Registry No.—1, 10565-20-5; 2, 102-09-0; 5, 58462-98-9; 6, 58462-99-0; 6 monoester analogue, 58463-00-6; 7, 14123-41-2; catechol, 120-80-9; dichloroacetyl chloride, 79-36-7; o-phenylene carbonate, 2171-74-6; o-hydroxy-α,α-dichloroacetophenone, 29003-58-5; o-hydroxy-α,α-dichloroacetophenone bis(2,4-dinitrophenylosazone), 58463-01-7; 2,4-DNPH, 119-26-6.

References and Notes

(1) Petroleum Research Fund Undergraduate Fellow, 1973–1974.
(2) M. K. Saxena and M. Bakadia, *Chem. Ind. (London)*, 666 (1966).
(3) H. Crompton and P. M. Triffitt, *J. Chem. Soc.*, 1874 (1921).
(4) A. B. Sen and A. K. Sen-Gupta, *J. Indian Chem. Soc.*, **33**, 437 (1956).
(5) D. S. Tarbell and P. E. Fanta, *J. Am. Chem. Soc.*, **65**, 2169 (1943).
(6) L. Ghosez, R. Montaigne, H. Vanlierde, and P. Mollet, *Tetrahedron*, **27**, 615 (1971).
(7) H. C. Stevens, D. A. Reich, D. R. Brandt, K. R. Fountain, and E. J. Gaughan, *J. Am. Chem. Soc.*, **87**, 5347 (1965).
(8) J. M. Lavanish, *Tetrahedron Lett.*, 6003 (1968).
(9) (a) W. T. Brady and P. L. Ting, *J. Org. Chem.*, **40**, 3417 (1975); (b) W. T. Brady, F. H. Parry, III, R. Roe, Jr., E. F. Hoff, Jr., and L. Smith, *ibid.*, **35**, 1515 (1970).
(10) G. L. Closs and G. M. Schwartz, *J. Am. Chem. Soc.*, **82**, 5723, 5729 (1960).
(11) A. C. Pierce and M. M. Joullie, *J. Org. Chem.*, **28**, 658 (1963).
(12) A. Einhorn and E. Lindenberg, *Justus Liebigs Ann. Chem.*, **300**, 141 (1898); R. S. Hanslick, W. F. Bruce, and A. Mascitti, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 788.
(13) Twinning of the carbonyl band of five-membered cyclic carbonates is apparently common. Cf. L. J. Bellamy, "The Infrared Spectra of Complex Organic Molecules", Vol. 1, 3d ed, Wiley, New York, N.Y., 1975, p 143.

Nucleosides. 98. Direct Introduction of an Acetamido Group into the Sugar Moiety of Nucleoside Epoxides[1]

Uri Reichman, David H. Hollenberg, Chung K. Chu, Kyoichi A. Watanabe, and Jack J. Fox*

Laboratory of Organic Chemistry, Sloan-Kettering Institute for Cancer Research, Sloan-Kettering Division of Cornell University Graduate School of Medical Sciences, New York, New York 10021

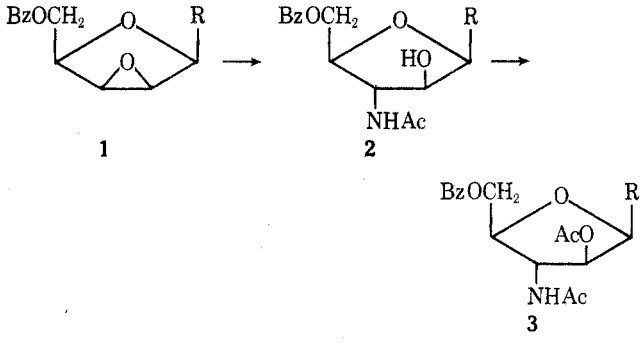
Received November 25, 1975

The interest in the synthesis of aminoglycosides (including amino nucleosides) has grown over the years owing to the antibiotic properties that many of them exhibit.[2] The most common method for the introduction of an amino group into a sugar is via nucleophilic displacement of a sulfonyloxy group by azide followed by reduction[3] or by opening an epoxide by ammonia.[4] In the case of nucleosides, an amino group may be introduced into the carbohydrate moiety by cyclization of nucleoside dialdehydes with nitromethane followed by reduction of the nitro group,[5] by replacement of a sulfonyloxy group,[6] or by opening an epoxide[7] or 2,2′-anhydro linkage[8] with azide and subsequent reduction of the azido function. Direct opening of nucleoside 2′,3′-epoxides with ammonia is also known.[9] We report herein a facile method for the *direct* introduction of an acylamino group into the sugar moiety of nucleosides by the use of boron trifluoride etherate in acetonitrile.

Treatment of the nucleoside 2′,3′-epoxides (**1**) with boron trifluoride etherate in acetonitrile followed by neutralization of the reaction mixture with saturated sodium hydrogen carbonate solution gave the corresponding 3′-acetamido-3′-deoxyarabinosyl nucleosides (**2**) which crystallized out in pure state from the reaction mixture (Chart I).

A plausible mechanism for the conversion of **1** → **2** via postulated intermediates **4** and **5** is shown (Chart II). This mechanism is somewhat akin to that proposed by Smith et al.[10] for the synthesis of oxazolines from epoxides. In the case of nucleoside 2′,3′-epoxides, however, anchimeric assistance from the 2′ oxygen in zwitterion **5** to form an oxazoline cannot occur. Hydrolysis of **5** results in the formation of 3′-acetamido-3′-deoxyarabinosyl nucleosides (**2**). It is noteworthy that TLC examination of the product **2** showed only one spot; no evidence for the formation of a 2′-acetamidoxylo nucleoside was obtained.

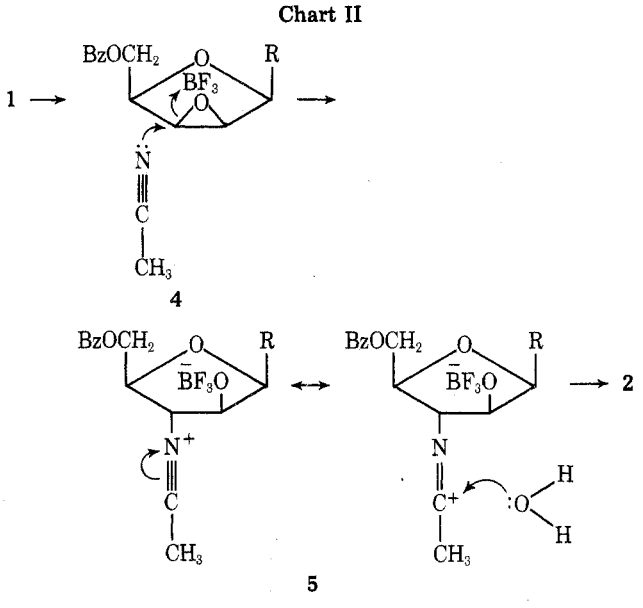
Chart I



1 2 3

a, R = uracil b, R = N^4-benzoylcytosine

Chart II



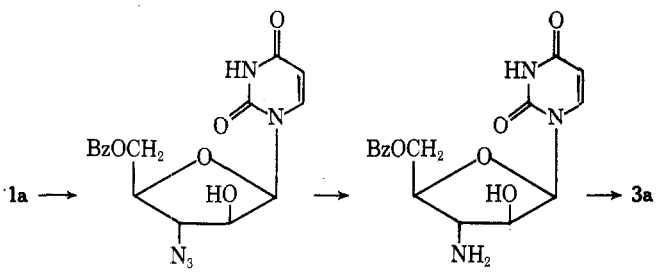
The structures of nucleosides **2** were established in the following manner: the position of the free hydroxyl group at C-2′ was confirmed by acylation of **2** to **3**, followed by NMR analyses of the acetylated products. In nucleosides **3** the sugar ring protons geminal to the acetoxy group are shifted downfield by ~1.2 ppm relative to their chemical shift in the parent compounds **2** (see NMR data in Experimental Section) and now appear as a triplet. Irradiation at the frequency of the triplet converted the doublet of the anomeric proton signal into a singlet. Upon irradiation at the frequency of the anomeric signal, the above mentioned triplet became a doublet. These decoupling experiments firmly allocate the hydroxyl substituent to C-2′ and, consequently, the acetamido function to C-3′ in **2** and **3**. Final proof was achieved by an unambiguous synthesis of 1-(3-acetamido-2-*O*-acetyl-5-*O*-benzoyl-3-deoxy-β-D-arabinofuranosyl)uracil and its identity with **3a** by NMR, ir, and mixture melting point. Thus, the lyxo epoxide **1a**[11] was treated with ammonium azide to afford **6** which was hydrogenolyzed to amino nucleoside **7** and acetylated to **3a** (Chart III).

Application of the boron trifluoride etherate–acetonitrile reagent combination to 2′,3′-epoxides of purine nucleosides is planned in our laboratory.

Experimental Section

NMR spectra were obtained on a JEOL J1M-PET-100 spectrometer with Me_4Si as reference. Chemical shifts are reported in parts per

Chart III



million (δ) and signals are described as s (singlet), d (doublet), t (triplet), and m (multiplet). Values given for coupling constants are first order. Ir spectra were recorded on a Perkin-Elmer Infracord using pressed KBr pellets. Melting points were determined on a Thomas-Hoover capillary apparatus. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

1-(2,3-Anhydro-β-D-lyxofuranosyl)cytosine. 2,2′-Anhydro-3′-*O*-mesylarabinofuranosylcytosine mesylate (2.0 g, 6 mmol)[12] was dissolved in water (20 ml) and potassium carbonate was added (1.0 g). After 2 h, more potassium carbonate was added (0.5 g) and the solution was allowed to stir at room temperature for 16 h. Excess Amberlite IRC-50 (H^+) was then added, and after stirring for 2 h the solution was filtered. The filtrate was concentrated and placed on a column of Dowex-50 (H^+). After washing thoroughly, the nucleoside was eluted with 1 N NH_4OH. Evaporation provided 0.9 g of an amorphous foam. TLC examination of the amorphous foam (90% ethanol) showed only two uv absorbing spots (R_f 0.46 and 0.20). Only the faster moving spot (major component) charred after sulfuric acid spray and also exhibited a positive test for epoxides with methyl red spray. This was used without further purification: NMR (Me_2SO-d_6) δ 3.59 (d, 2 H, H-5′, $J_{4',5'} \simeq 6$ Hz), 3.94–4.06 (two distorted doublets, 3 H, $J_{2',3'} \simeq 3$ Hz, superimposed on H-4′, J value not first order), 5.77 (d, 1 H, H-5, $J_{5,6} \simeq 8$ Hz), 6.08 (s, 1 H, H-1′), 7.57 (d, 1 H, H-6), 4.09 (broad s, 1 H, exchanged in D_2O), 7.20 (broad s, 2 H, exchanged in D_2O); uv λ_{max} (H_2O) 269 nm (neut), 277 nm (pH 1).

1-(2,3-Anhydro-5-*O*-benzoyl-β-D-lyxofuranosyl)-*N*⁴-benzoylcytosine (1b). The free epoxide (0.8 g) obtained above was treated with benzoic anhydride (2.5 g, 3 equiv) in dry pyridine (25 ml) for 12 h at room temperature and then for 3 h at 60 °C. The reaction mixture was poured into water (50 ml) and extracted with chloroform (50 ml × 3). The combined organic extracts were dried (sodium sulfate) and evaporated to dryness. The residue was crystallized from ethanol to afford **1b** as colorless needles, 0.62 g (40% based on crude epoxide), mp 187–190 °C.

Anal. Calcd for $C_{23}H_{19}N_3O_6$: C, 63.74; H, 4.38; N, 9.69. Found: C, 63.60; H. 4.29; N, 9.56.

1-(3-Acetamido-5-*O*-benzoyl-3-deoxy-β-D-arabinofuranosyl)uracil (2a). To a suspension of the epoxide **1a**[11] (2.0 g, 6 mmol) in acetonitrile (25 ml, dried over P_2O_5) was added 4 ml of boron trifluoride etherate solution (5 equiv). A clear solution was obtained in a few minutes after the addition. The solution was stirred for 12 h at room temperature, then poured onto 40 ml of saturated sodium hydrogen carbonate solution. Compound **2a** precipitated out as colorless crystals which were filtered and washed with water and acetone, 1.5 g (64%), mp 230–234 °C (dec): NMR (Me_2SO-d_6) δ 1.87 (s, 3 H, NAc), 4.11 (m, 3 H, H-2′, H-3′, H-4′), 4.52 (d, 2 H, H-5′, $J_{4',5'} \simeq 4.3$ Hz), 5.49 (d, 1 H, H-5, $J_{5,6} \simeq 8.2$ Hz), 5.88 (d, 1 H, 2′-OH, $J_{2',OH} \simeq 4.6$ Hz), 6.10 (d, 1 H, H-1′, $J_{1',2'} \simeq 4.0$ Hz), 7.76 (m, 5 H, benzoyl), 8.40 (d, 1 H, H-6, $J_{5,6} \simeq 8.2$ Hz).

Anal. Calcd for $C_{18}H_{19}N_3O_7$: C, 55.52; H, 4.89; N, 10.76. Found: C, 55.42; H, 4.83; N, 10.63.

1-(3-Acetamido-5-*O*-benzoyl-3-deoxy-β-D-arabinofuranosyl)-*N*⁴-benzoylcytosine (2b). By the same procedure as above, **2b** (1.95 g, 67.5%) was obtained as colorless crystals, mp 254–259 °C dec, from **1b** (2.6 g, 6 mmol): NMR (Me_2SO-d_6) δ 1.89 (s, 3 H, NAc), 4.20 (m, 3 H, H-2′, H-3′, H-4′), 4.56 (broad s, 2 H, H-5′), 5.89 (d, 1 H, 2′-OH, $J_{2'}$, OH $\simeq 4.6$ Hz), 6.21 (d, 1 H, H-1′, $J_{1',2'} \simeq 4.0$ Hz), 7.31 (d, 1 H, H-5, $J_{5,6} \simeq 7.3$ Hz), 7.81 (m, 10 H, benzoyl), 8.50 (d, 1 H, H-6, $J_{5,6} \simeq 7.3$ Hz).

Anal. Calcd for $C_{25}H_{24}N_4O_7$: C, 60.96; H, 4.87; N, 11.38. Found: C, 60.85; H, 4.92; N, 11.26.

1-(3-Acetamido-2-*O*-acetyl-5-*O*-benzoyl-3-deoxy-β-D-arabinofuranosyl)uracil (3a). Compound **2a** (380 mg, 1 mmol) was dissolved in pyridine (15 ml) and 1 ml of acetic anhydride was added. The mixture was stirred for 2 h and then poured onto an ice–water mixture (25 ml). The mixture was extracted with chloroform (75 ml × 3) and the organic layer was dried (over sodium sulfate), evaporated to dryness, and then coevaporated several times with ethanol to remove traces of pyridine. The residue was crystallized from ethanol to give 360 mg of **3a** (85%) as colorless crystals, mp 208–210 °C: NMR (Me_2SO-d_6) δ 1.87 (s, 3 H, NAc), 1.89 (s, 3 H, OAc), 4.16 (m, 1 H, H-4′), 4.39 (m, 1 H, H-3′), 4.56 (d, 2 H, H-5′), 5.30 (t, 1 H, H-2′, $J_{1',2'} \simeq J_{2',3'} \simeq 5.5$ Hz), 5.55 (d, 1 H, H-5, $J_{5,6} \simeq 7.9$ Hz), 6.28 (d, 1 H, H-1′, $J_{1',2'} \simeq 5.5$ Hz), 7.79 (m, 5 H, benzoyl), 8.47 (d, 1 H, H-6, $J_{5,6} \simeq 7.9$ Hz).

Anal. Calcd for $C_{20}H_{21}N_3O_8$: C, 55.68; H, 4.87; N, 9.74. Found: C, 55.80; H, 4.96; N, 9.67.

1-(3-Acetamido-2-*O*-acetyl-5-*O*-benzoyl-3-deoxy-β-D-arabinofuranosyl)-*N*⁴-benzoylcytosine (3b). Compound **2b** (100 mg, 0.25 mmol) was treated with acetic anhydride (1 ml) in pyridine (10 ml) for 2 h at room temperature and then poured onto water (20 ml). Colorless crystals precipitated, were collected and recrystallized from ethanol to give 86 mg of **3b** (80%), mp 136–141 °C: NMR (Me_2SO-d_6) δ 1.84 (s, 3 H, NAc), 1.89 (s, 3 H, OAc), 4.27 (m, 2 H, H-3′, H-4′), 4.60 (d, 2 H, H-5′), 5.45 (t, 1 H, H-2′, $J_{1',2'} \simeq J_{2',3'} \simeq 4.6$ Hz), 6.36 (d, 1 H, H-1′, $J_{1',2'} \simeq 4.6$ Hz), 7.35 (d, 1 H, H-5, $J_{5,6} \simeq 7.6$ Hz), 7.83 (m, 10 H, benzoyl), 8.58 (d, 1 H, H-6).

Anal. Calcd for $C_{27}H_{26}N_4O_8 \cdot H_2O$: C, 58.69; H, 5.07; N, 10.14. Found: C, 58.68; H, 4.96; N, 10.09.

The presence of H_2O was shown in NMR (Me_2SO-d_6) at δ 3.32.

1-(3-Azido-5-*O*-benzoyl-3-deoxy-β-D-arabinofuranosyl)uracil (6). Compound **1a** (1.0 g) was added to ethanol (25 ml) containing ammonium azide (0.3 g). The mixture was refluxed for 22 h and the solution was evaporated. The residue was crystallized from 80% EtOH to give 1.1 g of **6** as colorless crystals, mp 150–153 °C. Recrystallization from methanol provided an analytical sample with mp 154–156 °C: NMR ($CDCl_3$) δ 4.20 (broad s, 2 H, H-5′), 4.6–4.8 (m, 3 H, H-2′, H-3′, H-4′), 5.31 (d, 1 H, H-5, $J_{5,6} \simeq 8$ Hz), 5.43 (broad s, 1 H, exchangeable, 2′-OH), 6.14 (d, 1 H, H-1′, $J_{1',2'} \simeq 3$ Hz), 7.40–7.84 (m, 4 H, benzoyl), 8.04–8.12 (distorted doublet, 2 H, H-6, $J_{5,6} \simeq 8$ Hz, and benzoyl).

Anal. Calcd for $C_{16}H_{15}N_5O_6$: C, 51.48; H, 4.05; N, 18.76. Found: C, 51.23; H, 4.19; N, 18.68.

1-(3-Acetamido-2-*O*-acetyl-5-*O*-benzoyl-3-deoxy-β-D-arabinofuranosyl)uracil (3a). Compound **6** (159 mg) was dissolved in ethanol (15 ml) containing $CHCl_3$ (1 ml), and 10% Pd/C (90 mg) was added. The mixture was stirred at room temperature in a hydrogen atmosphere for 20 h and then filtered. The filtrate was decolorized with carbon and evaporated. The residue was dissolved in pyridine (5 ml) and acetic anhydride (1 ml) was added. After 5 h, methanol was added, and the solution was evaporated. The residue was crystallized from ethanol to yield **3a** (46 mg, mp 208–209 °C). The NMR, ir, and TLC behavior were identical with those for **3a** obtained as described above. The mixture melting point was undepressed.

Acknowledgment. The authors are indebted to Mr. Marvin Olsen for recording the NMR spectra.

Registry No.—**1a,** 14999-47-4; **1b,** 58540-92-4; **1b** free epoxide, 34989-27-0; **2a,** 58540-93-5; **2b,** 58540-94-6; **3a,** 58540-95-7; **3b,** 58540-96-8; **6,** 58540-97-9; 2,2′-anhydro-3′-*O*-mesylarabinofuranosylcytosine mesylate, 23463-73-2.

References and Notes

(1) This investigation was supported in part by funds from the National Cancer Institute, DHEW (Grants CA-08748, -17085, and -18601), the Westchester Division of the American Cancer Society, and the Hearst Fund.
(2) D. Horton, "The Amino Sugars", Vol. IA, R. W. Jeanloz and E. A. Balazs, Ed., Academic Press, New York, N.Y., 1969, p 2.
(3) D. H. Ball and F. W. Parrish, *Adv. Carbohydr. Chem.*, **24,** 139 (1969).
(4) D. Horton in ref 2, p 27.
(5) K. A. Watanabe, J. Beranek, H. A. Friedman, and J. J. Fox, *J. Org. Chem.*, **30,** 2735 (1965); J. Beranek, H. A. Friedman, K. A. Watanabe, and J. J. Fox, *J. Heterocycl. Chem.*, **2,** 188 (1965).
(6) J. P. Horwitz, J. Chua, and M. Noel, *J. Org. Chem.*, **29,** 2076 (1964); K. A. Watanabe, M. P. Kotick, and J. J. Fox, *ibid.*, **35,** 231 (1970).
(7) M. Hirata, T. Kobayashi, and T. Naito, *Chem. Pharm. Bull.*, **17,** 1188 (1969); M. Hubert-Habart and L. Goodman, *Can. J. Chem.*, **48,** 1335 (1970); A. P. Martinez, D. F. Calkins, E. J. Reist, W. W. Lee, and L. Goodman, *J. Heterocycl. Chem.*, **7,** 713 (1970).
(8) J. P. H. Verheyden, D. Wagner, and J. G. Moffatt, *J. Org. Chem.*, **36,** 250 (1971).
(9) B. R. Baker, R. E. Schaub, and H. M. Kissman, *J. Am. Chem. Soc.*, **77,** 5900 (1955).
(10) J. R. L. Smith, R. D. C. Norman, and M. R. Stillings, *J. Chem. Soc., Perkin Trans. 1,* 1200 (1975).
(11) J. F. Codington, R. Fecher, and J. J. Fox, *J. Org. Chem.*, **27,** 163 (1962).
(12) T. Kanai and M. Ichino, *Chem. Pharm. Bull.*, **16,** 1848 (1968).