

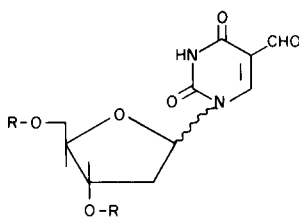
Synthesis of 5-Formyl-2'-deoxyuridine and the  $\alpha$ -Anomer (1)

Mathias P. Mertes and Mohammed T. Shipchandler

Department of Medicinal Chemistry, The University of Kansas

Sir:

The mechanism of the reductive methylation of 2'-deoxyuridine-5'-phosphate catalyzed by the enzyme thymidylate synthetase utilizes tetrahydrofolic acid as the cofactor (2). A model system for the study of this bio-transformation is the 5-formyl analog IIb.



- Ia, R *p*-Toluyyl,  $\alpha$ -anomer  
 Ib, R *p*-Toluyyl,  $\beta$ -anomer  
 IIa, R H,  $\alpha$ -anomer  
 IIb, R H,  $\beta$ -anomer

5-Formyluracil (3) (1 g.) was silylated by the method of Wittenburg (4) and condensed with 2-deoxy-3,5-di-*O*-*p*-toluyyl-D-ribofuranosyl chloride (5) (2.2 g.) in dry acetonitrile (25 ml.) in the presence of molecular sieves (1 g.) (6). After stirring at 25° for two days under anhydrous conditions, the reaction mixture was filtered, evaporated, and the resulting yellow oil treated with dry ethanol (10 ml.) to remove the silyl groups. A partial separation of the anomers was achieved on a silica gel column (300 g.). Elution with chloroform provided 0.4 g. of the  $\alpha$ -anomer (Ia), m.p. 188-189°, 0.26 g. of anomeric mixture and 0.17 g. of the  $\beta$ -anomer (Ib), m.p. 195-196° (total yield 31%) (7).

Transesterification of Ia in methanol-benzene catalyzed by sodium methoxide followed by neutralization with Dowex 50 provided the  $\alpha$ -nucleoside (IIa) as light yellow hygroscopic crystals, m.p. 92-95° (from ethanol-ethyl acetate); uv (1 *N* hydrochloric acid),  $\lambda$  max 282 ( $\epsilon$ , 13,000), 234 ( $\epsilon$ , 9,400),  $\lambda$  min 250 ( $\epsilon$ , 2,900); (water),  $\lambda$  max 281 ( $\epsilon$ , 12,100), 232 ( $\epsilon$ , 9,300),  $\lambda$  min 251 ( $\epsilon$ , 3,100); (1 *N* potassium hydroxide),  $\lambda$  max 283 ( $\epsilon$ , 9,100), 237 ( $\epsilon$ , 10,700),  $\lambda$  min 260  $\mu$ m ( $\epsilon$ , 5,800);  $[\alpha]_{\text{D}}^{25}$  +23.4° (c 1.40, water). The anomeric assignment is based on

nmr (deuterium oxide) analysis in which the 1' proton appeared as a quartet at 6.23  $\delta$  ( $J_{\text{H}2'\alpha} = 7$ ,  $J_{\text{H}2'\beta} = 2.5$ ,  $W_{1/2} = 10.5$  Hz) (8a). A first order splitting pattern of the 2' protons was consistent with that reported by Lemieux (8b). By selective decoupling experiments, a *cis* relationship between the 1'H and the 3'H was established.

Transesterification of Ib yielded the corresponding  $\beta$ -nucleoside (IIb) (9) as tan yellow crystals, m.p. 175-175.5° (from ethanol); uv (1 *N* hydrochloric acid),  $\lambda$  max 281 ( $\epsilon$ , 13,200), 232 ( $\epsilon$ , 10,000),  $\lambda$  min 251 ( $\epsilon$ , 3,100); (water),  $\lambda$  max 281 ( $\epsilon$ , 13,400), 231 ( $\epsilon$ , 10,400),  $\lambda$  min 250 ( $\epsilon$ , 3,100); (1 *N* potassium hydroxide),  $\lambda$  max 282 ( $\epsilon$ , 10,300), 238 ( $\epsilon$ , 11,600),  $\lambda$  min 261  $\mu$ m ( $\epsilon$ , 5,600);  $[\alpha]_{\text{D}}^{25}$  +33.0° (c 1.13, water). In the nmr (deuterium oxide) the anomeric proton appeared as a triplet at 6.30  $\delta$  ( $J = 6.5$ ,  $W_{1/2} = 13$  Hz) (8a); the spectrum of the remainder of the sugar protons resembled that of thymidine (8b).

## REFERENCES

- (1) This work was supported by Grants CA 5639 and CA 10,739 from the National Cancer Institute of the National Institutes of Health, Maryland.
- (2) M. Friedkin, *Ann. Rev. Biochem.*, **32**, 185 (1963).
- (3) R. Brossmer and D. Ziegler, *Tetrahedron Letters*, 5253 (1966).
- (4) E. Wittenburg, *Z. Chem.*, **4**, 303 (1964).
- (5) C. C. Bhat, "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, W. W. Zorbach and R. S. Tipson, Ed., J. Wiley and Sons, Inc., New York, N. Y., 1968, p. 521.
- (6) M. W. Winkley and R. K. Robins, *J. Org. Chem.*, **34**, 431 (1969).
- (7) Satisfactory elemental, ir and nmr analyses were obtained for I and II.
- (8a) M. J. Robins and R. K. Robins, *J. Am. Chem. Soc.*, **87**, 4934 (1965). (b) R. U. Lemieux, *Can. J. Chem.*, **39**, 116 (1961).
- (9) Compound IIb has been tentatively identified (chromatographic behavior and color reactions) as a product of platinum oxide oxidation of 5-hydroxymethyl-2'-deoxyuridine, R. E. Cline, R. M. Fink and K. Fink, *J. Am. Chem. Soc.*, **81**, 2521 (1959).

Received April 24, 1970

Lawrence, Kansas 66044