Note

Nucleosides. Part LXX. An unequivocal synthesis of 1-β-D-allopyranosyl-uracil and -cytosine*

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In a preliminary communication; Cron *et al.*[1] reported that the nitrous acid deamination of *O*-acetylated kanosamine (3-amino-3-deoxy-D-glucose) followed by reacetylation afforded α-D-glucose pentaacetate (no net inversion). Later, Watanabe *et al.*[2] reported that treatment of the tri-*O*-acetate of 1-(3-amino-3-deoxy-β-D-glucopyranosyl) uracil (**1**) with ethyl nitrite in acetic acid, followed by saponification with alcoholic ammonia gave in 32% yield a crystalline nucleoside which exhibited ultraviolet absorption spectral characteristics and elemental analyses consistent with a 1-hexosyluracil. However, since this product differed from 1-β-D-gluco- and -galacto-pyranosyluracils[3] with respect to chromatographic and electrophoretic behavior, m.p., i.r. spectrum, and optical rotation, it was tentatively assigned the *allo* configuration **3**. A plausible mechanism for the overall conversion (**1**→**3**) was proposed[2] in which the 2-carbonyl of the aglycon would stabilize the diazonium intermediate (as in structure **2**) and favor a rearward attack on C-3′ by solvent to give the *allo* nucleoside (**3**). Such a proposed mechanism (if valid) would be especially germane to such a class of nucleosides containing amino sugar moieties as the several recently-discovered nucleoside antibiotics[4]. It is therefore important that structure **3** be firmly established. In this report, we offer conclusive evidence for the structure of **3** by an unequivocal synthesis.

β-D-Allopyranose pentaacetate[5] (**4**) was synthesized from β-D-allose in an improved yield using acetic anhydride–pyridine at 0°. Compound **4** was treated according to the procedure of Niedballa and Vorgrüggen[6] with the 2,4-bis-(trimethylsilyl) derivative of N^4-acetylcytosine in the presence of stannic chloride to give the fully acylated cytosine nucleoside **5** as a syrup. The u.v. spectrum of **5** was consistent with that of a 1-substituted glycosylcytosine and the n.m.r. spectrum ($J_{1',2'}$, 10 c.p.s.) established the β-D configuration. Saponification of **5** with sodium methoxide in methanol afforded crystalline 1-β-D-allopyranosylcytosine (**6**). Treatment of **5** with 80% acetic acid under reflux conditions, according to the procedure of Brown

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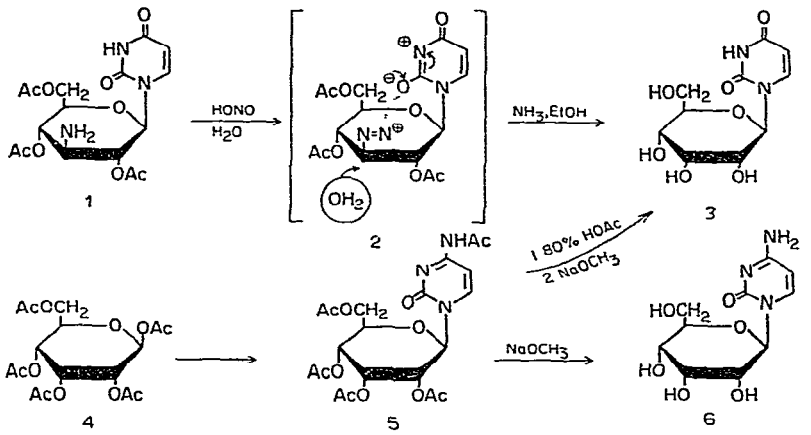
et al.[7], followed by saponification with sodium methoxide gave crystalline 1-β-D-allopyranosyluracil, which was identical with **3** previously obtained by nitrous acid treatment of **1**.



EXPERIMENTAL

General. — Melting points were determined on a Thomas–Hoover apparatus (capillary method) and are not corrected. The elementary analyses were performed by Galbraith Laboratories, Inc.. Knoxville, Tennessee. Thin-layer chromatography was performed on microscope slides coated with silica gel GF-254 (Merck) with: (A) 9:1 (v/v) benzene–methanol, and (B) butyl alcohol saturated with water. The compounds were detected by u.v. light, or by spraying with 20% (v/v) sulfuric acid in ethanol, followed by heating on a hot plate or by both methods. All evaporations were carried out *in vacuo* at 40–50°. N.m.r. spectra were determined on a Varian A-60 spectrometer, using tetramethylsilane or sodium 3-trimethylsilyl-1-propanesulfonate as an internal standard, i.r. spectra on a Perkin–Elmer model 221 spectrophotometer and u.v. spectra on a Unicam SP.800 spectrophotometer.

β-D-Allopyranose pentaacetate (**4**). — β-D-Allose[8] (10.8 g, 0.06 mole) was added to a stirred, cold (0°) solution of pyridine (100 ml) and acetic anhydride (50 ml, 54.5 g, 0.53 mole). The temperature of the stirred solution was allowed to rise to room temperature. After 18 h, the solution was cooled in an ice–water bath, and the excess acetic anhydride was decomposed with ethanol. Concentration of the solution *in vacuo* gave a pale-yellow syrup, to which ethanol was added and evaporated (2 × 100 ml) to remove traces of pyridine. The syrup was dissolved in ether, and petroleum ether (b.p. 30–60°) was added until turbidity occured. The yield of crystalline **4** was 16.0 g (68%), m.p. 95–96° $[\alpha]_D^{25}$ −15° (c 2.9, chloroform); lit. [5].m.p. 93–93.5°, $[\alpha]_D$ −13.7°.

1-(Tetra-O-acetyl-β-D-allopyranosyl)-N⁴-acetylcytosine (**5**). — Compound **4** (1.95 g, 5.0 mmoles) and 2,4-bis(trimethylsilyl)-*N*⁴-acetylcytosine (5.6 moles) in dry

1,2-dichloroethane (100 ml) were stirred in the presence of stannic chloride (10 ml, 8.0 mmoles) for 4 h at 22°. After the addition of saturated aqueous sodium hydrogen carbonate (100 ml), the organic layer was separated, washed with water (100 ml), and dried (sodium sulfate). Evaporation of the solvent gave a chromatographically pure (Solvent A, R_F 0.25) syrup (~2.0 g); n.m.r. data (dimethylsulfoxide-d_6): δ 1.90, 2.00, 2.02, and 2.12 (OAc, 12), 2.25 (NAc, 3), 4.00–4.50 and 5.00–5.85 (sugar ring and CH_2 protons, 6), 6.20 (H-1′, d, 1, $J_{1',2'}$ ~10 c.p.s.), 7.20 and 8.22 (H-5, H-6, d, 2, $J_{5,6}$ ~7.5 c.p.s.), and 10.82 (NH, 1); λ_{max}^{EtOH} 214, 250, 299 nm; λ_{min}^{EtOH} 226, 227 nm.

1-β-D-Allopyranosylcytosine (**6**). — Compound **5** (from 1.95 g sugar acetate) was dissolved in methanol (100 ml) containing sodium methoxide (100 mg) and kept for 3 h at 22°. The sodium ions were removed by stirring the solution with Amberlite IRC-50 (H^+) resin (10 g, dry weight) for 1 h, followed by filtration. The filtrate was concentrated to dryness, and the resulting syrup was applied to a column of Dowex 50 (H^+, 100–200 mesh, 30 ml). The column was washed with water (200 ml), and the nucleoside was eluted with 2.5M ammonia (250 ml). The eluent was concentrated to a small volume (~3 ml). Addition of ethanol (100 ml) gave a gummy residue which was dissolved by heating. Crystals formed at room temperature (730 mg in two crops, 53% based on sugar acetate); m.p. 185–220°; (dec.); $[\alpha]_D^{25}$ ~0° (c 2.2, water); t.l.c. (solvent B): R_F 0.1; n.m.r. data (D_2O): δ 3.85 (H-4′, H-5′, CH_2, m, 4), 3.95 (H-2′, m, 1), 4.31 (H-3′, m, 1), 5.90 (H-1′, d, 1, $J_{1',2'}$ ~10 c.p.s.), 6.05 and 7.65 (H-5, H-6, d, 2, $J_{5,6}$ ~8 c.p.s.); $\lambda_{max}^{0.1MHCl}$ 277, 218 nm, $\lambda_{min}^{0.1MHCl}$ 240 nm; $\lambda_{max}^{H_2O}$ 268, 236 nm, $\lambda_{min}^{H_2O}$ 252 nm.

Anal. Calc. for $C_{10}H_{13}N_3O_6$: C, 43.91; H, 5.53; N, 15.37. Found: C, 43.61; H, 5.94; N, 14.98.

1-β-D-Allopyranosyluracil (**3**). — Compound **5** (from 1.95 g of **4**) was heated at reflux with 80% aqueous acetic acid (100 ml) for 9 h, during which time most of the starting material was converted into a new material (t.l.c.: R_F 0.12 in solvent A). Evaporation of the solvent and subsequent additions and evaporations of toluene (2 × 100 ml) gave an acetic acid-free syrup, which was dissolved in methanol (100 ml) containing sodium methoxide (100 mg). The solution was stirred for 3 h at room temperature and the sodium ions were removed by stirring with Amberlite IRC-50 (H^+) resin (10 g, dry weight) for 1 h, followed by filtration. The filtrate was concentrated to dryness, the residue dissolved in water (10 ml), and the solution applied to a column of Dowex 50 (H^+, 100–200 mesh, 30 ml). The resin was washed with water (300 ml), and the eluent concentrated to a solid which was crystallized from 1:1 (v/v) ethanol–methanol (yield 36%, based on sugar acetate **4**, 500 mg in two crops); m.p. 246–248°; $[\alpha]_D$ ~−3° (c 1.1, water); n.m.r. data (D_2O): 3.85 (H-4′, H-5′, CH_2, m, 4), 3.97 (H-2′, m, 1), 4.30 (H-3′, m, 1), 5.82 (H-1′, d, 1, $J_{1',2'}$ ~10 c.p.s.), 5.90 and 7.75 (H-5 H-6 d, 2, $J_{5,6}$ ~8 c.p.s.); $\lambda_{max}^{H_2O}$ 208, 260 nm, $\lambda_{min}^{H_2O}$ 228 nm. The physical properties of this product with regard to i.r., u.v., optical rotation, electrophoretic mobility, and t.l.c. (solvent B, R_F 0.25) were identical with those observed on a sample of **3** obtained from **1** .A melting point of **3** (derived from **1**) observed recently was 246–248° (previously reported[2] to be 241–242°), and a mixed melting point of

samples of **3** derived from both synthetic routes (**1**→**3** and **4**→**5**→**3**) was undepressed (246–248°).

Elution of the Dowex 50 (H^+) column with 2.5M ammonia (300 ml) and evaporation of the eluent gave 300 mg (22% based on the sugar acetate) of the cytosine nucleoside **5**.

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