NUCLEIC ACID CHEMISTRY

Improved and New Synthetic Procedures, Methods, and Techniques

Part 3

EDITED BY

LEROY B. TOWNSEND
R. STUART TIPSON

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LEROY B. TOWNSEND

The University of Michigan
Ann Arbor, Michigan

R. STUART TIPSON

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PART THREE

PREFACE

This volume constitutes Part 3 of a projected four-part series, the first volume of which was published in 1978. Herein is a collection of new or improved synthetic procedures, methods, and techniques in the field of nucleic acid chemistry. These are subdivided under seven main topics: I, Heterocyclic Compounds; II, Carbohydrates; III, Nucleosides; IV, Nucleotides and Polynucleotides; V, Isotopically Labeled Compounds; VI, Reagents, Intermediates, and Miscellaneous Compounds; and VII, Instrumental or Analytical Techniques and Applications. They provide an up-to-date source of information on all the important aspects of the subject. Each contribution was written by experienced research workers to guide the reader by giving representative descriptions with ample details, so that even a novice will be able to apply the information.

Although intended primarily for the use of organic chemists, these books should prove valuable to medicinal chemists and biochemists, because the rapid expansion of these fields has produced an urgent need for a compilation of reliable methods. The extensive literature now makes it difficult, even for the expert in the field, to select a suitable procedure, but the detailed information given here exemplifies the most modern approaches to the various problems encountered. Most of the authors of the articles are investigators who either originated these methods or acquired detailed knowledge of them through extensive use in the laboratory. We thank all of them for their enthusiasm and their gratifying responses to our request for contributions. We also thank Ms. Julie Koppitsch, Ms. Patricia Kaiser, and Ms. Deanna VanSickle for typing camera ready copy, and Ms. Deanna VanSickle for compiling and typing the subject index. We also thank Ms. Margaret Perrin for handling all correspondence related to the publication of this volume and Ms. Laura Pearson and Ms. Pamela Crump for their help in the preparation of reaction schemes.

Part 4 will be divided into eight main topics: I, Heterocyclic Compounds; II, Carbohydrates; III, Nucleosides; IV, Nucleotides and Polynucleotides; V, Isotopically Labeled Compounds; VI, Chemical and Enzymic Syntheses; VII, Reagents, Intermediates, and Miscellaneous Compounds; and VIII, Instrumental or Analytical

Techniques and Applications. The reception accorded Parts 3 and 4 will determine whether this series will be continued.

LEROY B. TOWNSEND
R. STUART TIPSON

Ann Arbor, Michigan
Kensington, Maryland
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NUCLEIC ACID CHEMISTRY
PART THREE

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[1] 5-(DIETHYLAMINOMETHYL)-3-METHYLURACIL HYDROCHLORIDE

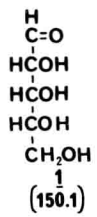
An Application of the Mannich Reaction to Pyrimidine Bases

Thomas J. Delia and Jerry D. Crandall

Malcolm H. Filson Laboratories, Department of Chemistry, Central Michigan University, Mt. Pleasant, MI 48859

INTRODUCTION

Extensive chemical modification at C-5 of pyrimidine bases, especially uracil and cytosine, has been conducted in the quest for chemotherapeutic agents. Less synthetic work has been aimed at introducing substituents directly at C-5 of nucleosides and other N-substituted pyrimidine bases. Our interest in the application of the Mannich reaction to pyrimidine com-



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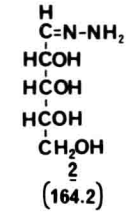

2 (164.2)

pounds[1] led us to investigate this reaction with 3-methyluracil (1). By using conditions modified from earlier work, we were able to obtain the title compound 2. This procedure is general, and can provide a variety of corresponding, 5-(substituted-aminomethyl) derivatives.

PROCEDURE

5-(Diethylaminomethyl)-3-methyluracil Hydrochloride (2)

To a 50 mL round-bottomed flask are added diethylamine hydrochloride (329 mg, 3 mmol), paraformaldehyde (90 mg, 3 mmol), and

glacial acetic acid (10 mL). The mixture is heated under reflux for 1 h at 100°, and then a solution of 3-methyluracil[2] (378 mg, 3 mmol) in glacial acetic acid (5 mL) is slowly added. The yellowish mixture is heated under reflux for 48 h at 125°, cooled to room temperature, and treated with Norit; filtration by gravity removes the colored impurities. The mixture is evaporated under diminished pressure to a transparent oil to which is added absolute methanol (3 mL); cooling overnight produces compound 2 (250 mg, 34%, m.p.[a] 205-206°); IR[b] KBr, s, 1650-1620, (Amide II, N-H bending); w, 320 (olefinic C-H stretch); s, 1430 (amide C-N ring stretch); s, 1720-1710, (C=O stretch). ^{1}H NMR[c] (D_2O, DSS[d]) δ 1.35 (t, 6 H, Me_2), 3.25 [q, 4 H, $N(CH_2)_2$], 4.10 (s, 2 H, $-CH_2-$), and 7.85 (s, 1 H, H-6).

Anal. Calcd. for $C_{10}H_{17}N_3O_2 \cdot HCl$: C, 48.49; H, 7.32; N, 16.96. Found:[e] C, 48.63; H, 7.53; N, 16.84.

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[a]Determined with a Mel-Temp apparatus, and uncorrected.

[b]Recorded with a Perkin-Elmer Model 597 spectrometer.

[c]Recorded with a Varian T-60 spectrometer, and reported as p.p.m.

[d]4,4-Dimethyl-4-silapentane-1-sulfonate.

[e]Performed by Galbraith Laboratories, Knoxville, TN.

[2] 5-VINYLURACIL

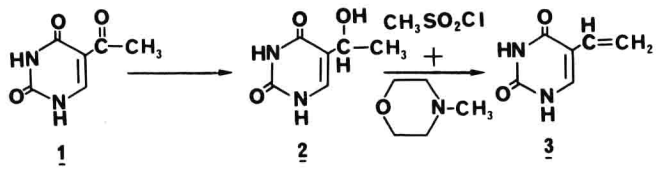
Reduction of 5-Acetyluracil to 5-(1-Hydroxyethyl)uracil, and Its Conversion under Basic Conditions into 5-Vinyluracil

A. Stanley Jones, Gordon P. Stephenson, and Richard T. Walker

Department of Chemistry, University of Birmingham, Birmingham, B15 2TT, United Kingdom

INTRODUCTION

The preparation of 5-vinyluracil (3) is accomplished by starting with 5-acetyluracil (1), which may be obtained commercially,[a] but, because of its expense, may be synthesized, for example, by the procedure described by Shaw *et al.*[1,2] In this, the starting materials are diketene and ethyl carbamate



1 (154.12) 2 (156.14) 3 (138.12)

(urethan), and the yield[b] of 1 is ~50%. By reduction with sodium borohydride, 5-acetyluracil is quantitatively converted into 5-(1-hydroxyethyl)uracil (2), and this is isolated in 70-80% yield by a slight modification of the published procedure.[3]

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[a]Commercial source: ICN Pharmaceuticals Inc., Life Sciences Group.

[b]We have carried out this synthesis as described in the references and have found the procedures to be satisfactory.

Treatment of 2 with methanesulfonyl chloride in 4-methylmorpholine, and then with more 4-methylmorpholine, gave 5-vinyluracil (3) in almost 90% yield.[4] The reaction presumably proceeds via the methanesulfonate, but this compound has not been identified. Two alternative procedures for the synthesis of 5-vinyluracil were published[5,6] at about the time that this method was being developed, but in those the overall yields were low (10-20%). The overall yield by the method described here is ~35%. Since this procedure[4] was published, another interesting synthesis of 3 has appeared in the literature.[7]

PROCEDURE

5-(1-Hydroxyethyl)uracil (2)

5-Acetyluracil[a, 1,2] is dissolved in 0.1 M sodium hydroxide (850 mL), sodium borohydride (9.5 g) is added, and the mixture is kept in the dark for 22 h at 20°. To the solution is added sufficient Zeo Karb 225 (H^+) sulfonic acid ion-exchange resin to decompose the excess of reducing agent and to neutralize the base. The resin is filtered off, and washed extensively with water (~4 L), the filtrate and washings are combined, and evaporated to dryness in a rotary evaporator, and most of the borate is removed by co-evaporation with methanol. A suspension of the residue in methanol (100 mL) is heated to boiling, and cooled, and the product is filtered off, washed with methanol, and dried. Alternatively, the residue is suspended in water (20 mL), and the solid is filtered off, washed with water, and dried (yield 70-80%). The product gives satisfactory elemental analyses; $\lambda_{max}^{pH\ 1}$ 263 nm, (ε_{mM} 7.65); $\lambda_{max}^{pH\ 13}$ 287 nm, (9.20); ^{1}H NMR [$(CD_3)_2SO$]: δ 10.95 (s, 2 H, NH), 7.23 (s, 1 H, H-6), 4.95 (s, 1 H, OH), 4.55 (q, 1 H, CHMe), and 1.22 (d, 3 H, Me).

5-Vinyluracil (3)

To a solution of 5-(1-hydroxyethyl)uracil (2; 6.24 g, 39.6 mmol)

in dry N,N-dimethylformamide (120 mL) are added 4-methylmorpholine (4.32 mL, 43.2 mmol) and methanesulfonyl chloride (3.12 mL, 39.6 mmol) and the solution kept for 22 h at 4°. An additional amount (4.32 mL) of 4-methylmorpholine is then added, and the solution is heated for 20 min at 100° and cooled; 0.1 M sodium hydroxide (300 mL) is added and the solution is concentrated to a small volume in a rotary evaporator. Sodium hydroxide (120 mL; 0.1 M) is then added, and the mixture is evaporated to dryness, to give a yellow solid.[c] To this is added water (70 mL),and the resulting white solid is filtered off, washed with water, and dried, to give 3 (4.9 g; 89% yield); $\lambda_{max}^{pH\ 1}$ 239 nm (ε_{mM} 12.30), 288 nm (ε_{mM} 6.90); $\lambda_{max}^{pH\ 14}$ 252 nm (ε_{mM} 12.40); 309 nm (7.90); ^{1}H NMR data [$(CD_3)_2SO$]: δ 11.20 (s, 2 H, NH), 7.65 (s, 1 H, H-6), 6.48 (q, 1 H, H-1'), 6.02 (2 d, 1 H, H-2'), and 5.14 (2 d, 1 H, H-2').

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[c] It is essential that, throughout the processing, the reaction mixture does not become acidic; if it does, the product dimerizes.