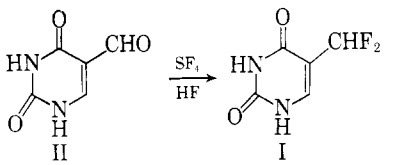
Thymine Analogs: The Synthesis of 5-Difluoromethyluracil[1]

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 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 tetrafluoride[6] (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 $C_5H_4F_2N_2O_2$: 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. Heidelberger[2] 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.

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(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).

(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-