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

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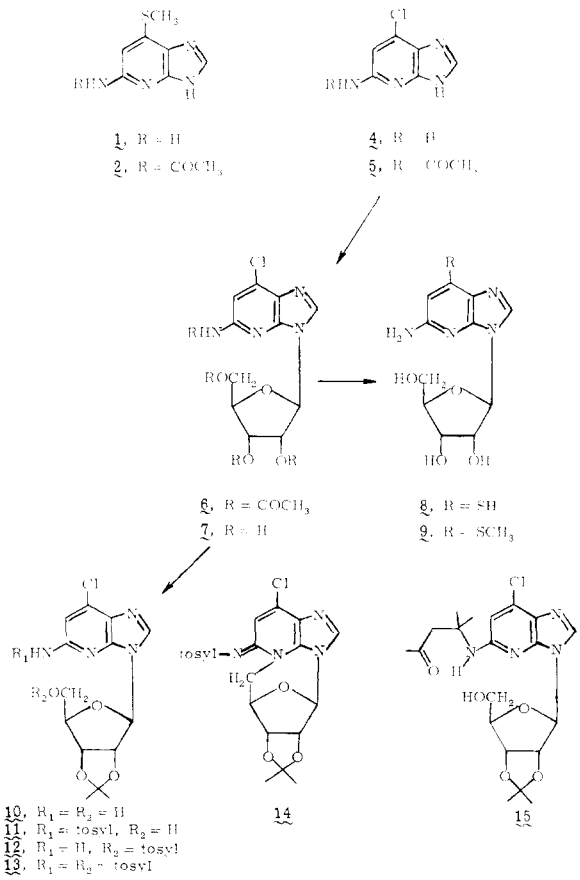
A synthesis of 1-deaza-6-thioguanosine (**8**) and 1-deaza-6-(methylthio)guanosine (**9**) from 2-amino-6-chloro-1-deazapurine (**4**) is described. The reaction of the N^2-acetyl derivative of **4** with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride in the presence of Linde 4A molecular sieve gave the 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 ^{1}H 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-thioguanine[1] and the nucleosides 6-thio-[2,3] and 6-(methylthio)guanosine[4] prompted our invesigation 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 chloride[5] (**3**). Acetylation of 7-(methylthio)-1*H*-imidazo[4,5-*b*]pyridin-5-amine[6] (**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-amine[7] (**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, ^{1}H 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 ^{13}C NMR spectrum of **7** indicates that the ribose must be attached at N_1 or N_3. The C_2 absorption shows two spin–spin couplings: $^1J_{C_2H_2} = 211.5 \pm 0.6$ Hz and $^3J_{C_2H_{1'}} = 3.4 \pm 0.6$ Hz. The latter coupling would not be present if the attachment were at N_4 or the 5-amino group.

The site of ribosylation and anomeric configuration of **7** was confirmed[9] 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 ^{1}H 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

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be very resistant to substitution by nucleophilic reagents.[7,12,13] Formation of an anion at N^3 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, ^{13}C 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 (ED_{50} = 1 μg/mL) and H.Ep.-2 cells[15] (ED_{50} = 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 (ED_{50} > 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 Me_2SO-d_6 with a Varian XL-100-15 spectrometer operating at 100 MHz (internal Me_4Si). 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 ^{13}C NMR spectra were determined in 5–10% w/v solutions in Me_2SO-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**·1.8HCl[6] (0.880 mmol) in Ac_2O (3 mL) was refluxed for 30 min and evaporated in vacuo. A stirred suspension of the residue in H_2O (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 H_2O, and dried in vacuo (P_2O_5): 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, CH_3CO), 2.60 (s, SCH_3), 7.97, 8.23 (s, s, 2, H_2 and H_6), 10.37 (s, 1, AcNH); mass spectrum m/e 222 (M^+). Anal. ($C_6H_{10}N_4OS$·0.3H_2O) C, H, N.

***N*-Acetyl-7-chloro-1*H*-imidazo[4,5-*b*]pyridin-5-amine (5).** A suspension of **4**[7] (3.00 g, 17.8 mmol) in Ac_2O (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 Et_2O, 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 H_2O was adjusted to pH 6 with 1 N HCl and the precipitate of **5** collected, washed with H_2O, and dried at 78 °C in vacuo (P_2O_5): yield 1.70 g (44%); mp 269 °C (lit.[8] mp 269–270 °C). Anal. ($C_6H_7ClN_4O$·0.25H_2O) 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), **3**[5] (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 $CHCl_3$, applied to eight preparative TLC plates, and developed with $CHCl_3$–CH_3OH (95:5). The major band was extracted with $CHCl_3$–CH_3OH (1:1) and evaporated to dryness in vacuo. A solution of the residue in $CHCl_3$ (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, CH_2, $H_{4'}$), 5.59 (d, 1, $H_{3'}$), 6.00 (t, 1, $H_{2'}$), 6.29 (d, 1, $J_{1',2'}$ = 3.0 Hz, $H_{1'}$), 8.24, 8.69 (s, s, 2, H_2, H_6), 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 H_2O. The combined filtrate and extract was evaporated to dryness in vacuo and a solution of the residue (591 mg) in $CHCl_3$ was applied to four preparative TLC plates. The plates were developed with $CHCl_3$–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 H_2O (5 mL) was lyophilized to give 438 mg (31% overall yield from **5**) of **7**: λ_{max}, nm (ε × 10^{-3}) (H_2O), 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 (CH_3 of EtOH), 3.60 (m, 2, $H_{5'}$), 3.92 (m, 1, $H_{4'}$), 4.14 (m, 1, $H_{3'}$), 4.50 (m, 1, $H_{2'}$), 5.87 (d, 1, $J_{1',2'}$ = 5.5 Hz, $H_{1'}$), 6.19 (s, 2, NH_2), 6.52 (s, 1, H_6), 8.23 (s, 1, H_2); ^{13}C NMR δ (±0.02) 61.42 ($C_{5'}$), 70.38 ($C_{3'}$), 73.36 ($C_{2'}$), 85.25 ($C_{4'}$), 86.97 ($C_{1'}$), 104.31 (C_6), 124.81 (C_{7a}), 134.35 (C_2), 139.12, 146.33 ($C_{3a,7}$), 157.20 (C_5); mass spectrum m/e 300 (M^+). Anal. ($C_{11}H_{13}ClN_4O_4$·0.1C_2H_6O·0.4H_2O) 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 H_2S (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 H_2O (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 Et_2O until cloudy and refrigerated. The precipitate of pure **8** was collected by filtration and dried in vacuo (P_2O_5): yield 155 mg (49%); λ_{max}, nm (ε × 10^{-3}) (H_2O), 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, $H_{5'}$), 3.92 (m, 1, $H_{4'}$), 4.15 (m, 1, $H_{3'}$), 4.56 (m, 1, $H_{2'}$), 5.12 (m, 2, $C_{3'}OH$), 5.36 (m, 1, $C_{2'}OH$), 5.88 (d, 1, $J_{1',2'}$ = 6 Hz, $H_{1'}$), 6.12 (s, 2, NH_2), 6.53 (s, 1, H_6), 8.24 (s, 1, H_2); mass spectrum m/e 298 (M^+). Anal. ($C_{11}H_{14}N_4O_4S$·H_2O) 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 H_2O (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 H_2O. 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 H_2O, lyophilized, and dried at 56 °C in vacuo (P_2O_5) to give pure **9** as a partial solvate with dioxane: yield 263 mg (76%); λ_{max}, nm ($\epsilon \times 10^{-3}$) (H_2O), 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, CH_3), 3.57 (m, $H_{5'}$ and dioxane), 3.91 (m, 1, $H_{4'}$), 4.13 (m, 1, $H_{3'}$), 4.52 (m, 1, $H_{2'}$), 5.85 (d, $J_{1',2'}$ = 6.5, $H_{1'}$), 6.27 (s, 1, H_6), 8.09 (s, 1, H_2); mass spectrum m/e 312 (M^+). Anal. ($C_{12}H_{16}N_4O_4S \cdot 0.5C_4H_8O_2$) C, H, N.

4,5′-Cyclonucleoside of 7-Chloro-4,5-dihydro-5-[[(4-methylphenyl)sulfonyl]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% $HClO_4$ (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 $NaHCO_3$ (840 mg) and evaporated to dryness in vacuo, and the residue was extracted with hot $CHCl_3$ (5 × 15 mL). The extract was concentrated and applied to a preparative TLC plate and developed two times with $CHCl_3$–MeOH (97:3) to give two major products. The faster moving major band was extracted with $CHCl_3$–MeOH (1:1) and the extract evaporated to dryness in vacuo. The residue in $CHCl_3$ (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*]pyridin-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, CMe_2), 3.93 (m, $H_{5'}$), 4.50 (m, 1, $H_{4'}$), 4.74 (s, 2, NH_2), 5.16 (m, 2, $H_{2',3'}$), 5.82 (d, 1, $J_{1',2'}$ = 4.7 Hz, $H_{1'}$), 6.52 (s, 1, H_6), 7.28 ($CHCl_3$), 7.81 (s, 1, H_2); 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, $OCMe_2$), 1.43, 1.44 (s, s, 6, $NCMe_2$), 1.98 (s, 3, COMe), 3.17 (d, 2, CH_2), 3.54 (t, 2, $H_{5'}$), 4.22 (m, 1, $H_{4'}$), 4.89 (m, 1, $H_{3'}$), 5.10 (m, 1, $O_{5'}H$), 5.33 (m, 1, $H_{2'}$), 6.12 (d, 1, J = 3.0 Hz, $H_{1'}$), 6.55 (s, 1, H_6), 6.62 (s, 1, NH), 8.22 (s, 1, H_2); ^{13}C NMR δ (±0.05, referenced to external Me_4Si) 25.04, 26.95 [$OC(CH_3)_2$], 27.34, 27.43 [$NC(CH_3)_2$], 31.40 ($COCH_3$), 50.45 ($NCMe_2$), 52.21 (CH_2Ac), 61.39 ($C_{5'}$), 81.07, 83.56 ($C_{2'}$, $C_{3'}$), 85.83 ($C_{4'}$), 89.60 ($C_{1'}$), 106.27 (C_6), 113.06 ($OCMe_2$), 123.89 (C_{7a}), 133.68 (C_{3a}), 138.32 (C_2), 145.42 (C_7), 155.82 (C_5); 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 $NaHCO_3$ solution (2.5 mL), and extracted with $CHCl_3$ (4 × 2.5 mL). The extract was dried ($MgSO_4$) 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 ($CDCl_3$) δ 1.34, 1.60 (s, s, 6, CMe_2), 2.34 (s, 3, CH_3 of tosyl), 5.97 (d, 1, $J_{1',2'}$ = 3.0 Hz, $H_{1'}$), 7.38 (s, H_6), 8.18 (s, 1, H_2); 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 $NaHCO_3$ solution (2.5 mL), and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) 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 ($CDCl_3$) δ 1.33, 1.56 (s, s, 6, CMe_2), 2.36 (s, 6, CH_3 of tosyl), 5.95 (d, 1, $J_{1',2'}$ = 2.4 Hz, $H_{1'}$), 7.19 (s, H_6), 7.98 (s, 1, H_2); mass spectrum m/e 648, 476 (M^+). A solution of **13** (55 mg) and Et_3N (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 (P_2O_5): 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, CMe_2), 2.36 (s, CH_3 of tosyl), 3.92, 5.39 (d of d, d of d, CH_2), 4.45, 4.79 (d, d, $H_{2',3'}$), 5.00 (m, $H_{4'}$), 6.58 (s, $H_{1'}$), 7.34, 7.78 (d, d, ArH), 7.37 (s, H_6), 8.29 (s, H_2); mass spectrum m/e 476 (M^+). Anal. ($C_{21}H_{21}ClN_4O_5S$) C, H, N.

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