1-(Adenin-9-yl)-2,5-anhydro-1-deoxy-D-allitol, A Homolog of Adenosine (1)

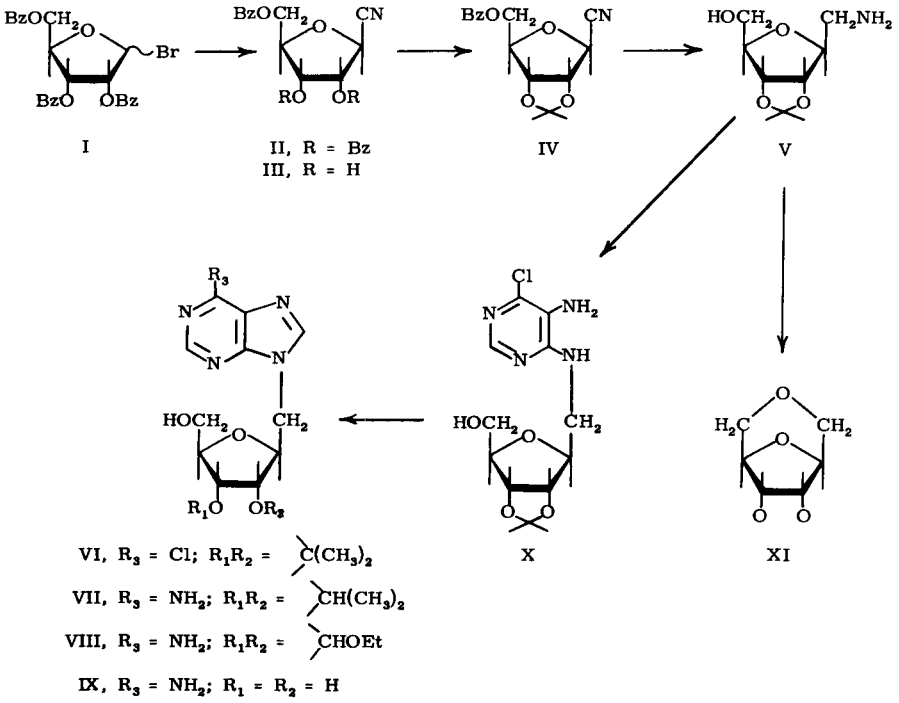
John A. Montgomery and Kathleen Hewson

Southern Research Institute, Kettering-Meyer Laboratory

Nucleoside analogs that might inhibit purine phosphoribosyltransferases are of interest for a number of reasons (2). 1-(Adenin-9-yl)-2,5-anhydro-1-deoxy-D-allitol (IX), a homolog of adenosine, was prepared for biologic evaluation in the following manner (3). Reaction of tri-*O*-benzoyl-D-ribofuranosyl bromide (I) with mercuric cyanide gave tri-*O*-benzoyl-D-ribofuranosyl cyanide (II) (4), presumed to have the β-configuration on the basis of the *trans* rule (5). Compound II was partially debenzoylated to 5-*O*-benzoyl-D-ribofuranosyl cyanide (III) by means of methanolic ammonia. Treatment of III with acetone in the presence of 2,2-dimethoxypropane and perchloric acid (6) gave 5-*O*-benzoyl-2,3-*O*-isopropylidene-D-ribofuranosyl cyanide (IV). Compound IV was reduced with lithium aluminum hydride to 1-amino-2,5-anhydro-1-deoxy-3,4-*O*-isopropylidene-D-allitol (V), which on treatment with nitrous acid gave the cyclic ether XI, thus unequivocally establishing that V is the β-anomer (7). Compound V was then allowed to react with 5-amino-4,6-dichloropyrimidine to give 2,5-anhydro-1-deoxy-3,4-*O*-isopropylidene-1-(5-amino-6-chloro-4-pyrimidinyl)amino-D-allitol (X) (8). Ring closure of X with ethyl orthoformate and acid (9) gave 2,5-anhydro-1-(6-chloropurin-9-yl)-1-deoxy-3,4-*O*-isopropylidene-D-allitol (VI) contaminated with some of the corresponding 3,4-*O*-ethoxymethylene compound. Ammonolysis of the mixture gave 1-(adenin-9-yl)-2,5-anhydro-1-deoxy-3,4-*O*-isopropylidene-D-allitol (VII) and a small amount of the 3,4-*O*-ethoxymethylene derivative VIII. Acid hydrolysis of the mixture of VII and VIII gave the title compound IX (10). The biological evaluation of this compound and related structures will be reported elsewhere.

EXPERIMENTAL

SilicAR-TLC-7 (Mallinckrodt) was used for column and thin-layer (1-mm. thick) chromatographic purifications. Silica gel H (Brinkmann) was used for thin-layer (0.25-mm. thick) analyses (tlc). Chromatographic homogeneity was established for all compounds using the solvent systems indicated. Spots were detected with either ultraviolet light (256 mμ) after spraying the plates with Ultraphor (WT, highly concentrated) (BASF Colors & Chemicals, Inc., Charlotte, N. C.) or heat charring after spraying with ammo-



nium sulfate. The ultraviolet spectra were determined in 0.1 *N* hydrochloric acid, 0.1 *N* sodium hydroxide and *p*H 7 buffer with a Cary Model 14 spectrophotometer, the infrared spectra were determined in pressed potassium bromide disks with a Perkin-Elmer Model 521 spectrophotometer. The pmr spectra were determined in the solvents specified with a Varian A-60A spectrometer using tetramethylsilane as an internal reference (11). The mass spectra were determined on a Hitachi-Perkin-Elmer RMU-7 double focusing mass spectrometer. Melting points, unless otherwise noted, were determined on a Kofler-Heizbank and are corrected.

5-*O*-Benzoyl-D-ribofuranosyl Cyanide (III).

A solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl cyanide (II, 3.5 g., 7.4 mmoles) (4) in methanolic ammonia (150 ml., saturated at 5°) was allowed to stand at 5° for 3 hours before it was evaporated to dryness *in vacuo*. The residue was triturated with ligroin (2 x 75 ml.) and then with benzene (3 x 100 ml.), followed by chloroform (100 ml.). The combined benzene and chloroform extracts were evaporated to dryness to give crude III, which was purified by high pressure column chromatography (1:1 benzene-ethyl acetate). The pure product was isolated as a light-sensitive solid: yield 710 mg. (36%); m.p. 118°; ν max in cm^{-1}: 3470 (OH), 2890 (CH), 2240 weak (C≡N), and 1705 (ester C=O), 1595 and 1580 (phenyl).

Anal. Calcd. for $C_{13}H_{13}O_5N$: C, 59.32; H, 4.98; N, 5.33. Found: C, 59.20; H, 5.07; N, 5.18.

5-*O*-Benzoyl-2,3-*O*-isopropylidene-D-ribofuranosyl Cyanide (IV).

Dimethoxypropane (0.98 ml.), acetone (35 ml. dried over magnesium sulfate), and 60% perchloric acid (1.32 ml.) were stirred 8 minutes before the addition of 5-*O*-benzoyl-D-ribofuranosyl cyanide (IV, 710 mg., 2.7 mmoles). The resulting reaction solution was stirred at room temperature for 50 minutes before it was neutralized with pyridine (1.35 ml.) and evaporated to dryness *in vacuo*. The residue was partitioned between chloroform (60 ml.) and water (60 ml.). The chloroform solution was washed with water (30 ml.) and dried over magnesium sulfate before it was evaporated to dryness *in vacuo* to give the homogeneous product as an oil, yield 807 mg. (98%); tlc (1:1 benzene:ether); ν max in cm^{-1}: 3070, 3010, 2950, 2878 (CH), 2240 weak (C≡N), 1720 and 1710 (ester C=O), 1600 and 1580 (phenyl).

1-Amino-2,5-anhydro-1-deoxy-3,4-*O*-isopropylidene-D-allitol (V).

A solution of 5-*O*-benzoyl-2,3-*O*-isopropylidene-D-ribofuranosyl cyanide (IV, 807 mg., 2.7 mmoles) in THF (8 ml., dried over Linde 4A sieve) was added dropwise under anhydrous conditions to a stirred suspension of LAH (640 mg.) in dry THF (6.7 ml.). The reaction mixture, which was cooled in an ice bath during addition of the sugar, was stirred at room temperature for 1 hour and then refluxed for 1.5 hours. The reaction mixture was cooled to room temperature and diluted cautiously with ethanol (5 ml.), water (2.66 ml.), and concentrated ammonium hydroxide (8 ml.). The insoluble gel that formed was removed by filtration and washed with 5 *N* ammonium hydroxide. The combined filtrate and washing was evaporated to dryness and dried *in vacuo* (0.05 mm./-25°) before the residue was triturated with chloroform. Evaporation of the chloroform extract to dryness gave the essentially homogeneous product: yield 514 mg. (92%); tlc (9:1 chloroform-methanol); δ in ppm (deuteriochloroform): 1.35 and 1.57 (2 s, CH_3), 2.97 (m, CH_2 of CH_2NH_2), 3.73 (m, CH_2 of CH_2OH), 3.97 (t, J_{23} ca 4Hz, C_2H) and 4.15 (q, C_4H), 4.64 (m, C_3H and C_4H), 2.72 (s, NH_2 and OH).

1-(5-Amino-6-chloro-4-pyrimidinyl)amino-2,5-anhydro-1-deoxy-3,4-*O*-isopropylidene-D-allitol (X).

A solution of 1-amino-2,5-anhydro-1-deoxy-3,4-*O*-isopropylidene-D-allitol (V, 500 mg., 2.5 mmoles) in *N* butanol (2.5 ml., dried over Linde 4A sieve) was added to a suspension of 5-amino-4,6-dichloropyrimidine (410 mg., 2.5 mmoles) in *N* butanol (7 ml.), and the mixture was stirred until homogeneous. Triethylamine (252 mg., 2.5 mmoles) was added and the reaction mixture was heated in a 100-110° bath for 48 hours before it was evaporated to dryness *in vacuo*. The crude product was purified by high pressure column chromatography (9:1 chloroform-methanol), and the homogeneous product was isolated as a glass, yield 500 mg. (60%); δ in ppm (deuteriochloroform): 1.31 and 1.52 (2 s, CH_3), 3.83 (m, $C_1'H_2$, $C_6'H_2$ and NH_2), 4.0 to 4.9 (2 m, $C_2'H$, $C_3'H$, $C_4'H$, $C_5'H$, OH), 5.75 broad (NH), 7.98 (C_2H).

1-(Adenin-9-yl)-2,5-anhydro-1-deoxy-3,4-isopropylidene-D-allitol (VII).

Concentrated hydrochloric acid (0.175 ml.) was added to a solution of 1-(5-amino-6-chloro-4-pyrimidinyl)amino-2,3-anhydro-1-deoxy-3,4-*O*-isopropylidene-D-allitol (X, 500 mg., 1.5 mmoles) in ethyl orthoformate (4 ml.), and the resulting solution was stirred at room temperature for 18 hours before it was evaporated to dryness and the residue dried *in vacuo* (0.05 mm./25°) overnight. The resulting crude 2,5-anhydro-1-(6-chloropurin-9-yl)-1-deoxy-3,4-*O*-isopropylidene-D-allitol (VI, λ max in nm: *p*H 1-264.5; *p*H 13-264) was dissolved in methanolic ammonia (30 ml. saturated at 5°), and the solution was heated at 100-110° for 18 hours. The reaction solution was evaporated to dryness *in vacuo*, and the resulting crude product was purified by thin-layer chromatography (9:1 chloroform-methanol), yield 280 mg. (58%). Tlc (9:1 chloroform-methanol) showed a compound spot which separated into two spots at low concentrations. Mass spectrometry confirmed the identity of the product as a mixture of the isopropylidene (VII, molecular ion at m/e 321) and the ethoxymethylene (VIII, molecular ion at m/e 337) derivatives. λ max in nm: *p*H 1-257; *p*H 7-260; *p*H 13-260.

1-(Adenin-9-yl)-2,5-anhydro-1-deoxy-D-allitol (IX).

1-(Adenin-9-yl)-2,5-anhydro-1-deoxy-2,4-*O*-isopropylidene-D-allitol (VII, 240 mg., 0.75 mmole) containing some VIII was dissolved in ethanol (2.5 ml.) and the solution diluted with water (5 ml.) and 0.6 *N* hydrochloric acid (2.5 ml.). The resulting reaction mixture was heated at 100° for 30 minutes before it was filtered through dry Celite. The filtrate was made basic with ammonium hydroxide and evaporated to dryness *in vacuo*. The resulting crude product was purified by thin-layer chromatography (1:1 chloroform-methanol. Recrystallization of the purified product (145 mg., 70%) from 95% ethanol (15 ml.) gave the pure product, yield 89 mg. (42%); m.p. 206°; $[\alpha]_D^{24}$ + 15.7 ±0.7 (*c* 1,07, 1:1 ethanol-water; λ max in nm (ϵ x 10^{-3}): *p*H 1-258 (14.3); *p*H 7, *p*H 13-261 (14.6).

Anal. Calcd. for $C_{11}H_{15}N_5O_4$: C, 46.96; H, 5.38; N, 24.91. Found: C, 46.79; H, 5.23; N, 24.64.

1,6;2,5-Dianhydro-3,4-*O*-isopropylidene-D-allitol (XI).

Sodium nitrite (22 mg., 0.32 mmoles) was added to a stirred solution of 1-amino-2,5-anhydro-1-deoxy-3,4-*O*-isopropylidene-D-allitol (V, 200 mg., 1 mmole) in 5% acetic acid (12 ml.) cooled in an ice bath. Additional sodium nitrite was added to the cold, stirred solution at intervals of 2, 18, 24, and 42 hours. Twenty hours after the final addition of nitrite, the mixture was filtered through dry Celite, and the filtrate was diluted with water (12 ml.) and extracted with chloroform (20 ml.). The chloroform solution

was washed with water before it was dried over magnesium sulfate and evaporated to dryness *in vacuo* to give the crude product as a volatile solid. Ethanol recrystallization of the crude product gave the pure material, m.p. 140-145° with sublimation; δ in ppm (deuteriochloroform), 1.36 and 1.49 (s 2, CH_3), complex multiplets between 3.4 and 4.25 (CH_2 and C_2H and C_3H), 4.82 (s, C_3H and C_4H).

Anal. Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.00; H, 7.72.

REFERENCES

(1) This work was supported by funds from the Southern Research Institute, the C. F. Kettering Foundation, and Chemotherapy, National Cancer Institute, National Institutes of Health, Contract No. PH43-64-51.

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(11) Chemical shifts listed for multiplets are not true chemical shifts, but are centers of the multiplets.

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