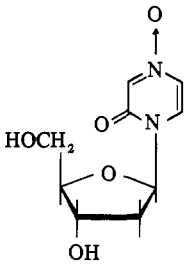
Communications to the Editor

Synthesis of 1,2-Dihydro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-2-oxopyrazine 4-Oxide, a Potent Analog of Deoxyuridine

Sir:

The uridine analog 1,2-dihydro-1-(β-D-ribofuranosyl)-2-oxopyrazine 4-oxide, which has recently been synthesized,[1] has demonstrated only moderate inhibitory activity against *Streptococcus faecium* and *Escherichia coli* B, the ED_{50} being 8×10^{-6} and 1×10^{-5} *M*, respectively, similar to that of the corresponding base, the antibiotic emimycin.[2] We have now prepared 1,2-dihydro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-2-oxopyrazine 4-oxide (I), the structural analog of 2'-deoxyuridine, and found it to be approximately 100,000 times more effective as an inhibitor of these microbial systems than is the ribonucleoside.



I

The synthesis was achieved by condensation of 2-(trimethylsilyl)oxypyrazine 4-oxide with 2-deoxy-3,5-di-*O*-*p*-chlorobenzoyl-α-D-*erythro*-pentofuranosyl chloride, followed by separation and hydrolysis of the resulting α and β anomers of the blocked nucleosides. 2-(Trimethylsilyl)-oxypyrazine 4-oxide, previously prepared[1] but not isolated, was synthesized more advantageously by a different route.

2-Chloropyrazine (0.2 mol) was oxidized with *m*-chloroperbenzoic acid (0.24 mol) in 550 ml of 1,2-dichloroethane at 65° for 24 hr to give an almost quantitative yield of 2-chloropyrazine 4-oxide. The crude product was hydrolyzed by refluxing (2 hr) with 2 equiv of NaOH in 80 ml of water. After neutralization, the aqueous reaction mixture was concentrated to dryness *in vacuo* and the residue was suspended in toluene. Traces of water were removed by azeotropic distillation using a Dean-Stark trap. Triethylamine (0.2 mol) and trimethylsilyl chloride (0.3 mol) were added and the mixture was refluxed for 6 hr. After filtration and removal of the toluene *in vacuo*, vacuum distillation of the residue afforded 2-(trimethylsilyl)oxypyrazine 4-oxide in 60% overall yield: bp 140° (8.8 mm); ir (CCl_4) 1255 ($SiMe_3$), 1220 (N→O), 869 cm^{-1} ($SiMe_3$, N→O); nmr ($CDCl_3$) 0.39 (s, 9 H), 7.73 (d, 1 H), 7.80 (d, 1 H), 7.98 ppm (d, 1 H).

An excess of this silyl compound (1.9 mmol) was allowed to react with 2-deoxy-3,5-di-*O*-*p*-chlorobenzoyl-α-D-*erythro*-pentofuranosyl chloride[3] (1.0 mmol) in benzene, at room temperature for 3 days, in the presence of 4A molecular sieves which was found necessary for the reaction to take place. After extraction with saturated aqueous $NaHCO_3$, column chromatography on silica gel with chloroform-ethyl acetate (3:2) gave 44% yield of an anomeric mixture (α/β = 1.2:1.0) of the blocked nucleosides. Crystallization from toluene gave 1,2-dihydro-1-(2-deoxy-3,5-di-*O*-*p*-chlorobenzoyl-α-D-*erythro*-pentofuranosyl)-2-oxopyrazine 4-oxide: yield 22% (based on the halogenose); mp 169–170° dec; $[\alpha]^{25}D$ −114° (*c* 0.5, $CHCl_3$); ir (KBr) 1715 (C=O, ester), 1650 (C=O, amide), 1235, 845 cm^{-1} (N→O); nmr ($CDCl_3$) $H_{1'}$ δ 6.37 ppm ("q", *J* = 2 and 6 Hz, peak width = 8 Hz). *Anal.* ($C_{23}H_{18}Cl_2N_2O_7$) C, H, Cl, N. Crystallization of the residue from toluene–petroleum ether gave 1,2-dihydro-1-(2-deoxy-3,5-di-*O*-*p*-chlorobenzoyl-β-D-*erythro*-pentofuranosyl)-2-oxopyrazine 4-oxide: yield 18% (based on the halogenose); mp 165–166° dec; $[\alpha]^{25}D$ +4.5° (*c* 1.0, $CHCl_3$); ir (KBr) 1710 (C=O, ester), 1655 (C=O, amide), 1230, 845 cm^{-1} (N→O); nmr ($CDCl_3$) $H_{1'}$ δ 6.38 ppm ("t", *J* = 6.5 Hz, peak width = 13 Hz). *Anal.* ($C_{23}H_{18}Cl_2N_2O_7$) C, H, Cl, N. Treatment of the blocked α anomer with MeOH–NH_3 at 5° for 13 hr, followed by recrystallization from ethanol, gave 1,2-dihydro-1-(2-deoxy-α-D-*erythro*-pentofuranosyl)-2-oxopyrazine 4-oxide (76%): mp 175° dec; $[\alpha]^{25}D$ −150° (*c* 0.2, MeOH); uv max (95% EtOH) 223 mμ (ε 20,080), 283 (9110), 335 (4680); ir (KBr) 3445, 3260 (OH), 1650 (C=O), 1210, 850 cm^{-1} (N→O); nmr (D_2O) $H_{1'}$ δ 6.35 ppm ("q", *J* = 2.5 and 6.5 Hz, peak width = 9 Hz). *Anal.* ($C_9H_{12}N_2O_5$) C, H, N. Treatment of the blocked β anomer with MeOH–HN_3 at 5° for 5 hr, followed by column chromatography on silica gel with chloroform–methanol (4:1), and crystallization from methanol–ether provided 1,2-dihydro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-2-oxopyrazine 4-oxide (I, 71%): mp 142–143° dec; $[\alpha]^{25}D$ +134° (*c* 0.25, MeOH); uv max (95% EtOH) 223 mμ (ε 21,690), 283 (9370), 335 (4820); ir (KBr) 3380–3280 (OH), 1650 (C=O), 1205, 845 cm^{-1} (N→O); nmr (D_2O) $H_{1'}$ δ 6.37 ppm ("t", *J* = 6.5 Hz, peak width = 13 Hz). *Anal.* ($C_9H_{12}N_2O_5$) C, H, N.

The anomeric configurations were assigned on the basis of the nmr spectra of the anomeric proton ($H_{1'}$) which clearly showed the characteristic "pseudo-triplet" ("t") for the β and the "multiplet of four" ("q") for the α anomers of both the blocked and free nucleosides, with similar values for the apparent coupling constants and "peak width" measurements as those reported previously for the corresponding anomeric 2'-deoxyribonucleosides of a variety of other heterocyclic bases.[4] However, assignments based on empirical nmr rules should be considered as tentative.

The β anomer I inhibited the growth of *S. faecium* and *E. coli* at 5×10^{-11} and 4×10^{-11} *M*, respectively. The α anomer was active in these systems at 4×10^{-5} and 1×10^{-4} *M*, respectively. The inhibition of growth by these nucleosides was prevented, to various extents, by the natural pyrimidines.

Such a large difference in the potency of a deoxyribonucleoside analog as compared to the corresponding ribonucleoside derivative is quite uncommon and puts greater emphasis on the preparation and evaluation of other deoxyribonucleoside analogs.

Acknowledgment. This work was supported by U. S. Public Health Service Grants CA 06695 and CA 12585 from the National Cancer Institute, NIH, and by a grant (IC-27) from the American Cancer Society.

References

(1) M. Bobek and A. Bloch, *J. Med. Chem.*, 15, 164 (1972).
(2) M. Terao, K. Karasawa, N. Tanaka, H. Yonehara, and H. Umezawa, *J. Antibiot., Ser. A.*, 13, 401 (1960); M. Terao, *ibid.*, 16, 182 (1963).
(3) M. P. Kotick, C. Szantay, and T. J. Bardos, *J. Org. Chem.*, 34, 3806 (1969); J. J. Fox, N. C. Yung, I. Wempen, and M. Hoffer, *J. Amer. Chem. Soc.*, 83, 4066 (1961).
(4) M. J. Robins and R. K. Robins, *ibid.*, 87, 4934 (1965); C. D. Jardetzky, *ibid.*, 83, 2919 (1961); R. U. Lemieux, *Can. J. Chem.*, 39, 116 (1961); P. Nuhn, A. Zschunke, D. Heller, and G. Wagner, *Tetrahedron*, 25, 2139 (1969).

Phillip T. Berkowitz, Thomas J. Bardos*
Department of Medicinal Chemistry, School of Pharmacy State University of New York at Buffalo, Buffalo, New York 14214

Alexander Bloch
Department of Experimental Therapeutics, Roswell Park Memorial Institute, New York State Department of Health Buffalo, New York 14203

Received September 25, 1972

Book Reviews

Luminescence Spectrometry in Analytical Chemistry. By James D. Winefordner, Stephen G. Schulman, and Thomas C. O'Haver. Wiley, New York, N. Y. 1972. xiii + 354 pp. 16 × 23.5 cm. $19.95.

This is a comprehensive and unified book covering the physical and analytical aspects of atomic and molecular luminescence spectroscopy. The treatment is unique, therefore, in that atomic fluorescence, molecular fluorescence, and phosphorescence are described in a single volume.

Approximately one-half of the monograph is devoted to theory. Though there is rather extensive mathematical development in this section, the authors demonstrate an exceptional ability to relate fundamental expressions and relationships to problems that can arise even in the most applied work. The remaining portion of the book includes discussions of instrumentation, methodology, and analytical use of luminescence spectroscopy. The treatment of molecular luminescence measurements is particularly good because sources of error in generating and interpreting data are well described. The last chapter contains tables listing detection limits for most of the elements using flame and solution fluorimetry. Included here as well are comparisons to data derived from other applicable methods (neutron activation analysis, spark source mass spectrometry). The utility of solution luminescence techniques in quantitative analysis of organic compounds is only briefly reviwed in the final chapter since a monograph exclusively devoted to applications is apparently planned in the "Chemical Analysis" series (edited by Elving and Kolthoff).

The text is relatively free of typographical errors. The notation used for chapters and subheadings is cumbersome and sometimes confusing. The authors consistently refer to extinction or molecular extinction coefficients instead of the more acceptable term, molar absorbtivity. These are minor objections. The book is generally well written and is recommended as a general reference. If its "companion" monograph on analytical applications is as well done, the combined volumes could serve as a current and useful treatise on luminescence spectrometry.

Division of Medicinal Chemistry
College of Pharmacy
The University of Iowa
Iowa City, Iowa 52240
Robert V. Smith

Studies of Neurotransmitters at the Synaptic Level. Edited by E. Costa, L. L. Iversen, and R. Paoletti. Advances in Biochemical Psychopharmacology. Vol. 6. Raven Press, New York, N. Y. 1972. viii + 248 pp. 16.4 × 24.3 cm. $15.95.

This symposium volume contains 14 original contributions to the chemistry, histochemistry, cell biology, enzymology, and pharmacology of neurotransmitters and the nerve terminals, with emphasis on novel methodology used in these researches. The work reported extends to the role and disposition of newly synthesized amines in central catecholaminergic neurons and drugs affecting monoamines in the basal ganglia. A description of inhibitors of monooxygenases and biochemical effects of dopa on *S*-adenosylmethionine and norepinephrine levels rounds out the sympathetic side of components of the nervous system. Studies on the isolation of the cholinergic receptor protein and the biochemical pharmacology of cholinergic function lead to the parasympathetic area. This also includes a new investigation of psychotomimetic anticholinergic agents of the Ditran type. The book, addressed to the neurobiochemist and neuropharmacologist, is printed especially beautifully, indexed well, and remarkably free of errors.

Chemistry Department
University of Virginia
Charlottesville, Virginia 22901
Alfred Burger

Stereochemistry and Its Application in Biochemistry. By W. L. Alworth. Wiley, New York, N. Y. 1972. xi + 311 pp. 15 × 23.5 cm. $16.95.

This presentation is intended to provide introductory biochemistry students an insight into the stereochemical principles that are involved in molecular interactions within biological systems. The areas covered, which are representative of the field but general in nature, are historical aspects of biological stereospecificity, introductory aspects of molecular symmetry, molecular disymmetry, optical activity, and biological stereospecificity, examples of stereochemical analysis, and numerous examples of biochemical differentiation between chemically like-paired groups. The latter sections of the book cover many of the classical examples of stereospecificity between chemically like-paired groups which are familiar to most students of biochemistry. Examples from the fundamental pathways of intermediate metabolism including TCA cycle, pyruvate metabolism, sterol biosynthesis, and ketose–aldose interconversions are discussed. In addition to the classical examples, the more recent experimental observations of biological stereospecificity between chemically like methyl hydrogens of chiral acetate and pyruvate are presented and discussed. The book is in no way meant to be an all encompassing review of the literature, but rather provides one with examples on which to build his knowledge and appreciation for the stereospecificity found in biological systems.

Utilization of the text at an advanced undergraduate level or an introductory graduate level course should provide the student with an appreciation for biological stereospecificity and will enable them to fully comprehend recent experimental results. It could also be highly recommended as a means of introduction or review of biological stereospecificity for practicing biochemists and chemists.

The author is to be commended for putting together a comprehensive introduction of the area of asymmetry in biological systems. The author's stated aims have been admirably achieved.

Department of Biochemistry
McCollum Laboratories
University of Kansas
Lawrence, Kansas 66044
Ronald T. Borchardt