

## 6-(Chlorinated-methyl)uracils

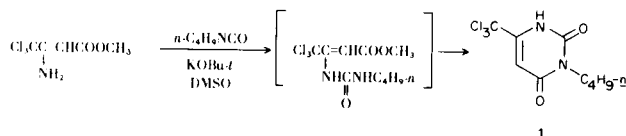
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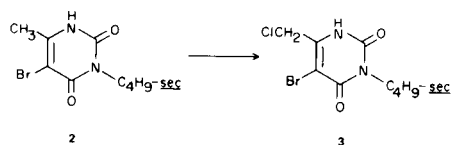
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Although examples of heterocycles substituted by trihalomethyl groups are known (1), no trichloromethyluracils appear to have been reported. Due to our interest in a related problem the synthesis of such a substituted uracil was required. We were particularly interested in preparing an *N*-3-alkylated-6-trichloromethyluracil.

One of the initial routes explored utilized the well-known route based on the condensation of a  $\beta$ -amino crotonate and an isocyanate (2). Although the desired 6-trichloromethyluracil (1) was isolated, the yield was only 3%. The synthesis had the advantage of requiring only one step; the customary isolation of the intermediate ureido compound was not necessary. In another attempt

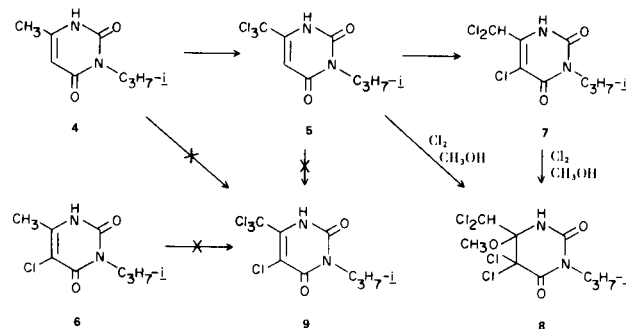


2 was allowed to react with phosphorus pentachloride-phosphorus oxychloride which gave a mixture of at least four compounds from which the 6-chloromethyl derivative (3) was isolated in low yield.



Recent publications have recommended for the preparation of 3-alkyl-5-chloro-6-methyluracils the use of sulfuryl chloride in glacial acetic acid containing sodium acetate (3) or in aprotic solvents such as chloroform (4a) or xylene (4b). Gershon *et al.* (5) have shown that 6-methyluracil is converted to 5-chloro-6-methyluracil in 97.5% yield in the presence of sulfuryl chloride in glacial acetic acid containing 10% acetic anhydride. In our experiments, quite surprisingly, 3-isopropyl-6-methyluracil (4) when warmed with sulfuryl chloride in this solvent mixture gave 6-trichloromethyl-3-isopropyluracil (5) rather than the expected 5-chloro-3-isopropyl-6-methyluracil (6).

The uniqueness of this chlorination mixture was demonstrated by failure to detect (tlc) any of the 5-chloro-6-methyluracil (6) as a co-product; nor was any 5 found when 4 was treated with sulfuryl chloride under the other conditions reported above.



Various experiments to improve the yield of 5 demonstrated that temperature, time, and molar ratios of reactants are important. For example, if the reaction medium is heated too long, a rearrangement occurs and 7 is formed. The 6-trichloromethyl compound (5) proved to be unstable in solution under neutral (acetone), acidic or basic conditions, readily rearranging to 7. The hydouracil (8) derived from 5 upon reaction with chlorine in methanol is the same compound as that obtained from the rearranged isomer (7). Attempts to prepare the 5-chloro-6-trichloromethyluracil (9) from 4, 5, 6, or 7 were uniformly unsuccessful, probably for steric reasons.

## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus in capillary tubes and are uncorrected. Nmr spectra were obtained on a Varian A-60 Spectrometer with TMS as the internal reference and deuteriodimethylsulfoxide as solvent unless otherwise stated. Elemental analyses were performed by Galbraith Laboratories, Inc. or the American Cyanamid Bound Brook Laboratory.

3-*n*-Butyl-6-trichloromethyluracil (1).

To a solution of potassium *t*-butoxide (5.1 g., 45.7 mmoles) in 50 ml. of dimethylsulfoxide at approximately 15° was added methyl 3-amino-4,4,4-trichlorocrotonate (6) (10.0 g., 45.7 mmoles)

in portions with cooling. The solution became dark brown. *n*-Butyl isocyanate (0.50 g., 50.3 mmoles) was then added all at once and the reaction mixture stirred at ambient temperatures for three hours. It was then poured into water (100 ml.), extracted with ether (extracts discarded), and the dark aqueous phase digested twice with activated charcoal and acidified. Ether extraction of the resulting mixture gave, after drying and stripping, a dark brown, tarry residue. This residue was partially purified by repeated extractions with warm cyclohexane and subsequent decantation from tar which separated out after the solution stood at room temperature. The combined cyclohexane extracts were concentrated to a small volume and allowed to stand overnight whereupon 0.80 g. of a light brown solid precipitated. This solid after chromatography on Brinkman silica gel with chloroform as eluent gave a major fraction, which after recrystallization from acetone, weighed 0.43 g. (3%) with m.p. 150-152°; nmr (deuteriochloroform), 386 Hz (ring H) 659 Hz (br, 1-NH).

*Anal.* Calcd. for  $C_9H_{11}Cl_3N_2O_2$ : C, 37.9; H, 3.9; Cl, 37.3; N, 9.8. Found: C, 37.8; H, 3.8; Cl, 37.3; N, 9.8.

The uv spectrum at pH 7 (absolute ethanol) showed absorption at 269  $m\mu$ , and at pH 13 (10% ethanol in 0.1 *N* sodium hydroxide) gave the expected bathochromic shift to 302.5  $m\mu$  for a 3-substituted uracil (7).

#### 5-Bromo-3-*sec*-butyl-6-(chloromethyl)uracil (3).

5-Bromo-3-*sec*-butyl-6-methyluracil (8) (5.0 g., 19.1 mmoles) was warmed to reflux with 10 g. phosphorus oxychloride and 10 g. of phosphorus pentachloride for 2 hours. The clear solution was poured into ice water, the organic material removed by ether extraction, the ether phase washed three times with water, dried and the solvent removed *in vacuo*. A solid weighing 4.2 g. remained which by tlc analysis (silica gel plate with two passes of 1:9 acetic acid:benzene) showed the presence of at least 4 compounds. Recrystallization from carbon tetrachloride gave 0.90 g. of a white solid which when recrystallized from carbon tetrachloride:chloroform gave 0.50 g. of product with m.p. 187-189°; nmr (deuteriochloroform) 258 Hz (2,  $ClCH_2$ ), 670 Hz (br, 1, 1-NH).

*Anal.* Calcd. for  $C_9H_{12}BrClN_2O_2$ : C, 36.6; H, 4.1; Br, 27.0; Cl, 12.0; N, 9.5. Found: C, 36.4; H, 4.3; Br, 26.8; Cl, 11.9; N, 9.2.

#### 3-Isopropyl-6-(trichloromethyl)uracil (5).

Sulfuryl chloride (36 g., 270 mmoles) was added to a solution of 3-isopropyl-6-methyluracil (8) (15 g., 90 mmoles) in 300 ml. of 10% acetic anhydride-acetic acid and warmed to 50-60° for 1 hour with stirring. The solution was then poured into 250 ml. of cold water, and the resulting fine white solid collected to give 15.4 g. (63%) of product homogeneous by tlc with m.p. 125-128°; nmr (deuteriochloroform) 391 Hz (ring H), 526 Hz (br, 1, 1-NH). The uv spectrum at pH 7 had  $\lambda$  max = 270  $m\mu$  (absolute ethanol) and pH 13 had  $\lambda$  max = 303.5  $m\mu$  (10% ethanol in 0.1 *N* sodium hydroxide), which confirmed that a rearrangement of the 3-isopropyl group to the 1-position had not occurred. Acetone solutions of this compound after standing for 24 hours showed the presence of 7.

*Anal.* Calcd. for  $C_8H_9Cl_3N_2O_2$ : C, 35.4; H, 3.3; Cl, 39.2; N, 10.3. Found: C, 35.7; H, 3.3; Cl, 39.1; N, 10.3.

#### 5-Chloro-3-isopropyl-6-dichloromethyluracil (7).

The reaction mixture described for 5 was warmed to 50-60° for 5 hours and allowed to stand overnight at ambient temperatures before working up. Tlc examination (chloroform, silica gel) of aliquots periodically removed showed the initial formation of 5 followed by its decreased concentrations as 7 appeared. At the end of the reaction period only 7 was present. Workup was as described above to give 2.55 g. of white solid with m.p. 187-190°; nmr 446 Hz (1,  $CHCl_2$ ), 722 Hz (br, 1, 1-NH). Additional product could be obtained by ether extraction of the aqueous filtrate, but no attempt was made to obtain the maximum yield.

*Anal.* Calcd. for  $C_8H_9Cl_3N_2O_2$ : C, 35.4; H, 3.3; Cl, 39.2; N, 10.3. Found: C, 35.3; H, 3.4; Cl, 39.5; N, 10.3.

#### 5,5-Dichloro-6-(dichloromethyl)-3-isopropyl-6-methoxyhydrouracil (8) from 5.

3-Isopropyl-6-(trichloromethyl)uracil (1.0 g., 3.7 mmoles) was dissolved in 10 ml. of methanol. Chlorine was bubbled into the solution until the temperature reached 40° and the solution retained a green color. The reaction was then allowed to reach room temperature and poured into water to give a white solid, which after recrystallization from 95% ethanol, gave 1.05 g. (84%) with m.p. 174-175°; nmr 219 Hz (3,  $CH_3O$ ), 412 Hz (1,  $CHCl_2$ ), 575 Hz (1, 1-NH).

*Anal.* Calcd. for  $C_9H_{12}Cl_4N_2O_3$ : C, 32.0; H, 3.6; Cl, 42.0; N, 8.3. Found: C, 32.2; H, 3.4; Cl, 42.2; N, 8.1.

#### 5,5-Dichloro-6-(dichloromethyl)-3-isopropyl-6-methoxyhydrouracil (8) from 7.

5-Chloro-3-isopropyl-6-dichloromethyluracil (0.30 g., 11 mmoles) was allowed to react with chlorine in methanol as above. When the reaction mixture was poured into water, a white solid precipitated which after drying weighed 0.35 g. (95%) with m.p. 172-174° and ir and nmr spectra identical to the previous preparation.

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