4,5-Bis(chloromethyl)uracil

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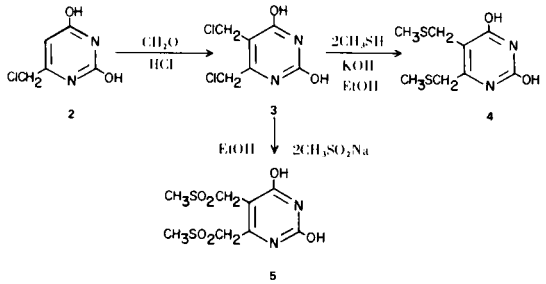
A one-step synthesis of 4,5-bis(chloromethyl)uracil from readily available starting materials has been accomplished. This substance is a stable, crystalline solid which undergoes facile nucleophilic attack to produce various di-substituted uracil derivatives.

J. Heterocyclic Chem., 13, 1135 (1976).

Functionalization of the 5-position of uracil by employing formaldehyde and hydrochloric acid to produce hydroxymethyl or chloromethyl derivatives is a well documented reaction (1a-d). Very few reports of this procedure being utilized with substituents in the 4-position have appeared: a notable exception is the recent report (2) of the preparation of 4-formyl-5-hydroxymethyluracil (**1**). Unfortunately, the preparation of **1** involves considerable synthetic effort and produces only modest overall yields.

We have been able to apply the chloromethylation reaction to 4-chloromethyluracil (**2**) (3) and thus produce in one step, an approximately 50% yield of 4,5-bis(chloromethyl)uracil (**3**). This intriguing compound is a relatively stable crystalline solid which can be stored for long periods of time without decomposition. Compound **3** undergoes rapid displacement of chloride when treated with nucleophilic reagents to yield other difunctional uracil derivatives such as **4** and **5** in good yield.

The ease of preparation of **3**, coupled with its stability, thus constitutes a powerful new tool for chemists to employ in the continuing study of pyrimidines (4) and their importance to biological systems.



EXPERIMENTAL (5)

4,5-Bis(chloromethyl)uracil (**3**).

A suspension of 16.0 g. (0.01 mole) of 4-chloromethyluracil, 3.3 g. (0.011 mole) of paraformaldehyde and 5 ml. of 40% formalin solution in 30 ml. of concentrated hydrochloric acid was stirred while gaseous hydrogen chloride was passed through the slurry. The temperature was raised to 80° and maintained until a clear yellow solution was obtained. After precipitation of **3** began, *ca.* 1 hour, the temperature was lowered to 70° and the reaction continued for an additional hour. The mixture was chilled and filtered, and the white solid was washed with a small portion of cold water. After air-drying there was obtained 11.3 g. (53%) of product, m.p. 190-194° dec., which did not require further purification before use. An analytical sample (6) was obtained by crystallization from acetonitrile and required several hours of chilling; nmr (DMSO): δ 4.52 (s, 4H), 9.65 (m, 2H, ex).

Anal. Calcd. for $C_6H_6Cl_2N_2O_2$: C, 34.48; H, 2.89; N, 13.40. Found: C, 34.96; H, 3.00; N, 13.69.

4,5-Bis(methylthiomethyl)uracil (**4**).

A solution of 1.24 g. (0.022 mole) of potassium hydroxide in 25 ml. of absolute ethanol was saturated with methylmercaptan. Dichloride **3**, 2.1 g. (0.01 mole), was added all at once to the well stirred solution of mercaptan. After the initial vigorous reaction, the mixture was refluxed for 15 minutes and then cooled. The solvent was removed under reduced pressure and the residue treated with 25 ml. of 10% hydrochloric acid. The solid was filtered, washed with water, and dried. Recrystallization from nitromethane gave 1.5 g. (65%), m.p. 193-195°; nmr (DMSO): δ 2.15 (s, 3H), 2.25 (s, 3H), 3.48 (s, 2H), and 3.62 (s, 2H).

Anal. Calcd. for $C_8H_{12}N_2O_2S_2$: C, 41.41; H, 5.21; N, 12.08. Found: C, 41.03; H, 4.99; N, 12.43.

4,5-Bis(methylsulfonylmethyl)uracil (**5**).

A mixture of 2.1 g. (0.01 mole) of **3** and 2.05 g. (0.02 mole) of sodium methanesulfinate (7) in 50 ml. of absolute ethanol was refluxed for 3 hours. The solution was cooled, diluted with 50 ml. of water and the product filtered. After crystallization from DMF-water there was obtained 2.2 g. (74%) of **5**, m.p. 288-289° dec.; nmr (DMSO): δ 2.95 (s, 3H), 3.20 (s, 3H), 4.28 (s, 2H),

and 4.48 (s, 2H).

Anal. Calcd. for $C_8H_{12}N_2O_6S_2$: C, 32.46; H, 4.09; N, 9.46. Found: C, 32.41; H, 4.18; N, 9.38.

REFERENCES AND NOTES

(1a) W. A. Skinner, M. G. Schelstraete and B. R. Baker, *J. Org. Chem.*, 25, 149 (1960); (b) J. A. Carbon, *ibid.*, **25**, 1731 (1960); (c) R. E. Cline, R. M. Fink and K. Fink, *J. Am. Chem. Soc.*, **81**, 2521 (1959); (d) J. H. Burckhalter, R. J. Seiwald and H. C. Scarborough, *ibid.*, **82**, 991 (1960).

(2) D. Ziegler and R. Brossmen, *Tetrahedron Letters*, 2055 (1973).

(3) Available from Aldrich Chemical Co., Inc., Milwaukee, Wisconsin; and Lonza Ltd., Basel, Switzerland.

(4) See *e.g.*, D. J. Brown, "The Chemistry of Heterocyclic Compounds, The Pyrimidines," Vol. 16 and Vol. 16 Supplement, A. Weissberger and E. C. Taylor, Eds., John Wiley & Sons, Inc., New York, N. Y., 1967 and 1970, respectively.

(5) Analyses were performed by Galbraith Labs, Knoxville, Tenn. Melting points are uncorrected. Nmr spectra were recorded on a Varian Associates T-60 instrument.

(6) M.p. 185° dec. Several samples which were analytically pure were found to melt at different temperatures: apparently, the rate of heating has an effect on the m.p. of **3**.

(7) Obtained from Parish Chemical Co., Provo, Utah.