hydrazone (2.3 g) which was sublimed at 140–150° (5×10^{-3} mm) to yield crystalline 1 (1 g, 48%), mp 135–137°. Recrystn from EtOH afforded 0.85 g, mp 137–138°. *Anal.* ($C_{16}H_{13}ClN_2O$) C, H, N.

Similarly prepd was **2** (65% yield), mp 229–230° (from $CHCl_3$–EtOH) *(Anal.* ($C_{15}H_{11}ClN_2O$) C, H, N), and, using 2-benzoyl-4,5-dimethoxyphenylacetic acid,[7] 1-phenyl-3-methyl-3,5-dihydro-7,8-dimethoxy-4*H*-benzo[2,3]diazepin-4-one (**3**) (40% yield) (from MeOH), mp 160–162° (*Anal.* ($C_{18}H_{18}N_2O_3$) C, H, N), and 1-phenyl-3,5-dihydro-7,8-dimethoxy-3*H*-benzo[2,3]diazepin-4-one (**4**) (75% yield) (from MeOH), mp 200–202° (*Anal.* ($C_{17}H_{16}N_2O_3$) C, H, N).

1-Methyl-3,5-dihydro-7,8-dimethoxy-4*H*-benzo[2,3]diazepin-4-one (5) and 1-Methyl-2-amino-2,3-dihydro-3-oxo-6,7-dimethoxyisoquinoline (8). 2-Acetyl-4,5-dimethoxyphenylacetic acid[8] (7.2 g, 30 mmoles) and hydrazine hydrate (1.5 g, 30 mmoles) in EtOH (200 ml) were heated under reflux for 2 hr, the solution was left overnight and concd to give the hydrazone **10** (5.3 g, 70%), mp 170–171° dec (from $CHCl_3$). *Anal.* ($C_{12}H_{16}N_2O_4$) C, H, N. The hydrazone (7.2 g, 28 mmoles) was heated at 180° (2×10^{-2} mm) for 4 hr; the cooled product was sepd into water-soluble and -insoluble parts. The latter was crystd from EtOH to give **5** (3.2 g, 45%), mp 210–212°. *Anal.* ($C_{12}H_{14}N_2O_3$) C, H, N.

The water-soluble fraction was crystd from MeOH to give **8** (1.8 g, 25%), mp 227–229°. *Anal.* ($C_{12}H_{14}N_2O_3$) C, H, N.

1-Phenyl-3-(γ-dimethylaminopropyl)-3,5-dihydro-8-chloro-4*H*-benzo[2,3]diazepin-4-one (6). A soln of **2** (0.9 g, 3.3 mmoles) in dry dioxane (25 ml) was stirred with 50% NaH suspension (0.2 g, 5 mmoles) in mineral oil at 50° for 1 hr and then treated with γ-dimethylaminopropyl chloride (0.7 g) in dioxane (10 ml). The mixture was stirred at 50° overnight and filtered, and the filtrate was stripped of solvent. The basic product was isolated through dil HCl and was obtained as an oil (0.5 g) which crystd from hexane, 0.4 g (34%), mp 84–86°. *Anal.* ($C_{20}H_{22}ClN_3O$) C, H, N.

1-Methyl-3-(β-dimethylaminoethyl)-3,5-dihydro-7,8-dimethoxy-4*H*-benzo[2,3]diazepin-4-one (**7**), characterized as a maleate (85% yield), was prepd in a similar manner from **5**, mp 155–157° (from EtOH–Et_2O). *Anal.* ($C_{20}H_{27}N_3O_7$) C, H, N.

2-Acetyl-4,5-dimethoxyphenylacetic Acid Guanylhydrazone (11). The acid (1.45 g, 6 mmoles) and aminoguanidine hydrogen carbonate (0.8 g, 6 mmoles) in EtOH (25 ml) were heated under reflux overnight to give the guanylhydrazone (1.1 g, 63%), mp 291° dec (*Anal.* ($C_{13}H_{18}N_4O_4$) C, H, N), forming a HCl salt, mp 210–212° (from EtOH) (*Anal.* ($C_{13}H_{19}ClN_4O_4$) C, H, N).

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Synthesis of 9-(3-Deoxy-3-fluoro-β-D-arabinofuranosyl)adenine

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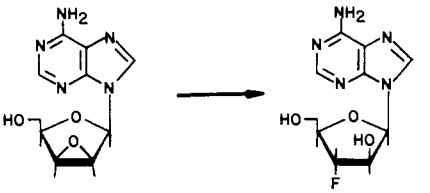
Modifications in the carbohydrate moiety of nucleosides that occur in the nucleic acids have led to structural analogs that possess important and useful biological properties. A significant example is 9-β-D-arabinofuranosyladenine (ara-A)[1] which has demonstrated significant antiherpes virus activity.[2,3] It was, therefore, of interest to prepare an ara-A analog (3-deoxy-3-fluoro-β-D-arabinofuranosyladenine, **2**) with a subtle modification in the carbohydrate moiety, in the hope that the antiviral activity might be maintained or increased with added selectivity.

The ring opening of the epoxide, 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine (**1**), seemed to provide the best approach



1 2

to the synthesis of **2**, since highly stereoselective scission of carbohydrate epoxides to the corresponding fluorohydrins has been observed[4-6] with KHF_2. Goodman and coworkers[7-9] have found, however, that 9-(2,3-anhydro-β-D-pentofuranosyl)adenines react with many nucleophiles to furnish mixtures of 2′- and 3′-substituted nucleosides. Treatment of **1** with KHF_2 in ethylene glycol at reflux gave a 41% yield of **2** as the single nucleoside product. As a result of the strenuous conditions required for displacement, there was considerable decomposition. Adenine was the only other isolable product; no other nucleosides were detected.

Exclusive opening of the epoxide at C-3 by fluoride ion was confirmed by elemental and chromatographic analysis as well as pmr spectral data for **2** which showed H-3′ as a pair of triplets ($J_{F,3'}$ = 53 Hz, $J_{3',4'}$ and $J_{2',3'}$ = 3.5 Hz) and H-1′ as a broadened doublet (fine splitting with fluorine) instead of a wide quartet ($J_{F,1'} \sim 18$ Hz), which would be expected if the fluorine were at C-2.[10] The mass spectral data indicated[11] from the presence of a *m/e* 178 (base + 44) peak, that the substituent at C-2 was a hydroxy group instead of fluorine.

Antiviral Evaluation.† *In vitro* cell culture experiments with herpes virus indicated that **2** possessed no significant antiviral activity, which suggests that the enzymatic site of action of ara-A[12] is extremely sensitive to changes in the carbohydrate moiety at C-3.

Experimental Section‡

9-(3-Deoxy-3-fluoro-β-D-arabinofuranosyl)adenine (2). A mixture of **1** (3.00 g, 12 mmoles) and KHF_2 (9.00 g) in ethylene glycol (45 ml) was heated to refluxing temperature for 55 min. The reaction mixture was cooled and applied directly on a column prepacked with silica gel (Merck 7734, 600 g) in EtOAc–*n*-PrOH–H_2O (4:1:2, upper phase). The product was eluted with the same solvent mixture and crystallized from water to give 1.33 g (41%) of needles: mp 261–262° dec; $[\alpha]^{25}D$ −12.7° (*c* 1.0, DMF); uv $\lambda_{max}^{pH\,1}$ 256 nm (ε 14,800), $\lambda_{max}^{pH\,7}$ 259 nm (ε 15,100), $\lambda_{max}^{pH\,11}$ 259 nm (ε 15,100); pmr (DMSO-d_6) δ 8.22 (s, 2, H_2+H_8), 7.30 (s, 2, NH_2), 6.38 [d (with

†The authors wish to thank Dr. R. W. Sidwell and his staff for the antiviral evaluation.

‡Melting point was determined on a Thomas-Hoover melting point apparatus and is uncorrected. The uv spectra were recorded on a Cary 15 spectrophotometer and optical rotation was determined with a Perkin-Elmer polarimeter 141. The infrared spectrum was recorded with a Perkin-Elmer 257 (KBr); nmr spectra were recorded with a Hitachi Perkin-Elmer R-20A nmr spectrometer (DSS); and the mass spectrum was recorded with a Perkin-Elmer 270 mass spectrometer. Satisfactory analytical data (C, H, N, F within ±0.4% of theoretical values) were obtained from Galbraith Laboratories, Inc., Knoxville, Tenn.

fine splitting ≤1 Hz), 1, $J_{1',2'}$ = 5.0 Hz, $H_{1'}$], 5.27 (two t, 1, $J_{2',3'} = J_{3',4'}$ = 3.5 Hz, $J_{3',F}$ = 53 Hz, $H_{3'}$), 4.62 (two q, 1, $J_{2',F}$ = 16.5 Hz, $H_{2'}$), 4.3 and 3.6 (m, 3, $H_{4'}$ and $H_{5'}$). *Anal.* ($C_{10}H_{12}N_5O_3F$) C, H, N, F.

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Book Reviews

Biochemical Aspects of Reactions on Solid Supports. Edited by G. R. Stark. Academic Press, New York, N. Y. 1971. x + 233 pp. $13.50.

This very useful little book presents five chapters on the preparation and uses of solid-support systems in protein chemistry and enzymology. The recent applications of solid-support technology to nucleic acid synthesis and degradation are included only in the form of a short list of references. The first chapter, by R. Goldman, L. Goldstein, and E. Katchalski, Water-Insoluble Enzyme Derivatives and Artificial Enzyme Membrances, is the largest and broadest one with a complete survey of methods of preparation of both covalent and noncovalent solid-support–enzyme derivatives. It also contains a brief analysis of the kinetic behavior of immobilized enzymes and a discussion of enzyme membranes and columns and their physical properties. The second chapter, by P. Cuatrecasas, Selective Absorbents Based on Biochemical Specificity, covers the whole exciting area of affinity chromatography, from the methods of preparation of affinity absorbants to the many and varied uses of these absorbants in biochemical research. Both chapters include extensive tabulation of what has been done in these areas and, in addition to giving a solid basis for further work, also impart to the reader a strong awareness of the very impressive potentials of these techniques. The next two chapters focus more directly on single purpose goals. Solid Phase Synthesis: The Use of Solid Supports and Insoluble in Peptide Synthesis by G. R. Marshall and R. B. Merrifield and Sequential Degradation of Peptides Using Solid Supports by G. S. Stark reinforce the solid-support applications from the previous chapters with the spectacular successes achieved in these areas. The last chapter by J. A. Patterson presents a survey of the preparation and properties of one of the most commonly used types of polymer supports: Preparation of Cross-Linked Polystyrenes and Their Derivatives for Uses as Solid Supports and Insoluble Reagents. Whereas most of the other topics in the book have been reviewed before, this chapter appears to be quite unique in the biochemical literature, and its subject is certainly of fundamental value to the theme of the book.

This book should have a most stimulating impact on the reader. The individual authors, all of whom have been active in developing this new field, have presented an impressive volume of information and ideas in an effective and very readable manner. Although the individual topics have been subject to previous reviews, there is an obvious advantage in having all topics assembled and brought up to date in a single volume. The book should be useful to anyone who wishes to inform himself of the concepts and specific applications of solid-support reactions and should also serve as an excellent starting point for the person who wishes to use these techniques in his own work.

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Biochemistry and the Central Nervous System. By Henry McIlwain and H. S. Bachelard. Fourth Edition. Churchill Livingstone, Edinburgh and London (The Williams and Wilkins Co., Baltimore, Md.). 1971. 616 pp. 24 × 16.5 cm. $26.50.

This fourth edition by Professor McIlwain was written for the first time with a coauthor, Dr. H. S. Bachelard, who is a Senior Lecturer at the same institution, University of London. This edition, as with the previous ones, is a well-written, succinct introduction to the titled subject. The new edition has increased in number of pages by about 50%, which reflects the large number of biochemical studies on this subject in recent years. The book contains two new chapters, one on metabolic regulation and the other on the metabolism of nucleic acids and proteins. Much of the information in these chapters was consolidated from material which was spread throughout the old editions. The consolidated information together with much new information has resulted in not only very fine treatises on these topics but convenient ones for the readers. In one of the chapters, regulatory mechanisms of glucose transport, glycogen metabolism, glycolysis, tricarboxylic acid cycle, and oxidative phosphorylation are discussed. Adequate discussions of cerebral RNA and protein synthesis and turnover and the regulatory roles of cyclic AMP and cyclic GMP are included in the other new chapter. Although the reader must go to other monographs for more extensive details, the chapters are well referenced with pertinent scientific papers.

There are other larger books and a few multivolume works on this subject but this reviewer heartily recommends this book as an excellent starting reference for students and research workers in neurochemistry and neurophysiology. The chapters involving acetylcholine, central biogenic amines, and neurotropic drugs should be of particular interest to the biochemical pharmacologists.

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Methods of Neurochemistry. Vol. 2. Edited by Rainer Fried. Marcel Dekker, New York, N. Y. 1972. ix + 294 pp. 15 × 22.6 cm. $18.50.

The minute amounts of neurochemicals obtainable from even large amounts of tissues, the instability of some of these materials, and the complexity of the tissue sources demand the greatest possible refinement of analytical methods for the detection and quantitative assays of neurohormones and similar substances. This volume presents a number of such methods for 5-HT, tryptophan-5-hydroxylase, cyclic AMP, and pyridoxal. Part of the analytical difficulties is the elaboration of source materials. Cell and tissue fractions must be prepared as closely circumscribed as possible so that contamination of the extracts with related substances is held to a minimum. How this condition is met is described in three chapters. One of them describes subcellular fractionation of brain tissue with special reference to the preparation of synaptosomes while another one discusses current approaches to the study of CNS receptors. An effort is made to differentiate between receptors and acceptors (other sites at which drugs can bind, be stored, and from which they can be released). Isotopically labeled nucleotides can be used to study incorporation into brain RNA and polysomes which are involved in short-term learning and training experiences in animals. Analytical techniques designed to follow the pathways of the isotope markers are described.

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