

# Imidazo[1,2-*c*]pyrimidine Nucleosides. Synthesis and Biological Evaluation of Certain 1-( $\beta$ -D-Arabinofuranosyl)imidazo[1,2-*c*]pyrimidines

David G. Bartholomew, John H. Huffman, Thomas R. Matthews, Roland K. Robins, and Ganapathi R. Revankar\*

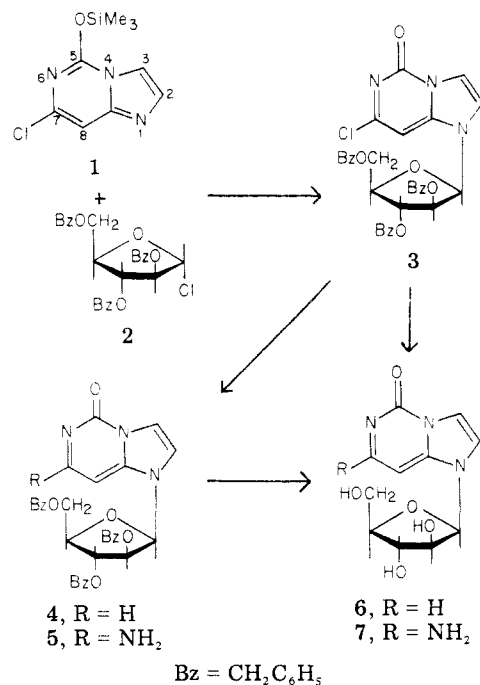
ICN Pharmaceuticals, Inc., Nucleic Acid Research Institute, Irvine, California 92715. Received November 14, 1975

The first chemical syntheses of the arabinosylhypoxanthine and arabinosylguanine analogues of the imidazo[1,2-*c*]pyrimidine series are described. Condensation of trimethylsilyl-7-chloroimidazo[1,2-*c*]pyrimidin-5-one (1) with 2,3,5-tri-*O*-benzyl- $\alpha$ -D-arabinofuranosyl chloride (2) gave 7-chloro-1-(2,3,5-tri-*O*-benzyl- $\beta$ -D-arabinofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one (3) which on catalytic dehalogenation furnished 1-(2,3,5-tri-*O*-benzyl- $\beta$ -D-arabinofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one (4). Amination of 3 gave 7-amino-1-(2,3,5-tri-*O*-benzyl- $\beta$ -D-arabinofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one (5). Reductive hydrogenolysis of 4 and 5 gave 1-( $\beta$ -D-arabinofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one (6), the arabinosylhypoxanthine analogue, and the corresponding 7-amino isomer 7, the arabinosylguanine analogue, respectively. The unequivocal assignment of the site of glycosylation and the anomeric configuration have been established. None of the compounds exhibited significant antiviral or antimicrobial activity in vitro.

During the past several years, there has been an increasing interest in nucleosides derived from  $\beta$ -D-arabinofuranose. The interesting biological properties of 1- $\beta$ -D-arabinofuranosylcytosine (ara-C),<sup>1-7</sup> 9- $\beta$ -D-arabinofuranosyladenine (ara-A),<sup>8-12</sup> and certain 5'-monophosphates of 9-D-arabinofuranosyladenine<sup>13-15</sup> and 9-D-arabinofuranosylhypoxanthine<sup>15-18</sup> have been amply documented. The physicochemical properties of 3-deazapurine nucleosides<sup>19-25</sup> and nucleotides<sup>24-26</sup> have been the subject of studies in a number of laboratories in recent years. The arabinofuranosyl derivatives of the imidazo[1,2-*c*]pyrimidines, which may be regarded as 3-deazapurines with a bridgehead nitrogen atom,<sup>27</sup> are, therefore, of potential biological interest. These nucleosides are also unique since they lack an N(H) function at position 1 of purine; therefore, hydrogen bonding of the Watson-Crick type would not be possible. The present report describes the synthesis and initial in vitro antiviral and antimicrobial testing of the inosine and guanosine analogues of the  $\beta$ -D-arabinofuranosylimidazo[1,2-*c*]pyrimidines.

**Chemistry.** The synthesis of 6 and 7 was approached by the direct glycosylation of the trimethylsilyl derivative of 7-chloroimidazo[1,2-*c*]pyrimidin-5-one (1). Treatment of 7-chloroimidazo[1,2-*c*]pyrimidin-5(6*H*)-one<sup>27</sup> with hexamethyldisilazane in the presence of ammonium sulfate, according to the general procedure described by Wittenburg,<sup>28</sup> gave the trimethylsilyl derivative 1 which without further purification reacted with 2,3,5-tri-*O*-benzyl- $\alpha$ -D-arabinofuranosyl chloride (2)<sup>29</sup> in boiling benzene. Under these conditions and after silicic acid column chromatography, a 91.6% yield of crystalline 7-chloro-1-(2,3,5-tri-*O*-benzyl- $\beta$ -D-arabinofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one (3) was obtained. Careful investigation of the mother liquor furnished chromatographic evidence of the formation of another nucleoside, which was not isolated, presumably anomeric 7-chloro-1-(2,3,5-tri-*O*-benzyl- $\alpha$ -D-arabinofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one, in a very small amount. Catalytic dehalogenation of 3 with 10% palladium on carbon in a hydrogen atmosphere at room temperature gave 1-(2,3,5-tri-*O*-benzyl- $\beta$ -D-arabinofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one (4) in 91.5% yield. Treatment of 3 with anhydrous methanol containing liquid ammonia at elevated temperature and pressure furnished, after silicic acid column chromatography, a 42.0% yield of 7-amino-1-(2,3,5-tri-*O*-benzyl- $\beta$ -D-arabinofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one (5) as light brown gum. Reductive hydrogenolysis of 3 and 5 over freshly reduced palladium black in 2-methoxyethanol gave the 3-deazainosine analogue 1-( $\beta$ -D-arabinofuranosyl)imidazo[1,2-*c*]pyrimidin-

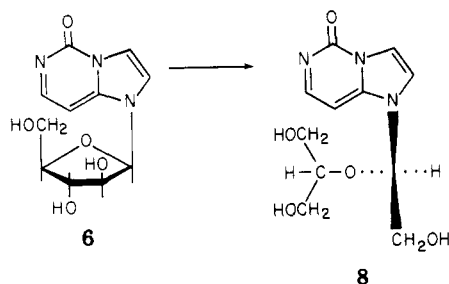
Scheme I



5-one (6) in 63.7% yield and 7-amino-1-( $\beta$ -D-arabinofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one (7), the 3-deazaguanosine analogue possessing a bridgehead nitrogen atom, in 74.4% yield, respectively (see Scheme I). Removal of the protecting benzyl groups of 4 with palladium black furnished 6 in 42.3% yield. The structural elucidation of these arabinosides was based on <sup>1</sup>H NMR, ir, and uv spectrometry and on elemental analysis. The purity was assured by the homogeneity in several thin-layer systems.

The site of glycosylation was established as N<sub>1</sub> by the direct comparison of the reported ultraviolet absorption spectra of 1-( $\beta$ -D-ribofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one<sup>27</sup> [ $\lambda$  max (pH 1) 244 nm ( $\epsilon$  5.0), 285 s (12.1), 292 (12.3), 305 s (7.9);  $\lambda$  max (pH 7) 251 nm ( $\epsilon$  6.4), 302 (14.9), 309 s (12.8);  $\lambda$  max (pH 11) 251 nm ( $\epsilon$  6.3), 302 (15.5), 309 s (14.1)] or 7-amino-1-( $\beta$ -D-ribofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one<sup>27</sup> [ $\lambda$  max (pH 1) 265 nm ( $\epsilon$  9.2), 301 (22.1);  $\lambda$  max (pH 7) 293 nm ( $\epsilon$  22.6);  $\lambda$  max (pH 11) 292 nm ( $\epsilon$  22.9)] with the ultraviolet absorption spectra observed for 6 or 7 (see Experimental Section), respectively, which are superimposable. The anomeric configuration was unequivocally established as  $\beta$  by subjecting 6 to periodate oxidation followed by reduction with sodium

borohydride.<sup>29</sup> Thus, compound 6,  $[\alpha]^{25}_D -3.75^\circ$ , produced the hydroxyethylglycerol compound 8 with  $[\alpha]^{25}_D +77.02^\circ$ . Similar oxidation and reduction of 1-( $\beta$ -D-ribofuranosyl)imidazo[1,2-c]pyrimidin-5-one,<sup>27</sup>  $[\alpha]^{25}_D -52.4^\circ$ , also produced 8 with  $[\alpha]^{25}_D +75.22^\circ$ . This change from negative to a large positive specific rotation indicated<sup>30</sup> the anomeric configuration of 6 and hence 3, 4, 5, and 7 as  $\beta$ .



**Biological Evaluation. Antiviral.** Antiviral activity was determined by observing the inhibition of virus-induced cytopathic effects (CPE). In this system, cultures of human carcinoma of the nasopharynx (KB) cells were grown in disposable plastic microplates.<sup>31</sup> Monolayers (18–24 h) of cells were exposed to 320 CCID<sub>50</sub> of virus and a series of concentrations of each compound ranging from 1000 to 1  $\mu$ g/ml was added within 15 min. The cells were observed for CPE development after a 72-h incubation at 37°. The degree of CPE inhibition and compound cytotoxicity were scored numerically and used in calculating a virus rating (VR) as described previously.<sup>31</sup> Significance of activity in terms of VR's has been assigned as follows: <0.5, slight activity; 0.5–0.9, moderate activity; and  $\geq 1.0$ , marked activity. Viruses used in this study were type 1 herpes simplex, type 3 parainfluenza, and type 13 rhino. Of all the compounds tested only 4 and 5 had slight antiviral activity against type 13 rhino (VR = 0.2) and the rest of the compounds were devoid of antiviral activity in these systems.

**Antimicrobial.** The compounds synthesized for this study were also assayed for antimicrobial activity. Clinical isolates of *Candida albicans* (Ca), *Escherichia coli* (Ec), *Klebsiella pneumonia* (Kp), *Proteus mirabilis* (Pm), *Staphylococcus aureus* (Sa), and *Trichophyton mentagrophytes* (Tm) were used for this study. In vitro sensitivity of these organisms to this series of arabinosyl-imidazo[1,2-c]pyrimidines was quantitatively determined by broth dilution assay.<sup>32</sup> Serial dilutions were prepared in chemically defined medium in a range from 0.4 to 0.005  $\mu$ mol/ml. The minimal inhibitory concentration (MIC) was recorded as the highest dilution of compound which prevented visible growth of the pathogen. Bacterial and yeast MIC's were read following 24 h of incubation at 35°. Dermatophyte inhibition was read after 48 h of incubation at 30°. Of the five compounds screened in vitro, only 4 and 5 exhibited slight activity against Sa and Tm [MIC ( $\mu$ mol/ml) Sa, 0.16; and Tm, 0.04]. All other compounds tested were inactive.

Thus, it could be concluded that this new class of the synthetic inosine and guanosine analogues of the  $\beta$ -D-arabinofuranosylimidazo[1,2-c]pyrimidines, which have close structural resemblance to both 9- $\beta$ -D-arabinofuranosylhypoxanthine (or guanine) and 3-deazainosine (or guanosine) is devoid of any significant antiviral or antimicrobial activity.

## Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Specific rotations were measured in a 1-dm tube with a Perkin-Elmer Model 141

automatic digital readout polarimeter. Nuclear magnetic resonance (<sup>1</sup>H NMR) spectra were recorded at 60 MHz on a Hitachi Perkin-Elmer R-20A spectrometer in Me<sub>2</sub>SO-*d*<sub>6</sub> using DSS as an internal standard. Ultraviolet spectra (uv,  $\epsilon \times 10^{-3}$ , s = shoulder) were recorded on a Cary Model 15 spectrophotometer and infrared spectra (ir) on a Perkin-Elmer 257 spectrophotometer (KBr pellets). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and the results are within  $\pm 0.4\%$  of the theoretical values. ICN-Woelm silica gel (70–230 mesh) was used for column chromatography. Chromatography solvent mixtures were by volume and the systems used were A, ethyl acetate–water–1-propanol (4:2:1, upper phase); B, chloroform–methanol (19:1). Detection of components on silica gel F-254 (EM Reagents) was by ultraviolet light and with 10% sulfuric acid in methanol spray followed by heating. Evaporations were carried out under reduced pressure with bath temperature below 30°.

**7-Chloro-1-(2,3,5-tri-O-benzyl- $\beta$ -D-arabinofuranosyl)-imidazo[1,2-c]pyrimidin-5-one (3).** 2,3,5-Tri-O-benzyl-1-O-(*p*-nitrobenzoyl)-D-arabinofuranose<sup>33</sup> (25.0 g, 44 mmol) was dissolved in anhydrous methylene chloride (350 ml) and the solution was cooled to 0° while a slow stream of dry hydrogen chloride gas was bubbled through for 2 h. The *p*-nitrobenzoic acid which had separated in almost quantitative yield (7.3 g) was removed by filtration and washed with methylene chloride (3  $\times$  25 ml). The filtrate and washings were evaporated to dryness and held at full pump vacuum for 2 h. The residual colorless syrupy 2,3,5-tri-O-benzyl- $\alpha$ -D-arabinofuranosyl chloride (2) was dissolved in benzene (300 ml, dried over sodium) and added to the trimethylsilyl compound 1 obtained by refluxing 7-chloro-imidazo[1,2-c]pyrimidin-5-one<sup>27</sup> (6.80 g, 40 mmol) in hexamethyldisilazane (HMDS, 25 ml) containing a catalytic amount of ammonium sulfate for 14 h, under anhydrous conditions, and distilling off the excess of HMDS in vacuo. The reaction mixture was heated under gentle reflux for 20 h with the exclusion of moisture. The cooled mixture was filtered to remove 0.30 g of unreacted heterocyclic base before it was evaporated to dryness. The solution of the dark residue in chloroform (500 ml) was washed with saturated aqueous sodium bicarbonate solution (2  $\times$  150 ml), followed by saturated aqueous sodium chloride solution (2  $\times$  100 ml), and finally with water (3  $\times$  100 ml) before it was dried over anhydrous sodium sulfate. The chloroform was evaporated to dryness and the residual foam (24.0 g) was chromatographed on a silica gel column (6.5  $\times$  70 cm) prepacked in chloroform and eluted with solvent B. The band carrying the product was collected and evaporated to dryness. The residual syrup was dissolved in methanol (25 ml); ether was added to the cloud point and refrigerated. The crystals that deposited were collected to yield 20.10 g (91.6%, based on the recovery of unreacted base), mp 98–100°. Recrystallization from ethanol afforded an analytically pure sample: mp 100–101°;  $[\alpha]^{25}_D +43.5^\circ$  (c 1.0, Me<sub>2</sub>SO); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>-D<sub>2</sub>O)  $\delta$  6.35 (d, *J* = 5.5 Hz, C<sub>1</sub>H), 6.90 (s, C<sub>8</sub>H), 7.63 (d, *J* = 3.5 Hz, C<sub>2</sub>H), 7.70 (d, *J* = 3.5 Hz, C<sub>3</sub>H) and sugar protons; uv  $\lambda$  max (pH 1) 252 nm ( $\epsilon$  5.09), 303 (14.15);  $\lambda$  max (pH 7) 255 nm, s ( $\epsilon$  15.29), 314 (16.69);  $\lambda$  max (pH 11) 255 nm, s ( $\epsilon$  12.52), 314 (16.17). Anal. (C<sub>32</sub>H<sub>30</sub>ClN<sub>3</sub>O<sub>5</sub>, 572.04) C, H, N.

**1-(2,3,5-Tri-O-benzyl- $\beta$ -D-arabinofuranosyl)imidazo[1,2-c]pyrimidin-5-one (4).** To a solution of 7-chloro-1-(2,3,5-tri-O-benzyl- $\beta$ -D-arabinofuranosyl)imidazo[1,2-c]pyrimidin-5-one (3, 2.5 g, 4.3 mmol) in ethanol (150 ml) containing concentrated ammonium hydroxide (1.0 ml) was added 10% palladium on carbon (0.35 g) and the mixture was hydrogenated at 40 psi at room temperature for 1.5 h. The mixture was flushed with nitrogen before filtering through a Celite pad. The filtrate was evaporated to dryness and the residue was chromatographed on a silica gel column (3.5  $\times$  50 cm) prepacked in chloroform and eluted with solvent B. The appropriate fractions were collected and evaporated to dryness to an oil: yield 2.15 g (91.5%);  $[\alpha]^{25}_D +11.4^\circ$  (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>)  $\delta$  6.45 (d, *J* = 5.0 Hz, C<sub>1</sub>H); uv  $\lambda$  max (pH 1) 245 nm, s ( $\epsilon$  4.60), 293 (9.20);  $\lambda$  max (pH 7) 250 nm ( $\epsilon$  5.62), 303 (11.25);  $\lambda$  max (pH 11) 250 nm ( $\epsilon$  4.60), 303 (10.74). Anal. (C<sub>32</sub>H<sub>31</sub>N<sub>3</sub>O<sub>5</sub>, 537.59) C, H, N.

**7-Amino-1-(2,3,5-tri-O-benzyl- $\beta$ -D-arabinofuranosyl)-imidazo[1,2-c]pyrimidin-5-one (5).** A solution of 7-chloro-1-(2,3,5-tri-O-benzyl- $\beta$ -D-arabinofuranosyl)imidazo[1,2-c]-

pyrimidin-5-one (3, 2.0 g, 3.4 mmol) in methanol (60 ml) containing liquid ammonia (20 ml) was heated in a sealed steel reaction vessel at 90–95° for 50 h. The resulting dark solution was evaporated to dryness and the residue was chromatographed on silica gel column (3.5 × 45 cm) prepacked in chloroform and eluted with solvent B. The appropriate fractions were pooled and the solvent was removed to yield a chromatographically homogeneous gum: 0.81 g (42.0%);  $[\alpha]^{25}_D +58.6^\circ$  (c 1.0,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$  6.10 (d,  $J = 5.0$  Hz,  $\text{C}_1\text{H}$ ); uv  $\lambda$  max (pH 1) 265 nm,  $s$  ( $\epsilon$  7.74), 302 (17.55);  $\lambda$  max (pH 7) 293 nm ( $\epsilon$  18.07);  $\lambda$  max (pH 11) 293 nm ( $\epsilon$  18.59). Anal. ( $\text{C}_{32}\text{H}_{32}\text{N}_4\text{O}_5$ , 552.61) C, H, N.

**1-( $\beta$ -D-Arabinofuranosyl)imidazo[1,2-c]pyrimidin-5-one (6).** Palladium chloride (2.0 g) was prereduced with hydrogen in 2-methoxyethanol (30 ml) at an initial pressure of 25 psi for 45 min. A solution of 7-chloro-1-(2,3,5-tri-*O*-benzyl- $\beta$ -D-arabinofuranosyl)imidazo[1,2-c]pyrimidin-5-one (3, 2.35 g, 4.1 mmol) in 2-methoxyethanol (45 ml) was added and the mixture was hydrogenated at an initial pressure of 50 psi for 55 min. The catalyst was removed by filtration through a Celite pad and washed with 2-methoxyethanol (2 × 20 ml). The combined filtrate and washings were neutralized by stirring with Dowex 1 X2 (carbonate form) ion-exchange resin. The clear, neutral solution, free from resin, was evaporated to dryness and the residue was triturated with water (5 ml) and stored at 5° overnight. The crystalline solid that separated was collected and dried to yield 0.70 g (63.7%). It was recrystallized from water as colorless needles: mp 216–218° dec;  $[\alpha]^{25}_D -3.75^\circ$  (c 1.0,  $\text{Me}_2\text{SO}$ );  $^1\text{H NMR}$  ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$  6.22 (d,  $J = 5.0$  Hz,  $\text{C}_1\text{H}$ ), 6.65 (d,  $J = 6.0$  Hz,  $\text{C}_8\text{H}$ ), 7.76 (d,  $J = 3.0$  Hz,  $\text{C}_3\text{H}$ ), 7.95 (d,  $J = 3.0$  Hz,  $\text{C}_2\text{H}$ ), 8.0 (d,  $J = 6.0$  Hz,  $\text{C}_7\text{H}$ ); uv  $\lambda$  max (pH 1) 244 nm ( $\epsilon$  4.86), 285 s (11.0), 292 (11.51);  $\lambda$  max (pH 7) 250 nm ( $\epsilon$  6.14), 301 (13.56), 309 s (11.26);  $\lambda$  max (pH 11) 250 nm ( $\epsilon$  5.88), 302 (14.59), 309 s (12.28); ir 1650  $\text{cm}^{-1}$  (C=O of heterocycle). Anal. ( $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_5$ , 267.23) C, H, N.

A similar debenzoylation of 4 (2.0 g, 3.7 mmol) under acidic conditions gave 0.42 g (42.3%) of 1-( $\beta$ -D-arabinofuranosyl)imidazo[1,2-c]pyrimidin-5-one (6) identical (melting point, mixture melting point, uv, ir,  $^1\text{H NMR}$ , optical rotation, TLC, etc.) with 6 prepared as above.

**7-Amino-1-( $\beta$ -D-arabinofuranosyl)imidazo[1,2-c]pyrimidin-5-one (7).** A solution of 7-amino-1-(2,3,5-tri-*O*-benzyl- $\beta$ -D-arabinofuranosyl)imidazo[1,2-c]pyrimidin-5-one (5, 0.50 g, 0.9 mmol) in 2-methoxyethanol (50 ml) was hydrogenated with prereduced palladium chloride (0.42 g) at 50 psi for 50 min and treated as described in 6 to yield 0.19 g (74.4%): mp 261–262° dec (sinters at 248–249°);  $[\alpha]^{25}_D +53.9^\circ$  (c 1.0,  $\text{H}_2\text{O}$ );  $^1\text{H NMR}$  ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$  5.82 (d,  $J = 5.0$  Hz,  $\text{C}_1\text{H}$ ), 6.34 (broad, s,  $\text{NH}_2$ ), 5.50 (s,  $\text{C}_8\text{H}$ ), 7.40 (d,  $J = 2.0$  Hz, 2 H,  $\text{C}_2\text{H}$  and  $\text{C}_3\text{H}$ ); uv  $\lambda$  max (pH 1) 270 nm,  $s$  ( $\epsilon$  9.94), 300 (19.61);  $\lambda$  max (pH 7) 292 nm ( $\epsilon$  20.18);  $\lambda$  max (pH 11) 292 nm ( $\epsilon$  20.46); ir 1630 (C=O of heterocycle), 3340  $\text{cm}^{-1}$  ( $\text{NH}_2$ ). Anal. ( $\text{C}_{11}\text{H}_{14}\text{N}_4\text{O}_5$ , 282.25) C, H, N.

**Periodate Oxidation and Sodium Borohydride Reduction.** To a solution of 1-( $\beta$ -D-arabinofuranosyl)imidazo[1,2-c]pyrimidin-5-one (6, 26.5 mg) in water (2.5 ml) was added 0.245 M sodium metaperiodate (0.60 ml) and the resulting mixture was left in the dark for 4 days with intermittent shaking. Excess periodate was removed by the addition of barium chloride (20 mg) before it was filtered. Sodium borohydride (50 mg) was added to the filtrate, followed after 2 h by 10% acetic acid (0.5 ml). The specific rotation was determined on this solution as  $[\alpha]^{25}_D +77.02^\circ$  based on the original weight of 6.

An identical oxidation and reduction of 1-( $\beta$ -D-ribofuranosyl)imidazo[1,2-c]pyrimidin-5-one<sup>27</sup> (26.5 mg) gave the specific rotation of the resulting solution as  $[\alpha]^{25}_D +75.22^\circ$ .

## References and Notes

- G. E. Underwood, *Proc. Soc. Exp. Biol. Med.*, **111**, 660 (1962).
- H. E. Kaufman and E. D. Maloney, *Arch. Ophthalmol.*, **69**, 626 (1963).
- R. D. Casey and R. R. Ellison, *Clin. Res.*, **13**, 337 (1965).
- T. C. Hall, J. Griffiths, G. Watters, R. Baringer, and S. Katz, *Pharmacologist*, **10**, 171 (1968).
- E. M. McKelvey and H. C. Kwaan, *Blood*, **34**, 706 (1969).
- M. D. Dowling, Jr., I. H. Krakoff, and D. A. Karnofsky in "Chemotherapy of Cancer", W. H. Cole, Ed., Lea and Febiger, Philadelphia, Pa., 1970, p 1.
- D. Prager, M. Bruder, and A. Sawitsky, *J. Pediat.*, **78**, 321 (1971).
- F. M. Schabel, Jr., *Chemotherapy*, **13**, 321 (1968).
- F. M. Schabel, Jr., and J. A. Montgomery in "Chemotherapy of Virus Diseases", Vol. 1, D. Bauer, Ed., Pergamon Press, Oxford, 1972, Chapter 4, p 231.
- B. E. Juel-Jensen and F. O. MacCallum in "Herpes Simplex, Varicella and Zoster", J. B. Lippincott Co., Philadelphia, Pa., 1972.
- L. T. Ch'ien, F. M. Schabel, Jr., and C. A. Alford, Jr., in "Selective Inhibitors of Viral Functions", W. A. Carter, Ed., CRC Press, Cleveland, Ohio, 1973, p 227.
- For a review of preliminary results, see *J. Am. Med. Assoc.*, **230**, 189 (Oct 14, 1974).
- R. W. Sidwell, L. B. Allen, J. H. Huffman, T. A. Khwaja, R. L. Tolman, and R. K. Robins, *Chemotherapy*, **19**, 325 (1973).
- A. M. Mian, R. Harris, R. W. Sidwell, R. K. Robins, and T. A. Khwaja, *J. Med. Chem.*, **17**, 259 (1974).
- G. R. Revankar, J. H. Huffman, L. B. Allen, R. W. Sidwell, R. K. Robins, and R. L. Tolman, *J. Med. Chem.*, **18**, 721 (1975).
- L. B. Allen, J. M. Thompson, J. H. Huffman, G. R. Revankar, R. L. Tolman, L. N. Simon, R. K. Robins, and R. W. Sidwell, *Antimicrob. Agents Chemother.*, **8**, 468 (1975).
- L. B. Allen, J. H. Huffman, G. R. Revankar, R. L. Tolman, L. N. Simon, R. K. Robins, and R. W. Sidwell, *Antimicrob. Agents Chemother.*, **8**, 474 (1975).
- R. W. Sidwell, L. B. Allen, J. H. Huffman, G. R. Revankar, R. K. Robins, and R. L. Tolman, *Antimicrob. Agents Chemother.*, **8**, 463 (1975).
- Y. Mizuno, T. Itoh, and K. Saito, *J. Org. Chem.*, **29**, 2611 (1964).
- J. A. Montgomery and K. Hewson, *J. Med. Chem.*, **9**, 105 (1966).
- R. J. Rousseau, L. B. Townsend, and R. K. Robins, *Biochemistry*, **5**, 756 (1966).
- Y. Mizuno, S. Tazawa, and K. Kageura, *Chem. Pharm. Bull.*, **16**, 2011 (1968).
- J. A. May, Jr., and L. B. Townsend, *J. Chem. Soc., Perkin Trans. 1*, 125 (1975).
- P. D. Cook, R. J. Rousseau, A. M. Mian, R. B. Meyer, Jr., P. Dea, G. Ivanovics, D. G. Streeter, J. T. Witkowski, M. G. Stout, L. N. Simon, R. W. Sidwell, and R. K. Robins, *J. Am. Chem. Soc.*, **97**, 2916 (1975).
- P. D. Cook, R. J. Rousseau, A. M. Mian, P. Dea, J. T. Witkowski, and R. K. Robins, *J. Am. Chem. Soc.*, **98**, 1492 (1976).
- M. Ikehara, T. Fukui, and S. Uesugi, *J. Biochem.*, **76**, 107 (1974).
- D. G. Bartholomew, P. Dea, R. K. Robins, and G. R. Revankar, *J. Org. Chem.*, **40**, 3708 (1975).
- E. Wittenburg, *Z. Chem.*, **4**, 303 (1964).
- C. P. J. Glaudemans and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 3004 (1963).
- G. R. Revankar and L. B. Townsend, *J. Heterocycl. Chem.*, **7**, 1329 (1970).
- R. W. Sidwell and J. H. Huffman, *Appl. Microbiol.*, **22**, 797 (1971).
- G. R. Revankar, T. R. Matthews, and R. K. Robins, *J. Med. Chem.*, **18**, 1253 (1975).
- R. Barker and H. G. Fletcher, Jr., *J. Org. Chem.*, **26**, 4605 (1961).