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Nucleoside Analogs. II. A Synthesis of 9-Adenyl-deoxyinositols

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Four 9-adenyl-deoxyinositols were prepared by a reaction between 4-amino-6-chloro-5-nitropyrimidine (**1**) and inosamines (**2a**, **2b**, **2c**, and **2d**), followed by a reduction and a cyclization. In the present article, 1-(6′-amino-9′-purinyl)-1-deoxy-*scyllo*-inositol (**5a**), 1-(6′-amino-9′-purinyl)-1-deoxy-*muco*-inositol (**5b**), 2-(6′-amino-9′-purinyl)-2-deoxy-*epi*-inositol (**5c**), and 2-(6′-amino-9′-purinyl)-2-deoxy-*myo*-inositol (**5d**) were described. These compunds exhibited an inhibitory effect against *piricularia oryzae*.

An alternation of a ribose moiety in naturally occurring adenosine may yield a biologically active nucleoside analog. Along this consideration, dihydroxycyclohexane analogs of the nucleoside have been described in a previous paper.[1)]

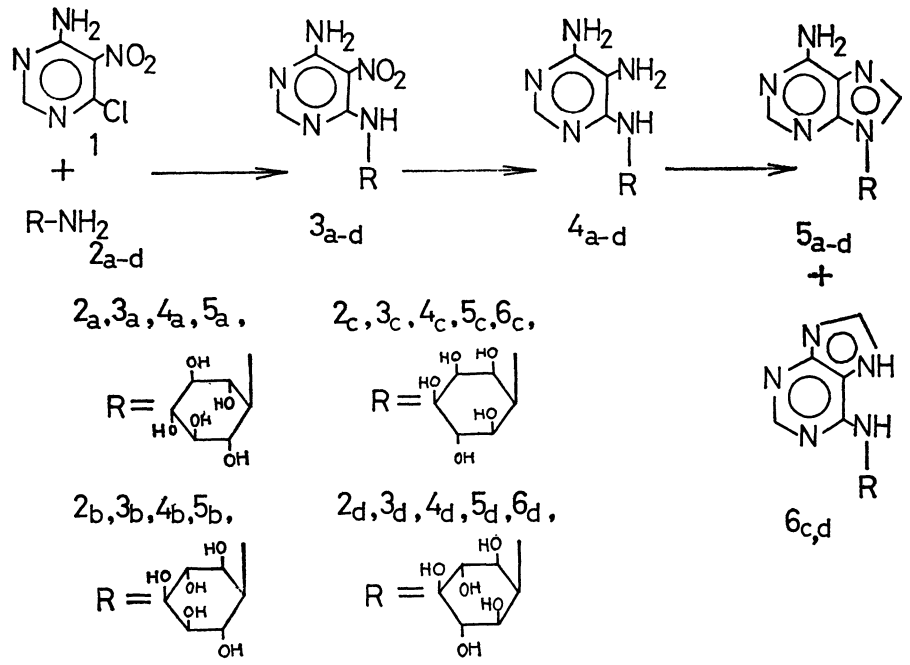
In connection with the previous paper of this series,[1)] four biologically active 9-adenyl-deoxyinositols (**5a**, **5b**, **5c**, and **5d**) have been prepared by a reaction between 4-amino-6-chloro-5-nitropyrimidine (**1**)[2)] and inosamines (**2a**, **2b**, **2c**, and **2d**), followed by reduction of a nitro group and cyclization of an imidazole ring, which will be described in the present article.

When a mixture of **1** and *scyllo*-inosamine (**2a**),[3,4)] was heated in 2-methoxyethanol under reflux for 20 hr, 1-(4′-amino-5′-nitro-6′-pyrimidinylamino)-1-deoxy-*scyllo*-inositol (**3a**) was obtained in 78% yield. Reduction of **3a** with zinc powder in boiling water afforded 1-(4′,5′-diamino-6′-pyrimidinylamino)-1-deoxy-*scyllo*-inositol (**4a**) in 87% yield, which was used for a successive synthesis without any further purification. Cyclization of **4a** was carried out by heating in formamide to give 1-(6′-amino-9′-purinyl)-1-deoxy-*scyllo*-inositol (**5a**) in a yield of 52%. The compound **5a** showed an ultraviolet absorption characteristic of an adenine at 263 mμ.[5)]

An analogous reaction beginning with *muco*-inosamine-1 (**2b**)[4)] and **1** afforded 1-(6′-amino-9′-purinyl)-1-deoxy-*muco*-inositol (**5b**) in 25% yield.

Reactions between *epi*-inosamine-2 (**2c**)[3,6,7)] and **1**

1) T. Suami, Y. Sato, Y. Fukai, and Y. Sakota, *J. Heterocycl. Chem.*, **6**, 663 (1969).
2) W. R. Boon, W. G. M. Jones, and G. R. Ramage, *J. Chem. Soc.*, **1951**, 99.
3) H. E. Carter, R. K. Clark, Jr., B. Lytle, and G. E. McCasland, *J. Biol. Chem.*, **175**, 683 (1948).
4) T. Suami, F. W. Lichtenthaler, and S. Ogawa, This Bulletin, **39**, 170 (1966).
5) R. K. Robins, K. J. Dille, C. H. Willits, and B. E. Christensen, *J. Amer. Chem. Soc.*, **75**, 263 (1953).
6) E. L. May and E. Mosettig, *J. Org. Chem.*, **14**, 1137 (1947).
7) T. Suami, S. Ogawa, Y. Nakashima, and H. Sano, This Bulletin, **40**, 2958 (1967).



and between *myo*-inosamine-2 (**2d**)[3,8,9] and **1** yielded 2-(6'-amino-9'-purinyl)-2-deoxy-*epi*-inositol (**5c**) and 2-(6'-amino-9'-purinyl)- 2-deoxy-*myo*-inositol (**5d**) respectively by an analogous after-treatment. In these reactions, besides the compounds **5c** and **5d**, 2-(6'-purinylamino)-2-deoxy-*epi*-inositol (**6c**) and 2-(6'-purinylamino)-2-deoxy-*myo*-inositol (**6d**) were obtained. These structural assignments were agreeable with their ultraviolet absorption maxima.[10-12]

The biological activities of 9-adenyl-deoxyinositols against *piricularia oryzae* will be reported elsewhere.

Experimental

Melting points were determined on a Mitamura Riken micro hot stage and uncorrected. The infrared spectra were determined in a potassium bromide disc with a Hitachi EPI-2 spectrometer. The ultraviolet absorption spectra were determined in water with a Hitachi EPS-2 spectrometer.

4-Amino-6-chloro-5-nitropyrimidine (1). The compound was prepared by the method of Boon and coworkers.[2]

Scyllo-*Inosamine (2a).* The compound was prepared by the method of Suami and coworkers.[4]

1-(4'-Amino-5'-nitro-6'-pyrimidinylamino)-1-deoxy-scyllo-*inositol (3a).* A mixture of 1.75 g of **1** and 1.79 g of **2a** in 200 m*l* of 2-methoxyethanol was heated under reflux in a presence of a small amount of triethylamine for 20 hr. After the mixture was settled overnight at room temperature, crystals were collected by filtration and washed with water to give 2.48 g (78% yield) of the product, mp above 300°C.

Found: C, 37.87; H, 4.90; N, 21.71%. Calcd for $C_{10}H_{15}N_5O_7$: C, 37.86; H, 4.77; N, 22.08%.

1-(4',5'-Diamino-6'-pyrimidinylamino)-1-deoxy-scyllo-*inositol (4a).* To a suspension of 60 g of zinc powder in 600 m*l* of boiling water, 1.0 g of **3a** was added with a mechanical agitation. The mixture was heated under reflux for 6 hr, and then it was filtered. The filtrate was evaporated under reduced pressure to a 100 m*l* volume. The residual solution was settled at room temperature to give pale yellow crystals. Crystals were collected by filtration to give 0.79 g (87% yield) of the product, mp 281—283°C (dec.).

1-(6'-Amino-9'-purinyl)-1-deoxy-scyllo-*inositol (5a).* A 0.5 g-portion of **4a** was heated with 10 m*l* of formamide under reflux for 40 min. After the mixture was settled overnight at room temperature, crystals were collected by filtration to give 0.39 g of a crude product. The product (200 mg) was dissolved in boiling water (200 m*l*) and the solution was decolorized with active charcoal. After cooling, the solution gave 0.14 g (53% yield) of crystals which were collected by filtration, mp above 300°C. UV λ_{max} (pH 1) 258; (pH 7) 263; (pH 13) 263 mμ.

Found: C, 44.42; H, 5.44; N, 23.81%. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.44; H, 5.09; N, 23.56%.

muco-*Inosamine-1 (2b).* Hexaacetyl *muco*-inosamine-1 was prepared by the method of Suami and coworkers.[4] A 6.0 g-portion of the hexaacetyl derivative was hydrolyzed in 6N hydrochloric acid and then treated with Amberlite IRA-400 to give 2.03 g (81% yield) of **2b**, mp 184—200°C (dec.).

1-(4'A-mino-5'-nitro-6'-pyrimidinylamino)-1-deoxy-muco-*inositol (3b).* A mixture of 0.49 g of **1** and 0.54 g of **2b** was heated in 2-methoxyethanol (40 m*l*) for 3 hr under reflux with a small amount of triethylamine. The mixture was evaporated *in vacuo* and the residue was crystallized in water. The crystals were collected by filtration and washed with chloroform to give 0.68 g (77% yield) of **3b**, mp 260—261°C.

Found: C, 37.77; H, 4.88; N, 21.88%. Calcd for $C_{10}H_{15}N_5O_7$: C, 37.86; H, 4.77; N, 22.07%.

1-(4',5'-Diamino-6'-pyrimidinylamino)-1-deoxy-muco-*inositol (4b).* A 1.0 g-portion of **3b** was reduced by analogous procedures as described in **4a** to give 0.73 g (81% yield) of **4b**, mp 166—171°C.

1-(6'-Amino-9'-purinyl)-1-deoxy-muco-*inositol (5b).* A

8) G. E. McCasland and E. C. Horswill, *J. Amer. Chem. Soc.*, **75**, 4020 (1953).

9) T. Suami, S. Ogawa, and M. Uchida, This Bulletin, **43**, 3577 (1970).

10) T. Okano, S. Goya, A. Takadate, and Y. Ito, *J. Pharm. Soc. Jap.* **86**, 649 (1966).

11) G. B. Elion, E. Burgi, and G. H. Hitchings, *J. Amer. Chem. Soc.*, **74**, 411 (1952).

12) J. A. Montgomery and L. B. Holum, *ibid.*, **80**, 404 (1958).

0.5 g-portion of **4b** was heated in formamide (10 ml) for 30 min. The mixture was treated analogously by the method as described in **5a** to give 0.27 g of a crude product. Recrystallization from water afforded 0.21 g (41% yield) of **5b**, mp 287—288.5°C. UV λ_{max} (pH 1) 259; (pH 7) 260; (pH 13) 261 mμ.

Found: C, 44.34; H, 5.35; N, 23.31%. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.44; H, 5.09; N, 23.56%.

epi-*Inosamine-2 (**2c**).* *epi*-Inosamine-2 hydrochloride was prepared by the method of Suami and coworkers.[7] The hydrochloride was treated with Amberlite IRA-400 to give **2c** in 90% yield. Mp 195—200°C (dec.).

2-(4'-Amino-5'-nitro-6'-pyrimidinylamino)-2-deoxy-epi-*inositol (**3c**).* A mixture of **1** (1.40 g) and **2c** (2.16 g) was heated in 2-methoxyethanol for 3 hr as described in **3a** to give 2.57 g of a crude product. Recrystallization from water afforded 2.36 g (93% yield) of **3c**, mp 264—265°C.

Found: C, 37.77; H, 4.90; N, 21.80%. Calcd for $C_{10}H_{15}N_5O_7$: C, 37.86; H, 4.77; N, 22.08%.

2-(4',5'-Diamino-6'-pyrimidinylamino)-2-deoxy-epi-*inositol (**4c**).* (A) **3c** (1.54 g) was reduced with zinc powder (10 g) in boiling water (100 ml) analogously as described in **4a** to give 1.07 g of a crude product. Recrystallization from water afforded 0.87 g (62% yield) of **4c**, mp 165—170°C. (B) To a mixture of ferrous sulfate (8.9 g) and barium hydroxide (10.6 g) in 100 ml of water, **3c** (1.0 g) was added with agitation and the mixture was heated at 90°C for 30 min. The warm mixture was filtered and the filtrate was evaporated under reduced pressure to 20 ml. The residual solution was settled in a refrigerator to give 0.73 g (81% yield) of **4c** as pale yellow crystals, mp 166—171°C.

2-(6'-Amino-9'-purinyl)-2-deoxy-epi-*inositol (**5c**) and 2-(6'-purinylamino)-2-deoxy*-epi-*inositol (**6c**).* **4c** (0.70 g) was heated in formamide (10 ml) for 30 min under reflux. The mixture was evaporated *in vacuo* and the residue was warmed in 0.4 N hydrochloric acid (14 ml) for 30 min at 50°C. The solution was passed through a column (1.5 cmφ) of Amberlite CG-120 (H^+ form) and subsequently the column was washed with water. The product was eluted from the column with 2.5N ammonia (100 ml) and the eluate was decolorized with active charcoal. The solution was evaporated under reduced pressure to a small volume, and the residue was settled in a refrigerator to give 0.38 g of a crude product. The product was recrystallized from water to give 0.11 g (15% yield) of **5c** as needle crystals, mp 282—283°C. UV λ_{max} (pH 1) 261; (pH 7) 262; (pH 13) 263 mμ.

Found: C, 44.50; H, 5.37; N, 23.70%. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.44; H, 5.09; N, 23.56%.

From the mother liquor of **5c**, another crop of crystal was obtained. Recrystallization from water afforded 0.19 g (26% yield) of crystals, mp above 310°C. The product was identified to be **6c**. UV λ_{max} (pH 1) 275; (pH 7) 268; (pH 13) 275 mμ.

Found: C, 44.64; H, 5.53; N, 23.38%. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.44; H, 5.09; N, 23.56%.

myo-*Inosamine-2 (**2d**).* Hexaacetyl *myo*-inosamine-2[3] was prepared by the method of Suami and coworkers[9] beginning with pentaacetyl 1-bromo-1-deoxy-*scyllo*-inositol.[8] **2d** was obtained from the hexaacetyl compound by an analogous method used for **2b**. Mp 263—265°C (dec.).

2-(4'-Amino-5'-nitro-6'-pyrimidinylamino)-2-deoxy-myo-*inositol (**3d**).* A mixture of **1** (0.35 g) and **2d** (0.40 g) was heated in 2-methoxyethanol for 3 hr as described in **3a** to give 0.57 g (90% yield) of crystals, mp 302—304°C (dec.).

Found: C, 37.76; H, 4.91; N, 21.98%. Calcd for $C_{10}H_{15}N_5O_7$: C, 37.86; H, 4.77; N, 22.07%.

2-(4',5'-Diamino-6'-pyrimidinylamino)-2-deoxy-myo-*inositol (**4d**).* A 1.0 g-portion of **3d** was reduced with zinc powder as described in **4a** to give 0.67 g (74% yield) of the product as pale yellow needles, mp 294—304°C (dec.).

2-(6'-Amino-9'-purinyl)-2-deoxy-myo-*inositol (**5d**) and 2-(6'-purinylamino)-2-deoxy*-myo-*inositol (**6d**).* A 2.5 g-portion of **4d** was heated in formamide (70 ml) for 1 hr in a nitrogen atomosphere. The reaction mixture was treated analogously as described in **5c** to give 0.82 g of a crude product. Recrystallization from water afforded 0.41 g (16% yield) of needles of mp 257—258.5°C (dec.), which was identified to be **6d**. UV λ_{mxa} (pH 1) 266; (pH 7) 270; (pH 13) 276 mμ.

Found: C, 44.44; H, 4.77; N, 23.81%. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.44; H, 5.09; N, 23.56%.

From the mother liquor, 0.15 g (6% yield) of crystals were obtained, which was identified to be **5d**. Mp 325—327°C (dec.). UV λ_{max} (pH 1) 260; (pH 7) 261; (pH 13) 262 mμ.

Found: C, 44.46; H, 5.20; N, 23.73%. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.44; H, 5.09; N, 23.56%.

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