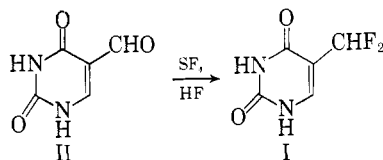


Thymine Analogs: The Synthesis of 5-Difluoromethyluracil¹

Sir:

One approach to more specific cancer chemotherapeutic agents is based on the essential metabolite, thymidylic acid, and its role in the synthesis of deoxyribonucleic acid. Recently, interest has been expressed in the fluoromethyl analogs of thymine as potential anticancer agents. 5-Trifluoromethyluracil has been reported to be effective in inhibiting growth of *Escherichia coli* and the deoxyribose analog is incorporated in DNA of bacteriophage T4 and human bone marrow cells.²

We wish to report the synthesis of 5-difluoromethyluracil (I), the difluoro analog of thymine. It has been noted that sulfur tetrafluoride is effective in the conversion of acids and carbonyls to the corresponding tri- and difluoro analogs.³ The addition of a catalyst, hydrofluoric acid (formed *in situ* from sulfur tetrafluoride and water) was utilized in the synthesis of 5-trifluoromethyluracil in high yield from uracil-5-carboxylic acid.⁴ This procedure was applied to the synthesis of 5-difluoromethyluracil from the corresponding aldehyde II. Selective attack of the aldehyde group without extensive decomposition of the ring was noted.



5-Formyluracil (II) was prepared by application of the Reimer-Tiemann reaction to uracil.⁵ Compound

(1) This work was supported in part by a grant (CY-5639) from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) C. H. Heidelberger, D. Parsons, and D. C. Remy, *J. Am. Chem. Soc.*, **84**, 3597 (1962); C. H. Heidelberger, H. Gottschling, G. D. Birnie, W. Szybalski, and N. K. Cohn, *Fed. Proc.*, **22**, 532 (1963).

(3) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *J. Am. Chem. Soc.*, **82**, 543 (1960).

(4) M. P. Mertes and E. Saheb, *J. Pharm. Sci.*, **52**, 508 (1963).

(5) R. H. Wiley and Y. Yamamoto, *J. Org. Chem.*, **25**, 1906 (1960).

II (0.711 g., 0.005 mole) was placed in a 300-ml. high pressure reaction vessel, 0.5 g. of water (0.03 mole) was added, and the vessel sealed. After cooling in a Dry Ice-acetone bath, 35 g. of sulfur tetrafluoride⁶ (0.32 mole) was admitted. The vessel was heated to 50° and agitated for 15 hr. and finally at 100° for 10 hr. After cooling, the volatile material was vented and decomposed in 20% potassium hydroxide solution. The residue in the bomb was removed and sublimed, yielding 0.488 g. (60%) of white powder, decomposing over the range 285–300°.

Anal. Calcd. for C₅H₄F₂N₂O₂: C, 37.03; H, 2.46; F, 23.46; N, 17.28. Found: C, 37.34; H, 2.50; F, 23.20; N, 17.40.

Paper chromatography on Whatman No. 1 showed one spot with an *R_f* value of 0.69 (ascending), utilizing the solvent system butanol-acetic acid-water (50:20:30). The ultraviolet absorption spectra in acid showed a hypsochromic shift of 12 mμ from the starting material.⁷ The following values for the product were recorded: pH 1, λ_{max} 263 mμ, ε molar 7450; pH 7, λ_{max} 265 mμ, ε molar 7340. In neutral media slow decomposition of 5-difluoromethyluracil was observed by a gradual shift in the ultraviolet maximum to longer wave lengths. The ultraviolet spectrum of the basic solution (pH 8.1) was superimposable with that of the starting aldehyde II. Hydrolysis to the starting material in *N* NaOH was confirmed by paper chromatography. Heidelberger² has reported a similar sensitivity of 5-trifluoromethyluracil in base.

Compound I has been submitted to the Cancer Chemotherapy National Service Center for antitumor screening.

(6) Organic Chemicals Dept., E. I. duPont de Nemours and Co., Inc.

(7) R. E. Cline, R. M. Fink, and K. Fink, *J. Am. Chem. Soc.*, **81**, 2521 (1959).

DEPARTMENT OF PHARMACEUTICAL CHEMISTRY
SCHOOL OF PHARMACY
UNIVERSITY OF KANSAS
LAWRENCE, KANSAS

MATHIAS P. MERTES
SOUHEIL E. SAHEB

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Book Reviews

Advances in Enzymology. Vol. XXIV. 572 pages. Interscience Publishers, Inc. (A Division of John Wiley and Sons), New York, N. Y., 1962. \$16.00.

The present volume admirably maintains the high standards of its predecessors both in terms of the interest of its contents and the quality of its contributors. The selection of articles reflects a number of points of immediate topical interest comprising, as it does, the biosynthesis of enzymes (H. Chantrenne), metabolism of spermatozoa (G. W. Salisbury and J. R. Lodge), chemical modifications of proteins and their significance in enzymology, immunochemistry, etc. (J. Sri Ram, M. Bier, and P. H. Maurer), structure and function of ribonuclease (H. A. Scheraga and J. A. Rupley), molecular properties and transformations of glycogen phosphorylase in animal tissues (E. G. Krebs and E. H. Fischer), distributions of enzymes between subcellular fractions in animal tissues (C. de Duve, R. Wattiaux, and P. Baudhuin), the effect of ionizing radiations on enzymes (L. G. Augenstine), identical and analogous peptide structure in proteins (F. Sorm), and mechanisms related to enzyme catalysis (F. H. Westheimer).

The volume also contains cumulative author and topic indexes for volumes I–XXIV.

The general point does however arise of what should be the main function of such articles: an exhaustive report of work in the field neglecting no reference, however trivial; a comprehensive account in which a certain amount of the wheat has been separated from chaff and emphasis laid on the more significant and important contributions; or a somewhat more speculative review of the contemporary interpretation of the available evidence? It would seem to this reviewer that the pendulum has swung perhaps a little too far over in the direction of the first category so that though all the information may well be gathered and a useful quarry thus provided, such articles hardly make enthralling reading for someone not wholly involved in the field in question—and he the person least in need of the article in any case!

It no doubt reflects the reviewers own prejudices that the most interesting and convincing articles appear to be those in which enzymological significance can be interpreted in terms of underlying chemical structure and specificity as in the chemical modi-

fication of proteins, the molecular properties and transformations of glycogen phosphorylase, identical and analogous peptide structures in proteins and in mechanisms related to enzyme catalysis. The excellent article by Professor Westheimer illustrates particularly forcibly the effect electronic theory in organic chemistry has had on the interpretation of enzyme action at least at the "active center" level. Equally, the vast recent strides in the application of physical methods to the elucidation of protein structure are admirably illustrated in the article on the structure and function of ribonuclease.

Somewhat more general and speculative, though in the best sense, is the article on the biosynthesis of enzymes—perhaps the most enthralling topic in contemporary enzymology. In addition, it serves usefully to underline the directions in which information is still greatly lacking, not least in cytoplasmic heredity and differentiation of enzyme biosynthesis. Another matter of pressing interest in more ways than one is the over-all effects of ionizing radiations and more particularly the extent to which these effects are bound up with the inactivation of enzyme systems. Dr. Augentine's article provides a fascinating survey of the ways in which damage can arise not only directly but also indirectly due to reactions between enzyme molecules and products produced by the action of radiation on the solvent.

The whole is an adequate index to the highly vigorous and healthy state of contemporary enzymology.

UNIVERSITY OF CAMBRIDGE
CAMBRIDGE, ENGLAND

PETER SYKES

Chemical Carcinogenesis. By DAVID B. CLAYSON, The University, Leeds. viii + 467 pp., 31 charts. Little, Brown and Co., Boston, Massachusetts, 1962.

This is the second thorough review of chemical carcinogens and environmental carcinogenesis within a few months (see J. C. Arcos and M. Arcos, "Molecular Geometry and Mechanism of Action of Chemical Carcinogens," in "Progress in Drug Research," reviewed in *J. Med. Chem.*, 6, 466 (1963)). The present volume covers, in addition to organic chemicals as carcinogens, a number of aspects not found in other reviews. The test procedures for carcinogenic activity are discussed critically, and the controversial case histories of induced cancers in man are well presented. It is understandable that the author draws on British source material first, but he does not neglect researches done elsewhere. Dr. Clayson appears to be as much at home in biostatistics, electron density calculations, interpretation of physical-chemical properties as related to carcinogenesis, the organic chemistry of diverse cancer producing agents, and the pharmacological, medical, immunological aspects, and preventive measures in this vast and rather amorphous area. It is fair to say that the literature has been highlighted adequately and that disputable theories have been compared dispassionately. Moreover, the reader is not left with the uncomfortable feeling that he himself has to make a choice which of several compounds, methods or hypotheses he should favor. The author gently but conservatively gives him the benefit of his obviously greater experience in such questions. This reviewer enjoyed the chapter

on theoretical aspects of carcinogenesis and the short concluding forecast of the direction of future researches. The many medicinal chemists interested in cancer chemotherapy will do well in reading these sections, and indeed the whole book. A pleasant style, good type, and ample documentation of the text will make such reading more enjoyable and profitable. The book is recommended to chemists, oncologists, immunologists, and others who want to get an up-to-date and comprehensive view of the field.

UNIVERSITY OF VIRGINIA
CHARLOTTESVILLE, VIRGINIA

ALFRED BERGER

Topics in Organic Chemistry. By LOUIS F. FIESER and MARY FIESER, Harvard University. xii + 668 pages. Reinhold Publishing Corp., New York, N. Y., 1963. \$10.00.

Every chemist who reads the current literature in his field likes to keep a card file of articles which interested him as he thumbed through the journals. The Fiesers must be voracious readers, and their card file should be something to behold. Since the publication of their text "Advanced Organic Chemistry" [see *J. Med. Pharm. Chem.*, 5, 882 (1962)], they have compiled references and information on major advances in many areas of organic chemistry and have now published over 250 supplements (over 300 references) covering the period, July 1, 1961, to December 13, 1962. These short articles are keyed with page references to the parent volume. Although highly up-to-date and written in the usual inimitable style of the authors, these supplements form a conglomerate of topics without a real trend, and without conclusions. The more fashionable fields are, of course, more thoroughly represented, especially large and small rings, carbenes, new rearrangements, stereochemistry, and new methodology of reactions furnishing much of the material. A good deal of the latter is a duplication of "Theilheimer," presented, however, in more readable form. An organic chemist who has found it difficult to squeeze in the overcrowded halls at symposia on topics of great current interest at ACS meetings will find these selected short articles of considerable value in keeping up-to-date.

The first portion of the book contains, in addition, surveys of nine topics which could not be placed in the parent volume because of lack of space. They are polynuclear hydrocarbons, aromatic heterocyclic compounds, alkaloids, terpenoids, steroids, vitamins, chemotherapy, synthetic polymers, and dyes. Some of these subjects, with which the authors are familiar through their own researches, are beautifully presented, especially the dyes, polynuclear hydrocarbons, and terpenoids. The section on heterocycles leaves something to be desired but shows up well enough in the framework of this book. The chapter on chemotherapy lists only facts without theory; the section on cancer chemotherapy, not written by the authors but delegated to an associate, is not worth reading.

On the whole, this book will be welcomed as a continuation of its parent volume and as a stimulating reminder of current highlights in organic chemical research.

UNIVERSITY OF VIRGINIA
CHARLOTTESVILLE, VIRGINIA

ALFRED BERGER