Synthesis of 9-(3-Amino-3-deoxy-β-D-arabinofuranosyl)- and 9-(2-Amino-2-deoxy-β-D-xylofuranosyl)adenine (1)

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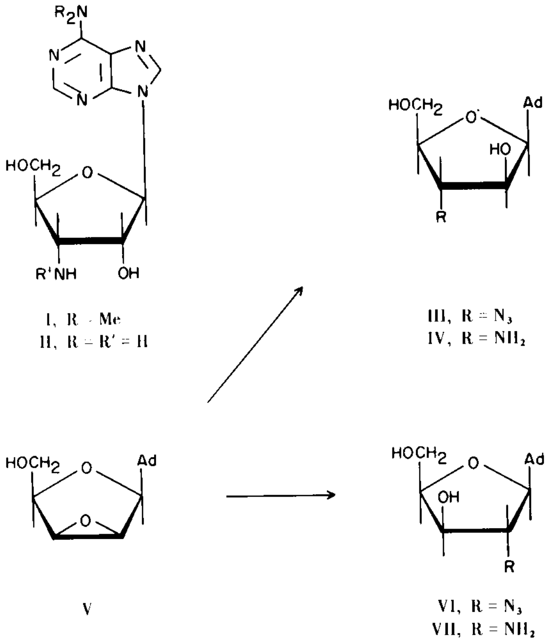
The aminonucleoside I, R′ = H, from puromycin (I, R′ = *p*-methoxy-L-phenylalanine) has antitumor activity (2) as does its adenine analog II (2). In continuing the search for biological activity among aminonucleosides we have synthesized IV and VII, which are also potential starting materials for other puromycin analogs. The azido precursors of IV and VII were successfully separated on Dowex 1 (OH) thus further illustrating the usefulness of Dekker's method of nucleoside separation (3).

The epoxide V (4) was opened mainly at the 3-position by sodium azide in hot methoxyethanol containing ammonium chloride to give 3′-azidonucleoside III as a crystalline, high melting solid. Passage of the mother liquors (containing all the inorganic salts) through a column of Dowex 1 (OH) (3) gave small amounts of the 2′-azidonucleoside VI. In a number of runs, changing the relative amount of inorganic salts:organic azides:ion exchange resin greatly affected the retention and reversed the order of elution of the azides III and VI. Such modification of the separation parameters may be useful in other separations. The ratio of III:VI was about 15:1 in several runs (5). Catalytic reduction of III and VI gave the desired amines IV and VII, respectively. As is generally the case, the *arabino* isomers (III and IV) were less soluble and higher melting than the *xylo* isomers (VI and VII).



I, R = Me
II, R = R′ = H

III, R = N_3
IV, R = NH_2

V

VI, R = N_3
VII, R = NH_2

EXPERIMENTAL (6)

9-(3-Azido-3-deoxy-β-D-arabinofuranosyl)adenine (III) and 9-(2-Azido-2-deoxy-β-D-xylofuranosyl)adenine (VI).

A mixture of 1.0 g. (4.02 mmoles) of crystalline 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine (V) (4), 1.00 g. (15.4 mmoles) of sodium azide, 0.23 g. (4.2 mmoles) of ammonium chloride in 160 ml. of 2-methoxyethanol and 11.0 ml. of water was heated for 20 hours in a bath kept at 75-80°. The clear reaction mixture was evaporated to dryness *in vacuo* and the residue was triturated for 30 minutes in 50 ml. of water. Filtration of this mixture gave a filtrate (designated as solution A) and a residue. This crystalline residue was dried to afford 0.91 g. (78%) of the 3′-azide III, homogeneous by paper chromatography, with ir like that of the analytical sample. Similar material from an earlier run was recrystallized from methanol (88% recovery) to give fine white needles of III, darkens at 235°, does not melt < 340°; $[\alpha]^{23.5}_{D}$ -23.0° (*c* 0.496, pyridine); $[\alpha]_{D}$ -41.5° (*c* 0.48, DMF); λ max (*p*H 1), 257 mμ (ε 15,100); λ max (*p*H 7), 259 (15,300); λ max (*p*H 13), 260 (16,800); R_{Ad} 1.2 in solvent A; R_{Ad} 1.2 in B; R_{Ad} 1.2 in C; ir (Nujol) μ 4.74 (azide, strong), 11.94 (broad); nmr H-1′ δ 6.15 (d, 1, $J_{1,2}$ 6 Hz); H-2 and H-8, 8.05 (s, 1) and 8.17 (s, 1).

Anal. Calcd. for $C_{10}H_{12}N_8O_3 \cdot 0.2\ H_2O$: C, 40.6; H, 4.23; N, 38.0; Found: C, 40.8; H, 4.23; N, 38.1.

The mother liquor (solution A) was evaporated to dryness *in vacuo*. The residue was dissolved in 10 ml. of aqueous methanol (1:1) and charged on a column (i.d. 22 mm) containing 100 g. of Dowex 1-X2 (OH), 200-400 mesh. Elution successively with 500 ml. of water, 500 ml. of 30% aqueous methanol, and 500 ml. of 60% methanol removed inorganic salts and trace materials. Elution with 250 ml. of methanol gave, after evaporation, 57.3 mg. (4.8%) of the 2′-azide VI, homogeneous by tlc in solvent D with R_f 0.20, multiple development (III, R_f 0.05 on same plate). Recrystallization of this white foam from methanol afforded 50 mg. (4.2%) of VI, m.p. 198-199°; $[\alpha]^{23}_{D}$ -53.9° (*c* 0.49, pyridine); $[\alpha]^{23}_{D}$ -40.2° (*c* 0.79, DMF); λ max (*p*H 1), 257 mμ (ε 14,600); λ max (*p*H 7), 259 (15,100); λ max (*p*H 13), 259 (15,000); ir distinguishable from III in the fingerprint region; ir (Nujol) μ 4.74 (azide, strong), 11.98 (sharp); nmr H-1′, δ 5.85 (d, 1, $J_{1,2}$ 4 Hz), H-2 and H-8, 8.09 (s, 1) and 8.25 (s, 1).

Anal. Calcd. for $C_{10}H_{12}N_8O_3$: C, 41.1; H, 4.14; N, 38.3. Found: C, 41.0; H, 4.12; N, 38.5.

Continued elution with methanol, 1 l., did not give any 3′-azide, III, but rather a small amount of solids that may have been dissolved from the ion exchange resin.

Several large scale runs using a total of 121.2 g. (0.487 mole) of V with the corresponding amount of inorganic salts (149 g.) afforded 122.4 (86%) of crystalline 3′-azide III, R_f 0.04 in D, multiple development. The filtrates were evaporated to dryness, and heated at 85° for 30 minutes in 250 ml. of water to afford 4.93 g. (3.47%) of the 2′-azide VI, m.p. 189-190°, containing traces of III. The filtrate and washes (total, 300 ml.) were chromatographed through 500 g. of Dowex 1 x 2 (OH^-) on a 4 x 50 cm column. The inorganic salts were eluted in 2.2 l. of water; III and traces of VI in the next 415 ml. of water. The final 1.14 l. of water gave, after evaporation, 3.10 g. (2.18%; total 5.65%) of the 2′-azide VI, homogeneous by tlc with R_f 0.20 (III, R_f 0.05, same plate) in solvent D with multiple development.

9-(3-Amino-3-deoxy-β-D-arabinofuranosyl)adenine (IV).

A 6.68 g. (22.8 mmoles) portion of 9-(3-azido-3-deoxy-β-D-arabinofuranosyl)adenine) (III) was stirred in 1 l. of water with 2.0 g. of 5% palladium-on-charcoal catalyst at room temperature and atmospheric pressure under hydrogen for 60 hours. The mixture was filtered through Celite, and the catalyst and Celite were Soxhlet extracted with 200 ml. water for 18 hours. The extract and filtrate were evaporated to dryness *in vacuo* to afford 4.97 g. (82%) of IV as a white solid, m.p. 245-247°. Further extraction with 200 ml. of water afforded another 0.26 g., m.p. 243-245° (total, 86%).

Product (82 mg.) from an earlier run was recrystallized from 3 ml. of water containing a few drops of methanol to give 69 mg. (76% recovery) of fine white needles of IV, m.p. 243.5-244.5° (corrected); $[\alpha]^{24}_{D}$ + 3.8°(*c* 0.50, H_2O); λ max (*p*H 1), 257 mμ (ε 14,300); λ max (*p*H 7), 259 (14,200); λ max (*p*H 13), 260 (14,600). It moved as a single spot with R_{Ad} 1.37, 0.28 and 0.60 in solvent systems A, B and C, respectively.

Anal. Calcd. for $C_{10}H_{14}N_6O_3 \cdot 0.7\ H_2O$: C, 43.0; H, 5.57; N, 30.1. Found: C, 43.2; H, 5.66; N, 30.1.

9-(2-Amino-2-deoxy-β-D-xylofuranosyl)adenine (VII).

Similar hydrogenation of 2.30 g. (7.87 mmoles) of the 2′-azide VI in 500 ml. of water with 0.70 g. of catalyst afforded, after crystallization from methanol, 1.24 g. (60%) of the 2′-amino VII, m.p. 193-194°; $[\alpha]^{23}_{D}$ -89.7° (*c* 0.50, DMF) and -79.4° (*c* 0.50, pyridine); λ max (*p*H 1), 256 mμ (ε 15,200); λ max (*p*H 7), 259 (15,200); λ max (*p*H 13), 259 (15,200); ir distinguishable from IV in the fingerprint region; ir (Nujol) μ 12.00 (VII, strong; IV, absent), 10.90 (IV, strong; VII, absent). It moved as a single spot with the same R_{Ad} as IV in solvents A, B and C.

Anal. Calcd. for $C_{10}H_{14}N_6O_3$: C, 45.1; H, 5.30; N, 31.6. Found: C, 44.9; H, 5.35; N, 31.5.

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REFERENCES

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(6) Melting points were determined on a Fisher-Johns apparatus and are not corrected. Samples were dried *in vacuo* (< 1 torr) at 100° overnight for analysis. Paper chromatography was run by the descending technique on Whatman No. 1 paper in solvent system A, 5% disodium hydrogen phosphate, *p*H 8.9; B, *n*-butanol-water (saturated); C, *n*-butanol-acetic acid-water (4:1:5). Thin-layer chromatography was run on Silica gel HF (E. Merck AG Darmstadt) in solvent D, ethyl acetate. All spots were detected by ultraviolet light. The nmr spectra were obtained on a Varian HA-100 instrument with DMSO-d_6 as solvent and TMS as external reference. Dowex 1 (OH) is a strongly basic ion exchange resin. of Dow Chemical Co.

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