Pyrimidines. XIII. Novel Pyrimidine to Pyrimidine Transformation Reactions (1,2)

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Novel pyrimidine to pyrimidine transformation reactions are described. 1,3-Dimethyl-(or diethyl)-uracil (**1**) are converted into isocytosine, 2-thiouracil or uracil derivatives by treatment with guanidine, thiourea or urea, respectively. The latter two cases require base catalysis. The effects of some substituents at C-5 and C-6 of 1,3-dialkylated uracils (**1a** → **1e**) on this transformation were examined and a plausible mechanism is offered for their reaction. The utility of this reaction is exemplified by the facile two-step conversion of pseudouridine into the antileukemic agent, pseudoisocytidine, in good overall yield.

J. Heterocyclic Chem., **14**, 537 (1977).

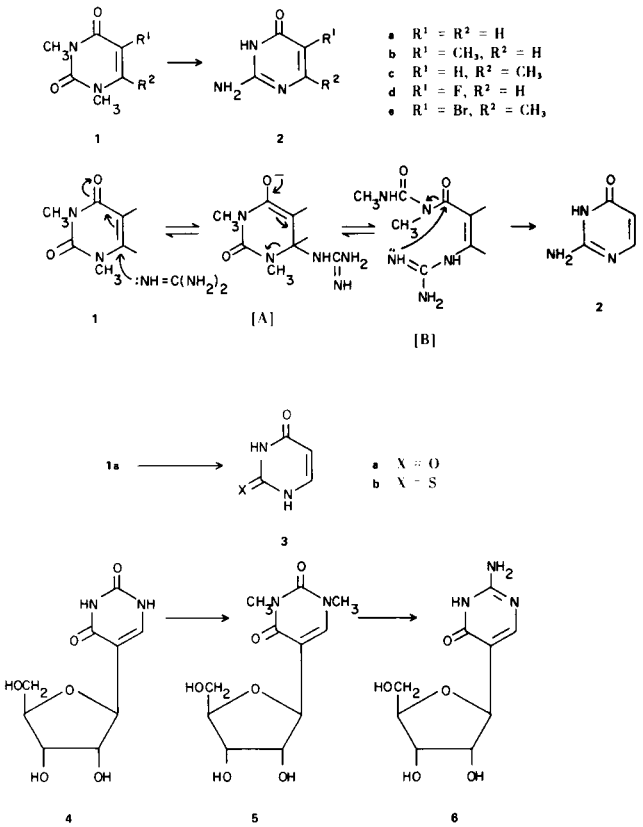
Sir:

It has long been known that pyrimidines undergo transformation to other heterocyclic ring systems by reaction with various nucleophilic reagents (3,4). Nucleophiles such as hydrazine or hydroxylamine react with pyrimidines giving rise to the corresponding pyrazoles or isoxazoles. These reactions have been employed extensively for the chemical modification of nucleic acids (5,6).

Pyrimidine → pyrimidine transformations by displacement of the 1,2,3 portion of a pyrimidine by a 1,3-ambident nucleophile such as guanidine, urea, or thiourea however have not been reported. In fact, when we treated uracil with guanidine, urea, or thiourea no reaction occurred.

In 1952, Shugar and Fox (7) reported on the instability of 1,3-dimethyluracil (**1a**) in 1*N* base. This instability is probably due to the susceptibility of **1a** to attack by hydroxyl ions at the 6 and 4 positions with the liberation eventually of 1,3-dimethylurea and formylacetate and products derived therefrom. Indeed, we have recently isolated a small amount of crystalline 1,3-dimethylurea from the reaction mixture of **1a** and *N* sodium hydroxide. The susceptibility of 1,3-dialkyluracils (**1**) to nucleophilic reagents was therefore investigated.

When 1,3-dimethyl-(or diethyl)-uracil was treated with ~ 7 molar excess of guanidine (8) in refluxing ethanol for several hours, 2-amino-4-oxopyrimidine (isocytosine, **2a**) was obtained in good yield. The reaction is highly dependent on the electronic nature of the substituent at C-5. Thus, while 5-fluoro-1,3-dimethyluracil (**1d**) was converted into 5-fluoroisocytosine (**2d**) (9) in a few



hours in refluxing ethanol, transformation of 1,3-dimethylthymine (**1b**) to 5-methylisocytosine (**2b**) required more stringent conditions, such as fusion with guanidine at 80-90°.

Methyl substitution at C-6 of 1,3-dimethyluracil also suppressed the reaction. 1,3,6-Trimethyluracil (**1c**) did

not undergo conversion to 6-methylisocytosine (**2c**) in refluxing ethanol and, again, fusion conditions with guanidine were required to effect this conversion. On the other hand, 5-bromo-1,3,6-trimethyluracil (**1e**) was readily converted into 5-bromo-6-methylisocytosine (**2e**) by treatment with guanidine in refluxing ethanol.

A plausible mechanism to explain the above results may be formulated as shown in the chart for the conversion of **1a** → **2a**. The initial step would be attack by the nucleophile (such as guanidine) at C-6 to give [A] followed by scission of the N1-C6 bond to [B]. Subsequent attack by the terminal guanidine nitrogen of [B] on C-4 with concommitant cleavage of the C4-N3 linkage would produce isocytosine **2** and 1,3-dimethylurea. Attempts to convert uracil, 1-methyl- or 3-methyl-uracils to the corresponding isocytosine derivatives by reaction with guanidine under various conditions were uniformly unsuccessful. These failures are readily explained by the fact that these compounds contain dissociable protons and, in the presence of a strong base such as guanidine, are in the anionic form which renders attack by nucleophiles more difficult.

Urea and thiourea, which contain less nucleophilic nitrogens, did not react with 1,3-dimethyluracil in ethanol. However, in the presence of sodium ethoxide, the reaction occurred smoothly with the formation of uracil (**3a**) and 2-thiouracil (**3b**), respectively, in ~ 60-70% yield. These latter reactions may have proceeded *via* a 2-aminooxazine or 2-aminothiazine intermediate.

The usefulness of this new pyrimidine → pyrimidine transformation is exemplified by a much simplified synthesis of an antileukemic agent, pseudoisocytidine (10) (**6**) from pseudouridine (11) (**4**). 1,3-Dimethylpseudouridine (12) (**5**, 82%, m.p. 174° from ethanol) was obtained by treatment of **4** at reflux temperature with dimethylformamide dimethylacetal. Direct fusion of **5** with guanidine at 80-90° for 50 minutes followed by removal of the excess guanidine by Amberlite IRC-50 (H^+) resin afforded pseudoisocytidine (**6**), m.p. 196-198° dec. (13) in crystalline form in 60% yield. The hydrochloride salt of **6** was identical with the known pseudoisocytidine hydrochloride (14). It is noteworthy that (unlike the experience with the previous synthetic route (14)) only the desired β-nucleoside isomer **6** is obtained by the pyrimidine → pyrimidine transformation procedure.

Further investigation of this reaction with other pyrimidines and nucleophiles is in progress.

REFERENCES AND NOTES

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(11) The authors wish to thank Kyowa Hakko Co., Inc., Tokyo, for pseudouridine used in this study.

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