A Facile Synthesis of 3-Alkyluracils and Thymines (1)

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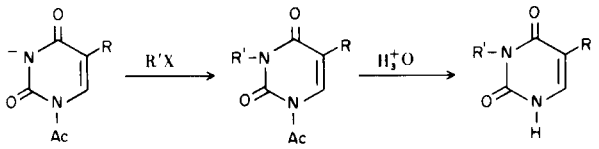
In the course of our work we encountered a need for substantial quantities of 3-alkyluracils and thymines. Direct mono-alkylation of uracil and thymine is a suitable route for 1-substituted uracils (3) but is not feasible for the preparation of the 3-substituted derivatives. The reported routes most commonly used for such derivatives involve principle synthesis (4) or alkylation of a pyrimidine which has been suitably blocked at the 1-position (5). The former route minimally involves three steps and requires the availability of suitable *N*-alkylureas; most blocking groups for the 1-position of pyrimidine-2,4-diones are somewhat tedious to introduce and remove.

SCHEME I



Pitha and Ts'o (6) have recently reported a preparation of 3-methyluracil by reaction of 1-acetyluracil with diazomethane followed by acidic hydrolysis. This procedure is advantageous because the acetyl blocking group may be specifically introduced at the *N*-1 position simply by treatment of the pyrimidine with hot acetic anhydride (7); further, the blocking group is quite labile and may be removed under very mild hydrolytic conditions. It occurred to us that an analogous procedure could be extended to the preparation of a variety of 3-alkylpyrimidine-1,4-diones if the 1-acetylpyrimidine could be converted to an anion which is sufficiently stable to permit reaction with alkyl halides (Scheme I). The procedure described here appears to be of general applicability, proceeds in high yield, and may be carried out with minimal effort.

1-Acetyluracil and 1-acetylthymine were prepared by the method of Spector and Keller (7) from the parent pyrimidines and acetic anhydride. Sodium hydride (10 mmoles) was added to a stirred solution of the 1-acetylpyrimidine (10 mmoles) in 10 ml. of dry DMF. After 15 minutes, the alkyl halide (11 mmoles of methyl iodide or 35 mmoles of *n*-butyl bromide) was added and the mixture stirred at ambient temperature for 12 hours protected from moisture. The solvent was evaporated *in vacuo* and the residue boiled for 15 minutes in 20 ml. of 0.05 *N* hydrochloric acid in 50% ethanol. The solvent was removed *in vacuo* and the residue was extracted with 50 ml. of chloroform. The extract was washed with water (2 x 50 ml.), dried (sodium sulfate) and evaporated. With the exception of 3-butylthymine (oil), products were recrystallized from hot water; yields and physical properties are given in Table I.

TABLE I

Compound	% Yield Isolated (a)	M.p. [lit. m.p. (ref.)]
3-Methyluracil	66 (b)	180-182 [180-182 (4)]
3-Methylthymine	62	201-203 [204-206 (8)]
3-*n*-Butyluracil	57	151-152 [152-153 (9)]
3-*n*-Butylthymine	90	oil (10)

(a) All products showed expected uv spectra (*ca.* 25-30 nm shift in λ max in going from neutral to basic solution) and a single spot on tlc (silica gel) using chloroform ethanol (3:1); for crystalline products, yields refer to once-recrystallized material. (b) Using 11 mmole potassium carbonate as acid acceptor an 84% yield was obtained.

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