), 4.9–6.2 (signals corresponding to 5 ring protons), 6.62 (3-proton singlet, OCH_3), 7.83, 7.96 (3-proton singlets, *O*-acetyl).

Anal. Calcd. for $C_{18}H_{21}NO_9$ (395.4): C, 54.65; H, 5.35; N, 3.54. Found: C, 54.61; H, 5.18; N, 3.64.

A sample of **4** (100 mg) was chromatographed on a column (1.5 × 30 cm) containing 20 g of silica gel (0.05–0.20 mm, E. Merck AG, Darmstadt, Germany) with carbon tetrachloride – ethyl acetate (2.0:1.5, v/v) as eluent. The effluent was monitored by t.l.c., and only a single compound appeared. Evaporation furnished crystalline nitroolefin **5** (63 mg, 85%), m.p. 187–188°, whose i.r. spectrum was superposable with that of an authentic sample; reported, m.p. 185–186° (9).

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Synthesis of 3-Deoxy-3-nitro-D-xylose[1]

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Crystalline 3-deoxy-3-nitro-α-D-xylose (**5**) was obtained in 40% over-all yield by periodate oxidation of 3-deoxy-1,2-*O*-isopropylidene-3-nitro-α-D-glucofuranose (**2**) followed by borohydride reduction and acid hydrolysis. In addition to the intermediate 3-deoxy-1,2-*O*-isopropylidene-3-nitro-α-D-xylofuranose (**4**), a small amount of an isomer probably having the D-*ribo* configuration was isolated. The title compound (**5**) was also obtained by hydrolysis of its methyl β-pyranoside (**1**).

Le déoxy-3 nitro-3 α-D-xylose (**5**) cristallisé, a été obtenu avec un rendement global de 40% par oxydation au periodate du déoxy-3 *O*-isopropylidène-1,2 nitro-3 α-D-glucofuranose (**2**), suivie par une réduction au borohydrure et hydrolyse acide. En plus du produit intermédiaire, le déoxy-3 *O*-isopropylidène-1,2 nitro-3 α-D-xylofuranose (**4**), une petite quantité d'un isomère ayant probablement la configuration du D-*ribo*, a été isolée. Le composé (**5**) a également été obtenu par hydrolyse de son méthyl β-pyranoside.

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For a study (1) on conformational and configurational equilibria in methyl 3-deoxy-3-nitropentopyranosides it was desirable to prepare the methyl β-pyranoside **1** of 3-deoxy-3-nitro-D-xylose (**5**). The glycoside was known to be a minor by-product in the nitromethane cyclization of L′-methoxydiglycolaldehyde; its formation had been revealed by isolation of the corresponding amine subsequent to catalytic hydrogenation, but the nitro glycoside itself had not been isolated (2). Although new efforts to separate **1** in crystalline condition from the products of nitromethane cyclization eventually proved successful (1), an independent synthesis of the parent sugar **5** was concurrently undertaken, and this synthesis, the first of a free nitro pentose, is recorded here.

3-Deoxy-1,2-*O*-isopropylidene-3-nitro-α-D-glucofuranose (**2**) (3) was oxidized with sodium metaperiodate and the resulting pentodialdose derivative **3**, which was not isolated, was reduced with sodium borohydride to give syrupy but sufficiently well-characterized 3-deoxy-1,2-*O*-isopropylidene-3-nitro-α-D-xylofuranose (**4**) as the main product. A crystalline by-product arose in small proportion and was revealed by analysis and spectroscopy to be an isomer of **4**. Although its configuration was not established by chemical means, it most likely was the D-*ribo* isomer, formed by alkali-catalyzed epimerization during the borohydride reduction.[2] The n.m.r. spectra of **4** and its isomer are in accord with this assumption and suggest, moreover, the T_2[3] conformation for both compounds, *i.e.* the same conformation that has been assigned (3) to the glucofuranose derivative **2**. As in the latter, the xylofuranose **4** exhibits zero coupling between H-2 and -3 and a coupling of 4 Hz between H-3 and -4. The isomer, on the other hand, shows coupling between H-2 and -3 (although its value could not be determined by first-order analysis), and it exhibits a 10 Hz coupling between H-3

[1]Part XXIV in a series on reactions of nitro sugars. For part XXIII see ref. 3.

[2]Compare the analogous, D-*gluco* → D-*allo* epimerization described in the preceding article (3).