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Note

Preparation of a substituted 3-acetamido-3-deoxy-D-ribofuranosyl bromide suitable for the synthesis of puromycin analogs*

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Extension of our work on the synthesis of adenine *C*-nucleosides[1] to the puromycin series necessitated the preparation of a substituted 3-amino-3-deoxy-D-ribofuranosyl halide capable of undergoing nucleophilic substitution with a nitrile Baker and co-workers[2] had synthesized substituted puromycins from 3-acetamido-1-*O*-acetyl-2,5-di-*O*-benzoyl-3-deoxy-D-ribofuranosyl chloride–titanium chloride and from 2,5-di-*O*-benzoyl-3-deoxy-3-phthalimido-D-ribofuranosyl chloride, but we found that these halides were not satisfactory for the synthesis of the substituted 4-amino-2,5-anhydro-4-deoxy-D-allononitrile and -allonic acid needed in our *C*-nucleoside synthesis Accordingly, we tried three other methods of preparing glycosyl halides, and found one that was satisfactory and that led to the preparation of a crystalline HBr salt of 3-acetamido-2-*O*-acetyl-3-deoxy-5-*O*-*p*-nitrobenzoyl-D-ribofuranosyl bromide, this could be converted into 4-acetamido-3-*O*-acetyl-2,5-anhydro-4-deoxy-5-*O*-*p*-nitrobenzoyl-D-allonic acid (**8**), an adequate starting material for the *C*-nucleoside synthesis

The synthesis started with the known 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-D-ribofuranose (**1**), prepared by the procedure of Brimacombe and Mofti[3] On *p*-nitrobenzoylation, compound **1** yielded crystalline 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-5-*O*-*p*-nitrobenzoyl-α-D-ribofuranose (**2**) To remove the isopropylidene group, we used the procedure of Christensen and Goodman[4] employing 90% aqueous trifluoroacetic acid. The reaction required 4 h for completion (instead of the customary 5–10 min, and yielded the desired 3-acetamido-3-deoxy-5-*O*-*p*-nitrobenzoyl-D-ribofuranose (**3**) This syrupy compound could be converted into three crystalline derivatives potentially capable of forming the glycosyl halide with hydrogen

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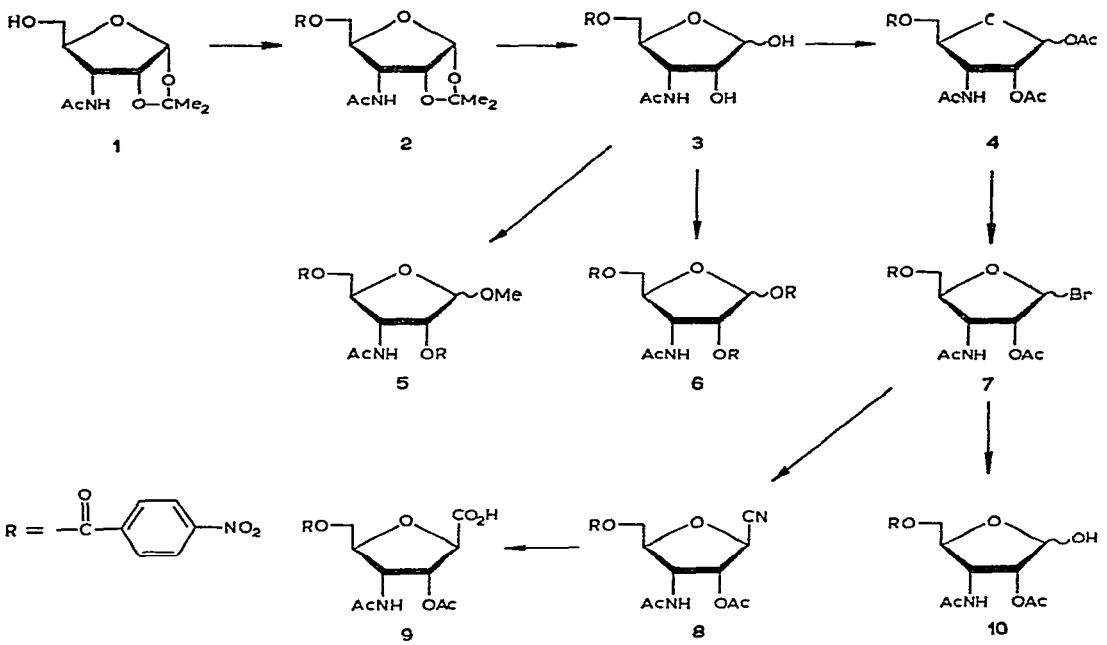
halide, however, the first two failed to give halide in satisfactory yield Thus, treatment of compound **3** with methanolic hydrogen chloride, followed by *p*-nitrobenzoylation of the methyl glycoside, converted compound **3** into the anomeric methyl 3-acetamido-3-deoxy-2,5-di-*O*-*p*-nitrobenzoyl-D-ribofuranosides (**5**) Alternatively, compound **3** was *p*-nitrobenzoylated to give the 3-acetamido-3-deoxy-1,2,5-tri-*O*-*p*-nitrobenzoyl-D-ribofuranoses (**6**) Attempts to prepare the glycoside halides from compounds **5** or **6** failed to give crystalline derivatives, and t l c of the reaction product revealed the presence of at least five compounds



It was, therefore, decided to proceed *via* the 1,2-di-*O*-acetyl derivatives (**4**), which could be obtained either by acetylating compound **3**, or (better) by treating compound **2** directly with a mixture of acetic anhydride and concentrated sulfuric acid. Compounds **4** showed two anomeric protons, a singlet at δ 5 0 and a doublet at δ 5 2 (J 4 5 Hz), for the β and α anomers, respectively Treatment of the di-*O*-acetyl derivatives **4** with acetyl bromide and hydrogen bromide in dichloromethane gave a hydrated HBr salt of 3-acetamido-2-*O*-acetyl-3-deoxy-5-*O*-*p*-nitrobenzoyl-D-ribofuranosyl bromide (**7**) On treatment with mercuric cyanide in nitromethane, compound **7** afforded a nitrile (**8**), which was hydrolyzed to the desired 4-acetamido-3-*O*-acetyl-2,5-anhydro-4-deoxy-5-*O*-*p*-nitrobenzoyl-D-allonic acid (**9**) Partial hydrolysis of compound **7** gave a crystalline 3-acetamido-2-*O*-acetyl-3-deoxy-5-*O*-*p*-nitrobenzoyl-D-ribofuranose (**10**)

EXPERIMENTAL

General — Melting points were determined on a Kofler block and are uncorrected. Evaporations were conducted under diminished pressure in a rotary evaporator at 40–45° Specific rotations were measured, in a 0 2-dm tube, with a Bendix-NPL polarimeter Infrared spectra were recorded, for potassium bromide pellets, with a Perkin–Elmer, model 621, grating, infrared spectrophotometer. N.m r. spectra were recorded at 60 and 100 MHz with Varian T-60 and HA-100 spectrometers, respectively Mass spectra were recorded with a Varian M-66 mass spectrometer by Mr M. P. Gilles Thin-layer chromatography (t l c) was performed either on plates of Merck Silica Gel G or plates of silica gel precoated with a fluorescent indicator (Eastman Kodak catalog No 6060), with sulfuric acid spray and u v light, respectively, for detection For column chromatography, silica gel (60–200 mesh, J T Baker) was used with a Gibson automatic fraction-collector. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan, U S A

*3-Acetamido-3-deoxy-1,2-*O*-isopropylidene-5-*O*-p-nitrobenzoyl-α-*D*-ribofuranose* (**2**) — A solution of 3-acetamido-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose[2] (**1**) (9 3 g, 0 04 mole) in a mixture of dichloromethane (20 ml) and pyridine (50 ml) was cooled to 0°. *p*-Nitrobenzoyl chloride (8 1 g, 0 04 mole) was then added, and the mixture was kept for 24 h at 20°, and then poured onto crushed ice (100 ml) The mixture was extracted with dichloromethane, and the extract successively washed with saturated sodium hydrogen carbonate (300 ml) and water (100 ml), filtered through a column (2 × 10 cm) of silica gel, and evaporated, to afford compound **2**, which crystallized from ethanol (10 ml) in needles, yield 86 28%, m p 118°, $[\alpha]_D^{20}$ −15 5° (*c* 1, chloroform), R_F 0 40 (1 1 benzene–ethyl acetate), ν_{max}^{KBr} 3350 (NH), 1725 (OAc), and 1650 cm^{-1} (NAc)

Anal Calc for $C_{17}H_{20}N_2O_8$ C, 53 68, H, 5 30, N, 7 37 Found C, 53 80, H, 5 32, N, 7 37

*3-Acetamido-3-deoxy-5-*O*-p-nitrobenzoyl-*D*-ribofuranoses* (**3**) — A suspension of compound **2** (0 4 g) in 9 1 trifluoroacetic acid–water (5 5 ml) was stirred for 4 h at room temperature and then evaporated under diminished pressure to a syrup which was dried by successive co-evaporation with dichloromethane and toluene The acidic syrup was dissolved in 1 1 water–acetone (50 ml), and the solution was made neutral with sodium hydrogen carbonate, and filtered The filtrate was evaporated to a syrup which was filtered through silica gel, and the solid washed with ethyl acetate The filtrate and washings were combined, and evaporated to a syrup, which was dried under diminished pressure, yield 0 45 g (71 0%), t l c (11·5 2 chloroform–methanol–benzene) R_F 0 71 (major) and 0 58 (minor), (2 3 petroleum ether–acetone) R_F 0 40 (major) and 0 33 (minor)

*3-Acetamido-1,2-di-*O*-acetyl-3-deoxy-5-*O*-p-nitrobenzoyl-*D*-ribofuranoses* (**4**) — To a solution of compounds **3** (2 8 g) in a mixture of acetic acid (42 ml) and acetic anhydride (4 2 ml) was added sulfuric acid (2 56 ml), dropwise, with stirring at 10°.

After addition was complete, the mixture was kept for 20 h at room temperature, poured slowly into ice-cold water, and the mixture extracted with chloroform (3 × 60 ml), the extracts were combined, successively washed with aqueous sodium hydrogen carbonate and water, dried (magnesium sulfate), and evaporated under diminished pressure to a syrup which crystallized from acetone–petroleum ether Compound **4** (yield 89%) crystallized in needles, m p 144°, $[\alpha]_D^{20}$ +24 4° (*c* 1, chloroform), R_F 0 40 (11 9 acetone–petroleum ether), ν_{max}^{KBr} 1740–1760 (OAc, CO_2R) and 1660 cm^{-1} (NAc)

Anal Calc for $C_{18}H_{20}N_2O_{10}\cdot 0\,5H_2O$ C, 49 89, H, 4 88, N, 6 46 Found C, 50 03, H, 4 74, N, 6 16

Methyl 3-acetamido-3-deoxy-2,5-di-O-p-*nitrobenzoyl*-D-*ribofuranosides* (**5**) — A solution of syrupy **3** (0 35 g) in a mixture of methanol (11 ml) and concentrated hydrochloric acid (0 2 ml) was kept for 9 h at room temperature, made neutral with sodium hydrogen carbonate, and evaporated under diminished pressure The residue was mixed with ether, the suspension filtered from the insoluble salt, and the filtrate evaporated, and dried by co-evaporation with toluene The residue was dissolved in anhydrous pyridine (10 ml), and treated overnight with *p*-nitrobenzoyl chloride (0 4 g) at 0°. A few drops of water were added, and the mixture was stirred for 0 5 h and then poured onto crushed ice The solution was extracted with chloroform, and the extract was washed successively with dilute hydrochloric acid, 2M sodium hydrogen carbonate, and water, dried (magnesium sulfate), and evaporated under diminished pressure, to yield compound **5**, which crystallized from benzene in needles, m p 228–231°

Anal Calc for $C_{22}H_{21}N_3O_{11}$ C, 52 49, H, 4 20, N, 8 35 Found C, 52 32, H, 4 40, N, 8 21

3-Acetamido-3-deoxy-1,2,5-tri-O-p-*nitrobenzoyl*-D-*ribofuranoses* (**6**) — A solution of compound **3** (3 0 g) in pyridine (30 ml) was cooled, *p*-nitrobenzoyl chloride (3 3 g) was added, and the mixture was kept for 20 h at 20° It was then poured onto ice (100 ml), and extracted with ethyl acetate (4 × 10 ml) The extracts were combined, successively washed with sodium hydrogen carbonate solution (2 × 50 ml) and water (2 × 50 ml), and dried The dark-brown suspension was filtered through silica gel, and the solid washed with ethyl acetate (300 ml), the filtrate and washings were combined, and concentrated to 10 ml The crystals that separated were recrystallized from ethyl acetate (yield 1 1 g, 17 2%) as needles, m p 204–206°, $[\alpha]_D^{20}$ +72 3° (*c* 0 31, chloroform), R_F 0 513 (2 3 petroleum ether–acetone)

Anal. Calc for $C_{28}H_{22}N_4O_{14}$· C, 52 67, H, 3 47, N, 8 77 Found· C, 52 74; H, 3 58, N, 8 42

3-Acetamido-2-O-*acetyl-3-deoxy-5*-O-p-*nitrobenzoyl*-D-*ribofuranosyl bromide* (**7**) — Thoroughly dried **4** (2 g) was dissolved in a hot mixture of dichloromethane (15 ml) and acetyl bromide (5 ml), the solution was cooled to 0°, hydrogen bromide gas was slowly bubbled through for 15 min, and the mixture was kept for 5 days at 0° under anhydrous conditions Ether (50 ml) was then added to precipitate the product, which was washed with 3 1 dichloromethane–ether (10 ml), and then dissolved in dichloro-

methane and precipitated with ether (yield 2 5 g) Compound 7 crystallized from a mixture of chloroform and dichloromethane as a hydrated salt, m p 144–147°; R_F 0 28 (9.11 petroleum ether–acetone)

Anal. Calc. for $C_{16}H_{17}BrN_2O_8 \cdot 0\,25\,HBr\ 0\,25\,H_2O$ C, 38 85; H, 3 77, N, 5.66. Found· C, 38.87; H, 4 08, N, 6.06

*4-Acetamido-3-*O*-acetyl-2,5-anhydro-4-deoxy-6* O-p-*nitrobenzoyl*-D-*allonic acid* (**9**) — Mercuric cyanide (7 5 g) in nitromethane (65 ml) was distilled azeotropically with benzene (20 ml) to remove any moisture present, the mixture was cooled to 0°, compound **7** (2 3 g) was added, and the mixture was stirred for 70 h at room temperature and processed as usual. The syrupy 4-acetamido-3-*O*-acetyl-2,5-anhydro-4-deoxy-6-*O*-*p*-nitrobenzoyl-D-allononitrile (**8**) (1.7 g) was hydrolyzed at room temperature with M hydrochloric acid, and the solution was then chromatographed on a column (2 × 32 cm) of silica gel with mixtures of petroleum ether (b p 90–110°) and acetone in the ratios of 3 1 (450 ml), 2 1 (300 ml), and 1 1 (450 ml) Fractions (15 ml each) were collected, and monitored by t l c (9 11 petroleum ether–acetone) Fractions 30–80 were combined, and crystallized from ethanol in needles, m p 136°, $[\alpha]_D^{20}$ +64 0° (*c* 1, chloroform), ν_{max}^{KBr} 3540 (OH), 3315 (NH), 1755 (COO), and 1655 cm^{-1} (CONH), n m r. data· δ 8 25 (aromatic), 4 88 (singlet; anomeric), 2 01 (OAc), and 2 20 (NAc), m s data *m/e* 466 ($M-CO_2$; 100%), 260 ($M-COC_6H_4NO_2$, 80%), and 150 ($COC_6H_4NO_2$ 75%)

Anal Calc. for $C_{17}H_{18}N_2O_{10}$· C, 49 76, H, 4 42, N, 6 82 Found C, 50 06, H, 4.72, N, 6 58

*3 Acetamido-2-*O*-acetyl-3-deoxy-5-*O*-p-nitrobenzoyl*-D-*ribofuranose* (**10**) — A solution of compound 7 (3 g) in chloroform (250 ml) was stirred with saturated sodium hydrogen carbonate solution (500 ml) for 2 h at room temperature. The chloroform layer was then separated, dried, and filtered through a short column of silica gel, which was washed with chloroform and acetone The filtrate and washings were combined, and evaporated to a syrup (3 1 g), which crystallized from 4 1 dichloromethane–ether in needles, yield 1.5 g, m p 165–167°, $[\alpha]_D^{20}$ +45.7° (*c* 1, acetone), R_F 0 33 (9 11 petroleum ether–acetone)

Anal Calc for $C_{16}H_{18}N_2O_3$ C, 50 26, H, 4 74, N, 7 32 Found C, 49 81, H, 4.70, N, 7 09

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