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PHOTOAMIDATION OF UNSATURATED CARBOHYDRATES. SYNTHESIS OF 1-(3-*C*-CARBAMOYL-3-DEOXY-β-D-GLUCOPYRANOSYL)-THYMINE AND -CYTOSINE*

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ABSTRACT

The acetone-initiated photochemical addition of formamide to 1,2,4,6-tetra-*O*-acetyl-3-deoxy-α-D-*erythro*-hex-2-enopyranose (**1**) afforded 1,2,4,6-tetra-*O*-acetyl-3-*C*-carbamoyl-3-deoxy-α-D-glucopyranose (**2**), 1,2,4,6-tetra-*O*-acetyl-3-*C*-carbamoyl-3-deoxy-α-D-allopyranose (**3**), 1,2,4,6-tetra-*O*-acetyl-3-*C*-carbamoyl-3-deoxy-α-D-altropyranose (**4**), and 1,2,4,6-tetra-*O*-acetyl-3-deoxy-3-*C*-(1-hydroxy-1-methylethyl)-α-D-mannopyranose (**5**), in 46, 13, 1, and 7% yields, respectively. Condensation of 2,4,6-tri-*O*-acetyl-3-*C*-carbamoyl-3-deoxy-α-D-glucopyranosyl bromide (produced from **2** with hydrogen bromide) with 2,4-bis(trimethylsilyl)thymine afforded 1-(2,4,6-tri-*O*-acetyl-3-*C*-carbamoyl-3-deoxy-β-D-glucopyranosyl)thymine (**6**) in 40% yield. Deacetylation of **6** with sodium methoxide in methanol yielded the pure unprotected nucleoside **7**. Similar condensation of the bromide from **2** with 2,4-bis(trimethylsilyl)-N^4-acetylcytosine afforded the protected cytosine nucleoside **8** in 55% yield, which was converted into 1-(3-*C*-carbamoyl-3-deoxy-β-D-glucopyranosyl)cytosine (**9**).

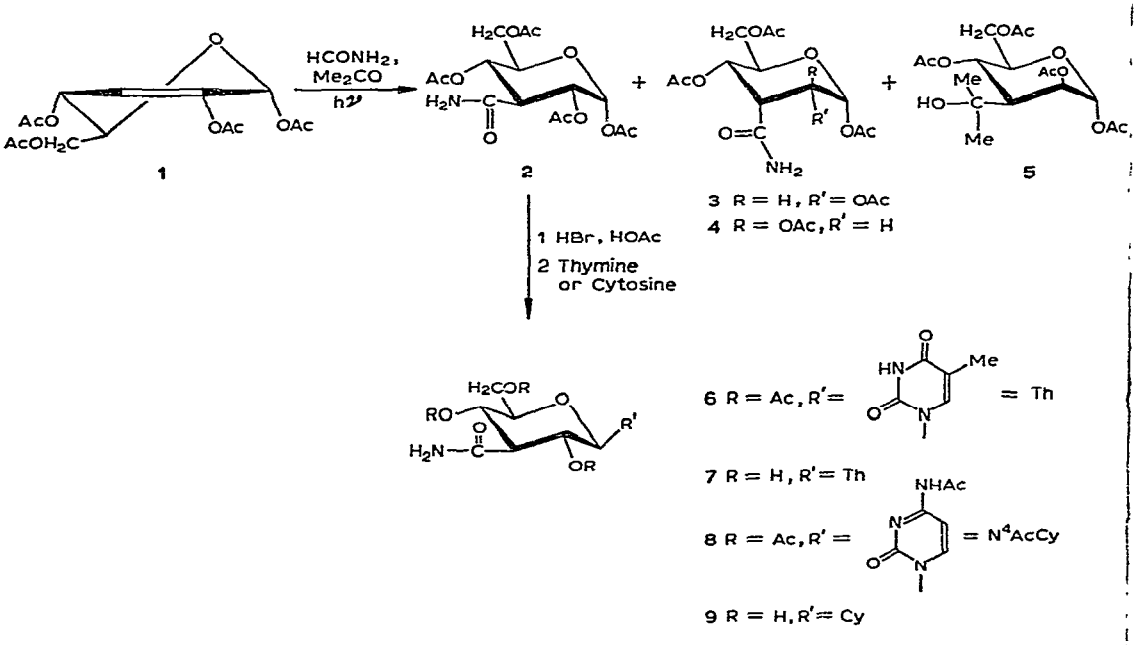
DISCUSSION

The photoamidation[1,2] of unsaturated carbohydrates provides a facile procedure for achieving anti-Markovnikov hydrocarbamoylation (hydrogen and carbamoyl [O=C–NH_2]) of carbon–carbon double bonds. Thus, application of this reaction to 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose[3] afforded branched-chain products in which the carbamoyl group had added exclusively to C-3, and *trans* addition of the addends occurred. When both carbon atoms of the unsaturated group bear hydrogen, the addition is non-selective.[4]

For some time we have been interested in synthesizing branched-chain analogues of gougerotin[5], a nucleoside antibiotic containing a carbamoyl group attached to C-5 of the D-glucopyranose ring. In this communication we report the results of studies on the photoamidation of 1,2,4,6-tetra-*O*-acetyl-α-D-*erythro*-hex-2-enopyranose[6] (**1**), and the subsequent use of the photoamidation product in the synthesis of branched-chain carbamoyl sugar nucleosides.

*Part of a series: Branched-Chain Sugar Nucleosides.

When a solution of compound **1** in acetone containing formamide and *tert*-butyl alcohol was irradiated through a Pyrex filter for 24 h according to the previously published procedure[3,4], a mixture of four products, **2**, **3**, **4**, and **5**, was formed (Scheme 1) in 46, 13, 1, and 7% yields, respectively. The principal product **2** was readily obtained pure by fractional crystallization of the product mixture from benzene–petroleum ether (b.p. 30–60°). Column chromatography of the mixture on silica gel with 10:5:1 benzene–ethyl ether–ethanol readily afforded the remaining components in pure form.



The structures of the photoproducts were readily deduced by analysis of their i.r. and p.m.r. spectra. Compounds **2**, **3**, and **4** showed amide peaks at 3475 and 1690 cm^{-1}, whereas **5** exhibited a hydroxyl peak at 3600 cm^{-1} and no amide peaks. The p.m.r. spectra of **2**, **3**, **4**, and **5** (see Experimental section) clearly indicated a single methine hydrogen, thus establishing that the carbamoyl and ketyl radical [$(CH_3)_2COH$] had added exclusively to C-3 of **1**. In the p.m.r. spectrum of compound **2**, the lone high-field triplet at τ 7.02 clearly displayed two very large coupling constants of 12 Hz, which were assigned to $J_{3,4}$ and to $J_{2,3}$. Confirmation of the $J_{2,3}$ doublet was provided by a first-order analysis of the H-2 signal, which was observed at τ 4.75 and showed $J_{2,3} = 12$ Hz. The large magnitude of the coupling constants of H-3 shows that the carbamoyl and the C-2 acetoxyl group must be in the equatorial orientation[7]. Further confirmation of the assignment of configuration of C-2 was provided by the fact that the H-1 signal has a coupling constant of 3.4 Hz, which corroborates the *cis*-arrangement of the C-1 and C-2 acetoxyl groups. The *trans*-diaxial arrangement of H-2, H-3, and H-4 was confirmed by double-irradiation

experiments. Therefore, compound **2** must be 1,2,4,6-tetra-*O*-acetyl-3-*C*-carbamoyl-3-deoxy-α-D-glucopyranose.

A similar first-order analysis of the p.m.r. spectrum of the carbamoyl product **3** in chloroform-*d* solution indicated that **3** is an epimer of **2** differing only in its configuration at C-3. The magnitude of $J_{1c,2}$ (3.9 Hz) of compound **3** was similar to that of compound **2**, thus indicating the *cis* arrangement of the C-1 and C-2 acetoxyl groups. The H-2 signal of compound **3** was a quartet at τ 4.77 that showed a much smaller $J_{2,3}$ value (6 Hz) than did compound **2** (12 Hz), thus suggesting that H-3 is equatorially oriented. Confirmation of this assignment was provided by the fact that the H-3 quartet at τ 6.62 consisted of two doublets of spacing 6 and 5 Hz. Irradiation of H-3 at τ 6.62 changed the H-2 quartet to a doublet having $J_{1,2}$ 3.9 Hz and collapsed the H-4 quartet at τ 5.02 to a doublet having J 9.5 Hz. This wide doublet was assigned to $J_{4,5}$. The magnitude of $J_{3,4}$ (5 Hz) confirmed that H-3 must be equatorially oriented. The H-6 signal was observed as a multiplet at τ 5.84. Irradiation at the latter frequency collapsed the H-5 sextet to a doublet showing $J_{4,5}$ 9.5 Hz, thus confirming the assignment of H-4, which was essential for corroboration of the assignment of H-3. Thus, compound **3** is 1,2,4,6-tetra-*O*-acetyl-3-*C*-carbamoyl-3-deoxy-α-D-allopyranose.

Compound **4**, which was isolated in only about 1% yield, is tentatively assigned the *altro* configuration (the C-2 epimer of compound **3**) on the basis of the following spectral evidence. The H-1 signal was a much narrower doublet (at τ 4.0) having $J_{1,2}$ 2.5 Hz, thus indicating that H-1 and H-2 were diequatorial. Because the H-2 quartet at τ 4.66 exhibited this doublet in addition to a doublet of $J_{2,3}$ 5 Hz, it was considered that H-3 must be in an equatorial orientation. This was confirmed by a first-order analysis of the H-3 quartet at τ 6.83, which showed two doublets of 5 and 5.4 Hz. Furthermore, irradiation at τ 6.83 collapsed the H-2 signal to a doublet having $J_{1,2}$ 2.5 Hz, and also collapsed the quartet at τ 4.70 (assigned to H-4) to a doublet having $J_{4,5}$ 7.0 Hz. Irradiation at τ 4.66 (H-4 and H-2 signals) collapsed the H-3 signals to a singlet. This assignment of structure of compound **4** is based on the premise that it exists in the $^4C_1$(D) conformation, a premise that is certainly tenuous, as the molecule contains three axial and only two equatorial substituents. Possibly the acetoxymethyl group, which is larger and equatorial, has a much greater influence than the carbamoyl group in determining conformation.

The complete structure of the branched-chain hydroxyisopropyl sugar derivative **5** was similarly deduced from its p.m.r. spectrum. The very small ($J_{1,2}$ 1.9 Hz) coupling constant of H-1 clearly indicated that H-2 must be in the equatorial orientation. Irradiation of H-1 at τ 4.02 collapsed the H-2 triplet to a doublet at τ 4.80 that showed $J_{2,3}$ 2.5 Hz. The H-3 quartet at τ 7.60 showed $J_{2,3}$ of 2.5 Hz and $J_{3,4}$ 10 Hz. Irradiation at τ 4.80 collapsed the latter quartet to a doublet having a spacing of 10 Hz, and also collapsed the H-1 doublet to a singlet. Irradiation at τ 7.60 collapsed the H-4 signal at τ 4.75 to a doublet showing $J_{4,5}$ 12 Hz, and the H-2 signal collapsed to a doublet having J 1.9 Hz. Thus **5** must be 1,2,4,6-tetra-*O*-acetyl-3-deoxy-3-*C*-(2-hydroxy-2-propyl)-α-D-mannopyranose. Presumably, **5** must have been been formed via a trans addition of the ketyl group and a hydrogen atom to **1**.

By inspection of a molecular model, it may be seen that the least-hindered approach of the carbamoyl or ketyl group to C-3 of the double bond of the α-D-anomer[8] **1** is from above the double bond, because of the steric hindrance of the C-4 acetoxyl group. Addition of the carbamoyl or ketyl free-radical (in equatorial orientation) to C-3 is followed by addition of hydrogen to C-2 of compound **1**. In this last step there appears to be no product-stability control.

The branched-chain sugar **2** was allowed to react with hydrogen bromide in glacial acetic acid and dichloromethane to yield 2,4,6-tri-*O*-acetyl-3-*C*-carbamoyl-3-deoxy-α-D-glucopyranosyl bromide. The latter compound was immediately condensed with 2,4-bis(trimethylsilyl)thymine for 30 min at 135–140° according to a known procedure[9] to afford, after column chromatography on silica gel with 5:5:1 dichloromethane–ethyl acetate–ethanol as developer, the crystalline, protected nucleoside **6** in 40% yield. Assignment of the structure of **6** was based on the following: (*a*) u.v. absorption data of **6** substantiate the site of glycosylation[10] at N-1, (*b*) the *trans* rule[11] indicates that **6** has a β-configuration, and (*c*) p.m.r. evidence (H-1′ gave a doublet showing $J_{1',2'}$ 9 Hz) clearly corroborates the β-anomeric configuration of **6**.

Attempts to condense 2,4,6-tri-*O*-acetyl-3-*O*-carbamoyl-3-deoxy-α-D-glucopyranosyl bromide with 6-benzamidochloromercuripurine in the presence of cadmium carbonate, in boiling xylene under reflux, gave a mixture of unsaturated carbohydrates. Condensation of 1,2,4,6-tetra-*O*-acetyl-3-*C*-carbamoyl-3-deoxy-α-D-glucopyranose with 6-benzamidochloromercuripurine by the titanium tetrachloride method[12] afforded anomerized and epimerized starting material.

Treatment of the protected nucleoside **6** with sodium methoxide in anhydrous methanol, followed by deionization of the product over Amberlite IR-120 (H^+), readily afforded, after crystallization from ethanol–methanol, 1-(3-*C*-carbamoyl-3-deoxy-β-D-glucopyranosyl)thymine (**7**). The unsubstituted nucleoside exhibited circular dichroism (c.d.) values of +3777 and −2260 at 274 and 243 nm, respectively, thus further substantiating the β-anomeric configuration of the pyrimidine nucleosides[13].

Condensation of 2,4,6-tri-*O*-acetyl-3-*C*-carbamoyl-3-deoxy-α-D-glucopyranosyl bromide with 2,4-bis(trimethylsilyl)-N^4-acetylcytosine for 20 min at 97° afforded the fully acylated, crystalline, cytosine nucleoside **8** in 55% yield. The u.v. spectrum of **8** was consistent with that of a 1-substituted glycosylcytosine, and the n.m.r. spectrum ($J_{1',2'}$ 10 Hz) established the β-D configuration. Saponification of **8** with sodium methoxide in methanol, followed by purification of the unprotected nucleoside on Bio-Rad AG1-X2 (OH^-) resin according to the procedure of Dekker[14], gave crystalline 1-(3-*C*-carbamoyl-3-deoxy-β-D-glucopyranosyl)cytosine (**9**).

EXPERIMENTAL

General methods. — Irradiations were made under oxygen-free nitrogen with a 450-W Hanovia medium-pressure mercury vapour lamp fitted with a Pyrex filter. The reaction mixture was stirred magnetically and cooled internally with running water. Purified nitrogen was bubbled through the reaction mixture for at least 8 h before

irradiation. The progress of the reactions was checked by t.l.c. on Silica Gel G, with 5:5:1 benzene–ethyl acetate–ethanol. Mondray silica was used for column chromatography. I.r. spectra were recorded in Nujol with a Perkin–Elmer Model 337 spectrometer, and n.m.r. spectra were determined in chloroform-*d* solution or $(CD_3)_2SO$ solution with Me_4Si as the internal standard by using a Varian XL-100 spectrometer. Mass spectra were obtained with an HMS-9 spectrometer. Optical rotations were measured at room temperature with a Perkin–Elmer Model 141 automatic polarimeter, and circular-dichroism data were obtained with a JASCO Model CD/uv-207 spectropolarimeter at room temperature. All melting points are corrected. Elemental analyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver.

Irradiation of 1,2,4,6-tetra-O-*acetyl-3-deoxy*-α-D-erythro-*hex-2-enopyranose* (**1**). — Following an established procedure[4], a mixture of compound **1** (8.7g), formamide (30 ml), *tert*-butyl alcohol (15 ml), and acetone (15 ml) was added dropwise during 1 h to a mixture of formamide (200 ml), *tert*-butyl alcohol (10 ml), and acetone contained in the photolysis cell. Irradiation was continued during the addition and prolonged for 48 h (or until all of the starting material had disappeared, as evidenced by t.l.c.). After the solution had been concentrated to remove *tert*-butyl alcohol and acetone by evaporation (30 torr at 50°), the resulting mixture was diluted with saturated aqueous sodium chloride (200 ml). The resulting solution was then extracted with dichloromethane (4 × 200 ml). The combined dichloromethane extract was concentrated to 100 ml and the resulting solution was washed with saturated aqueous sodium chloride (50 ml), dried over anhydrous sodium sulfate, filtered, and evaporated under diminished pressure to a syrup (9.0 g). The main product **2** (3.0 g, 35%) was obtained by fractional crystallization from benzene–petroleum ether (b.p. 30–60°). A second recrystallization of **2** from the same solvent mixture afforded analytically pure **2**; m.p. 190–191°, $[\alpha]_D^{26}$ +108° (*c* 0.1, chloroform); i.r. 3475 and 1690 cm^{-1} (NH); n.m.r. data ($CDCl_3$): τ 3.9–4.3 (d, 2, NH_2, exchanges with D_2O), 3.63 (d, 1, $J_{1,2}$ 3.4 Hz, H-1), 4.75 (q, 1, $J_{2,3}$ 12 Hz, H-2), 7.02 (t, 1, $J_{3,4}$ 12 Hz, H-3), and 7.8–8.1 (3 s, 12, OAc).

Anal. Calc. for $C_{15}H_{21}NO_{10}$: C, 48.00; H, 5.64; N, 3.73. Found: C, 48.05; H, 5.72; N, 4.00.

After product **2** had been removed from the recrystallization solvents, the mother liquor was evaporated to a syrup. An aliquot (1.0 g) of this syrup was chromatographed on t.l.c.-grade silica gel (26.5 × 6 cm), with 10:5:1 benzene–ethyl ether–ethanol as developer, to afford the *gluco* amide **2** (200 mg, 11.4%), the *allo* amide **3** (220 mg, 12.7%), the *altro* amide **4** (18 mg, 1.0%), and the *manno* alcohol **5** (120 mg, 6.9%).

Compound **3** was recrystallized from ethyl acetate–petroleum ether (b.p. 30–60°); m.p. 41–42.5°, $[\alpha]_D^{26}$ +42.7° (*c* 1.0, chloroform); n.m.r. data (in $CDCl_3$): τ 3.85 (d, 1, $J_{1,2}$ 3.9 Hz, H-1), 3.87–4.2 (broad doublet, 2, NH_2, exchanges with D_2O), 4.77 (q, 1, $J_{2,3}$ 6 Hz, H-2), 5.08 (t, 1, $J_{4,5}$ 5 Hz, H-4), 6.62 (q, 1, $J_{3,4}$ 5 Hz, H-3), and 8.2 (4 s, 12, 4 OAc).

Anal. Calc. for $C_{15}H_{21}NO_{10}$: C, 48.00; H, 5.64; N, 3.73. Found: C, 48.29; H, 5.80; N, 3.18.

Compound **4** could not be obtained crystalline: $[\alpha]_D^{26}$ +32.7° (*c* 0.5, chloroform); n.m.r. data (in $CDCl_3$): τ 4.00 (d, 1, $J_{1,2}$ 2.5 Hz, H-1), 4.1–4.4 (broad singlet, 2, NH_2, exchanges with D_2O), 4.64 (q, 1, $J_{2,3}$ 5 Hz, H-2), 4.70 (q, 1, $J_{4,5}$ 7 Hz, H-4), 6.83 (q, $J_{3,4}$ 5.4 Hz, H-3), and 7.80–7.90 (2 s, 12, 4 OAc),

Anal. Calc. for $C_{15}H_{21}NO_{10}$: C, 48.00; A, 5.64; N, 3.73. Found: C, 47.95; H, 6.00; N, 3.48.

Compound **5** was recrystallized from ethanol–petroleum ether (b.p. 30–60°); m.p. 94–95°, $[\alpha]_D^{20}$ +20.0° (*c* 0.3, chloroform); ν_{max}^{Nujol} 3600 (OH); n.m.r. data (in $CDCl_3$): τ 4.02 (d, 1, $J_{1,2}$ 1.9 Hz, H-1), 4.80 (t, 1, $J_{2,3}$ 2.5 Hz, H-2), 7.60 (q, 1, $J_{3,4}$ 11 Hz, H-3), 7.95 (broad s, 1, OH, exchanges with D_2O), 7.8–8.1 (3s, 12, 4 OAc), and 8.75 (2s, 6, 2 Me).

Anal. Calc. for $C_{17}H_{26}O_{10}$: C, 52.30; H, 6.71. Found: C, 52.49; H, 6.92.

1-(2,4,6-Tri-O-acetyl-3-C-carbamoyl-3-deoxy-β-D-glucopyranosyl)thymine (**6**). — 1,2,4,6-Tetra-*O*-acetyl-3-*C*-carbamoyl-3-deoxy-α-D-glucopyranose (**2**, 0.2 g) was dissolved in 1 ml of anhydrous dichloromethane, cooled to 0°, and treated with (1 ml) of cold glacial acetic acid saturated with anhydrous hydrogen bromide. After the mixture had been stirred for 1 h at room temperature, the solvent was removed under diminished pressure. Toluene (3 × 2 ml) was added to, and evaporated from, the product to remove all hydrogen bromide. The resulting halide (0.25 g) and 2,4-bis-(trimethylsilyl)thymine[9] (0.236 g) were intimately mixed, placed in the flask, evacuated to 15 torr and the flask then sealed. The reaction mixture was slowly heated to 135–140° and maintained at that temperature for 30 min. After the reaction product had been triturated with 4:1 methanol–saturated aqueous sodium hydrogen carbonate (5 ml) the volatile components were removed under diminished pressure. The residue was then extracted with hot ethanol (5 × 5 ml) and the combined extracts were evaporated to yield a light brown syrup (0.232 g). This syrup was chromatographed on t.l.c.-grade silica gel (10 × 2 cm), with 5:5:1 dichloromethane–ethyl acetate–ethanol as developer, to give solid **6** (88 mg, 40%) which was recrystallized from ethanol–methanol; m.p. 144–145°, $[\alpha]_D^{24}$ −7.2° (*c* 0.2, methanol); λ_{max}^{MeOH} 207 (ε 7140) and 260 nm (7050); m.s. calc. 441.140179, found: 441.138329; c.d. (*c* 0.004, ethanol) $[\theta]_{270}$ +3290, $[\theta]_{245}$ −657; n.m.r. data (in Me_2SO-d_6): τ 1.0 (s, NH, N-3), 2.30 (s, 1, H-6), 2.40 (s, 1, O=CNH_2, exchanges with D_2O), 2.90 (s, 1, O=C–NH_2, exchanges with D_2O), 4.20 (d, 1, $J_{1',2'}$ 9 Hz, H-1'), 4.80 (overlapping peaks, 2, H-2', H-4'), 7.00 (t, 1, $J_{2',3'}$ 10 Hz, H-3'), and 8.0–8.25 (3s, 12, 3 OAc and 1 Me).

Anal. Calc. for $C_{18}H_{23}N_3O_{10}(CH_3OH)$; C, 48.20; H, 5.75; N, 8.87. Found: C, 48.30; H, 5.78; N, 8.61.

2,4,6-Tri-*O*-acetyl-3-*C*-carbamoyl-3-deoxy-α-D-glucopyranosyl bromide when treated with 6-benzamidochloromercuripurine in the presence of cadmium carbonate in boiling xylene under reflux, gave only unsaturated carbohydrates. Attempts to condense 1,2,4,6-tetra-*O*-acetyl-3-*C*-carbamoyl-3-deoxy-α-D-glucopyranose with 6-

benzamidochloromercuripurine by the titanium tetrachloride method[10] yielded only anomerized and epimerized starting material.

1-(3-C-Carbamoyl-3-deoxy-β-D-glucopyranosyl)thymine (**7**). — Compound **6** (0.04 g) was dissolved in anhydrous methanol (1 ml) containing sodium methoxide (about 1 mg) and the solution was kept for 4 h at room temperature. The sodium ions were removed by stirring with Amberlite IR-120 (H^+) resin, followed by filtration. The filtrate was evaporated to dryness and the resulting syrup (0.029 g) was crystallized from ethanol–methanol; m.p. 187–188°, $[\alpha]_D^{24}$ +22.6° (*c* 0.2, methanol); λ_{max}^{MeOH} 264 (ε 6310), 208 (6210); c.d. (*c* 0.06, methanol), $[\theta]_{274}$ +3777°, $[\theta]_{243}$ −2260°; n.m.r. data (in Me_2SO-d_6): τ 5.22 (s, 1, H-6), 3.46 (s, 1, O=C–NH_2, exchanges with D_2O), 3.75 (s, 1, O=C–NH_2, exchanges with D_2O), 5.08 (d, 1, $J_{1',2'}$ 11 Hz, H-1'), 7.60 (t, 1, $J_{2',3'}$ 9.8 Hz, H-3'), and 8.05 (s, 3, Me).

Anal. Calc. $C_{12}H_{17}N_3O_7(H_2O)$: C, 43.24; H, 5.75; N, 12.61. Found: C, 43.50; H, 5.58; N, 12.60.

1-(2,4,6-Tri-O-acetyl-3-C-carbamoyl-3-deoxy-β-D-glucopyranosyl)-N^4-acetylcytosine (**8**). — 1,2,4,6-Tetra-*O*-acetyl-3-*C*-carbamoyl-3-deoxy-β-D-glucopyranose (**2**, 0.385 g) was dissolved in anhydrous dichloromethane (2 ml), and hydrogen bromide-saturated glacial acetic acid (10 ml) was added at 0° with stirring. The flask was sealed and allowed to warm to room temperature and was stirred for an additional 1 h. The solution was then evaporated to dryness under diminished pressure and any remaining acetic acid removed by successive azeotroping with toluene (2 × 5 ml) under diminished pressure. The resulting syrup was immediately dissolved in anhydrous dichloromethane (5 ml) containing 2,4-bis(trimethylsilyl)-N^4-acetylcytosine (0.40 g) and the solvent removed under diminished pressure. This homogenous syrup was then heated for 20 min to 97° at 6 torr. Methanol saturated with sodium hydrogen carbonate (20 ml) was added after cooling, and the solution filtered through sintered glass. Removal of the solvent under diminished pressure yielded a brown syrup (0.4 g). Column chromatography of the product on silica (40 g, 3 × 20 cm) under pressure, with 1:1 ethyl acetate–ethanol as the eluent, afforded 1-(2,4,6-tetra-*O*-acetyl-3-*C*-deoxy-β-D-glucopyranosyl)-N^4-acetylcytosine (**8**), (0.255 g, 55% yield) (based on the amount of sugar acetate used). An analytical sample of **8** was prepared by crystallization from ethanol–petroleum ether (b.p. 30–60°); m.p. 163–164.5°; $[\alpha]_D^{25}$ +35° (*c* 0.2, methanol); λ_{max}^{MeOH} 250 (ε 17,000), 208 (15,700), 298 nm (6850); c.d. (*c* 0.004 methanol), $[\theta]_{275}^{25}$ +10,890°, $[\theta]_{235}^{25}$ −11,600°; n.m.r. data (in Me_2SO-d_6): τ 1.78 (d, 1, $J_{5,6}$ 7.6 Hz, H-6), 2.78 (d, 1, H-5), 2.36–2.88 (s, 2 O=CNH_2, disappears on addition of D_2O), 3.99 (d, 1, $J_{1,2}$ 10 Hz, H-1') 4.5–5.1 (overlapping peaks), 5.5–6.3 (overlapping peaks), 6.94 (t, 1, $J_{2,3} \approx J_{3,4} = 10.4$ Hz, H-3) 7.82, 7.94, 7.96, and 8.14 (s, 4 OAc).

Anal. Calc. for $C_{19}H_{24}N_4O_{10}$: C, 48.72; H, 5.16; N, 11.96. Found: C, 48.89; H, 5.00; N, 11.69.

1-(3-C-Carbamoyl-3-deoxy-β-D-glucopyranosyl)cytosine (**9**). — The fully acetylated nucleoside **8** was dissolved in anhydrous methanol (10 ml) and a catalytic amount of sodium methoxide solution was added (10 μl of an 0.3mM solution of

sodium methoxide). This solution was kept for 8 h at room temperature, after which time it was neutralized with IR-120 (H^+) resin. T.l.c. of the product on silica gel, developed with 1:1 methanol–ethyl acetate, showed two products, having R_F 0.45 and 0.37. After filtering off the resin, removal of the solvent left a clear syrup (0.40 g). Column chromatography of the product, with the same solvent, on silica gel (4.0 g, 13 × 1 cm) afforded the major zone (20 mg, 65% yield). The unprotected nucleoside **9** was purified by chromatography according to the procedure of Dekker[14].

An analytical sample of **9** was crystallized from ethanol–methanol; m.p. 185.5–187°, $[\alpha]_D^{24}$ +20.4° (*c* 0.56, methanol); $\lambda_{max}^{0.1\,M\,HCl}$ 210 (ε 6770), 274 nm (9250), $\lambda_{min}^{0.1\,M\,HCl}$ 234; λ_{max}^{MeOH} 209 (ε 6740), 237 (5620), 267 nm (5399); c.d. (*c* 0.004, methanol), $[\theta]_{274}^{25}$ +8,000, $[\theta]_{236}^{25}$ −4,045; n.m.r. data (in D_2O): τ 2.10 (1, d, $J_{5,6}$ 8 Hz, H-6), 3.70 (1, d, H-5), (irradiation of H-6 at τ 2.10 collapsed the doublet at τ 3.70 to a singlet), 4.33 (1, d, $J_{1',2'}$ 9.5 Hz, H-1'), 6.10 (q, $J_{2',3'}$ 10 Hz, H-2'), 5.95–6.20 (overlapping peaks, H-4, H-5, and H-6), 7.06 (1, unresolved quartet, $J_{2,3} = J_{3,4} = 10$ Hz, H-3'), and 3.9–4.1 (broad peak, exchanges slowly with D_2O after 10 min, $O{=}CNH_2$).

Anal. Calc. for $C_{11}H_{16}N_4O_6(H_2O)$: C, 41.51; H, 5.70; N, 17.60. Found: C, 41.61; H, 5.30; N, 17.00.

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