7c, 52540-17-7; 8, 52540-18-8; 9, 52540-42-8; 3-phenylphthalide, 5398-11-8.

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The Synthesis of 2-Substituted Derivatives of 5-Amino-1-β-D-ribofuranosylimidazole-4-carboxamide. Ring Opening Reactions of 2-Azapurine Nucleosides

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The reaction of 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**1a**) with *N*-bromoacetamide gave the corresponding 2-bromo nucleoside (**3**). The latter compound was ring closed with nitrous acid to afford 6-bromo-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (**5**). The bromine of **5** was displaced by various nucleophiles to give 6-substituted imidazo[4,5-*d*]-*v*-triazine nucleosides such as 6-azido-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazine-(3*H*)4-one (**6**), 6-methoxy-7-β-D-ribofuranosylimidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (**9**), 7-β-D-ribofuranosylimidazo[4,5-*d*]-*v*-triazine-4,6-dione (**11**), and 6-thio-7-β-D-ribofuranosylimidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (**12**). Compound **6** in the presence of hydrogen and Pd/C was reduced to corresponding 6-amino-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (**7**). Compounds **7** and **9** under the influence of hydrogen and Raney Ni were ring opened to give previously unreported 2,5-diamino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**8**) and 5-amino-2-methoxy-1-β-D-ribofuranosylimidazole-4-carboxamide (**10**), respectively.

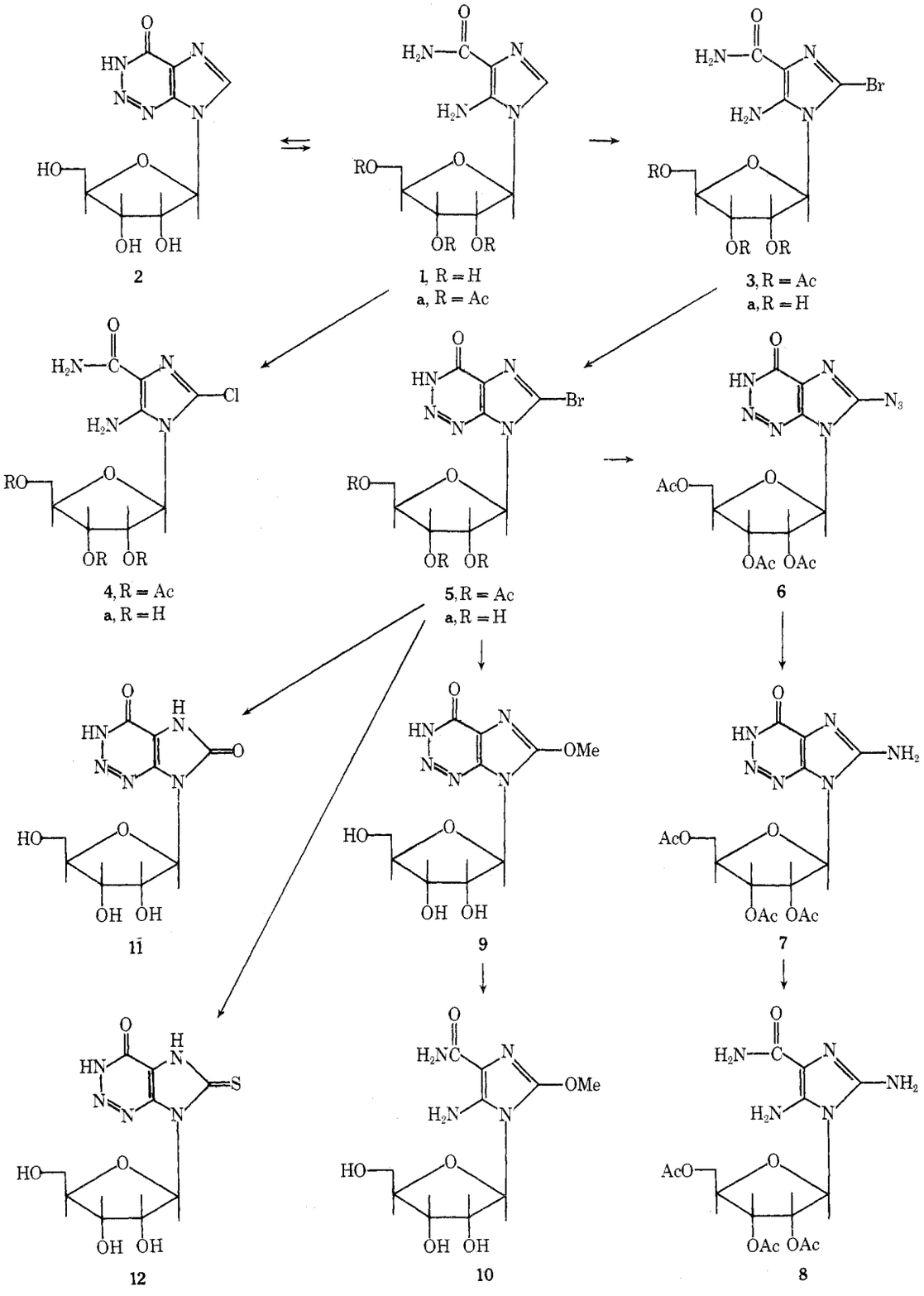
During the past few years, based on the original work of Buchanan and his colleagues,[1] there have been series of significant papers by Shaw and coworkers[2,3] on the synthesis of imidazole nucleosides related to the key intermediates in the *de novo* purine biosynthetic pathway. Relatively few studies have been made on the chemical modifications of these intermediates due to their difficult accessibility.[4] 5-Amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICA riboside) (**1**) is of special interest due to its central role[1] and recent commercial availability.[5]

Several of the procedures described in the literature, for the synthesis of AICA riboside[6,7] and its derivatives[8–10] include the ring opening of purine nucleosides. Ikehara and Muneyama[11] reported the formation of a 2-methylsulfonyl AICA riboside derivative by the cleavage of the pyrimidine ring of 8-methylsulfonylguanosine with sodium *tert*-butoxide but the precise structure of the product was never determined. Thus, 2-substituted derivatives of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide are until now unknown. In the present work we describe a novel and convenient route for the synthesis of certain 2-substituted AICA riboside derivatives by (1) direct electrophilic substitution and (2) by the ring opening of substituted 2-azapurine nucleosides.

Direct attempts to brominate 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (**1**) in various solvents were discouraging, and resulted mainly in unidentified oxidation products. However, when 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide[12] (**1a**) was treated with *N*-bromoacetamide in anhydrous tetrahydrafuran at −10°, crystalline 5-amino-2-bromo-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**3**) was obtained in 70% yield. Subsequent deacetylation with a catalytic amount of sodium methoxide in methanol afforded the nucleoside, 5-amino-2-bromo-1-β-D-ribofuranosylimidazole-4-carboxamide (**3a**). In a similar experiment, using *N*-chlorosuccinimide as the halogenating agent, the corresponding 5-amino-2-chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**4**) and 5-amino-2-chloro-1-β-D-ribofuranosylimidazole-4-carboxamide (**4a**) were prepared.

As expected, the direct displacement of bromine atom from **3** or **3a** by various nucleophiles was unsuccessful, *e.g.*, several hours reflux of **3** with excess 2 *M* methanolic sodium methoxide showed the presence of **3a** as the only reaction product. The ease by which the bromine would be displaced in such a molecule would depend upon lowering the electron density at the C-2 position. An earlier report from this laboratory[13] described the ring annulation of AICA riboside (**1**) *via* diazotization to give 7-(β-D-ribofuranosyl)imidazo-[4,5-*d*]-*v*-triazin-4-one (**2**, 2-azainosine). We subsequently discovered that 2-azainosine could readily be ring opened and reconverted into AICA riboside by hydrogenation in the presence of Raney Ni. In a similar experiment, when Raney Ni was replaced by Pd/C (10%) the starting material was recovered unchanged. Thus it was expected that 2-bromo-AICA riboside (**3a**) could be first converted to 6-bromo-7-(β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-4-one (**5a**) which renders the bromine susceptible to nucleophilic attack. Subsequent hydrogenolysis in the presence of Raney Ni should provide the required 2-substituted derivative of AICA riboside.

Scheme I



Indeed, treatment of **3a** with nitrous acid at −25° in 6 *N* hydrochloric acid afforded **5a** in 50–60% yield. In order to simplify the isolation of the nucleoside, the protected nucleoside **3** was similarly ring closed to 6-bromo-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (**5**). The product **5** was isolated by extraction and purified by column chromatography. Subsequent treatment of **5** with methanolic ammonia left the bromine at the C-6 position still intact and afforded the corresponding deacetylated product, 6-bromo-7-(β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (**5a**) in 85% yield.

Treatment of **5** with sodium azide in Me_2SO furnished the corresponding 6-azido-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (**6**). The catalytic hydrogenation studies of this molecule are of special interest. The Pd/C catalyzed hydrogenation of **6** selectively reduced the azido function to give 6-amino-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-(3*H*)4-

one (7) showing the stability of the *v*-triazine ring under these conditions. In contrast, during hydrogenolysis of 7 in the presence of Raney Ni as the catalyst the *v*-triazine was ring opened to give 2,5-diamino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (8). Treatment of 5 with excess methanolic sodium methoxide furnished 6-methoxy-7-(β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (9). In this reaction introduction of the methoxyl and the removal of the acetyl groups were accomplished simultaneously. Catalytic hydrogenolysis of 9 in the presence of Raney Ni afforded 5-amino-2-methoxy-β-D-ribofuranosylimidazole-4-carboxamide (10).

The replacement of the bromine atom at C-6 of **5a** by two other nucleophiles further illustrates the versatility of this intermediate. When 6-bromo-7-(β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one was treated with aqueous sodium hydroxide it gave the desired 7-(β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazine-4,6-dione (11). In a similar experiment when sodium hydroxide was replaced by sodium hydrosulfide the corresponding 6-thio-7-(β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-4-one (12) was obtained. In these experiments the base-catalyzed deacetylation was achieved *in situ*.

Experimental Section

The ir spectra were obtained with a Perkin-Elmer Model 257 spectrophotometer (KBr). Nmr spectra were determined on a Hitachi Perkin-Elmer Model R-20A spectrometer using DSS as an internal standard. Where indicated by elemental analyses, hydration was confirmed by nmr spectroscopy in absolute Me_2SO-d_6 by exchange with D_2O and reintegration. Melting points were obtained on a Thomas Hoover apparatus and are uncorrected. Elemental analyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo. The uv spectra were recorded on a Cary 15 ultraviolet spectrometer. Baker analyzed silica gel powder (60–200 mesh) was used for column chromatography. The homogeneity of the compounds was checked by thin-layer chromatography using precoated (250 μ) ICN (Life Science Group) Woelm tlc plates (silica gel F-254). Short-wave ultraviolet light (mineralight UVS 11) was used to detect the spots. A Parr apparatus was used for hydrogenation reactions.

5-Amino-1-β-D-ribofuranosylimidazole-4-carboxamide (1). Ring Opening of 2-Azainosine. To a solution of 2-azainosine (54 mg, 0.2 mmol) in water (12 ml) was added Raney Ni (wet, 180 mg) and the mixture was hydrogenated at 44 psi for 22 hr. The catalyst was removed by filtration through a Celite pad and washed with water. The filtrate and washings were concentrated to dryness. The residue was crystallized from ethanol–water to give 28 mg (54%) of 1 as colorless needles, mp 211–212° (lit.[14] 213–214°). An authentic sample[5] and the product had the same mixture melting point (211–212°) and their uv and ir were identical in all respects.

5-Amino-2-bromo-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (3). 5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**1a**) (3.84 g, 10 mmol) was dissolved in dry tetrahydrofuran (THF) and treated with a solution of *N*-bromoacetamide (1.41 g, 11 mmol) (in 50 ml of dry THF) at −10°. After 30 min at −10° the solvent was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (50 ml), extracted with H_2O (4 × 100 ml), dried (Na_2SO_4), evaporated to dryness, and recrystallized from aqueous EtOH to yield 3.32 g (70%): mp 169–170°; nmr (Me_2SO-d_6) δ 6.93 (s, 2, NH_2), 5.91 (s, 2, NH_2), 4.39 (br s, 3, H-4′, H-5′); λ_{max} (MeOH) 271 mμ.

Anal. Calcd for $C_{15}H_{19}N_4O_8Br$: C, 38.89; H, 4.13; N, 12.09. Found: C, 38.89; H, 4.15; N, 12.01.

5-Amino-2-bromo-1-β-D-ribofuranosylimidazole-4-carboxamide (3a). Compound 3 (463 mg, 1 mmol) was dissolved in freshly prepared 0.01 *M* methanolic sodium methoxide. After 10-min reflux it was kept at room temperature for 2 hr and then treated with excess Amberlite IRC 50 (in H^+ form). The resin was removed by filtration and the solution was evaporated to dryness. The residue was crystallized from EtOH to yield 205 mg (61%): mp 159–161°; nmr (Me_2SO-d_6–D_2O) δ 5.69 (d, 1, $J_{1',2'}$ = 6.5 Hz, H-1′); $\lambda_{max}^{pH\ 1}$ 272 mμ (ε 19,900); $\lambda_{max}^{pH\ 11}$ 272 (19,900).

Anal. Calcd for $C_9H_{13}N_4O_5Br \cdot 0.5C_2H_5OH$: C, 33.31; H, 4.48; N, 15.25. Found: C, 33.30; H, 4.44; N, 15.09.

5-Amino-2-chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (4). A solution of **1a** (1.92 g, 5 mmol) in dry THF (30 ml) at −15° was treated with *N*-chlorosuccinimide (0.75 g, 5.5 mmol). After 2 hr at room temperature the solvent was evaporated under reduced pressure and the residue was dissolved in a mixture of EtOAc–$CHCl_3$ (4:1, 10 ml) and kept at −20° for 16 hr. Colorless crystals of succinimide deposited and were removed by filtration. The filtrate was evaporated to dryness and the residue recrystallized from boiling H_2O to yield 2.01 g (81%) of desired product: mp 189–190°; nmr (Me_2SO-d_6) δ 5.90 (d, 1, $J_{1',2'}$ = 6 Hz, H-1′), 4.35 (br s, 3, H-4′, H-5′); λ_{max} (MeOH)271 mμ.

Anal. Calcd for $C_{15}H_{19}N_4O_8Cl$: C, 42.98; H, 4.54; N, 13.74. Found: C, 42.81; H, 4.66; N, 13.52.

5-Amino-2-chloro-1-β-D-ribofuranosulimidazole-4-carboxamide (4a). Compound 4 (255 mg, 0.5 mmol) was deacetylated by refluxing it with a freshly prepared 0.01 *M* solution of methanolic sodium methoxide (10 ml) for 10 min. After 2 hr at room temperature it was treated with excess Amberlite IRC 50 (H^+ form), the resin was removed by filtration, and the solvent evaporated slowly *in vacuo* to a small volume (~1 ml). After the mixture had cooled to room temperature crystalline material deposited which was recrystallized from aqueous MeOH to yield 124 mg (84%): mp 175–176°; nmr (Me_2SO-d_6) δ 6.83 (s, NH_2), 6.37 (s, NH_2), 5.66 (d, 1, $J_{1',2'}$ = 6.0 Hz, H-1′), $\lambda_{max}^{pH\ 1}$ 272 mμ (ε 17,700); $\lambda_{max}^{pH\ 11}$ 272 (17,7000).

Anal. Calcd for $C_9H_{13}N_4O_5Cl \cdot H_2O$: C, 35.00; H, 4.85; N, 18.00. Found: C, 35.02; H, 4.89; N, 18.15.

6-Bromo-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo-[4,5-*d*]-*v*-triazin-(3*H*)4-one (5). Compound 3 (4.63 g, 10 mmol) was dissolved in cold (−25°) 6 *N* HCl (50 ml). A saturated aqueous solution of $NaNO_2$ (2.1 g, 30 mmol) was added dropwise to the rapidly stirred solution over a period of ~30 min. After an additional 30 min stirring the pH of the reaction mixture was adjusted to 4.5 with concentrated NH_4OH. Up to this point the temperature was carefully kept between −22 and −25°. The product was extracted with EtOAc (4 × 100 ml) and the combined EtOAc fractions were dried (Na_2SO_4) and evaporated to dryness. The resulting light tan foam was applied to a column of silica gel (3 × 30 cm) packed in $CHCl_3$. The product was eluted with $CHCl_3$–EtOAc (8:6). The fractions containing the major product were combined and evaporated to dryness to yield amorphous, slightly yellowish material, 3.16 g (64%): nmr (Me_2SO-d_6) δ 15.66 (s, 1, 3-NH); λ_{max} (MeOH) 298 mμ.

Anal. Calcd for $C_{15}H_{16}N_5O_8Br$: C, 37.99; H, 3.40; N, 14.76. Found: C, 38.06; H, 3.33; N, 14.58.

6-Bromo-7-β-D-ribofuranosylimidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (5a). Compound 5 (2.84 g, 6 mmol) was added to saturated (0°) methanolic ammonia (200 ml). It was kept at 25° for 16 hr, then evaporated to dryness. The residue was dissolved in H_2O (20 ml) and extracted with EtOAc (4 × 50 ml). The pH of the aqueous solution was adjusted with Dowex 50 (H^+ form) to 4, the resin was removed by filtration, and the solvent evaporated *in vacuo*. The product was recrystallized from boiling EtOH to yield 1.95 g (85%): mp 94–95°; nmr (D_2O) δ 6.16 (d, 1, $J_{1',2'}$ = 5.0 Hz, H-1′); $\lambda_{max}^{pH\ 1}$ 293 mμ (ε 7300); $\lambda_{max}^{pH\ 11}$ 298 (9350).

Anal. Calcd for $C_9H_{10}N_5O_5Br \cdot (C_2H_5OH)$: C, 33.21; H, 4.07; N, 17.74. Found: C, 33.30; H, 4.11; N, 17.57.

6-Azido-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo-[4,5-*d*]-*v*-triazin-(3*H*)4-one (6). Compound 5 (4.74 g, 10 mmol), NaN_3 (1.95 g, 30 mmol), and Me_2SO (20 ml) were stirred at room temperature for 3 days, in the dark. H_2O (200 ml) was added and then the solvent was removed by azeotropic vacuum distillation. The dark residue was dissolved in $CHCl_3$ (20 ml) and applied to a column of silica gel, Baker (4 × 50 cm), packed in $CHCl_3$. The desired product was eluted with $CHCl_3$–EtOAc (7:3). The uv-absorbing fractions were combined and evaporated to dryness to yield an amorphous solid, 1.62 g (37%): ir 2150 cm^{-1} (N_3); $\lambda_{max}^{pH\ 1}$ 308 mμ (ε 9000) and 264 (sh) (7200); $\lambda_{max}^{pH\ 11}$ 307 (9900) and 265 (sh) (6530).

Anal. Calcd for $C_{15}H_{16}N_8O_8$: C, 41.28; H, 3.89; N, 25.61. Found: C, 41.33; H, 4.07; N, 25.40.

6-Amino-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo-[4,5-*d*]-*v*-triazin-(3*H*)4-one (7). Compound 6 (0.436 g, 1 mmol) was dissolved in 96% EtOH (20 ml). Pd/C (10%, 100 mg) was added and the mixture hydrogenated at 25° and 1 atm of pressure. After 45 min the catalyst was removed by filtration and the filtrate evaporated to dryness. A crystalline product was obtained by recrystallization from EtOH to yield 244 mg (60%): mp 173–176°; nmr (Me_2SO-d_6) δ 7.47 (s, 2, 6-NH_2); $\lambda_{max}^{pH\ 1}$ 323 mμ (ε 8200); $\lambda_{max}^{pH\ 11}$ 310 (10,050).

Anal. Calcd for $C_{15}H_{18}N_6O_8$: C, 43.88; H, 4.38; N, 20.47. Found: C, 44.01; H, 4.29; N, 20.21.

2,5-Diamino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (8). Raney Ni (500 mg) was added to a solution of **7** (80 mg) in 50% aqueous ethanol. The mixture was shaken under 40 psi of H_2 for 1 hr at 70°. The catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The material was purified by preparative thin-layer chromatography (20 cm × 20 cm × 2 mm silica gel plate) using an ethyl acetate–methylene chloride–methanol (6:3:1) system. Compound **8** was obtained as hygroscopic amorphous solid: 32 mg (40%); nmr (Me_2SO-d_6) δ 7.28 (s, 2, 2-NH_2); (Me_2SO-d_6–D_2O) δ 5.94 (s, 1, $J_{1',2'}$ = 6 Hz, H-1'); $\lambda_{max}^{pH\ 1}$ 276 mμ (ε 9700); $\lambda_{max}^{pH\ 11}$ 284 (12,600).

Anal. Calcd for $C_{15}H_{21}N_5O_8$: C, 45.11; H, 5.30; N, 17.54. Found: C, 45.02; H, 5.46; N, 17.38.

6-Methoxy-7-β-D-ribofuranosylimidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (9). Compound **5** (142 mg, 0.3 mmol) was refluxed with freshly prepared 0.35 *M* methanolic sodium methoxide (6 ml) for 2 hr. After 16 hr at room temperature it was treated with Dowex 50 (H^+ form) to remove the sodium, filtered, and evaporated to dryness to yield an amorphous product, 78 mg (62%): mp 114–116°; nmr (Me_2SO-d_6) δ 5.87 (d, 1, $J_{1',2'}$ = 6 Hz, H-1'), 4.22 (s, 3, OCH_3); $\lambda_{max}^{pH\ 1}$ 306 mμ (ε 10,500); $\lambda_{max}^{pH\ 11}$ 299 (12,200).

Anal. Calcd for $C_{10}H_{13}N_5O_6$: C, 40.07; H, 4.34; N, 23.33. Found: C, 40.16; H, 4.19; N, 23.11.

5-Amino-2-methoxy-1-β-D-ribofuranosylimidazole-4-carboxamide (10). Raney Ni (500 mg) was added to a solution of **9** (299 mg, 1 mmol) in H_2O (10 ml). It was hydrogenated at 30 psi and 25° for 40 hr. The catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was triturated with EtOH, giving a crystalline product which was recrystallized from EtOH–H_2O giving 171 mg (59%) of **10**: mp 182–184°; nmr (D_2O) δ 5.66 (d, 1, $J_{1',2'}$ = 6 Hz, H-1'), 4.00 (s, 3, OCH_3); $\lambda_{max}^{pH\ 1}$ 272 mμ (ε 11,800); $\lambda_{max}^{pH\ 11}$ 281 (14,400).

Anal. Calcd for $C_{10}H_{16}N_4O_6$: C, 41.66; H, 5.59; N, 19.44. Found: C, 41.42; H, 5.79; N, 19.25.

7-β-D-Ribofuranosylimidazo[4,5-*d*]-*v*-triazine-4,6-dione (11). Compound **5a** (174 mg, 0.5 mmol) was treated with 6 ml of 3% NaOH for 16 hr at 4°, then passed through a column (1 × 15 cm) of Amberlite IRC 50 ([H^+], 100–200 mesh). The column was washed with H_2O (30 ml) and the combined eluates were evaporated to a small volume (1 ml) *in vacuo* and then applied to a column (2 × 30 cm) of microcrystalline cellulose (Avicel). The product was eluted with H_2O. A colorless, amorphous solid, 98 mg (67%), was obtained by lyophilizing the fractions containing the product: nmr (Me_2SO-d_6) δ 5.95 (d, 1, $J_{1',2'}$ = 5 Hz, H-1'); $\lambda_{max}^{pH\ 1}$ 297 mμ (ε 3560); $\lambda_{max}^{pH\ 11}$ 305 (5700).

Anal. Calcd for $C_9H_{11}N_5O_6$: C, 37.92; H, 3.86; N, 24.56. Found: C, 38.10; H, 3.77; N, 24.33.

6-Thio-7-β-D-ribofuranosylimidazo[4,5-*d*]-*v*-triazin-(3*H*)4-one (12). Compound **5a** (348 mg, 1 mmol) was added to a freshly prepared 2 *M* aqueous solution of NaSH (5 ml), stirred at 4° for 16 hr, and then diluted with H_2O (5 ml) and MeOH (15 ml). The pH of the solution was brought to 4 with Dowex 50 (H^+ form), the resin was removed by filtration, and the filtrate was evaporated to dryness. The product was recrystallized from aqueous EtOH to yield 261 mg (75%): mp 228–231°; nmr (Me_2SO-d_6) δ 5.90 (d, 1, $J_{1',2'}$ = 6.0 Hz, H-1'); $\lambda_{max}^{pH\ 1}$ 283 mμ (ε 9600), 341 (3600); $\lambda_{max}^{pH\ 11}$ 334 (7500).

Anal. Calcd for $C_9H_{11}N_5O_5S \cdot H_2O$: C, 33.83; H, 4.08; N, 21.95. Found: C, 33.91; H, 4.08; N, 21.98.

Registry No.—**1,** 2627-69-2; **1a,** 23274-21-7; **2,** 36519-16-1; **3,** 52906-34-0; **3a,** 52906-35-1; **4,** 52906-36-2; **4a,** 52906-37-3; **5,** 52906-38-4; **5a,** 52906-39-5; **6,** 52906-40-8; **7,** 52906-41-9; **8,** 52906-42-0; **9,** 52951-30-1; **10,** 52906-43-1; **11,** 52906-44-2; **12,** 52906-45-3.

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A General Synthesis of N-Glycosides. I.[1] Synthesis of Pyrimidine Nucleosides

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Reaction of silylated hydroxy-, amino-, and mercaptopyrimidines as well as 6-azapyrimidines (1,2,4-triazines) with protected 1-*O*-acetyl as well as 1-*O*-methyl sugars in the presence of Friedel–Crafts catalysts gave the corresponding pyrimidine nucleosides, generally in excellent yields. The scope and limitations of this new synthetic procedure are discussed.

Because we wanted to prepare larger quantities of 6-azauridine, we investigated and compared the known methods for the preparation of pyrimidine nucleosides,[2] especially the silyl Hilbert–Johnson reaction.[3-8] After early synthetic studies by different groups,[9] Cristescu[10] and Wittenburg[11] had prepared 6-azauridine 2′,3′,5′-tri-*O*-benzoate in 60% yield by the benzenemercuric salt modification of the silyl Hilbert–Johnson reaction. Using this procedure we obtained varying yields of a rather impure substance which had to be purified by column chromatography. However the resulting crystalline product was still contaminated by mercuric compounds.

Since the Hilbert–Johnson reaction involves an attack of a sugar cation on the aromatic pyrimidine ring, we carried out the reaction in the presence of Friedel–Crafts catalysts, which are known[12] to convert acylated 1-acyloxy sugars into their corresponding acylated glycosyl halides.

Friedel–Crafts catalysts have been used by Baker[13] and later by Furukawa and Honjo[14] for the synthesis of purine nucleosides, but, strangely enough, the more obvious use of