the product obtained by method A.

***cis*-6-[2-[(2-Hydroxyethyl)thio]vinyl]uracil (6a).** Compound **3** (82 mg, 0.60 mmol) was dissolved in hot H_2O (8 mL) and cooled to room temperature prior to the addition of 2-mercaptoethanol (0.042 mL, 0.60 mmol). The solution was stirred for 24 h at room temperature, additional 2-mercaptoethanol (0.01 mL) was added, and the mixture was stirred overnight. The precipitate was removed by centrifugation, washed with H_2O (2.5 mL), and dried. The light tan powder (99 mg, 77%) obtained was shown by NMR to consist of a mixture of cis/trans isomers approximately 5:1, mp 235–239 °C. Crystallization and recrystallization of 61 mg of the solid from hot H_2O yielded analytically pure **6a** (37 mg) as fine, light yellow needles: mp 245–246 °C; NMR (Me_2SO-d_6) δ 2.99 (t, 2, CH_2S, J = 6.0 Hz), 3.61 (q, 2, CH_2OH, J = 5.7 Hz), 4.93 (t, 1, OH, J = 5.3 Hz), 5.58 (s, 1, C_5 H), 5.92 (d, 1, vinylic CH, J = 11.1 Hz), 7.17 (d, 1, vinylic CH, J = 11.1 Hz), 10.67 and 10.86 (m, 2, NH). The quartet at δ 3.61 collapses to a triplet (J = 6.0 Hz) after D_2O exchange: UV (pH 7.5) λ_{max} 325 nm (ϵ 13 000), 291 (ϵ 9300); MS, m/e 214 (13, M^+), 169 (84), 126 (100), 98 (44). Anal. ($C_8H_{10}N_2O_3S$) C, H, N, S.

The combined supernatant and washings remaining after initial removal of the isomers was lyophilized, dissolved in MeOH, and concentrated to give a yellow solid (23 mg). By NMR, this material was indicated to consist of approximately a 1:1:1 mixture of the cis isomer (**6a**), trans isomer, and oxidized 2-mercaptoethanol: NMR (Me_2SO-d_6, trans isomer) δ 2.87 (m, CH_2S), 3.58 (m, CH_2OH), 4.80 (br m, OH), 5.42 (s, C_5 H), 6.00 (d, vinylic CH, J = 15.7 Hz), 7.61 (d, vinylic CH, J = 15.7 Hz), 10.72 (br m, NH).

Cysteine-6-Ethynyluracil Addition Product. L-Cysteine hydrochloride hydrate (113 mg, 0.64 mmol) was dissolved in H_2O (0.4 mL), neutralized with 1 N NaOH, and added to a solution of **3** (73 mg, 0.54 mmol) in H_2O (7 mL) at room temperature. The flask was flushed with N_2, and the mixture was stirred at room temperature overnight. TLC of the ensuing supernatant showed the absence of **3**. The precipitate was removed by centrifugation, washed with a 2.5- and a 1.5-mL aliquot of H_2O, and dried to give a light tan solid (113 mg), which appeared as a single spot on TLC (B). NMR indicated the presence of cis and trans isomers: NMR (Me_2SO-d_6) δ 5.50 (s, C_5 H, trans), 5.65 (s, C_5 H, cis), 5.98 (d, vinylic CH, cis, J = 11.2 Hz), 6.14 (d, vinylic CH, trans, J = 16.0 Hz), 7.25 (d, vinylic CH, cis, J = 11.2 Hz), 7.71 (d, vinylic CH, trans, J = 16.0 Hz); UV (pH 7.5) λ_{max} 321 nm, 290 (sh).

Biological Assay Procedures. Evaluation of the effect of the agents on the growth of leukemia L1210 was carried out by previously described procedures.[10] B-16 melanoma and lewis lung carcinoma were grown in monolayer cultures in RPMI 1640 medium containing 5% heat-inactivated calf serum and 20 mM Hepes buffer. The initial innoculum of 2.5×10^4 cells was incubated at 37 °C for 1 day before addition of drug, at which time the number of cells had approximately doubled. After 3 days of further incubation, the growth medium was poured off, the cells were rinsed twice with saline, and protein was determined by the Lowry procedure.[11] The lewis lung carcinoma cells were scraped from the disks with a rubber policeman and washed twice with saline with centrifugation for 3 min at 1500 rpm, and Lowry protein determinations were performed on the washed pellets.

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Synthesis of 4-Amino-1-β-D-ribofuranosyl-1*H*-pyrrolo[2,3-*b*]pyridine (1-Deazatubercidin) as a Potential Antitumor Agent

Ippolito Antonini, Francesco Claudi, Gloria Cristalli, Palmarisa Franchetti, Mario Grifantini,* and Sante Martelli

Institute of Pharmaceutical and Organic Chemistry, University of Camerino, 62032 Camerino, Italy.
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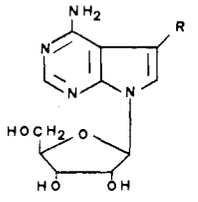
The synthesis of 4-amino-1-β-D-ribofuranosyl-1*H*-pyrrolo[2,3-*b*]pyridine, a deaza analogue of the antitumor antibiotic tubercidin, starting from 1*H*-pyrrolo[2,3-*b*]pyridine (7-azaindole), is described. It was evaluated against L1210 and S-180 cells in culture and found to be inactive.

Several natural nucleosides produced by different streptomyces species are derivatives of pyrrolo[2,3-*d*]pyrimidine. Among these, tubercidin (7-deazaadenosine) (**1a**), toyocamycin (**1b**), and sangivamycin (**1c**) have been



1 a: R = H
b: R = CN
c: R = $CONH_2$

particularly studied.[1,2] Biological tests performed with such compounds have pointed out their antitumor, antibacterical, and antiviral activities. On the other hand, much effort has been made to synthesize deaza-, dideaza-, and trideazaadenosine analogues as potential chemotherapeutic agents.[3-7]

In this paper we report the synthesis of 1,7-dideazaadenosine (1-deazatubercidin; **15**), the first example of dideazaadenosine containing only one nitrogen atom in each of the two heterocyclic rings.

Chemistry. The synthesis of 4-amino-1-β-ribofuranosyl-1*H*-pyrrolo[2,3-*b*]pyridine was carried out by the sequence shown in the Scheme I.

4-Amino-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine (**8**), a key intermediate in our synthesis, was prepared by hy-

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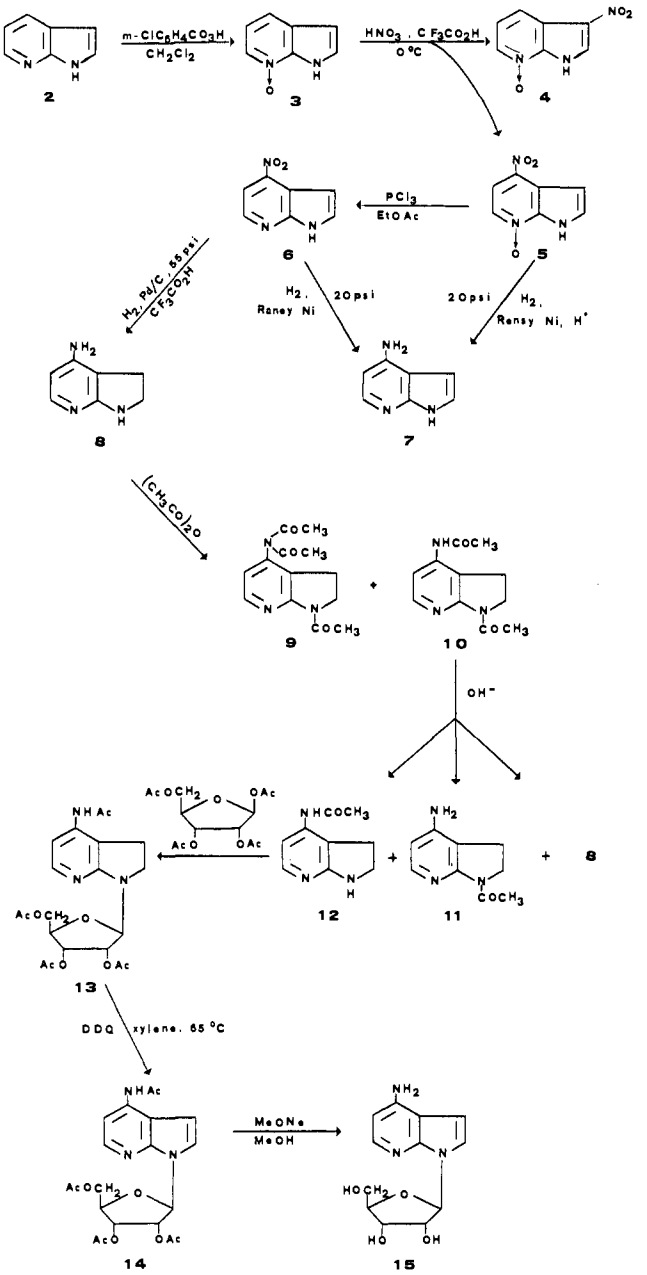
Scheme I



drogenation of 4-nitro-1*H*-pyrrolo[2,3-*b*]pyridine (**6**) in trifluoroacetic acid at 55 psi with 10% palladium on charcoal as catalyst. We found that by such a method the double bond at the 2,3-position of 1*H*-pyrrolo[2,3-*b*]-pyridine derivatives may be easily reduced, whereas methods previously described require hydrogenation under high pressure.[8,9]

Synthesis of **6** was performed in three steps, starting from 1*H*-pyrrolo[2,3-*b*]pyridine (**2**), as shown in Scheme I. Oxidation of **2** with *m*-chloroperbenzoic acid in dichloromethane solution readily gave the *N*-oxide derivative **3**, already described in the literature.[10]

Nitration of **3** with HNO_3 in trifluoroacetic acid at 0 °C gave the 4-nitro-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (**5**), together with a small amount of the 3-nitro isomer **4**. A more complex synthesis of **5** was recently reported by Schneller and Luo starting from 1*H*-pyrrolo[2,3-*b*]-pyridine-3-carbonitrile.[11] In their paper, the authors reported that the nitration of **3** with HNO_3 in sulfuric acid at 0 °C gave exclusively the 3-nitro isomer **4**. This result indicates that under such conditions the directive influence of the pyrrole ring nitrogen on the electrophilic substitution exceeds that of the *N*-oxide. The different orientation of the electrophile in the nitration of **3** in sulfuric or in trifluoroacetic acid may be rationalized by considering that sulfuric acid may protonate to a greater extent the *N*-oxide function; in this way, the pyridine ring is deactivated in comparison with the pyrrole ring.

By deoxygenation of the nitro *N*-oxide **5** with PCl_3 in ethyl acetate, compound **6** was obtained in high yield. The hydrogenation of **5** or **6** with Raney nickel in methanol and acetic acid at 20 psi gave the 4-amino-1*H*-pyrrolo[2,3-*b*]-pyridine (**7**) as a solid, whose picrate was identical with that described by Schneller and Luo.[11]

Several attempts to obtain **15** by direct glycosylation of **7** failed. For this reason, the alternative route shown in Scheme I, starting from the 2,3-dihydro derivative **8**, was followed.[6,12] Acetylation of **8** with acetic anhydride gave a mixture of triacetyl and diacetyl derivatives, which were separated by silica gel chromatography. Partial hydrolysis of **10** with diluted NaOH in ethanol gave a mixture of the compounds **8**, **11**, and **12**, which were separated by silica gel chromatography. The structure of the two monoacetyl isomers **11** and **12** was assigned on the basis of the IR and NMR spectra. In fact the infrared spectrum of **12** showed a C=O absorption shifted to higher frequency (1697 vs. 1635 cm^{-1}); on the other hand, the NMR signals in deuterated dimethyl sulfoxide for hydrogens exchangeable by D_2O treatment included a NH_2 singlet at δ 5.98 for compound **11** and two NH singlets at δ 6.06 and 9.67 for compound **12**.

The 4-*N*-acetyl derivative **12** was then treated with tetra-*O*-acetyl-β-D-ribofuranose in the presence of a catalytic amount of *p*-toluenesulfonic acid at 135 °C in vacuo for 40 min. Crude 1-β-D-ribofuranosyl derivative **13** was purified by silica gel chromatography. Oxidation of **13** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in boiling xylene produced the ribofuranosyl derivative **14**. The acyl blocking groups in **14** were catalytically removed with sodium methoxide in methanol, giving the desired 4-amino-1-β-D-ribofuranosyl-1*H*-pyrrolo[2,3-*b*]pyridine (**15**). The ultraviolet spectrum of compound **15**, showing absorption maxima at 229, 273, 293, and 301 nm, was very similar to that of the 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine; on the other hand, it was very different from the spectrum of 7-methyl-1*H*-pyrrolo[2,3-*b*]pyridine.[13] These data confirm that compound **12** has been ribosylated on N-1 and not on N-7. The reaction of the nucleoside **15** with acetone and *p*-toluenesulfonic acid gave to corresponding 2′,3′-*O*-isopropylidene derivative **16**. Its ^1H NMR spectrum in Me_2SO-d_6 shows a difference of 0.23 ppm between the chemical shift of the two methyl signals of the isopropylidene group. This value is characteristic of the β configuration according to the "isopropylidene rule".[14]

Biological Evaluation. Compound **15** was tested against murine leukemia L1210 and murine sarcoma S-180 cells in culture as described by Lin et al.[15] Murine L1210

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cells were maintained as a suspension culture in Fisher's medium supplemented with 10% horse serum at 37 °C in a humidified atmosphere of 5% CO_2–95% air. Under these conditions, the generation time for L1210 cells is approximately 18 h. Murine sarcoma 180 cells were processed in the same way, and their generation time is approximately 16 h. Compound **15** was added to L1210 and to sarcoma 180 cells ($\sim 10^{-4}$ cells/mL) at concentrations ranging between 1×10^{-7} to 1×10^{-4} M. The increase in cell number of the drug-free culture (control), as well as that of cultures supplemented with the tested compound, was determined after 24, 48, and 72 h of growth. The cell growth in the presence of the nucleoside **15** did not differ from that of the control. This result suggests that the nitrogen atom at position 1 of the pyrimidine ring of tubercidin is important for antitumor activity.

Experimental Section

Melting points were determined with a Büchi apparatus and are uncorrected. NMR spectra were obtained with a Varian EM-390 90-MHz spectrometer, with tetramethylsilane as internal standard. IR spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. UV spectra were obtained with a Perkin-Elmer Model 575 spectrophotometer. TLC were carried out on precoated TLC plates with silica gel 60 F-254 (Merck). For column chromatography, silica gel 60 (Merck) was used. Microanalytical results are indicated by atomic symbols and are within ±0.4% of theoretical values. 1*H*-Pyrrolo[2,3-*b*]pyridine was purchased from Aldrich Chemical Co. (European Division).

1*H*-Pyrrolo[2,3-*b*]pyridine 7-Oxide (3). 1*H*-Pyrrolo[2,3-*b*]pyridine (**2**; 20 g, 0.169 mol) in 150 mL of CH_2Cl_2 was added dropwise to a cooled solution of *m*-chloroperbenzoic acid (60 g, 0.34 mol) in 600 mL of CH_2Cl_2. The mixture was allowed to warm slowly to room temperature. After 6 h the reaction mixture was filtered, and the filtrate was evaporated in vacuo. The residue was neutralized with saturated K_2CO_3 solution and then extracted continuously with chloroform. The extract was dried over Na_2SO_4 and evaporated in vacuo. The crude compound was crystallized from benzene to give 15.5 g of **3** (60%): mp 138–139 °C (lit.[10] mp 134–135 °C; lit.[11] mp 101–103 °C).

4-Nitro-1*H*-pyrrolo[2,3-*b*]pyridine 7-Oxide (5) and 3-Nitro-1*H*-pyrrolo[2,3-*b*]pyridine 7-Oxide (4). To a stirred and ice-cooled solution of compound **3** (6.3 g, 0.047 mol) in 50 mL of trifluoroacetic acid was added 22 mL of fuming nitric acid. As soon as addition of the nitric acid was completed, the mixture was rapidly poured into ice, and 110 mL of 12 N NaOH was added dropwise to obtain a yellow precipitate. The reaction mixture was allowed to stand for 30 min at room temperature, and then the solid was filtered, washed with cold water, and dried in vacuo to yield 6.5 g of a mixture of **4** and **5**. Recrystallization from water gave 5 g (60%) of compound **5**: mp 229–230 °C dec; ^{1}H NMR (Me_2SO) δ 7.04 (1 H, d, J = 3 Hz, 3-H), 7.82 (1 H, d, J = 3 Hz, 2-H), 8.02 (1 H, d, J = 6 Hz, 5-H), 8.31 (1 H, d, J = 6 Hz, 6-H), 13.47 (1 H, large s, 1-H). Anal. ($C_7H_5N_3O_3$) C, H, N.

The mother liquor was evaporated, and the residue was chromatographed on a silica gel column eluting with EtOAc–MeOH (7:3) to yield 1 g (12%) of **4**, which was recrystallized from water: mp >340 °C (this melting point is very different from that reported by Schneller and Luo,[11] mp 276–277.5 °C); ^{1}H NMR (Me_2SO) δ 7.22 (1 H, t, $J_{4,5}$ = 8 Hz, $J_{5,6}$ = 7 Hz, 5-H), 8.04 (1 H, d, 4-H), 8.28 (2 H, overlapped signals, 2-H and 6-H). Anal. ($C_7H_5N_3O_3$) C, H, N.

4-Nitro-1*H*-pyrrolo[2,3-*b*]pyridine (6). To 5 g (0.028 mol) of **5** in 100 mL of EtOAc was added 20 mL of PCl_3. The reaction mixture was allowed to boil for a few minutes, then was cooled to 0 °C, and carefully neutralized with saturated Na_2CO_3 solution. The mixture was extracted several times with EtOAc, and the combined extracts were dried (Na_2SO_4) and evaporated under vacuum. The residue was crystallized from water to give 3.7 g (80%) of **6**: mp 109–110 °C; ^{1}H NMR (Me_2SO) δ 7.04 (1 H, d, J = 3 Hz, 3-H), 7.96 (2 H, m, 2-H and 5-H), 8.55 (1 H, d, J = 5 Hz, 6-H). Anal. ($C_7H_5N_3O_2$) C, H, N.

4-Amino-1*H*-pyrrolo[2,3-*b*]pyridine (7). Method A. A mixture of 0.5 g (2.85 mmol) of **5** in 20 mL of MeOH, 1 g of Raney nickel (washed with water), and 0.3 mL of glacial acetic acid was shaken with hydrogen at 20 psi for 2 h. The catalyst was removed, the filtrate was evaporated, and the residue was neutralized with 2 N NaOH. The aqueous solution was extracted several times with EtOAc, and the organic layers were collected, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica gel column; elution with EtOAc–MeOH (6:4) gave a solid, which was crystallized from benzene to yield 190 mg (50%) of **7**, mp 134–136 °C.

Method B. A mixture of 0.5 g (3.06 mmol) of **6** in 20 mL of MeOH, 1 g of Raney nickel (washed with water), and 0.3 mL of glacial acetic acid was stirred with hydrogen at 20 psi for 1 h. After the catalyst was removed, the filtrate was evaporated, neutralized with 2 N NaOH, and extracted with EtOAc as above. The organic phase was dried (Na_2SO_4) and evaporated to give a residue, which was chromatographed on a silica gel column. Elution with $CHCl_3$–MeOH–NH_3 (90:8:2) yielded 0.38 g (93%) of **7** as a pure solid: mp 134–136 °C; ^{1}H NMR (Me_2SO) δ 6.03 (2 H, s, 4-NH_2), 6.14 (1 H, d, J = 5 Hz, 5-H), 6.5 (1 H, d, J = 3 Hz, 3-H), 7.05 (1 H, d, J = 3 Hz, 2-H), 7.75 (1 H, d, J = 5 Hz, 6-H), 11.13 (1 H, large s, 1-H); UV (C_2H_5OH) λ_{max} 226 nm (log ϵ 4.45), 272 (3.93), 290 (3.99), 298 (3.93). Anal. ($C_7H_7N_3$) C, H, N.

4-Amino-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine (8). To a solution of 7.5 g (0.044 mol) of **6** in 140 mL of trifluoroacetic acid was added 5 g of 10% Pd/C, and the mixture was shaken with hydrogen at 55 psi for 5 h. The catalyst was removed by filtration, the filtrate was evaporated, and the residue was made basic with 12 N NaOH. The solution was extracted several times with EtOAc, and then the combined extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on a silica gel column eluting with EtOAc–MeOH–NH_3 (85:12:3). Crude compound **8** (5.7 g) was crystallized from EtOAc (5 g, 84%): mp 146–147 °C; ^{1}H NMR (Me_2SO) δ 2.72 (2 H, t, J = 8 Hz, 3-H), 3.37 (2 H, t, J = 8 Hz, 2-H), 4–5 (1 H, large s, 1-H), 5.4 (2 H, s, 4-NH_2), 5.84 (1 H, d, J = 5.5 Hz, 5-H), 7.36 (1 H, d, J = 5.5 Hz, 6-H); UV (C_2H_5OH) λ_{max} 228 nm (log ϵ 4.52), 286 (3.72). Anal. ($C_7H_9N_3$) C, H, N.

1-Acetyl-4-(diacetylamino)-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine (9) and 1-Acetyl-4-(acetylamino)-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine (10). A mixture of 2.4 g (17.7 mmol) of **8** and 30 mL of acetic anhydride was heated under reflux for 30 min. After the solvent was removed, the resulting solid was neutralized with saturated Na_2CO_3 solution and extracted several times with EtOAc. The extracts were dried (Na_2SO_4) and evaporated, and the residue was chromatographed on a silica gel column eluting with EtOAc–MeOH (9:1) to give 850 mg (3.16 mmol) of **9** and 2.4 g (10.9 mmol) of **10**: total yield 80%. Analytical samples, from absolute ethanol, of **9** and **10** had mp 116–117 and 204–206 °C, respectively. **9**: ^{1}H NMR (Me_2SO) δ 2.25 (6 H, s, 2 CH_3), 2.59 (3 H, s, CH_3), 2.88 (2 H, t, J = 8 Hz, 3-H), 4.00 (2 H, t, J = 8 Hz, 2-H), 7.02 (1 H, d, J = 6 Hz, 5-H), 8.23 (1 H, d, J = 6 Hz, 6-H). Anal. ($C_{13}H_{15}N_3O_3$) C, H, N. **10**: ^{1}H NMR (Me_2SO) δ 2.13 (3 H, s, CH_3), 2.53 (3 H, s, CH_3), 2.99 (2 H, t, J = 8 Hz, 3-H), 3.97 (2 H, t, J = 8 Hz, 2-H), 7.58 (1 H, d, J = 6 Hz, 5-H), 8.01 (1 H, d, J = 6 Hz, 6-H). Anal. ($C_{11}H_{13}N_3O_2$) C, H, N.

1-Acetyl-4-amino-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine (11) and 4-(Acetylamino)-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]-pyridine (12). To a solution of 6.9 g (31.48 mmol) of **10** in 130 mL of EtOH was added 50 mL of 2 N NaOH. The reaction mixture was stirred for 13 h at room temperature and then extracted with EtOAc (250 mL × 3). The extracts were processed in the usual manner, and the residue was chromatographed on a silica gel column. Elution with EtOAc–MeOH–NH_3 (85:14:1) yielded 1 g (18%) of **11** (R_f 0.71), 1.7 g (30.5%) of **12** (R_f 0.45), and 1.6 g (37.5%) of **8** (R_f 0.29). Analytical samples, from EtOAc, of **11** and **12** had mp 187–188 and 190–191 °C, respectively. **11**: ^{1}H NMR (Me_2SO) δ 2.51 (3 H, s, CH_3), 2.75 (2 H, t, J = 8 Hz, 3-H), 3.92 (2 H, t, J = 8 Hz, 2-H), 5.98 (2 H, s, 4-NH_2), 6.25 (1 H, d, J = 6 Hz, 5-H), 7.61 (1 H, d, J = 6 Hz, 6-H); IR ν_{max} 3468, 3410, 3340, 3240 (NH_2), 1635 (C=O) cm^{-1}. Anal. ($C_9H_{11}N_3O$) C, H, N. **12**: ^{1}H NMR (Me_2SO) δ 2.12 (3 H, s, CH_3), 2.97 (2 H, t, J = 8 Hz, 3-H), 3.5 (2 H, t, J = 8 Hz, 2-H), 6.06 (1 H, s, 4-NH),

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7.02 (1 H, d, J = 6 Hz, 5-H), 7.66 (1 H, d, J = 6 Hz, 6-H), 9.67 (1 H, s, 1-H); IR ν_{max} 3410, 3245, 3170, 3100 (NHCOCH$_3$, NH) 1697 (C=O) cm^{-1}. Anal. ($C_9H_{11}N_3O$) C, H, N.

4-(Acetylamino)-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine (13). An intimate mixture of **12** (0.9 g, 5 mmol), 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (3.2 g, 10 mmol), and *p*-toluenesulfonic acid (50 mg) was heated at 135 °C with stirring in vacuo (25 mm) for 40 min. The resulting solid was neutralized with saturated K_2CO_3 solution and extracted with chloroform (150 mL × 3). The residue of the chloroform layer concentration was chromatographed on a silica gel column eluting with EtOAc–MeOH (95:5) to give 0.6 g (28%) of **13** (R_f 0.58) and 0.55 g (50%) of **10** (R_f 0.38): ^{1}H NMR ($CDCl_3$) δ 2.06, 2.08, 2.1, and 2.17 (12 H, 4 s, four CH_3), 2.93 (2 H, m, 3-H), 3.7 (2 H, m, 2-H), 4.22 (3 H, s, 4′-H and 5′-CH_2), 5.2–5.5 (2 H, m, 3′-H and 2′-H), 6.15 (1 H, d, J = 7 Hz, 1′-H), 7.24 (2 H, m, 5-H and 4-NH), 7.91 (1 H, d, J = 6 Hz, 6-H). Anal. ($C_{20}H_{25}N_3O_8$) C, H, N.

4-(Acetylamino)-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-1*H*-pyrrolo[2,3-*b*]pyridine (14). A mixture of 0.7 g (1.6 mmol) of **13**, dissolved in 35 mL of dry xylene, and 0.36 g (1.6 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was heated under reflux for 1.5 h and then cooled to room temperature. The solid was removed and washed three times with EtOAc, and the filtrate was concentrated. The residue was chromatographed on a silica gel column eluting with EtOAc to give 250 mg (35%) of **14** (R_f 0.54): ^{1}H NMR ($CDCl_3$) δ 2.00, 2.07, 2.1, and 2.21 (12 H, 4 s, 4 CH_3), 4.35 (3 H, s, 4′-H and 5′-CH_2), 5.57 (1 H, m, 3′-H), 5.78 (1 H, m, 2′-H), 6.58 (2 H, m, 1′-H and 3-H), 7.25 (1 H, d, J = 3 Hz, 2-H), 7.92 (1 H, d, J = 5 Hz, 5-H), 8.23 (1 H, d, J = 5 Hz, 6-H), 8.39 (1 H, s, 4-NH). Anal. ($C_{20}H_{23}N_3O_8$) C, H, N.

4-Amino-1-β-D-ribofuranosyl-1*H*-pyrrolo[2,3-*b*]pyridine (15). A mixture of 140 mg (0.323 mmol) of **15**, 10 mL of methanol, and 3 mL of 1 N methanolic sodium methoxide solution was refluxed for 2 h. The solution was cooled and neutralized with IRC 50 (H^+ form). The resin was removed by filtration, and the filtrate was concentrated to dryness to give a residue, which was chromatographed on a silica gel column. Elution with EtOAc–MeOH (7:3) yielded **15** as an oil, which crystallized from absolute ethanol to give 55 mg (0.207 mmol, 64%): mp 252–253 °C dec; ^{1}H NMR (Me_2SO) δ 3.58 (2 H, m, 5′-CH_2), 3.92 (1 H, m, 4′-H), 4.1 (1 H, m, 3′-H), 4.58 (1 H, m, 2′-H), 4.8–5.3 (3 H, large s, 2′,3′,5′-OH), 5.96 (1 H, d, J = 6 Hz, 1′-H), 6.33 (3 H, m, 5-H and 4-NH_2), 6.58 (1 H, d, J = 3 Hz, 3-H), 7.28 (1 H, d, J = 3 Hz, 2-H), 7.72 (1 H, d, J = 5 Hz, 6-H); UV (C_2H_5OH) λ_{max} 229 nm (log ε 4.41), 273 (3.92), 293 (4.02), 301 (3.97). Anal. ($C_{12}H_{15}N_3O_4$) C, H, N.

4-Amino-1-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-1*H*-pyrrolo[2,3-*b*]pyridine (16). A suspension of **15** (50 mg, 0.188 mmol) in dry acetone (10 mL) was mixed with *p*-toluenesulfonic acid monohydrate (71 mg, 0.37 mmol) and stirred at room temperature for 1 h. Then solid sodium hydrogen carbonate (580 mg) was added, and stirring was continued for 24 h. The solid was filtered off, and the filtrate was evaporated to dryness. The residue was chromatographed on a silica gel column eluting with EtOAc to give 40 mg (0.133 mmol, 70%) of **16**: ^{1}H NMR (Me_2SO) δ 1.31 and 1.54 [each 3 H, s, $C(CH_3)_2$], 3.55 (2 H, m, 5′-CH_2), 4.11 (1 H, m, 4′-H), 4.93 (1 H, m, 3′-H), 5.16 (2 H, m, 2′-H and 5′-OH), 6.17 (2 H, m, 5-H and 1′-H), 6.27 (2 H, s, 4-NH_2), 6.6 (1 H, d, J = 3 Hz, 3-H), 7.3 (1 H, d, J = 3 Hz, 2-H), 7.73 (1 H, d, J = 5 Hz, 6-H). Anal. ($C_{15}H_{19}N_3O_4$) C, H, N.

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2-Acetylpyridine Thiosemicarbazones. 4. Complexes with Transition Metals as Antimalarial and Antileukemic Agents[1,2]

John P. Scovill, Daniel L. Klayman,* and Charles F. Franchino

Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC 20012.
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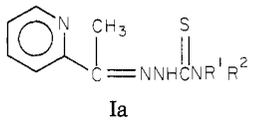
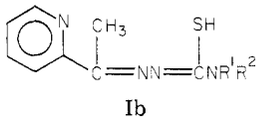
Reaction of the 2-acetylpyridine thiosemicarbazones, 3-azabicyclo[3.2.2]nonane-3-thiocarboxylic acid 2-[1-(2-pyridyl)ethylidene]hydrazide (IIIa), its selenium analogue (IIIb), 1*H*-hexahydroazepine-1-thiocarboxylic acid 2-[1-(2-pyridyl)ethylidene]hydrazide (IV), and 1*H*-octahydroazocine-1-thiocarboxylic acid 2-[1-(2-pyridyl)-ethylidene]hydrazide (V) with Cu(II), Ni(II), Fe(III), and Mn(II) salts gave crystalline complexes. Relative to the free ligands, these complexes show reduced antimalarial activity in mice infected with *Plasmodium berghei*; however, antileukemic properties are enhanced by coordination with the above-mentioned metals.

We have recently reported on a series of 2-acetylpyridine thiosemicarbazones (Ia) that possess significant antimalarial activity.[3,4] The molecular features that have been shown to be essential for antimalarial activity are the presence of a 2-pyridylalkylidene moiety[4] and a thiocarbonyl[4] or selenocarbonyl[1] group (in contrast to a carbonyl group). These features would also be expected to promote effective transtion-metal chelating properties.[5] In addition, we have observed that the presence of certain bulky groups at position N^4 of the thiosemicarbazone moiety greatly enhances antimalarial activity.[4] The formation of complexes with transition metals has been implicated in the mechanism of action of the structurally related 2-formylpyridine thiosemicarbazones.[6,7]



Ia



Ib

Saryan et al.[8] have shown that the iron complexes of some α-N-heterocyclic thiosemicarbazones are three- to

(1) For paper 3 in this series, see Klayman, D. L.; Scovill, J. P.; Bartosevich, J. F.; Mason, C. J. *Eur. J. Med. Chem.* **1981**, *16*, 317.
(2) This is contribution no. 1640 to the Army Research Program on Malaria.
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