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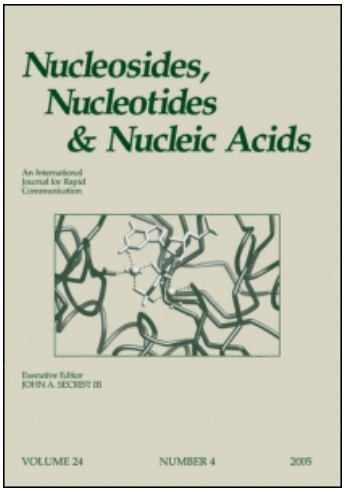

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The Synthesis of Coformycin from 5-Amino-1-β-D-ribofuranosylimidazole-4-carboxamide

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The Synthesis of Coformycin from 5-Amino-1-β-D-ribofuranosylimidazole-4-carboxamide

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A convenient synthesis of coformycin from commercially available 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide is described.

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An ongoing program in our laboratory is devoted to the synthesis of nucleosides substituted at $C_{5'}$ with groups capable of reacting with the nucleophilic binding sites of nucleotide metabolizing enzymes.[1] We have shown that one such nucleoside, 5'-bromoacetamido-5'-deoxythymidine, inactivates thymidylate synthetase in the manner of an active-site-directed-irreversible inhibitor.[2] Coformycin[3] appeared to be an excellent candidate for derivatization since it inhibits not only adenosine deaminase but also AMP deaminase with a K_i for the latter enzyme of 2-5 x 10^{-8}M.[4,5] This reversible binding should be sufficiently tight to allow efficient inactivation to occur, and better inhibitors of AMP deaminase have become of considerable interest. Coformycin, originally isolated together with formycin from the culture filtrate of N. interforman and S. haviharaensis SF-557,[3] has been synthesized by the reaction of the silyl derivative of 6,7-dihydroimidazo-[4,5-d]diazepin-8(3H)-one with 2,3,5-tri-O-benzoyl-D-ribofuranosyl chloride followed by removal of the benzoyl groups and reduction of the carbonyl function, which gave a mixture of coformycin and its 8S epimer (**12**).[6]

We have now developed a more convenient route to coformycin starting with the commercially available 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide, which

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is converted to 5-amino-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylic acid (1) by a literature procedure.[7] Reaction of the acid **1** with N,N-dimethylchloroforminium chloride gave the acid chloride **2**, which was allowed to react with ethereal diazomethane to give the diazoacetylimidazole **3**. Treatment of **3** with methanolic ammonia gave 4-diazoacetyl-5-(dimethylaminomethylene)amino-1-β-D-ribofuranosylimidazole (**4**) as a yellow crystalline solid. Reduction of **4** with hydrogen (5% Pd/C) in water gave the acetylimidazole **7** [FAB M.S. 313 $(M + 1)^+$] containing some of the desired amino compound **9** [FAB M.S. 328 $(M + 1)^+$]. Treatment of compound **4** with dry hydrogen chloride in tetrahydrofuran at 0 °C resulted in sugar cleavage as well as conversion to the chloromethylketone. The solid obtained was purified by TLC followed by recrystallization from methanol to give a sample that analyzed as a partial hydrochloride hydrate of 4-chloroacetyl-5-(dimethylaminomethyleneamino)imidazole (**5a**). The triacetate **3** was converted to the chloroacetylimidazole **5** by bubbling dry hydrogen chloride into a solution of it in methylene chloride at 0-3 °C. Apparently, the O-acetyl groups prevented the sugar cleavage observed with **4**[8]. Reaction of syrupy **5** with sodium azide in DMF gave the azidoacetylimidazole **6**, which was carefully deacetylated with a catalytic amount of sodium methoxide in methanol to give **8**. Catalytic (5% Pd/C) reduction of **8** gave the aminomethylketone **9**. Cyclization of **9** was accomplished with 1N sodium methoxide in methanol giving the desired 3-β-D-ribofuranosyl-6,7-dihydroimidazo[4,5-d][1,3]diazepin-8(3H)-one (**11**) of 93% purity (HPLC). The ^1H NMR spectrum of **11** is in good agreement with published data.[6] Reduction of **11** with sodium borohydride gave coformycin and its 8S epimer (**12**) which could be separated by HPLC as reported. Again, the ^1H NMR and UV data are in good agreement with the literature values.[6] The impurity in **11** could not be isolated from it, but could be separated from **12** after the reduction. It was identified by its elemental analyses, mass spectrum, UV spectrum, and ^1H and ^{13}C NMR spectra as 4-(N-formylaminoacetyl)-5-amino-1-β-D-ribofuranosylimidazole (**10**), which must have resulted from the base catalyzed ring-opening of **11**.[10] In the proton-coupled spectrum, the ^{13}C signal at 161.1 ppm appears as a doublet of quartets with a $^1J_{C,H}$ of 191.0 Hz. This large one-bond coupling constant suggests that this carbon is the carbonyl of a formamide.[12] The formyl-carbon coupling collapses to give a doublet of doublets when the non-sugar CH_2 protons are selectively decoupled. Therefore, the formyl carbon is two or three bonds from the protons of this CH_2 group. The identification of **10** suggested that more stringently

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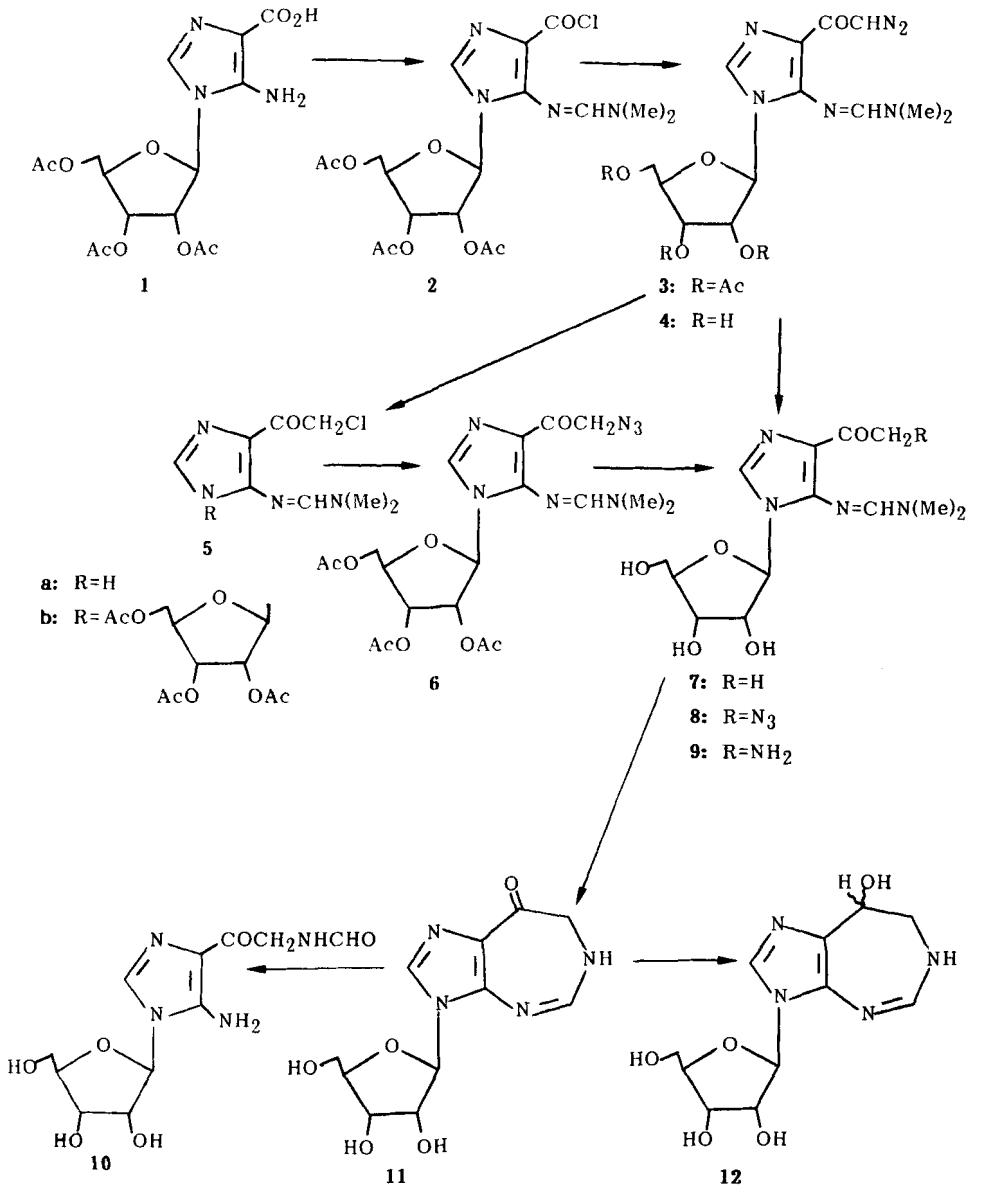

anhydrous conditions be used in the ring closure. When the reaction was carried out in anhydrous methanol (ChromAR HPLC, Mallinckrodt; dried over Linde 3A molecular sieves) containing sodium methoxide generated by the addition of metallic sodium, it gave **11** (93% pure by HPLC) and no **10**.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. The UV absorption spectra were determined in the solvents specified with a Cary 17 spectro-

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photometer. ^{1}H NMR spectra were recorded on a Varian XL-100-15 spectrometer or a Nicolet NMC 300NB spectrometer. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. When microanalytical data are on a solvate, the solvents were seen in the proper amounts in the NMR spectrum. Microanalyses were performed with a Perkin-Elmer Model 240 Elemental Analyzer. TLC analyses were carried out on Analtech silica gel SGF (250 microns) plates using the solvents and detection methods given for each compound. Unless otherwise indicated, compounds were TLC homogeneous. The HPLC analyses were carried out with an ALC-242 liquid chromatograph (Waters Associates), using a μBondapak C_{18} column with UV monitoring. Mass spectra were recorded on a Varian MAT 311A mass spectrometer in the fast-atom-bombardment (FAB) mode.

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1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-4-diazoacetyl-5-(dimethylaminomethyleneamino)imidazole (3). To a suspension of 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-5-aminoimidazole-4-carboxylic acid[7] (**1**, 432 mg, 1.12 mmol) in anhydrous tetrahydrofuran (15 mL) was added N,N-dimethylchloroforminium chloride (432 mg, 3.37 mmol). A complete solution was obtained after 10 min of stirring. After 1 h, the solution was added slowly under anhydrous conditions to a stirred solution of ethereal diazomethane (25 mL, ca 17 mmol) maintained at -10 °C. After addition was complete, the mixture was allowed to warm up to ambient temperature, kept there for 20 h, then filtered, and evaporated to dryness in vacuo. A syrup was obtained: yield 324 mg (67%); TLC (EtOAc, NBP positive); mass spectrum m/z 259 $(sugar)^+$, 465 $(M + 1)^+$; ^{1}H NMR (Me_2SO-d_6 δ 2.03, 2.06, 2.08 (3s, 9H, CH_3 of CH_3CO), 2.99, 3.08 (2s, 6H, $(CH_3)_2N$), 4.18 (dd, $J_{4',5'a}$=5.2 Hz, $H_{5'a}$), 4.26 (m, H-4'), 4.33 (dd, $J_{4',5'a}$=3.3 Hz, $J_{5'a,5'b}$=11.5 Hz, H-5'b), 5.39 (ψt, $J_{3',4'}$=5.7 Hz, H-3'), 5.73 (dd, $J_{2',3'}$=6.0 Hz, H-2'), 5.91 (d, $J_{1',2'}$=5.0 Hz, H-1'), 6.39 (s, CHN_2), 7.62 (s, H-2), 8.61 (s, CH=N).

4-Diazoacetyl-5-dimethylaminomethyleneamino-1-β-D-ribofuranosylimidazole (4). A solution of 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-4-diazoacetyl-5-(dimethylaminomethyleneamino)imidazole (**3**, 2.00 g, 4.30 mmol) in ethanolic-ammonia (saturated at 0 °C) (150 mL) was kept at 0-3 °C for 5 days and evaporated to dryness in vacuo. The residue was recrystallized from methanol-ether. A yellow solid, **4**, was obtained: yield 424 mg (29%); m.p. 164-166 °C dec; TLC [$CHCl_3$-MeOH (3:1), NBP positive]; UV λ_{max} in nm

(ϵ x 10^{-3}): pH 1-unstable, pH 7-245 (18.9), 286 (11.1) and 342 (13.6), pH 13-246 (18.6), 289 (11.0), and 342 (13.2); mass spectrum m/e 339 $(M + 1)^+$; ^1H NMR (Me_2SO-d_6) δ 2.98, 3.06 (2s, 6H,$(CH_2)_2N$), 3.50 (m, H-5'a), 3.60 (m, $J_{5'a,5'b}$=11.7 Hz, H-5'b), 3.82 (ψq, $J_{4',5'a}=J_{4',5'b}$=3.5 Hz, H-4'), 4.04 (ψq, $J_{3',4'}$=4.3 Hz, H-3'), 4.22 (ψq, $J_{2',3'}$=4.7 Hz, H-2'), 4.95 (ψt, $J_{5'a,5'b,OH}$=5.4 Hz, $J_{5'b,OH}$=4.5 Hz, exchanges, 5'-OH), 5.07 (d, $J_{3',OH}$=5.0 Hz, exchanges, 3'-OH), 5.31 (d, $J_{2',OH}$=5.4 Hz, exchanges, 2'-OH), 5.67 (d, $J_{1',2'}$=5.1 Hz, H-1'), 6.37 (s, CHN_2), 7.66 (s, H-2), 8.6 (s, CH=N). Anal. calcd. for $C_{13}H_{18}N_6O_5$: C, 46.15; H, 5.36; N, 24.84. Found: C, 46.35; H, 5.54; N, 24.81.

4-Chloroacetyl-5-(dimethylaminomethyleneamino)imidazole (5a). A suspension of 4-diazoacetyl-5-dimethylaminomethyleneamino-1-β-D-ribofuranosylimidazole (**4**, 160 mg, 0.47 mmol) in anhydrous tetrahydrofuran (25 mL) was diluted with 20 mL of tetrahydrofuran saturated at 0 °C with HCl. The color of the suspension changed from yellow to white with bubbling. When the bubbling ceased, the solid was collected by filtration: yield 30 mg. It was purified by preparative tlc on Brinkmann 2-mm plates developed in chloroform-methanol (4:1). The faster moving product (**5a**) was obtained as a white solid: yield 12 mg. The slower moving, 4-chloroacetyl-5-dimethylaminomethyleneamino-1-(β-D-ribofuranosyl)imidazole, was obtained as a white solid: yield 9 mg (2.6%); mass spectrum m/z 347 $(M + 1)^+$; TLC [$CHCl_3$-MeOH (3:1)].

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Dilution of the mother liquor with ether gave a second crop of **5a** which was recrystallized from methanol: yield 42 mg. Total yield: 20%; TLC [$CHCl_3$-MeOH (9:1), NBP positive]; UV λ_{max} (ϵ x 10^{-3}); 231 and 304 nm at pH 1 (14.1 and 11.8); 243 and 336 nm at pH 7 (13.9 and 16.7); 253 and 346 nm at pH 13 (14.0 and 13.7); mass spectrum m/z 215 $(M + 1)^+$; ^1H NMR (Me_2SO-d_6) δ 3.15 (s, CH_3), 3.22 (s, CH_3), 3.32 (s, H_2O), 4.99 (s, CH_2), 8.76 (m, CH=N), 8.79 (d, CH of imidazole). Anal. calcd. for $C_8H_{11}ClN_4O \cdot 0.7\ HCl \cdot 1.7\ H_2O$: C, 35.47; H, 5.57; N, 20.69. Found: C, 35.72; H, 5.62; N, 20.49.

1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-4-chloroacetyl-5-(dimethylaminomethyleneamino)imidazole (5b). Anhydrous hydrogen chloride was bubbled for 3 min into a cold (0-3 °C) solution of 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-4-diazoacetyl-5-(dimethylaminomethylamino)imidazole (**3**, 324 mg, 0.70 mmol) in anhydrous methylene chloride

(25 mL). The solution was then washed with water until neutral, dried over magnesium sulfate, and evaporated to dryness in vacuo. A syrup was obtained: yield 175 mg (55%); TLC (EtOAc, NBP positive); mass spectrum m/z 259 $(sugar)^+$, 473 $(M + 1)^+$; ^1H NMR (Me_2SO-d_6) δ 2.05, 2.07, 2.09 (3s, CH_3 of Ac), 3.03, 3.12 (2s, CH_3 of $(CH_3)_2N$), 4.19 (dd, $H_{5'}$), 4.30 (m, $H_{4'}$,$H_{5'}$), 4.85 (s, CH_2Cl), 5.39 (ψt, $H_{3'}$), 5.75 (ψt, $H_{2'}$), 5.93 (d, $J_{1',2'}$=3 Hz, $H_{1'}$), 7.72 (s, N=CH), 8.58 (s, H_2).

1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-4-azidoacetyl-5-(dimethylaminomethyleneamino)imidazole (6). A solution of 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-4-chloroacetyl-5-(dimethylaminomethyleneamino)imidazole (**5**, 175 mg, 0.37 mmol) in dimethylacetamide containing sodium azide (72 mg, 1.11 mmol) was stirred at ambient temperature for 20 h, filtered, and evaporated to dryness in vacuo. An ethyl acetate solution of the residue was washed with water, dried over magnesium sulfate, and evaporated to dryness in vacuo. A syrup was obtained: yield 149 mg (84%); TLC (EtOAc, ninhydrin positive); mass spectrum m/z 259 $(sugar)^+$, 480 $(M + 1)^+$; ^1H NMR (Me_2SO-d_6) δ 2.07 (3s, CH_3 of acetyls), 3.03, 3.12 (2s, CH_3 of $(CH_3)_2N$), 4.19 (dd, $H_{5'}$), 4.30 (m, $H_{4'}$, $H_{5'}$), 4.52 (s, CH_2N_3), 5.40 (ψt, $H_{3'}$), 5.75 (ψt, $H_{2'}$), 5.93 (d, $H_{1'}$, $J_{1',2'}$=2Hz), 7.70 (s, N=CH), 8.59 (s, H_2).

4-Azidoacetyl-5-dimethylaminomethyleneamino-1-β-D-ribofuranosylimidazole (8). To a solution of 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-4-azidoacetyl-5-(dimethylaminomethyleneamino)imidazole (**6**,2.90 g, 6.0 mmol) in anhydrous methanol (170 mL) was added 0.6 mL of 1N sodium methoxide in methanol. After 3 min, when the pH of the solution was no longer basic, 0.6 mL more sodium methoxide was added. After 45 min at ambient temperature, the solution was examined by TLC and showed no starting material. The solution was treated with Amberlite IR-120(H^+) ion exchange resin to remove Na^+ ions and then evaporated to dryness in vacuo. The crystalline residue was recrystallized from methanol-acetone. A white solid was obtained: yield 1.63 g (77%); m.p. 121-122 °C dec.

The analytical sample was obtained from another reaction: m.p. 121-123 °C dec; TLC [$CHCl_3$-MeOH (9:1), ninhydrin positive]; UV λ_{max} ($\epsilon \times 10^{-3}$) 222 and 260 nm at pH 1 (16.6 and 8.50), 234, 305 (sh), and 337 nm at pH 7 (19.6, 6.00, and 8.56); 236, 305 (sh), and 337 nm at pH 13 (19.3, 6.07, and 8.19); mass spectrum m/z 354 $(M + 1)^+$; ^1H NMR (Me_2SO-d_6) δ 3.01, 3.11 (2s, CH_3), 3.27 (s, H_2O), 3.52, 3.60 (2m, $J_{5',5'}$=12 Hz, 2 $H_{5'}$), 3.83

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(dd, $J_{4',5'}$=3.7 and 4.0, $H_{4'}$), 4.04 (dd, $J_{3',4'}$=4.4, $H_{3'}$), 4.43 (dd, $J_{2',3'}$=5.0 $H_{2'}$), 4.50 (s, $C\underline{H}_2N_3$), 4.97 (ψt, $J_{5',5'\text{-}OH}$=5.3, $O_{5'}$-H), 5.09 (d, $J_{3',3'\text{-}OH}$=5.2, $O_{3'}$-H), 5.33 (d, $J_{2',2'\text{-}OH}$=5.9, $O_{2'}$-H), 7.74 (s, N=C$\underline{H}$), 8.58 (s, H_2). Anal. calcd. for $C_{13}H_{19}N_7O_5 \cdot 0.5\ H_2O$: C, 43.09; H, 5.56; N, 27.06. Found: C, 43.22; H, 5.68; N, 27.03.

4-Aminoacetyl-5-dimethylaminomethyleneamino-1-β-D-ribofuranosylimidazole (9). A solution of 4-azidoacetyl-5-dimethylaminomethyleneamino-1-(β-D-ribofuranosyl)-imidazole (353 mg, 1.0 mmol) in methanol (50 mL), containing 5% palladium-on-carbon catalyst (100 mg) was hydrogenated at ambient temperature and atmospheric pressure. After ½ h, the system was recharged with hydrogen. After 1½ h more, the catalyst was removed by filtration and washed well with methanol followed by water. The combined filtrate and wash was evaporated to dryness in vacuo. Trituration of the residue with ethanol gave a crystalline solid weighing 320 mg. It was recrystallized from boiling ethanol: yield 133 mg (41%); m.p. 171-172 °C dec; TLC [CH_3CN-IN NH_4OH (13:7), ninhydrin positive]; UV λ_{max} (ϵ x 10^{-3}) 223 and 265 nm at pH 1 (16.0 and 7.68); 232, 300 (sh), and 335 nm at pH 7 (19.1, 5.27, and 8.28); 232, 300, and 330 (sh) at pH 13 (16.3, 6.52, and 5.85); mass spectrum m/z 196 $(B + 2H)^+$, 328 $(M + 1)^+$; ^1H NMR (Me_2SO-d_6) δ 1.06 (t, CH_3 of ethanol), 1.64 (broad s, NH_2), 2.98, 3.07 (2s, $2CH_3$), 3.46 (q, CH_2 of EtOH), 3.50 and 3.60 (m, 3.50, 3.60 (2dd, $J_{4',5'}$=3.4 Hz, $J_{4',5'}$=3.8 Hz, $J_{5',5'}$=11.7 Hz, 2-$H_{5'}$), 3.81 (s, $C\underline{H}_2NH_2$), 4.04 (ψt, $J_{3',4'}$=4.3, $H_{3'}$), 4.22 (ψt, $J_{2',3'}$=5.1, $H_{2'}$), 4.95 (broad, $O_{5'}H$), 5.09 (broad, $O_{3'}H$), 5.31 (broad, $O_{2'}H$), 5.66 (d, $J_{1',2'}$=5.2, $H_{1'}$), 7.68 (s, N=C$\underline{H}$), 8.57 (s, H_2). Anal. calcd. for $C_{13}H_{21}N_5O_5 \cdot 0.1\ C_2H_5OH$: C, 47.76; H, 6.56; N, 21.10. Found: C, 47.74; H, 6.64; N, 20.86.

4-(N-Formylaminoacetyl)-5-amino-1-β-D-ribofuranosylimidazole (10). 3-β-D-Ribofuranosyl-6,7-dihydroimidazo[4,5-$\underline{d}$][1,3]diazepin-8(3H)-one containing 4-(N-formylaminoacetyl)-5-amino-1-β-D-ribofuranosylimidazole (**10**) was reduced to coformycin and its R isomer (**12**). Coformycin was separated from its R isomer and from compound **10** by flash chromatography on a Bonded Octadecyl (C_{18}) 100-mL column (Baker, 20 g) with water followed by chromatography on Brinkmann silica gel plates developed in 65 MeCN:35 1$\underline{N}$ NH_4OH. Compound **10** was eluted and recrystallized from methanol. UV pH 1-294 (113), pH 7-303 (11.1), pH 13-304 (11.1); ^1H NMR (Me_2SO-d_6) δ 3.59 (ψt, 2H, H-5'), 3.92

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(ψq, $J_{4',5'}$=2.8 Hz, H-4'), 4.04 (ψq, $J_{3',4'}$=2.6 Hz, H-3'), 4.28 (ψq, $J_{2',3'}$=5.1 Hz, H-2'), 4.34 (d, J=5.6 Hz, ccllapses to a singlet on addition of D_2O, 2H, $COCH_2N$), 5.18 (d, $J_{3',OH}$=4.1 Hz, exchanges, 3'-OH), 5.35 (t, $J_{5',OH}$=4.7 Hz, exchanges, 5'-OH), 5.41 (d, $J_{2',OH}$=6.6 Hz, exchanges, 2'-OH), 5.53 (d, $J_{1',2'}$=6.6 Hz, H-1'), 6.82 (br s, exchanges, NH_2), 7.36 (s, H-2), 8.11 (br s, collapses to a sharp singlet upon addition of D_2O, HCO), 8.14 (br t, J=5.6 Hz, exchanges, CONH). ^{13}C NMR (75.6 MHz, Me_2SO-d_6) δ 42.8 (t of d, $^1J_{C,H}$=131.8 Hz, $^3J_{C,\underline{C}HO}$=4.6 Hz, CH_2), 61.0 (t, $^1J_{C,H}$=139.7 Hz, C-5'), 70.3 (d, $^1J_{C,H}$=150.5 Hz, C-3'), 72.7 (d, $^1J_{C,H}$=147.6 Hz, C-2'), 85.3 (d, $^1J_{C,H}$=147.9 Hz, C-4'), 87.3 (d, $^1J_{C,H}$=160.7 Hz, C-1'), 118.7 (d, $^3J_{C\text{-}4,\ H\text{-}2}$=10.0 Hz, C-4), 130.0 (dd, $^1J_{C\text{-}2,\ H\text{-}2}$=214.9 Hz, $^3J_{C\text{-}2,H\text{-}1'}$=3.6 Hz, C-2), 145.8 (t, $^3J_{C\text{-}5,\ H\text{-}1'}$=3.2 Hz, $^3J_{C\text{-}5,H\text{-}2}$=3.8 Hz, C-5), 161.1 (d of q, $^1J_{C,H}$=191 Hz, $^2J_{C,NH}$=$^3J_{C,CH_2}$=3.7 Hz, NHCHO), 187.1 (t, $^2J_{C,H}$=4.1 Hz, $\underline{C}OCH_2$). Anal. calcd. for $C_{11}H_{16}N_4O_6$: C, 44.00; H, 5.37; N, 18.66. Found: C, 43.87; H, 5.39; N, 18.40.

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3-β-D-Ribofuranosyl-6,7-dihydroimidazo[4,5-d][1,3]diazepin-8(3H)-one (11). After standing 20 h at room temperature, a solution of 4-aminoacetyl-5-(dimethylaminomethylene)amino-1-β-D-ribofuranosyl)imidazole (**9**, 100 mg, 0.3 mmol) in 11 mL of 0.1 N sodium methoxide in dry methanol was neutralized with solid CO_2 and evaporated to dryness in vacuo. The residue was purified by flash chromatography on a 100-mL silica gel column (3 $CHCl_3$:1 MeOH). The resulting white glass was triturated with EtOH and dried: yield 48 mg (56%). This material was shown by HPLC to contain **11** (93%) and **10** (7%). ^1H NMR (Me_2SO-d_6) δ 3.8, 3.87 (ddd, 2 H-5'), 4.02 (s, 2H, $COCH_2$), 4.22 (dd, H-4'), 4.38 (ψt, $H_{3'}$), 4.66 (ψt, $H_{2'}$), 5.97 (d, $H_{1',2'}$=4.5 Hz, H-1'), 7.45 (s, H-2), 7.9 (s, N=CH).

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