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Note

A simple approach to new 5-butenylidene-imidazolin-2-ones from 2-amino-2-deoxy-D-glucose

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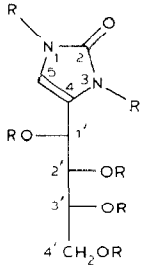
During studies of the synthesis of 1,2-cyclic urea derivatives of sugars[1] as analogues of building units of Cinodine antibiotics[2,3], attention was turned to the reaction of 2-amino-2-deoxy sugars with salts of cyanic acid.

The reaction[4] of 2-amino-2-deoxy-D-glucose hydrochloride with silver cyanate was believed to produce an acyclic sugar imidazolinone (**1**), but the product was proved[5] to be the 1,2-cyclic urea derivative (**2**) of D-glucofuranose.

In contrast, when 2-amino-2-deoxy-D-glucose hydrochloride was treated with potassium cyanate, a multicomponent mixture was formed from which, after acetylation, 1,3-diacetyl-4-(1,2,3,4-tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)-1,3-dihydro-2*H*-imidazol-2-one (**3**, 14%) and 3,5,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucofurano-[1,2-*d*]imidazolidin-2-one[5] (**4**, 27%) were isolated.



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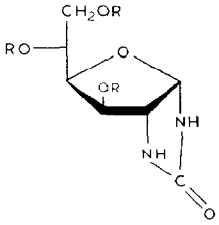
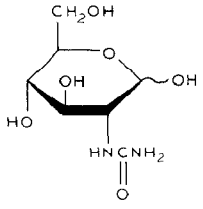
3 R = Ac



2 R = H
4 R = Ac



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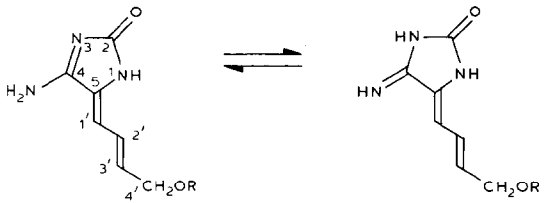
The structure of **3** was supported by the ^{1}H-n.m.r. spectrum, which exhibited singlets for four OAc (δ 2.10, 2.07, 2.00, and 1.97) and two NAc (δ 2.63 and 2.57) groups and indicated a 4,5-double bond (δ 6.87, s, H-5) as part of the imidazoline ring. Furthermore, a zigzag conformation of the acyclic sugar moiety was inferred from the low values of $J_{1',2'}$, $J_{3',4'a}$, and $J_{3',4'b}$ (*gauche* relationships), and the high value of $J_{2',3'}$ (antiperiplanar relationship), which are similar to those of the analogous guanidino derivative[6]. The structure of **3** was corroborated also by the ^{13}C-n.m.r. spectrum, the assignment of which was supported by a 2D ^{13}C,^{1}H correlation map[7].

The formation of **3** and **4** probably proceeds *via* 2-deoxy-2-ureido-D-glucose[8,9] (**5**). Support for this assumption was provided by the observation that, following storage of an aqueous solution of **5** for 24 h, concentration and acetylation of the products afforded **3** and **4**.

Attempts to prepare **1** by deacetylation of **3** were unsuccessful. With methanolic sodium methoxide, a complex mixture of unidentified products was formed, whereas treatment with ethanolic aqueous ammonia for 3 days afforded 4-amino-(*Z*)-5-[4-hydroxy-(*E*)-but-2-enylidene]-1,5-dihydro-2*H*-imidazol-2-one (**6**) isolated as the crystalline hydrate. When the reaction of **3** with ammonia was stopped after 1 h, the acetoxy derivative **7** was the main product and only a small proportion of **6** was present.



6a R = H **6b**

7a R = Ac **7b**

The ^{1}H-n.m.r. spectrum of **7** indicated the presence of one OAc group (δ 2.03) and revealed the $AcOCH_2$ group to be linked to an acyclic chain of three vicinal –CH= units in which, according to the $^3J_{H,H}$ values (15.0 and 11.5 Hz), H-1',2',3' were antiperiplanar (*trans*-butadiene). The relative configuration of the *exo*-butenylidene substituent at C-5 of the imidazole ring was determined by measurement of n.O.e. differences[10]: the proximity of H-2' and NH-1 was proved by the increase of the intensity of the signal for H-2' (δ 6.59 dd) caused by irradiation at the sharp singlet of NH (δ 10.07). Two additional NH signals appeared at δ 8.20 and 8.02 with $W_{1/2}$ values of 56 and 38 Hz, respectively, indicative of a rapid exchange process.

The ^{1}H-n.m.r. spectrum of **6** revealed a diamagnetic shift of 0.56 p.p.m. for the CH_2O signal. The *Z* configuration of the side chain at C-5, as for **7**, was supported by n.O.e. enhancements, namely, an increase of 4.0% in the intensity of

the signal for H-2′ (δ 6.53 dd) by irradiation at the sharp NH signal (δ 9.88 s). Also, there were three NH signals, which indicated the preponderance of the 4-imino-imidazolidinone tautomers (**6b** and **7b**, respectively) in $(CD_3)_2SO$. The same structure can be concluded from the couplings (9 Hz and 4.5 Hz, respectively) of the C=O signal (dd) with the two vicinal NH in the ^{13}C-n.m.r. spectrum of **6**.

In contrast, evidence for the 4-aminoimidazolin-2-one structure (**6a**) in the crystal of **6** was provided by X-ray diffraction studies[11].

The mechanism of the formation of **7** appears to involve, instead of the expected *O*-deacetylation of AcO-1′,2′,3′, *N*-deacetylation of the *N,N′*-diacetyl-imidazolin-2-one moiety followed by nucleophilic attack of ammonia on the imidazole ring, accompanied by stepwise elimination of AcO-1′,2′,3′, affording the butadiene side-chain. The formation of **6** from **7** involves a normal *O*-deacetylation process.

EXPERIMENTAL

General. — T.l.c. was performed on Silica Gel F_{254} (Merck) with *A*, chloroform–acetone (3:2); or *B*, ethyl acetate–ethanol–water (7:2:1). Silica Gel 60 (230–400 mesh) was used for preparative t.l.c. Optical rotations were measured with a Zeiss Polamat A polarimeter and i.r. spectra with a Zeiss Specord 75 spectrometer. The n.m.r. spectra were recorded with a Bruker AM-400 spectrometer. The δ and *J* values for ^1H resonances were calculated as first-order spectra at 400 MHz. 1D-N.O.e and 2D correlation spectra were recorded by using the standard Bruker software packages.

*1,3-Diacetyl-4-(1′,2′,3′,4′-tetra-*O*-acetyl-*D*-arabino-tetritol-1′-yl)-1,3-dihydro-2H-imidazol-2-one* (**3**) *and 3,5,6-tri-*O*-acetyl-1,2-dideoxy-α-*D*-glucofurano[1,2-d]-imidazolidin-2-one* (**4**). — (*a*) A solution of 2-amino-2-deoxy-D-glucose hydrochloride (10.6 g, 49.2 mmol) and potassium cyanate (6.1 g, 75.3 mmol) in water (20 mL) was stirred for 3 h at room temperature, then kept in the dark for 4 days, and concentrated to dryness at 40°. Toluene was evaporated repeatedly from the residue, which was then acetylated conventionally with pyridine (120 mL) and acetic anhydride (60 mL) at room temperature for 3 days, to give **3** (3.05 g, 14%), m.p. 141–143° (from ethanol), $[\alpha]_D$ +3° (*c* 3, chloroform), R_F 0.7 (solvent *A*); ν_{max}^{KBr} 1770–1720 cm^{-1} (OAc, NAc, CO). N.m.r. data ($CDCl_3$): ^1H (400 MHz) δ 6.87 (s, 1 H, H-5), 6.47 (t, 1 H, $J_{5,1'}$ 1.5, $J_{1',2'}$ 1.5 Hz, H-1′), 5.47 (dd, 1 H, $J_{2',3'}$ 9.5 Hz, H-2′), 5.27 (ddd, 1 H, H-3′), 4.24 (dd, 1 H, $J_{3',4'a}$ 2.4 Hz, H-4′a), 4.14 (dd, 1 H, $J_{3',4'b}$ 4.8, $J_{4a,4'b}$ 12.5 Hz, H-4′b), 2.63, 2.57, 2.10, 2.07, 2.00, and 1.97 (6 s, each 3 H, 2 NAc, 4 OAc); ^{13}C (100 MHz), 170.5, 170.4, 169.9, 169.7, 169.4, 167.3 (Ac), 149.7 (NCON), 122.2 (C-4), 108.0 (C-5), 68.9 (C-2′), 67.2 (C-3′), 66.0 (C-1′), 62.2 (C-4′), 25.6, 24.2 ($NHCOCH_3$), and 20.6 p.p.m. ($OCOCH_3$).

Anal. Calc. for $C_{19}H_{24}N_2O_{11}$: C, 50.00; H, 5.30; N, 6.14. Found: C, 49.94; H, 5.30; N, 5.92.

Extraction of the aqueous mother liquor with chloroform gave, after concen-

tration, a gum (9.4 g). T.l.c. (solvent *A*) revealed one main product (R_F 0.25). Crystallisation of the residue from ethanol afforded **4** (3.3 g, 20%), m.p. 170–172°, $[\alpha]_D$ +22° (*c* 1, chloroform), R_F 0.25 (solvent *A*); lit.[5] m.p. 166–168°, $[\alpha]_D$ +22° (chloroform).

The ethanolic mother liquor of **4** was concentrated and the residue was subjected to preparative t.l.c. (solvent *A*), to give more **4** (1.12 g; total yield, 4.42 g, 27%), R_F 0.25 (solvent *A*).

(*b*) A solution of 2-deoxy-2-ureido-D-glucose[8,9] (**5**; 0.18 g, 0.81 mmol) in water (4 mL) was stored for 24 h at room temperature, then concentrated, and dried, and the residue was acetylated conventionally to give **3** (9 mg), m.p. 138–140°, R_F 0.7 (solvent *A*). The aqueous mother liquor was extracted with chloroform, and the material in the extract was subjected to preparative t.l.c. as in (*a*), to give more **3** (22 mg; total yield, 8%), m.p. 140–141°, $[\alpha]_D$ +3° (*c* 2, chloroform), R_F 0.7 (solvent *A*); and **4** (82 mg, 31%), m.p. 168–170°, $[\alpha]_D$ +23° (*c* 2, chloroform), R_F 0.25 (solvent *A*).

4-Amino-(Z)*-5-[4'-hydroxy-*(E)*-but-2'-enylidene]-1,5-dihydro-2*H*-imidazol-2-one* (**6**). — To a stirred suspension of **3** (1.82 g, 4 mmol) in ethanol (10 mL) was added aqueous 25% ammonia (10 mL). After 10 min, yellow crystals separated and stirring was continued for 6 h. The mixture was stored for 3 days, cooled to 0–5°, and then filtered to give crude **6** (0.384 g, 52%), R_F 0.35 (solvent *B*). Crystallisation from water (50 mL) containing potassium carbonate (0.2 g) gave **6** monohydrate as pale-yellow needles (0.337 g, 45%), m.p. >300°; ν_{max}^{KBr} 3600–3250 (H_2O, OH), 3200–3000 (NH), 1660 cm^{-1} (CO). N.m.r. data [$(CD_3)_2SO$]: ^1H (400 MHz) δ 9.88 (s, 1 H, NH-1), 8.06 (s, 1 H, NH-3), 7.93 (s, 1 H, C=NH), 6.53 (dd, 1 H, $J_{2',3'}$ 15.2 Hz, H-2'), 6.18 (d, 1 H, $J_{1',2'}$ 11.5 Hz, H-1'), 5.92 (dt, 1 H, $J_{3',4'}$ 5.4 Hz, H-3'), 4.88 (t, 1 H, $J_{4',OH}$ 5.1 Hz, OH), 4.03 (dd, 2 H, H-4'a,4'b); ^{13}C (100 MHz), 170.3 ($J_{C\text{-}2,NH}$ 9 and 4.5 Hz, C-2), 167.5 (C-4), 138.2 (C-3'), 131.4 (C-5), 124.2 (C-2'), 105.4 (C-1'), and 61.5 p.p.m. (C-4').

Drying at 100°/20 mmHg gave anhydrous **6**.

Anal. Calc. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.22; H, 5.48; N, 25.05.

4-Amino-(Z)*-5-[4'-acetoxy-*(E)*-but-2'-enylidene]-1,5-dihydro-2*H*-imidazol-2-one* (**7**). — To a stirred suspension of **3** (1.82 g, 4 mmol) in ethanol (9 mL) at 20° was added aqueous 25% ammonia (9 mL). The crystals were collected after 1 h at 20° to give crude **7** (0.334 g, 40%), R_F 0.5 (solvent *B*), which contained a bright-yellow contaminant (R_F 0.55). A solution of the crude product in water (30 mL) was acidified with conc. hydrochloric acid, then filtered, neutralised with potassium carbonate to pH 8, and cooled to 5°. The precipitate was collected, and washed with cold water and ethanol to give **7** as pale-yellow crystals, m.p. >300°, R_F 0.5 (solvent *B*); ν_{max}^{KBr} 3440 (NH_2), 3200–2900 (NH), 1720 (OAc), 1645 cm^{-1} (CO). N.m.r. data [$(CD_3)_2SO$]: ^1H (400 MHz), δ 10.07 (s, 1 H, NH-1), 8.20 (s, 1 H, NH-3), 8.02 (s, 1 H, C=NH), 6.59 (dd, 1 H, $J_{2',3'}$ 15.0 Hz, H-2'), 6.18 (d, 1 H, $J_{1',2'}$ 11.5 Hz, H-1'), 5.87 (dt, 1 H, $J_{3',4'}$ 5.7 Hz, H-3'), 4.59 (d, 2 H, H-4'a,4'b), and 2.03

(s, 3 H, OAc); ^{13}C (100 MHz), 170.3 (C-2), 170.2 (Ac), 167.5 (C-4), 132.7 (C-5), 130.4 (C-3′), 127.4 (C-2′), 104.2 (C-1′), 63.8 (C-4′), and 20.7 p.p.m. ($OCOCH_3$).

Anal. Calc. for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.90. Found: C, 51.75; H, 5.20; N, 19.97.

The mother liquor was stored for 2 days, then cooled, and filtered to give **6** (0.170 g, 23%), m.p. >300°, R_F 0.35 (solvent *B*). Crystallisation from water gave **6** as the monohydrate.

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