

- Ward, R. C. Cykiert, T. S. Lin, D. C. Ward, and W. H. Prusoff, *J. Invest. Ophthalmol.*, **15**, 470 (1976).
- (13) C. A. Puliafito, N. L. Robinson, D. M. Albert, T. S. Lin, D. C. Ward, and W. H. Prusoff, *Proc. Soc. Exp. Biol. Med.*, in press.

- (14) M. S. Chen, D. C. Ward, and W. H. Prusoff, *J. Biol. Chem.*, **251**, 4833 (1976).
- (15) J. J. Fox and N. C. Miller, *J. Org. Chem.*, **28**, 936 (1963).
- (16) J. P. Horwitz, J. Chua, J. A. Urbanski, and M. Noel, *J. Org. Chem.*, **28**, 942 (1963).

Synthesis of 1-Deaza-6-thioguanosine and 1-Deaza-6-(methylthio)guanosine

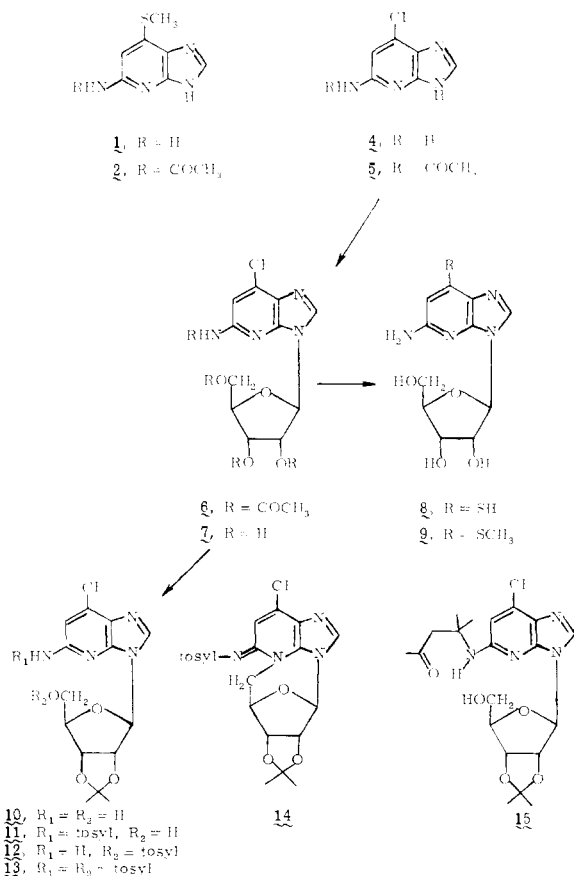
Robert D. Elliott* and John A. Montgomery

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205. Received August 22, 1977

A synthesis of 1-deaza-6-thioguanosine (8) and 1-deaza-6-(methylthio)guanosine (9) from 2-amino-6-chloro-1-deazapurine (4) is described. The reaction of the *N*²-acetyl derivative of 4 with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride in the presence of Linde 4A molecular sieve gave the blocked nucleoside 6. Deacetylation of 6 gave the chloro nucleoside 7 which was treated at high temperature with hydrogen sulfide and methyl mercaptan to give 8 and 9, respectively. The structure of 7 was confirmed by ¹H NMR and by conversion to the cyclonucleoside 14. Compound 4 gave a 79% increase in life span in the L1210 mouse leukemia screen.

The reported antitumor activity of 6-thioguanine¹ and the nucleosides 6-thio-^{2,3} and 6-(methylthio)guanosine⁴ prompted our investigation of synthetic routes to 5-amino-3,4-dihydro-3-β-D-ribofuranosyl-7*H*-imidazo[4,5-*b*]pyridine-7-thione (1-deaza-6-thioguanosine, 8) and 7-(methylthio)-3-β-D-ribofuranosyl-3*H*-imidazo[4,5-*b*]pyridin-5-amine [1-deaza-6-(methylthio)guanosine, 9].

An initial attempt was made to prepare 9 by a nucleoside coupling reaction between *N*-acetyl-7-(methylthio)-1*H*-imidazo[4,5-*b*]pyridin-5-amine (2) and 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride⁵ (3). Acetylation of 7-(methylthio)-1*H*-imidazo[4,5-*b*]pyridin-5-amine⁶ (1) in refluxing acetic anhydride gave 2 which was heated with 3 in 1,2-dichloroethane at 75 °C in the presence of Linde 4A molecular sieve for 6 days. Thin-layer chromatography indicated negligible nucleoside formation.



The successful route to 8 and 9 involved nucleophilic displacement of the chlorine from 7-chloro-3-β-D-ribofuranosyl-3*H*-imidazo[4,5-*b*]pyridin-5-amine (7). 7-Chloro-1*H*-imidazo[4,5-*b*]pyridin-5-amine⁷ (4) was treated with acetic anhydride to give a diacetylation product which was partially hydrolyzed to give the monoacetyl derivative 5. This compound was identified by comparison of physical properties (melting point, ¹H NMR, IR) with those described for 5 prepared by a different route.⁸ Condensation of 5 with 3 in 1,2-dichloroethane containing Linde 4A molecular sieve gave the tetraacetyl nucleoside 6 which was deblocked with sodium methoxide in methanol to give 7.

The proton-coupled ¹³C NMR spectrum of 7 indicates that the ribose must be attached at N₁ or N₃. The C₂ absorption shows two spin-spin couplings: ¹J_{C₂H₂ = 211.5 ± 0.6 Hz and ³J_{C₂H₁ = 3.4 ± 0.6 Hz. The latter coupling would not be present if the attachment were at N₄ or the 5-amino group.}}

The site of ribosylation and anomeric configuration of 7 was confirmed⁹ by conversion to the cyclonucleoside 14. Treatment of 7 with acetone, 2,2-dimethoxypropane, and perchloric acid gave the isopropylidene derivative 10. Tosylation of 10 in pyridine with 1 equiv of tosyl chloride gave the tosylamide 11 rather than the expected tosylate ester 12. Tosylation of guanosine under the same conditions gives the 5'-*O*-tosyl ester.¹⁰ The difference is apparently due to the increased basicity of the amino group of 10. Evidence for structure 11 is based on NMR data, a mass ion of *m/e* 494 (M⁺), and a UV spectrum different from 10 and similar to 5 at pH 1. Treatment of 11 with additional tosyl chloride in pyridine gave the crude ditosyl derivative 13 which was identified by ¹H NMR, a mass ion of *m/e* 648 (M⁺), and a UV spectrum similar to 11. The cyclonucleoside 14 was readily formed by heating a solution of 13 with triethylamine in benzene at 50 °C. The structure of the product is based on elemental analysis, a mass ion of *m/e* 476 (M⁺), a UV spectrum different from 10 or 11, and NMR data. There is a large (1.47 ppm) difference in the chemical shifts of the H_{5'} bridge protons due to the difference in magnetic environments in which they are held by the cyclic structure. In the related guanosine cyclonucleoside the remote possibility that cyclization of C_{5'} with the 2-amino group may occur has been considered by Reist et al.¹⁰ and Chambers et al.;¹¹ however, Dreiding stereomodels strongly favor the 3-5' ring structure for cycloguanosine and 14 (purine numbering).

The chlorine of the deazapurine 4 has been reported to

be very resistant to substitution by nucleophilic reagents.^{7,12,13} Formation of an anion at N³ could exert a repelling effect on approaching nucleophiles and in part explain the stability of 4. The ease of displacement of chlorine from 7 was, however, expected to be greater than that of 4 because anion formation is not possible at the 3 position of 7. The reaction of 7 with hydrogen sulfide in ethanol containing sodium methoxide in a sealed tube at 114 °C gave a 49% yield of 1-deaza-6-thioguanosine 8. A similar reaction of 7 with methyl mercaptan gave a 76% yield of 1-deaza-6-(methylthio)guanosine 9. Spectral data and elemental analyses were consistent with the proposed structures for 8 and 9.

In the conversion of 7 to 10 a second product was isolated and tentatively identified as structure 15 based on UV, ¹H NMR, ¹³C NMR, infrared absorption at 1700 cm⁻¹ (C=O), and a mass ion of *m/e* 438 (M⁺). This product may have been formed by addition of 10 to the acetone condensation product mesityl oxide.

Biological Results. Compounds 1, 2, 4, 5, 7-9, and 14 were evaluated for their ability to inhibit the growth of KB cells in culture;¹⁴ and compounds 1, 2, 4, 5, and 7-9 were evaluated for their ability to inhibit leukemia L1210 in mice.¹⁴ 2-Amino-6-chloro-1-deazapurine (4) extended the life of leukemic mice 79% at 33 mg/kg administered on days 1-9 and was active over the range of 14-75 mg/kg. Compound 4 is cytotoxic to KB cells (ED₅₀ = 1 μg/mL) and H.Ep.-2 cells¹⁵ (ED₅₀ = 0.3 μg/mL) in culture; and the cytotoxicity is not reversed by 5-amino-1*H*-imidazole-4-carboxamide, indicating no interference with de novo biosynthesis of inosinic acid,¹⁶ but is reversed by hypoxanthine, suggesting that competition for hypoxanthine phosphoribosyl transferase may prevent conversion of 4 to its ribonucleotide and that this conversion may be a prerequisite for activity. The other compounds tested showed low cytotoxicity (ED₅₀ > 22 μg/mL) and no significant L1210 activity (less than 15% increase in life span).

Experimental Section

Melting points were determined on a Kofler Heizbank, and absence of melting point data indicates an indefinite melting point. The ultraviolet absorption spectra were determined with a Cary Model 17 spectrophotometer. Each compound was dissolved in the solvent indicated in parentheses and diluted tenfold with 0.1 N HCl, pH 7 buffer, and 0.1 N NaOH. The ¹H NMR spectra were determined in 1-9% w/v solutions in Me₂SO-*d*₆ with a Varian XL-100-15 spectrometer operating at 100 MHz (internal Me₄Si). The relative peak areas are given to the nearest whole number, and chemical shifts quoted in the case of multiplets are measured from the approximate center. The ¹³C NMR spectra were determined in 5-10% w/v solutions in Me₂SO-*d*₆ with a Varian XL-100-15 spectrophotometer operating at 25.160 MHz and equipped with a Digilab FTS NMR-3 pulser and data system. Mass spectral data were taken with a Varian MAT 311A instrument equipped with a combination EI/FI/FD ion source. Merck 2-mm silica gel 60F-254 preparative TLC plates (8 × 8 in.) were used for preparative TLC purifications. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.3% of the theoretical values.

N-Acetyl-7-(methylthio)-1*H*-imidazo[4,5-*b*]pyridin-5-amine (2). A solution of 1.1.8HCl¹⁶ (0.880 mmol) in Ac₂O (3 mL) was refluxed for 30 min and evaporated in vacuo. A stirred suspension of the residue in H₂O (5 mL) was treated dropwise with 4 N NaOH until the pH remained constant at pH 8.5 for 10 min. The solution was filtered and the filtrate taken to pH 6 with 1 N HCl and refrigerated. The crystalline product was collected, washed with cold H₂O, and dried in vacuo (P₂O₅): yield 130 mg (65%); mp 252 °C; λ_{max}, nm (ε × 10⁻³) (EtOH), in 0.1 N HCl 208 (11.9), 245 (16.6), 296 (22.2), in pH 7 245 (17.5), 290 (18.3) (br), in 0.1 N NaOH 243 (17.5), 301 (16.9); ¹H NMR δ 2.13 (s, 3,

CH₃CO), 2.60 (s, SCH₃), 7.97, 8.23 (s, s, 2, H₂ and H₆), 10.37 (s, 1, AcNH); mass spectrum *m/e* 222 (M⁺). Anal. (C₆H₁₀N₄O·0.3H₂O) C, H, N.

N-Acetyl-7-chloro-1*H*-imidazo[4,5-*b*]pyridin-5-amine (5). A suspension of 4⁷ (3.00 g, 17.8 mmol) in Ac₂O (25 mL) was refluxed until solution occurred and heated an additional 30 min at this temperature. The solution was refrigerated and the crude diacetyl derivative (C=O absorption at 1690 and 1740 cm⁻¹) collected by filtration, washed with Et₂O, and dried at 78 °C in vacuo. A solution of this solid (2.50 g) in ethanol (60 mL) was treated with 1 N KOH (10 mL), stirred for 18 h, and evaporated to dryness in vacuo. A suspension of the residue in H₂O was adjusted to pH 6 with 1 N HCl and the precipitate of 5 collected, washed with H₂O, and dried at 78 °C in vacuo (P₂O₅): yield 1.70 g (44%); mp 269 °C (lit.⁸ mp 269-270 °C). Anal. (C₆H₇ClN₄O·0.25H₂O) C, H, N.

7-Chloro-3-β-D-ribofuranosyl-3*H*-imidazo[4,5-*b*]pyridin-5-amine (7). A mixture of 5 (903 mg, 4.20 mmol), 3⁵ (4.20 mmol), Linde 4A molecular sieve (21 g), and dichloroethane (210 mL) was stirred in a 62 °C oil bath for 6 days. The mixture was cooled to 25 °C, filtered, and evaporated to dryness in vacuo. A solution of the residue in benzene (25 mL) was filtered and evaporated to give 1.53 g of crude 6 which was dissolved in CHCl₃, applied to eight preparative TLC plates, and developed with CHCl₃-CH₃OH (95:5). The major band was extracted with CHCl₃-CH₃OH (1:1) and evaporated to dryness in vacuo. A solution of the residue in CHCl₃ (10 mL) was filtered and evaporated to give 1.04 g of 6 as a foam containing only minor traces of impurities (TLC): ¹H NMR δ 2.02-2.16 (m, Ac), 4.08-4.5 (m, 3, CH₂, H₄), 5.59 (d, 1, H₃), 6.00 (t, 1, H₂), 6.29 (d, 1, J_{1,2} = 3.0 Hz, H₁), 8.24, 8.69 (s, s, 2, H₂, H₆), 10.65 (s, 1, NH). A solution of 6 and NaOMe (0.52 g, 9.62 mmol) in MeOH (200 mL) was stirred at 62 °C for 16 h, cooled to 25 °C, neutralized with Amberlite IR-120 H⁺ ion-exchange resin, and filtered and the resin was extracted with MeOH and H₂O. The combined filtrate and extract was evaporated to dryness in vacuo and a solution of the residue (591 mg) in CHCl₃ was applied to four preparative TLC plates. The plates were developed with CHCl₃-MeOH (4:1) and the principal band was extracted with MeOH. The extract was evaporated and the residue dissolved in EtOH (10 mL), filtered, and evaporated to dryness. A solution of this solid in H₂O (5 mL) was lyophilized to give 438 mg (31% overall yield from 5) of 7: λ_{max}, nm (ε × 10⁻³) (H₂O), in 0.1 N HCl 218 (22.1), 318 (11.0), in pH 7 220 (19.3), 249 (6.38), 256 (sh) (5.52), 311 (10.8), in 0.1 N NaOH 249 (5.85), 256 (sh) (5.10), 311 (11.0); ¹H NMR δ 1.05 (CH₃ of EtOH), 3.60 (m, 2, H₅), 3.92 (m, 1, H₄), 4.14 (m, 1, H₃), 4.50 (m, 1, H₂), 5.87 (d, 1, J_{1,2} = 5.5 Hz, H₁), 6.19 (s, 2, NH₂), 6.52 (s, 1, H₆), 8.23 (s, 1, H₂); ¹³C NMR δ (±0.02) 61.42 (C₅), 70.38 (C₃), 73.36 (C₂), 85.25 (C₄), 86.97 (C₁), 104.31 (C₆), 124.81 (C_{8a}), 134.35 (C₂), 139.12, 146.33 (C_{3a,7}), 157.20 (C₅); mass spectrum *m/e* 300 (M⁺). Anal. (C₁₁H₁₃ClN₄O₄·0.1C₂H₅O·0.4H₂O) C, H, N.

5-Amino-3,4-dihydro-3-β-D-ribofuranosyl-7*H*-imidazo[4,5-*b*]pyridine-7-thione (8). A solution of 7 (337 mg, 1.00 mmol), liquid H₂S (3 mL), NaOMe (108 mg, 2.00 mmol), and EtOH (13 mL) was heated in a sealed tube in an oil bath at 114 °C for 45 h. The tube was cooled, opened, and warmed slowly to 25 °C. The resulting solution was diluted with H₂O (10 mL), concentrated to 10 mL in vacuo (rotary evaporator), adjusted to pH 6 with Amberlite IR-120 H⁺ ion-exchange resin, filtered, and lyophilized. A solution of the solid in hot EtOH (5 mL) was filtered and allowed to cool to 25 °C. The precipitate of crude 7 (62 mg) was removed by filtration, and the filtrate was diluted with Et₂O until cloudy and refrigerated. The precipitate of pure 8 was collected by filtration and dried in vacuo (P₂O₅): yield 155 mg (49%); λ_{max}, nm (ε × 10⁻³) (H₂O), in 0.1 N HCl 223 (14.3), 226 (7.27), 327 (7.91), in pH 7 213 (15.6), 228 (15.1), 261 (8.85), 268 (8.64) (sh), 317 (8.36), in 0.1 N NaOH 243 (11.1), 299 (16.4); ¹H NMR δ 3.61 (m, 2, H₅), 3.92 (m, 1, H₄), 4.15 (m, 1, H₃), 4.56 (m, 1, H₂), 5.12 (m, 2, C₃-OH), 5.36 (m, 1, C₂-OH), 5.88 (d, 1, J_{1,2} = 6 Hz, H₁), 6.12 (s, 2, NH₂), 6.53 (s, 1, H₆), 8.24 (s, 1, H₂); mass spectrum *m/e* 298 (M⁺). Anal. (C₁₁H₁₄N₄O₄S·H₂O) C, H, N.

7-(Methylthio)-3-β-D-ribofuranosyl-3*H*-imidazo[4,5-*b*]pyridin-5-amine (9). A solution of 7 (337 mg, 1.00 mmol), liquid MeSH (3 mL), NaOMe (108 mg, 2.00 mmol), and EtOH (13 mL) was heated in a sealed tube in an oil bath at 115 °C for 42 h. The tube was cooled in a dry ice-acetone mixture, opened, and warmed

slowly to 25 °C. The resulting solution was filtered, concentrated under water-aspirator vacuum, diluted with H₂O (20 mL), and adjusted to pH 6 with Amberlite IR-120 H⁺ ion-exchange resin. The solution was filtered and the resin washed well with H₂O. The filtrate and wash was lyophilized to a white powder. A solution of the powder in dioxane (10 mL) was filtered and evaporated to dryness, and the residue was redissolved in H₂O, lyophilized, and dried at 56 °C in vacuo (P₂O₅) to give pure **9** as a partial solvate with dioxane: yield 263 mg (76%); λ_{\max} , nm ($\epsilon \times 10^{-3}$) (H₂O), in 0.1 N HCl 209 (14.9), 237 (10.2), 243 (9.14) (sh), 284 (13.9), 316 (10.9), in pH 7 214 (16.0), 241 (15.9), 273 (13.0), 308 (9.87), in 0.1 N NaOH 241 (15.4), 273 (13.1), 308 (10.1); ¹H NMR δ 2.50 (s, CH₃), 3.57 (m, H₅ and dioxane), 3.91 (m, 1, H₄), 4.13 (m, 1, H₃), 4.52 (m, 1, H₂), 5.85 (d, $J_{1,2} = 6.5$, H₁), 6.27 (s, 1, H₆), 8.09 (s, 1, H₂); mass spectrum m/e 312 (M⁺). Anal. (C₁₂H₁₆N₄O₄S·0.5C₄H₈O₂) C, H, N.

4,5'-Cyclonucleoside of 7-Chloro-4,5-dihydro-5-[[4-methylphenylsulfonyl]imino]-3-[2,3-O-(1-methylethylidene)- β -D-ribofuranosyl]-3-H-imidazo[4,5-b]pyridine (14). A solution of 2,2-dimethoxypropane (0.116 mL, 1.35 mmol), anhydrous acetone (25 mL), and 60% HClO₄ (0.155 mL, 1.11 mmol) was stirred for 5 min, added to **7** (100 mg, 0.296 mmol), and stirred for 20 min. The solution was neutralized by addition of NaHCO₃ (840 mg) and evaporated to dryness in vacuo, and the residue was extracted with hot CHCl₃ (5 \times 15 mL). The extract was concentrated and applied to a preparative TLC plate and developed two times with CHCl₃-MeOH (97:3) to give two major products. The faster moving major band was extracted with CHCl₃-MeOH (1:1) and the extract evaporated to dryness in vacuo. The residue in CHCl₃ (3 mL) was evaporated under high vacuum to give 59 mg (54% yield) of a solvate of **7-chloro-3-[2,3-O-(1-methylethylidene)- β -D-ribofuranosyl]-3-H-imidazo[4,5-b]pyridine-5-amine (10)**: λ_{\max} , nm (EtOH), in 0.1 N HCl 218, 319, in pH 7 219, 249, 255 (sh), 312, in 0.1 N NaOH 220, 249, 255, 312; ¹H NMR δ 1.37, 1.64 (s, s, 6, CMe₂), 3.93 (m, H₅), 4.50 (m, 1, H₄), 4.74 (s, 2, NH₂), 5.16 (m, 2, H_{2,3}), 5.82 (d, 1, $J_{1,2} = 4.7$ Hz, H₁), 6.52 (s, 1, H₆), 7.28 (CHCl₃), 7.81 (s, 1, H₂); mass spectrum m/e 340 (M⁺).

The slower moving band was extracted and isolated as above to give 54 mg of **15**: λ_{\max} , nm (EtOH), in 0.1 N HCl 223, 255 (sh), 330, in pH 7 and 0.1 N NaOH 225, 258, 321; IR (KBr) 1700 cm⁻¹; ¹H NMR δ 1.31, 1.55 (s, s, 6, OCMe₂), 1.43, 1.44 (s, s, 6, NCMe₂), 1.98 (s, 3, COMe), 3.17 (d, 2, CH₂), 3.54 (t, 2, H₅), 4.22 (m, 1, H₄), 4.89 (m, 1, H₃), 5.10 (m, 1, O₅H), 5.33 (m, 1, H₂), 6.12 (d, 1, $J = 3.0$ Hz, H₁), 6.55 (s, 1, H₆), 6.62 (s, 1, NH), 8.22 (s, 1, H₂); ¹³C NMR δ (± 0.05 , referenced to external Me₄Si) 25.04, 26.95 [OC(CH₃)₂], 27.34, 27.43 [NC(CH₃)₂], 31.40 (COCH₃), 50.45 (NCMe₂), 52.21 (CH₂Ac), 61.39 (C₅), 81.07, 83.56 (C₂, C₃), 85.83 (C₄), 89.60 (C₁), 106.27 (C₆), 113.06 (OCMe₂), 123.89 (C_{7a}), 133.68 (C_{3a}), 138.32 (C₂), 145.42 (C₇), 155.82 (C₅); mass spectrum m/e 438 (M⁺).

A solution of **10** (63 mg, 0.170 mmol), *p*-toluenesulfonyl chloride (38.8 mg, 0.204 mmol), and anhydrous pyridine (1 mL) was prepared at 0 °C and stirred at 25 °C for 18 h. The solution was cooled to 0 °C, diluted with cold saturated NaHCO₃ solution (2.5 mL), and extracted with CHCl₃ (4 \times 2.5 mL). The extract was dried (MgSO₄) and evaporated in vacuo to give crude **11** (92 mg): λ_{\max} , nm (EtOH), in 0.1 N HCl 215, 299, in pH 7 225, 253, 315, in 0.1 N NaOH 225, 253, 316; ¹H NMR (CDCl₃) δ 1.34, 1.60 (s, s, 6, CMe₂), 2.34 (s, 3, CH₃ of tosyl), 5.97 (d, 1, $J_{1,2} = 3.0$ Hz, H₁), 7.38 (s, H₆), 8.18 (s, 1, H₂); mass spectrum m/e 494 (M⁺). A solution of **11** (70 mg) and *p*-toluenesulfonyl chloride (30 mg) in anhydrous pyridine (1 mL) was stirred at 25 °C for 18 h, cooled to 0 °C, neutralized with cold, saturated NaHCO₃ solution (2.5 mL), and extracted with CHCl₃. The extract was dried (MgSO₄) and evaporated in vacuo to give a residue of **13** containing unreacted **11**. This mixture was tosylated by the procedure described above to give 70 mg of crude **13** containing a trace of **14** (TLC): λ_{\max} , nm (EtOH), in 0.1 N HCl 218, 299, in pH 7 225, 255, 316,

in 0.1 N NaOH 225, 255, 317; ¹H NMR (CDCl₃) δ 1.33, 1.56 (s, s, 6, CMe₂), 2.36 (s, 6, CH₃ of tosyl), 5.95 (d, 1, $J_{1,2} = 2.4$ Hz, H₁), 7.19 (s, H₆), 7.98 (s, 1, H₂); mass spectrum m/e 648, 476 (M⁺). A solution of **13** (55 mg) and Et₃N (0.7 mL) in benzene (14 mL) was heated at 50 °C in an oil bath for 21 h and refrigerated. The white crystalline **14** was collected, washed with benzene, and dried in vacuo (P₂O₅): yield 15 mg; mp 295 °C dec (Mel-Temp). An additional 7 mg of product was obtained by evaporation of the mother liquor and trituration of the residue with benzene: λ_{\max} , nm (EtOH), in 0.1 N HCl 224 (22.6), 223 (22.0) (sh), 262 (10.2) (sh), 348 (21.1), in pH 7 224 (22.4), 233 (21.9) (sh), 262 (10.1) (sh), 348 (21.3); ¹H NMR δ 1.20, 1.44 (s, s, CMe₂), 2.36 (s, CH₃ of tosyl), 3.92, 5.39 (d of d, d of d, CH₂), 4.45, 4.79 (d, d, H_{2,3}), 5.00 (m, H₄), 6.58 (s, H₁), 7.34, 7.78 (d, d, ArH), 7.37 (s, H₆), 8.29 (s, H₂); mass spectrum m/e 476 (M⁺). Anal. (C₂₁H₂₁ClN₄O₅S) C, H, N.

Acknowledgment. This investigation was supported by the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare, Contract No. NO1-CM-43762. The authors are indebted to Dr. C. Temple, Jr., and Mr. Buford H. Smith for the synthesis of **1** and **5**, to Dr. W. C. Coburn, Jr., and Mrs. M. C. Thorpe, who interpreted NMR data, to other members of the Molecular Spectroscopy Section of Southern Research Institute, who performed most of the microanalytical and spectral determinations reported, and to Dr. L. L. Bennett, Jr., for the cytotoxicity data reported.

References and Notes

- (1) G. A. LePage and T. L. Loo in "Cancer Medicine", J. F. Holland and E. Frei, III, Ed., Lea and Febiger, Philadelphia, Pa., 1973, p 754.
- (2) A. Goldin, H. B. Wood, Jr., and R. R. Engle, *Cancer Chemother. Rep., Part 2*, 1, 1 (1967).
- (3) J. J. Fox, I. Wempen, A. Hampton, and I. L. Doerr, *J. Am. Chem. Soc.*, **80**, 1669 (1958).
- (4) C. W. Noell and R. K. Robins, *J. Med. Pharm. Chem.*, **5**, 1074 (1962).
- (5) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 967 (1948).
- (6) C. Temple, Jr., B. H. Smith, Jr., C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, **41**, 3784 (1976).
- (7) C. Temple, Jr., B. H. Smith, Jr., and J. A. Montgomery, *J. Org. Chem.*, **38**, 613 (1973).
- (8) J. E. Schelling and C. A. Salemink, *Recl. Trav. Chim. Pays-Bas*, **93**, 160 (1974).
- (9) After completion of the structure proof of **7**, a different synthesis and structure proof of **7** was published [B. L. Cline, R. P. Panzica, and L. B. Townsend, *J. Heterocycl. Chem.*, **12**, 603 (1975)]. This communication gave no physical properties of **7** for comparison.
- (10) E. J. Reist, P. A. Hart, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **26**, 1557 (1961).
- (11) R. W. Chambers, J. G. Moffatt, and H. G. Khorana, *J. Am. Chem. Soc.*, **79**, 3747 (1957).
- (12) D. G. Markees and G. W. Kidder, *J. Am. Chem. Soc.*, **78**, 4130 (1956).
- (13) J. E. Schelling and C. A. Salemink, *Recl. Trav. Chim. Pays-Bas*, **91**, 650 (1972).
- (14) R. I. Geran, N. H. Greenberg, M. M. Macdonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, **3** (no. 2) (1972).
- (15) L. L. Bennett, Jr., M. H. Vail, P. W. Allan, and S. C. Shaddix, *Biochem. Pharmacol.*, **22**, 1221 (1973).
- (16) J. A. Nelson, J. W. Carpenter, L. M. Rose, and D. J. Adamson, *Cancer Res.*, **35**, 2872 (1975).