Reaction of 2,3:5,6-Di-*O*-isopropylidene-D-mannose Oxime with Some Dehydrating Agents

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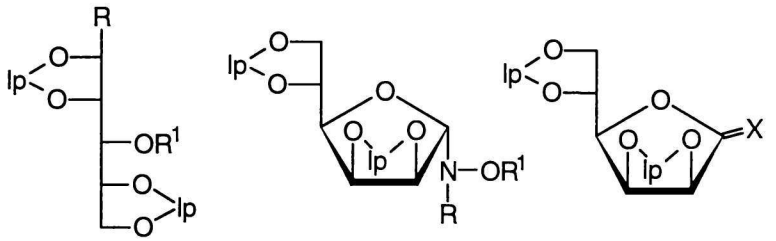
Dedicated to Professor H. S. Mosher, in honour of his 80th birthday

Reaction of 2,3:5,6-di-*O*-isopropylidene-D-mannose oxime with some dehydrating agents (acetic anhydride, phenyl isocyanate, phosphorus pentoxide) was studied. The presence of one free hydroxyl group at C-4 atom as well as the possibility of existence of hydroxylamino tautomer of the title compound with α-D configuration are responsible for the formation of different products depending on dehydrating agent and the reaction conditions used. The isolated compounds were characterized by the NMR and mass spectral data.

It is well known that aldoximes may be converted to the nitriles by dehydration using such reagents as acetic anhydride, phosphorus pentachloride, thionyl chloride, phosphorus pentoxide, triethyl orthoformate, benzoyl chloride, phenyl isocyanate, *etc.* [1—8]. Some of these we have used with an intention to convert 2,3:5,6-di-*O*-isopropylidene-D-mannose oxime (*I*) into corresponding nitrile *II*. The presence of one free hydroxyl group at C-4 carbon atom as well as the possibility of existence of the hydroxylamino tautomer *III* of the title compound [9, 10] with α-D-configuration are responsible for the formation of different products depending on dehydrating agent and reaction conditions used.

Thus, using acetic anhydride at room temperature, *N*-acetoxy-*N*-acetyl-2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosylamine (*IV*) was formed preferably. At higher temperature, a mixture (x_r = 8 : 1) of diacetate *IV* and 4-*O*-acetyl-2,3:5,6-di-*O*-isopropylidene-D-mannononitrile (*V*) was obtained. When *I* was heated with acetic anhydride in the presence of pyridine, a mixture (x_r = 1 1) of *IV* and *V* resulted. Finally, keeping *I* in pyridine at room temperature for 48 h and subsequent addition of acetic anhydride under reflux afforded *IV* and *V* in the ratio x_r of 1 : 2. These observations indicate that in the presence of base the proportion of oxime tautomer *I* is favoured. Products *IV* and *V* can be easily separated on a column of silica gel. The NMR spectral data of *V* are in a good accordance with those given for corresponding 4-*O*-methylsulfonyl [7], 4-*O*-benzoyl [8], and 4-*O*-dimethoxyphosphoryl [11] analogues. An attempt to prepare *II* by deacetylation of *V* under usual conditions (MeONa, MeOH) led to the formation of known 2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone (*VI*) [12].

Reaction of *I* with one equivalent of phenyl isocyanate at room temperature afforded *N*-(2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)-*N*-phenylcarbamylhydroxylamine (*VII*) almost quantitatively. The structure of α-anomer of the furanose form was confirmed on the basis of ^{1}H NMR spectra where characteristic singlet ($J_{1,2}$ = 0) of anomeric hydrogen atom at δ = 5.74 and $J_{2,3}$ = 6.0 Hz were observed [9, 12—15]. Moreover, the absence of the signal corresponding to the oxime carbon atom in the ^{13}C NMR spectra is also confirmative. The use of three equivalents of phenyl isocyanate and catalytic amount of triethylamine resulted in the formation of a mixture of three products.



I R = CH=NOH, R^1 = H
II R = CN, R^1 = H
V R = CN, R^1 = Ac
VIII R = CN, R^1 = CONHPh

III R = R^1 = H
IV R = R^1 = Ac
VII R = CONHPh, R^1 = H

VI X = O
IX X = NOCONHPh

Ip = isopropylidene

Two of them (major) with higher R_f in TLC were isolated and identified as 2,3:5,6-di-*O*-isopropylidene-4-*O*-phenylcarbamyl-D-mannononitrile (*VIII*) and 2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone *O*-phenylcarbamyloxime (*IX*). The lowest moving third product was unidentified. Finally, from the reaction of *I* and phosphorus pentoxide in benzene only a small amount of lactone *VI* was isolated. The gummy residue represented probably polymerization and decomposition products.

EXPERIMENTAL

Starting 2,3:5,6-di-*O*-isopropylidene-D-mannose oxime (*I*) was prepared according to the known procedure [8, 9]. The other used chemicals were commercially available products (Fluka, Buchs; Lachema, Brno; Merck, Darmstadt).

Melting points were determined with a Boetius PHMK 05 microscope. ^{1}H and ^{13}C NMR spectra (in $CDCl_3$ or $(CD_3)_2SO$, internal standard Me_4Si) were measured with a Bruker AM-300 spectrometer operating at 300.13 MHz and 75.46 MHz working frequencies, respectively. The quaternary carbon atoms were identified on the basis of semiselective INEPT experiment [16] and 1D INADEQUATE pulse sequence technique [17]. For compounds *IV*, *V*, and *VI*, the EI mass spectra (70 eV) were recorded with a Finigan MAT SSQ 710 spectrometer using SP 2330 column. The other spectra were obtained with a Jeol JMS-100D spectrometer applying direct sample-introduction technique. Elemental analyses were performed on a Perkin—Elmer 240 analyzer. Optical rotations were measured with a Perkin—Elmer 141 polarimeter (10-cm cell). All reactions were monitored routinely by TLC on silica gel 60 F_{254} (Merck) plates using ethyl acetate—hexane (φ_r = 3 : 2, eluent A). Visualization was effected with sulfuric acid, UV_{254} light, or iodine vapour. Column chromatography was performed as flash chromatography on silica gel 60 (Merck, "230—400 mesh") with the same eluent.

N-Acetoxy-*N*-acetyl-2,3:5,6-di-*O*-isopropylidene-D-mannofuranosylamine (*IV*)

A mixture of 2,3:5,6-di-*O*-isopropylidene-D-mannose oxime (*I*) (0.55 g; 2 mmol) and acetic anhydride (5 cm^3) was stirred at room temperature for 3 h. Methanol (5 cm^3) was then added dropwise and the mixture was stirred for 1 h. The solvents were evaporated under diminished pressure, resulting crude product was dissolved in ether (25 cm^3) and decolourized with charcoal. After evaporation of ether, *IV* (0.66 g, 92 %) was obtained as colourless sirup, $[\alpha]$(D, 20 °C, ρ = 10 g dm^{-3}, CH_3OH) = + 81° ^{1}H NMR spectrum ($CDCl_3$), δ: 5.11 (bs, 1H, H-1), 4.93 (d, 1H, $J_{2,3}$ = 5.7 Hz, H-2), 4.90 (dd, 1H, $J_{3,4}$ = 3.8 Hz, H-3), 4.32 (ddd, 1H, $J_{4,5}$ = 7.3 Hz, $J_{5,6}$ = 6.0 Hz, $J_{5,6'}$ = 4.7 Hz, H-5), 4.24 (dd, 1H, H-4), 4.07 (dd, 1H, $J_{6,6'}$ = 8.7 Hz, H-6), 4.00 (dd, 1H, H-6'), 2.23 (s, 3H, CH_3CO), 2.06 (s, 3H, CH_3CON), 1.49, 1.45, 1.37, 1.34 (4s, each 3H, 4 × CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ: 169.5 (C=O), 167.9 (C=O), 112.7, 110.0 (2 × $\underline{C}Me_2$), 94.6 (C-1), 84.5 (C-4), 83.9 (C-2), 80.4 (C-3), 73.2 (C-5), 66.4 (C-6), 26.7, 25.8, 25.0, 24.2 (4 × CH_3), 20.9 ($\underline{C}H_3COO$), 18.2 ($\underline{C}H_3CON$). EI mass spectrum, *m/z* (*I*/%): 344 (24, $[M - CH_3]^+$), 301 (20, $[M - Me_2CO]^+$), 286 (37, $[M - CH_3 - Me_2CO]^+$), 244 (67), 243 (35, $[M - Me_2CO - Me_2CO]^+$), 101 (44), 43 (100). For $C_{16}H_{25}NO_8$ (M_r = 359.55) w_i(calc.): 53.44 % C, 7.02 % H, 3.93 % N; w_i(found): 53.21 % C, 7.10 % H, 3.90 % N.

4-*O*-Acetyl-2,3:5,6-di-*O*-isopropylidene-D-mannononitrile (*V*)

Oxime *I* (1.1 g; 4 mmol) was dissolved in dry pyridine (10 cm^3) and left standing for 48 h. Then, the solution was heated under reflux, acetic anhydride (10 cm^3) was added dropwise and heating continued for additional 1 h. The solvents were distilled off at reduced pressure, resulting dark sirup was dissolved in ether (20 cm^3) and decolourized with charcoal. After usual work-up, TLC revealed the presence of *IV* (R_f = 0.50) and *V* (R_f = 0.62, eluent A). These were separated on a column of silica gel (eluent A) giving 0.36 g (25 % based on *I*) of *IV* and 0.61 g (51 %) of *V* (colourless sirup), $[\alpha]$(D, 20 °C, ρ = 10 g dm^{-3}, CH_3OH) = + 41°. ^{1}H NMR spectrum ($CDCl_3$), δ: 5.29 (dd, 1H, $J_{3,4}$ = 6.8 Hz, $J_{4,5}$ = 7.9 Hz, H-4), 4.88 (d, 1H, $J_{2,3}$ = 5.3 Hz, H-2), 4.34 (dd, 1H, H-3), 4.11 (ddd, 1H, $J_{5,6}$ = 6.2 Hz, $J_{5,6'}$ = 8.7 Hz, H-5), 4.08 (dd, 1H, $J_{6,6'}$ = 11.9 Hz, H-6), 3.89 (dd, 1H, H-6'), 2.13 (s, 3H, CH_3), 1.57, 1.46, 1.40, 1.35 (4s, each 3H, 2 × CMe_2). ^{13}C NMR spectrum ($CDCl_3$), δ: 169.5 (C=O), 116.6 (CN), 111.6, 110.3 (2 × $\underline{C}Me_2$), 76.9 (C-5), 74.4 (C-3), 71.1 (C-2), 67.1 (C-6), 65.8 (C-4), 26.6, 25.8, 25.7, 25.2 (2 × CMe_2), 20.5 (CH_3). EI mass spectrum, *m/z* (*I*/%): 284 (61, $[M - CH_3]^+$), 226 (30, $[M - CH_3 - Me_2CO]^+$), 184 (22), 101 (44), 43 (100). For $C_{14}H_{21}NO_6$ (M_r = 299.36) w_i(calc.): 56.21 % C, 7.02 % H, 4.68 % N; w_i(found): 56.14 % C, 7.07 % H, 4.65 % N.

2,3:5,6-Di-*O*-isopropylidene-D-mannono-1,4-lactone (*VI*)

A solution of nitrile *V* (0.6 g; 2 mmol) and catalytic amount of sodium methoxide in dry methanol (10 cm^3) was stirred for 3 h at room temperature. Subsequently, it was neutralized with acetic acid and the solvent was evaporated under diminished pressure. Usual work-up (decolourizing in ether) afforded lactone *VI* (0.38 g, 74 %) having the same analytical constants as described [12]. ^{1}H NMR spectrum ($CDCl_3$), δ: 4.81

(dd, 1H, $J_{2,3}$ = 5.3 Hz, $J_{3,4}$ = 3.1 Hz, H-3), 4.78 (d, 1H, H-2), 4.36 (ddd, 1H, $J_{4,5}$ = 8.0 Hz, $J_{5,6}$ = 5.6 Hz, $J_{5,6'}$ = 3.8 Hz, H-5), 4.31 (dd, 1H, H-4), 4.08 (dd, 1H, $J_{6,6'}$ = 9.3 Hz, H-6), 4.00 (dd, 1H, H-6'), 1.42, 1.40, 1.36, 1.33 (4s, each 3H, 2 × CMe_2). ^{13}C NMR spectrum ($CDCl_3$), δ: 173.4 (C=O), 114.4, 109.8 (2 × $\underline{C}Me_2$), 78.1 (C-4), 76.0 (C-2), 75.8 (C-3), 72.5 (C-5), 66.4 (C-6), 26.9, 26.7, 25.9, 25.1 (2 × CMe_2). EI mass spectrum, *m/z* (*I*/%): 243 (38, [M − CH_3]$^+$), 185 (12, [M − CH_3 − Me_2CO]$^+$), 101 (80), 43 (100).

N-(2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranosyl)-*N*-phenylcarbamylhydroxylamine (*VII*)

To a stirred solution of *I* (1.4 g; 5 mmol) in dry toluene (50 cm^3), phenyl isocyanate (0.6 g; 5 mmol) was added dropwise at room temperature. Filtration of white crystals which separated after 5 min afforded 1.9 g (96 %) of *VII*, m.p. = 171—172 °C, [α](D, 20 °C, ρ = 10 g dm^{-3}, CH_3OH) = + 93°. EI mass spectrum, *m/z* (*I*/%): 293 (10), 243 (26), 185 (23), 101 (48), 43 (100). ^{1}H NMR spectrum (DMSO-d_6), δ: 10.00 (s, 1H, OH), 9.16 (s, 1H, NH), 7.00—7.62 (m, 5H, H_{arom}), 5.74 (s, 1H, H-1), 4.98 (d, 1H, $J_{2,3}$ = 6.0 Hz, H-2), 4.84 (dd, 1H, $J_{3,4}$ = 3.9 Hz, H-3), 4.37 (dd, 1H, $J_{4,5}$ = 6.5 Hz, H-4), 4.18 (dd, 1H, $J_{5,6}$ = 5.8 Hz, $J_{6,6'}$ = 12.3 Hz, H-6), 3.96 (ddd, 1H, $J_{5,6'}$ = 8.4 Hz, H-5), 3.82 (dd, 1H, H-6'), 1.41, 1.31, 1.29, 1.25 (4s, each 3H, 2 × CMe_2). ^{13}C NMR spectrum (DMSO-d_6), δ: 156.6 (C=O), 138.8 (C-1'), 128.6 (C-3', C-5'), 123.0 (C-4'), 119.9 (C-2', C-6'), 111.8, 108.2 (2 × $\underline{C}Me_2$), 92.1 (C-1), 83.7 (C-3), 83.3 (C-2), 80.5 (C-4), 73.2 (C-5), 65.8 (C-6), 26.7, 26.1, 25.2, 24.5 (4 × CH_3). For $C_{19}H_{26}N_2O_7$ (M_r = 394.47) w_i(calc.): 57.85 % C, 6.66 % H, 7.10 % N; w_i(found): 57.63 % C, 6.72 % H, 7.07 % N.

2,3:5,6-Di-*O*-isopropylidene-4-*O*-phenylcarbamyl-D-mannononitrile (*VIII*) and 2,3:5,6-Di-*O*-isopropylidene-D-mannono-1,4-lactone *O*-Phenylcarbamyloxime (*IX*)

Phenyl isocyanate (1.8 g; 15 mmol) was added dropwise at room temperature to a stirred mixture of *I* (1.4 g; 5 mmol), toluene (50 cm^3), and catalytic amount of triethylamine. Then the mixture was heated under reflux for 4 h. The separated 1,3-diphenylurea was filtered off and toluene evaporated at diminished pressure. The crude product was decolourized (charcoal) in ether and chromatographed on a column of silica gel (eluent A) yielding first *VIII* (0.87 g, 46 %) and then *IX* (0.67 g, 34 %). For *VIII* m.p. = 169—170 °C, [α](D, 20 °C, ρ = 10 g dm^{-3}, CH_3OH) = + 47°. ^{1}H NMR spectrum ($CDCl_3$), δ: 8.94 (bs, 1H, NH), 7.07—7.61 (m, 5H, H_{arom}), 5.27 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 7.5 Hz, H-4), 4.89 (d, 1H, $J_{2,3}$ = 5.1 Hz, H-2), 4.35 (dd, 1H, H-3), 4.02—4.17 (m, 3H, H-5, H-6, H-6'), 1.61, 1.49, 1.40, 1.37 (4s, each 3H, 4 × CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ: 153.4 (C=O), 137.1 (C-1'), 128.9 (C-3', C-5'), 124.4 (C-4'), 120.6 (C-2', C-6'), 116.7 (CN), 111.8, 110.6 (2 × $\underline{C}Me_2$), 77.4 (C-5), 74.6 (C-3), 72.6 (C-2), 67.5 (C-6), 66.1 (C-4), 26.9, 26.0, 25.9, 25.4 (4 × CH_3). EI mass spectrum, *m/z* (*I*/%): 376 (16, [M]$^+$), 361 (23, [M − CH_3]$^+$), 318 (5, [M − Me_2CO]$^+$), 303 (5, [M − CH_3 − Me_2CO]$^+$), 119 (100, [PhNCO]$^+$), 101 (51), 43 (57). For $C_{19}H_{24}N_2O_6$ (M_r = 376.45) w_i(calc.): 60.62 % C, 6.44 % H, 7.44 % N; w_i(found): 60.45 % C, 6.50 % H, 7.37 % N. For *IX* m.p. = 139—140 °C, [α](D, 20 °C, ρ = 10 g dm^{-3}, CH_3OH) = + 55° ^{1}H NMR spectrum ($CDCl_3$), δ: 8.43 (s, 1H, NH), 7.02—7.48 (m, 5H, H_{arom}), 4.67 (dd, 1H, $J_{2,3}$ = 8.6 Hz, $J_{3,4}$ = 0.9 Hz, H-3), 4.56 (d, 1H, H-2), 3.92—4.01 (m, 3H, H-4, H-5, H-6), 3.80 (dd, 1H, $J_{5,6'}$ = 3.4 Hz, $J_{6,6'}$ = 8.3 Hz, H-6'), 1.56 (s, 3H, CH_3), 1.36 (s, 6H, 2 × CH_3), 1.27 (s, 3H, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ: 171.8 (O—CN), 150.3 (CO), 137.1 (C-1'), 128.9 (C-3', C-5'), 120.2 (C-2', C-6'), 110.6, 109.5 (2 × $\underline{C}Me_2$), 77.0 (C-4), 75.7 (C-2), 74.9 (C-3), 69.0 (C-5), 67.0 (C-6), 26.9, 26.1, 25.3, 24.0 (4 × CH_3). EI mass spectrum, *m/z* (*I*/%): 392 (8, [M]$^+$), 377 (8, [M − CH_3]$^+$), 242 (42), 137 (38), 119 (45, [PhNCO]$^+$), 101 (53), 43 (100). For $C_{19}H_{24}N_2O_7$ (M_r = 392.45) w_i(calc.): 58.14 % C, 6.18 % H, 7.14 % N; w_i(found): 58.01 % C, 6.22 % H, 7.10 % N.

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