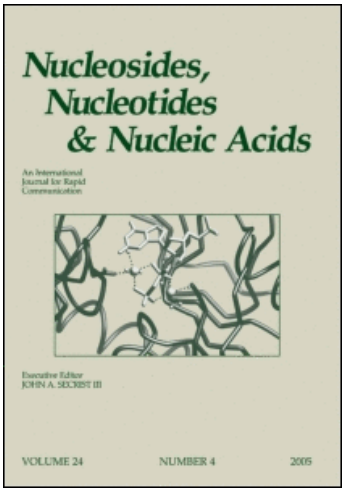

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Cook, Alan F. and Holman, Michael J.(1984) 'Synthesis of the Natural Product 5'-Deoxy-5-iodotubercidin and Related Halogenated Analogs', Nucleosides, Nucleotides and Nucleic Acids, 3: 4, 401 — 411
To link to this Article: DOI: 10.1080/07328318408081278
URL: http://dx.doi.org/10.1080/07328318408081278

NUCLEOSIDES & NUCLEOTIDES, 3(4), 401-411 (1984)

SYNTHESIS OF THE NATURAL PRODUCT 5'-DEOXY-5-IODOTUBERCIDIN AND RELATED HALOGENATED ANALOGS

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Abstract: 5'-Deoxy-5-iodotubercidin, a novel nucleoside recently isolated from a marine source, has been synthesized in four steps from tubercidin. The intermediate 5'-deoxytubercidin was also used to prepare the 5-bromo and 5-chloro derivatives, as well as a series of 5,6-dihalo compounds.

Introduction

Although pyrrolo[2,3-d]pyrimidine nucleosides are relatively rare in nature, several examples have been isolated from natural sources. The most well known compounds are tubercidin, toyocamycin and sangivamycin which have been isolated from a variety of strains of Streptomyces, and which have stimulated considerable interest on account of their powerful antibacterial, antifungal and antitumor properties.[1] Other examples of pyrrolo[2,3-d]pyrimidines in nature include nucleoside Q, which was isolated from the degradation of tRNA,[2] and cadeguomycin, isolated from Streptomyces hygroscopicus.[3] Recently a new pyrrolo[2,3-d]pyrimidine nucleoside 5'-deoxy-5-iodotubercidin (1) was isolated from an extract of the marine red alga Hypnea valendiae,[4] and shown to produce muscle relaxation and hypothermia in mice as well as being a potent inhibitor of the enzyme adenosine kinase. This compound is unusual in several respects, since 5'-deoxynucleosides are extremely rare in nature[5] and this compound appears to be the first iodinated nucleoside to be isolated

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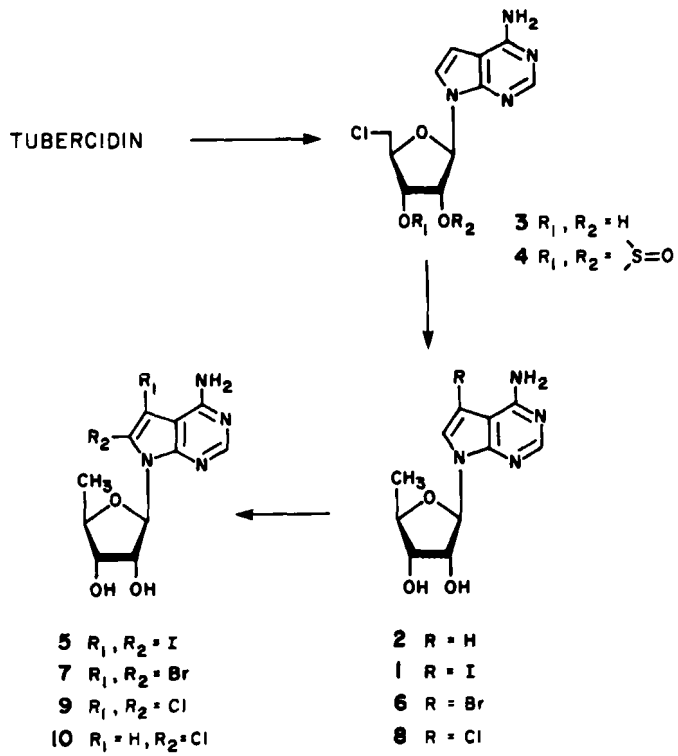
Scheme 1



from natural sources. Since the isolation procedure yielded relatively small amounts of 1, and a reisolation attempt produced another less active isomer,[4] the synthesis of 1 and some closely related analogs was undertaken in order to provide sufficient material for a more systematic study.

Results and Discussion

Tubercidin was used as the starting material, and the planned route (Scheme 1) involved conversion to the 5'-deoxy compound 2 followed by iodination of the pyrrole ring. Our initial route to the 5'-deoxy compound 2 employed the procedure of Anzai and Matsui,[6] in which the tubercidin molecule was fully protected, and the 5'-deoxy moiety was introduced by hydrogenation of an intermediate 5'-iodo compound. Although this procedure was improved so that 2 could be

obtained in an overall yield of 34% from tubercidin, this route required seven steps, including three column chromatographic separations, and a shorter route was therefore sought.

Iodination of 2',3'-O-isopropylidene tubercidin with methyl triphenoxyphosphonium iodide yielded a less polar product, presumably the 5'-iodo compound, which could not be isolated in pure form, but which was rapidly converted into the 1,5'-cyclonucleoside salt; the latter, as the tosylate salt, was also obtained by Anzai and Matsui when 2',3'-O-isopropylidene-5'-tosyl-tubercidin was stored at room temperature.[6] Direct 5'-iodination of tubercidin followed by catalytic reduction did produce small amounts of the 5'-deoxy compound **2**, although this method was not considered to be of practical value.

A variety of 5'-deoxynucleosides, including 5'-deoxytoyocamycin and 5'-deoxysangivamycin have been previously synthesized by chlorination using thionyl chloride, followed by reduction with tributyltin hydride.[7] In view of the simplicity of this procedure, together with the reasonably good yields reported, it was evaluated for the synthesis of 5'-deoxytubercidin. Reaction of tubercidin with thionyl chloride in hexamethylphosphoramide overnight at room temperature produced the 5'-chloro compound **3** in 85% yield, a substantial improvement over that previously reported.[8] When the excess reagent was hydrolyzed with water but not neutralized by the addition of base, crystals were obtained and characterized as the 2',3'-cyclic sulfite **4**; the formation of this cyclic intermediate presumably blocks the 2'- and 3'-positions of the molecule and thus accounts for the selectivity of the reaction. Reduction of **3** using tributyltin hydride proceeded well to give 5'-deoxytubercidin in an overall yield of 67% from tubercidin. Other reducing agents appeared to be less satisfactory; lithium triethyl borohydride required approximately 6 days for complete reaction at room temperature, and lithium aluminum hydride produced the 1,5'-cyclonucleoside as a major product.

Since trial experiments on the iodination of **2** using iodine or iodine monochloride did not appear to be promising, iodination was

carried out by the method of Bergstrom et al.[9] which involved a 5-mercuri intermediate. The mercuri salt of **2** was isolated as an amorphous solid, and was investigated by NMR; the absence of C_5-H together with a singlet for C_6-H at δ 7.86 indicated that the mercuri substituent was situated at the C_5 position as was described by Bergstrom and Schweickert for tubercidin.[10] Reaction of the mercuri derivative with iodine in DMF produced the required 5-iodo nucleoside **1** as the major product, which was isolated in 29% yield after column chromatography. ^1H and ^{13}C NMR spectral comparison of this sample of **1** against data reported for the material isolated from natural sources[4] indicated that these samples were indeed identical. The NMR spectrum clearly indicated the presence of a 5-iodo compound since the absence of the C_5-H absorbtion normally observed in the region of δ6.6, together with the C_6-H absorbtion observed as a singlet at δ7.59 is particularly diagnostic for 5-substituted derivatives. The presence of the 5'-deoxy moiety was clearly indicated by the three proton doublet at δ 1.25 as has been observed for a variety of other 5'-deoxy nucleosides. The UV spectrum of **1** was closely similar to that of 5-iodotubercidin, a sample of which was prepared as previously described,[9] and elemental analysis indicated that the compound contained one atom of iodine per molecule.

During the iodination of the 5-mercuri compound it was observed that an additional less polar byproduct, suspected to be the diiodo derivative **5**, was also produced. Trial experiments indicated that this material could also be prepared by direct iodination of the monoiodo compound **1**, but treatment of **2** under the same conditions did not produce any di-iodo compound. The most convenient method for the synthesis of the di-iodo compound was determined to be via treatment of the 5-mercuri derivative of **2** with an excess of iodine in DMF, and under these conditions **5** was obtained in 39% yield. The NMR spectrum of **5** indicated the absence of hydrogens at both C_5 and C_6, thus indicating that iodination had taken place at both these positions.

The 5-bromo analog **6** could be prepared directly from **2**, rather than employing a mercuri derivative as an intermediate, as was

necessary for synthesis of the 5-iodo compound. N-Bromoacetamide (1·1 equiv.) was used as the brominating agent, and trial reactions indicated that dioxane was the preferred solvent. After a reaction time of 1.5h the mixture was purified by column chromatography to give **6** in 56% yield, and small amounts of the dibromo compound were also formed under these conditions. Use of a larger excess of brominating agent substantially increased the proportion of dibromo compound **7** which could be obtained in 37% yield when 3 equiv. of reagent were employed.

The chloro analogs **8** and **9** were prepared by reaction of **2** with N-chlorosuccinimide in THF; the monochloro compound **8** was the major product when one equiv. of reagent was employed, whereas an excess of reagent produced the dichloro compound **9** as the major product. In one reaction a small amount of the 6-chloro compound **10** was produced as a byproduct. Bergstrom and Brattesani have previously reported the preparation of 5-chloro, and 5,6-dichlorotubercidin using the same reagent.[11]

Experimental

5'-Chloro-5'-deoxytubercidin (**3**). Tubercidin (5 g, 18.8 mmol) was added to a stirred 0° solution of thionyl chloride (7.5 mL) in hexamethylphosphoramide (7.5 mL) and the reaction was stirred overnight at room temperature. The solution was evaporated to dryness, and the yellow oil was dissolved in methanol/water (9:1; 100 mL) and adjusted to pH 8.2 with conc. ammonium hydroxide. The solution was stored overnight at 5° and a crystalline precipitate was removed by filtration and rinsed with methanol. The filtrate was impregnated onto silica gel (50 g) and applied to the top of a silica column (500 g) which was packed and eluted with methylene chloride/methanol (10:1). Tubes 185-240 (20 mL fractions) were combined, evaporated to a white solid and recrystallized from water to give **3**, 4.55 g (85%). mp 169-174°, lit.[8] mp 165-167°. UV(H_2O) λ_{max} 204 nm (ε27,400) 269 (11,300). NMR (Me_2SO-d_6) δ 8.06 (s, 1, H-2), 7.31 (d, 1, H-6, $J_{1',2'}$ = 4 Hz), 7.0 (s, 2, NH_2), 6.52 (d, 1, H-5,

J = 4 Hz), 6.10 (d, 1, H-1', J = 6 Hz), 5.6 (m, 2, 2 x OH), 4.46 (m, 1, H-2'), 4.05 (m, 2, H-3', H-4'), 3.84 (m, 2, H-5'). Anal. C 46.62, H 4.60, N 19.84, Cl 12.23. Calcd. for $C_{11}H_{13}ClN_4O_3$: C 46.41, H 4.60, N 19.68, Cl 12.45.

Another reaction (3.76 mmol scale) was carried out under identical conditions except that after overnight treatment with thionyl chloride the reaction was cooled to 0°, crushed ice (25 mL) was added, and the mixture was stirred for 2h. The crystals were collected, washed with ether and dried in vacuo to give **4** as the hydrochloride salt, 665 mg (47%). mp 124-140° (indefinite). Anal. C 34.96, H 3.53, N 15.03, S 8.16, Cl 19.11. Calcd. for $C_{11}H_{11}ClN_4O_3S.HCl.1.5\ H_2O$: C 34.93, H 3.99, N 14.81, S 8.48, Cl 18.75.

5'-Deoxytubercidin (**2**). A solution of **3** (4.46 g, 15.7 mmol) in dry dioxane (300 mL) was treated with 2,2'-azobis (2-methylpropane nitrile) (1.5 g) followed by tri-n-butyltin hydride (16.6 mL, 62.7 mmol), and the reaction was heated under reflux for 3h. Methanol (200 mL) was added to the cooled reaction mixture and the solution was impregnated onto silica gel (50 g). The impregnated silica was applied to the top of a silica column (500 g) which was packed and eluted with methylene chloride/methanol (10:1). Tubes 280-550 (20 mL fractions) were combined, evaporated and recrystallized from water to give **2**, 3.09 g (79%). mp 190°. UV (H_2O) λ_{max} 206 nm (ϵ28,200), 269-70 (11,620). NMR (Me_2SO-d_6) δ 8.05 (s, 1, H-2), 7.25 (d, 1, H-6, $J_{1',2'}$ = 4 Hz) 6.95 (brs, 2, NH_2), 6.60 (d, 1, H-5, J = 4 Hz) 6.01 (d, 1, H-1', J = 5 Hz), 5.24 (d, 1, OH), 5.02 (d, 1, OH) 4.35 (m, 1, H-2'), 3.86 (m, 2, H-3', H-4') 1.27 (d, 3, H-5', J = 6 Hz). Anal. C 52.83, H 5.72, N 22.40. Calcd. for $C_{11}H_{14}N_4O_3$: C 52.79, H 5.64, N 22.39.

5'-Deoxy-5-iodotubercidin (**1**). A stirred solution of 5'-deoxytubercidin (**2**, 1.78 g, 7.11 mmol) and sodium acetate (2.9 g, 21.4 mmol) in water (175 mL) was heated to 65° under a nitrogen atmosphere. A solution of mercuric acetate (2.27 g, 7.12 mmol) in

water (50 mL) was added dropwise during a ten minute period, and the solution was stirred at 65° for an additional 4h. The mixture was cooled, and adjusted to pH 7.2 with N ammonium hydroxide. The orange precipitate was collected, washed with water (2 x 50 mL), methanol (2 x 50 mL) and finally ether (2 x 50 mL), and dried in vacuo to give the crude mercuri derivative of **2**, 2.85 g (85%).

A suspension of the mercuri derivative (2.63 g, 5.56 mmol) in DMF (25 mL) was treated with iodine (1.7 g) for 6h at room temperature. The solution was evaporated to an oil, extracted with methanol (3 x 50 mL) and the combined extracts were impregnated onto silica (40 g). The impregnated silica was applied to the top of a silica column (500g) which was eluted with methylene chloride/methanol (10:1). Tubes 201-355 (22 mL fractions) were combined, evaporated to dryness and recrystallized from methanol to give **1**, 0.61 g (29%). mp 230-232°. UV (H_2O) λ_{max}205 nm (ε21,000) 283 (8,200); in 0.1N HCl λ_{max}203 nm (ε19,450), 240 (18,850), 287 (8,000); in 0.1N KOH λ_{max}282 nm (ε8,400). Mass spectrum, m/e 377, 376 (M^+) 303,289,261,260,233. NMR (Me_2SO-d_6) δ 8.13 (s, 1, H-2), 7.62 (s, 1, H-6), 6.68 (s, 2, NH_2), 6.00 (d, 1, H-1', $J_{1',2'}$= 5 Hz), 5.33 (d, 1, OH), 5.10 (d, 1, OH), 4.40 (m, 1, H-2'), 3.88 (m, 2, H-3', H-4'), 1.28 (d, 3, H-5', J = 6 Hz). ^{13}C NMR (Me_2SO-d_6) 157.07 (s, C-4), 151.97 (d, C-2), 150.23 (s, C-8), 126.80 (d, C-6), 103.03 (s, C-9), 86.86 (d, C-1'), 79.17, 74.45, 73.28 (d, C-2', C-3', C-4'), 52.19 (s, C-5), 18.99 (q, C-5'). Anal: C 35.30, H 3.17, N 15.09, I 33.67. Calcd. for $C_{11}H_{13}IN_4O_3$: C 35.12, H 3.48, N 14.90, I 33.74.

5'-Deoxy-5,6-diiodotubercidin (5). A portion of the crude mercuri salt of **2** (2.36 g, 4.98 mmol) was suspended in dry DMF (50 mL), treated with a solution of iodine (6.35 g, 25 mmol) in dry DMF (50 mL), and stirred at room temperature. After 4 h the mixture was evaporated to an oil, dissolved in methanol (300 mL) and treated with a saturated aqueous solution (15 mL) of sodium thiosulfate to discharge the iodine. This solution was impregnated onto silica (60g), and applied to the top of a silica column (600g). The column was eluted with ethyl acetate, and tubes 52-110 (20 mL fractions)

were combined, evaporated to dryness. The residue was dissolved in hot methanol, and crystals were deposited on cooling. The crystals were collected and dried in vacuo to give the di-iodo compound **5**, 473 mg. Fractions 116-200 were combined, evaporated to an oil, triturated with boiling methanol (50 mL) and on storage overnight crystals were deposited. The crystals were collected and dried in vacuo to give additional **5**, 509 mg. Total yield 39%. mp 199° (decomp). UV (MeOH) λ_{max} 204 nm (ε26,550), 224 (21,200), 288 (12,580). NMR (Me_2SO-d_6) δ 8.06 (s, 1H, H-2), 6.73 (s, 2H, NH_2), 5.90 (d, 1H, H-1', $J_{1',2'}$ = 4 Hz), 5.23 and 4.97 (2d, 2H, 2'OH, and 3'OH), 5.08 (m, 1H, H-2'), 4.13 (m, 1H, H-3'), 3.84 (m, 1H, H-4'), 3.15 (s, CH_3OH), 1.27 (d, 3H, H-5'). Anal: C 26.74, H, 2.87, N 10.22, I 48.12. Calcd. for $C_{11}H_{12}I_2N_4O_3 \cdot 0.75\ CH_3OH$: C 26.83, H, 2.87, N 10.65, I 48.25.

5-Bromo-5'-deoxytubercidin (**6**). A solution of the hydrochloride of **2** (574 mg, 2 mmol) in dioxane (100 mL, dried over 4A molecular sieve) was treated with N-bromoacetamide (303 mg, 2.2 mmol) for 1.5h at room temperature, and the solution was then poured onto a silica column (50 g) which had been packed in ethyl acetate. The column was eluted with ethyl acetate (600 mL) followed by ethyl acetate/methanol (10:1, 100 mL) and fractions of 15 mL were collected. Tubes 10-46 were pooled, evaporated to dryness, and the residue was crystallized from methanol with charcoal treatment. Recrystallization from methanol yielded pure **6** (103 mg), and a second crop (140 mg) could be obtained from water. A third crop could be obtained by repeated recrystallization of the residues. Total yield 371 mg (56%). mp 245-247° (decomp.). UV (MeOH) λ_{max} 209 nm (ε24,400), 279-281 (10,000). NMR (Me_2SO-d_6) δ 8.11 (s, 1H, H-2), 7.58 (s, 1H, H-6), 6.74 (s, 2H, NH_2), 6.01 (d, 1H, H-1', $J_{1',2'}$ = 5 Hz), 5.29 and 5.06 (2d, 2H, 2'-OH and 3'-OH), 4.38 (m, 1H, H-2'), 3.89 (m, 2H, H-3', H-4'), 1.27 (d, 3H, H-5'). Anal. C 39.96, H 3.97, N 17.10, Br 24.30. Calcd. for $C_{11}H_{13}BrN_4O_3$: C 40.14, H 3.98, N 17.02, Br 24.28.

5'-Deoxy-5,6-dibromotubercidin (7). A solution of 2 (1 g, 4 mmol) and N-bromoacetamide (1.72 g, 12.3 mmol) in dioxane (200 mL, dry) was heated with stirring under reflux for 20 min and then cooled to room temperature. The dark brown solution was impregnated onto silica (15g) and applied to a silica column (125g). The column was eluted with ethyl acetate (2.4 L) followed by ethyl acetate/acetic acid (100:1, 1 L) and then ethyl acetate/methanol/acetic acid (100:10:1, 1L). Tubes 51-130 (19 mL fractions) were evaporated and recrystallized twice from ethanol to give **6**, 76 mg. The combined liquors were evaporated and crystallized from ethanol/water (1:1, 25mL) to give additional material (366 mg). Tubes 131-205 were combined, evaporated and triturated with water to give a brown solid, which was crystallized from ethanol/water (1:1, 45 mL) with charcoal treatment to give a third crop, 123 mg. The three crops of crystals were combined and recrystallized from ethanol/water (1:1, 60 mL) to give pure **7**, 613 mg (38%). mp 209°. UV (MeOH) λ_{max} 217 nm (ε16,210), 283 (9,680). NMR (Me_2SO-d_6) δ 8.13 (s, 1H, H-2), 7.38 (s, 2H, NH_2) 5.93 (d, 1H, H-1', $J_{1',2'}$ = 4 Hz), 5.30 and 5.07 (2d, 2H, H-2' and H-3'), 4.98 (m, 1H, H-2'), 4.10 (m, 1H, H-3'), 3.85 (m, 1H, H-4') 1.28 (d, 3H, H-5'). Anal. C 31.87, H 3.07, N 13.34, Br 38.30. Calcd. for $C_{11}H_{12}Br_2N_4O_3 \cdot 0.5\ H_2O$: C 31.68, H 3.14, N 13.43, Br 38.32.

5-Chloro-5'-deoxytubercidin (8). A solution of 2 (1.0 g, 4 mmol) and N-chlorosuccinimide (534 mg, 4 mmol, recrystallized) in tetrahydrofuran (100 mL, dried over 4A molecular sieve) was heated under reflux for 2h. A small amount of crystalline material was removed by filtration, and the filtrate was impregnated onto silica gel (10 g), and applied to the top of a silica column (130 g) which had been packed in methylene chloride-methanol (10:1). The column was eluted with the same solvent, and 15 mL fractions were collected. Fractions 23-60 were combined, evaporated to dryness, impregnated onto silica (10 g) and applied to a second silica column (250 g) which was eluted with ethyl acetate-methanol (25:1). Tubes 80-200 (24 mL fractions) were combined, evaporated and crystallized from

water (250 mL) to give **8**, 0.47 g, (41%). mp 239° (decomp.). UV (MeOH) λ_{max} 207 nm (ε26,590), 279-280 (10,180). NMR (Me_2SO-d_6) δ 8.11 (s, 1H, H-2), 7.52 (s, 1H, H-6), 6.82 (s, 2H, NH_2), 6.03 (d, 1H, H-1', $J_{1',2'}$ = 5 Hz), 5.29 and 5.06 (2d, 2H, 2'-OH and 3'-OH), 4.37 (m, 1H, H-2'), 3.88 (m, 2H, H-3', H-4'), 1.27 (d, 3H, H-5'). Anal. C 46.32, H 4.66, N 19.58, Cl 12.52. Calcd. for $C_{11}H_{13}ClN_4O_3$: C 46.41, H 4.60, N 19.68, Cl 12.45. Earlier fractions were evaporated to an oil which crystallized on trituration with ethyl acetate to give the 6-chloro compound **10** (25 mg). mp 198-199°. UV (MeOH) λ_{max} 209 nm (ε28,250), 270-1 (15,200). NMR (Me_2SO-d_6) δ 8.11 (s, 1, H-2), 7.15 (s, 2, NH_2), 6.70 (s, 1, H-5), 5.88 (d, 1, H-1', $J_{1',2'}$ = 6 Hz) 5.30 (d, 1, OH), 5.04 (d, 1, OH), 4.09 (m, 1, H-3'), 3.84 (m, 1, H-4'), 1.27 (d, 3, H-5', J = 6 Hz). Anal. C 46.35, H 4.78, N 19.56, Cl 12.16. Calcd. for $C_{11}H_{13}ClN_4O_3$: C 46.40, H 4.60, N 19.68, Cl 12.45.

5'-Deoxy-5,6-dichlorotubercidin (**9**). A suspension of **2** (1.5 g, 6 mmol) and N-chlorosuccinimide (800 mg, 6 mmol) in tetrahydrofuran (150 mL, dry) was heated under reflux. After 1h additional N-chlorosuccinimide (800 mg, 6 mmol) was added, and the solution was heated under reflux for an additional 2h, cooled, filtered through celite, and evaporated to dryness. The residue was dissolved in boiling ethanol (50 mL), and the solution was treated with charcoal, filtered through celite, and on cooling crystals were deposited. Recrystallization from ethanol (35 mL) gave pure **9**, 474 mg. The combined liquors were impregnated onto silica (15 g) and applied to a silica column (100 g). The column was eluted with ethyl acetate, and tubes 6-100 (22 mL fractions) were pooled, evaporated to dryness and recrystallized twice from ethanol to give additional **9**, total yield 0.884 g (46%). mp 202-204°. UV (MeOH) λ_{max} 213-214 nm (ε23,700), 279-280 (11,900). NMR (Me_2SO-d_6) δ 8.16 (s, 1H, H-2), 7.04 (s, 2H, NH_2), 5.94 (d, 1H, H-1', $J_{1',2'}$ = 5 Hz), 5.36 and 5.08 (2d, 2H, 2'-OH and 3'-OH), 4.94 (m, 1H, H-2'), 4.05 (m, 1H, H-3'), 3.87 (m, 1H, H-4'), 1.27 (d, 3H, H-5'). Anal. C 41.33, H 3.45, N 17.09, Cl 22.31. Calcd. for $C_{11}H_{12}Cl_2N_4O_3$: C 41.40, H 3.79, N 17.56, Cl 22.22.

Acknowledgment: We wish to thank Dr. E. Lee and associates, Biotechnology Process Research and Development Department, Hoffmann-La Roche Inc. for preparing a supply of tubercidin, the Physical Chemistry Department, Hoffmann-La Roche Inc. for providing spectral data, and Dr. F. Scheidl and associates for providing microanalyses.

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Received May 21, 1984