Pyrimidines. 16. Novel *s*-Triazine to Pyrimidine Ring Transformation Reaction[1]

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Ring transformations of heterocyclic systems by nucleophilic reactions are an important area of chemistry from theoretical as well as practical viewpoints.[3] Thus, hydrazine or hydroxylamine, which converts pyrimidine into pyrazole or oxazole, has been used extensively in the modification of nucleic acids.[4] Pseudoisocytidine,[5] a potential antileukemic agent,[6] has been prepared successfully from commercially available pseudouridine in two steps by exploitation of a new pyrimidine to pyrimidine transformation discovered in our laboratory.[7] Recently, we also reported a novel pyrimidine to pyridine ring transformation reaction.[8]

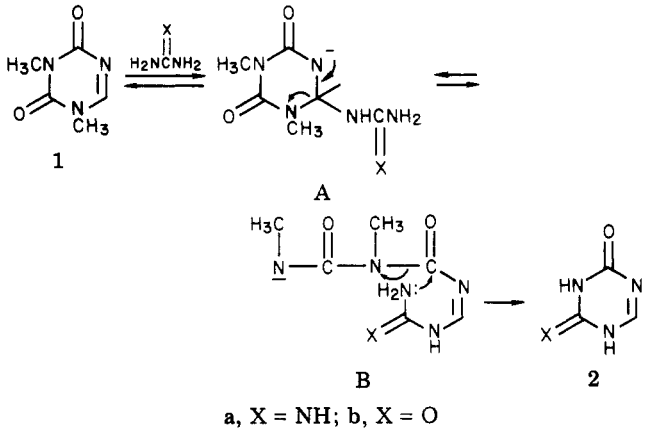
van der Plas et al.[9,10] reported a pyrimidine to *s*-triazine ring transformation by treatment of 4-chloro-2-substituted-pyrimidines with potassium amide in liquid ammonia. The reverse reaction, i.e., the conversion of an *s*-triazine to pyrimidine, has not been reported. This report deals with the first successful *s*-triazine to pyrimidine transformation and some related reactions.

We had found[7] that 1,3-dimethyluracils can be readily converted into the corresponding isocytosine, 2-thiouracil, or uracil derivatives by treatment with guanidine, thiourea, or urea under basic conditions. A mechanism for these reactions was proposed[7] in which the first step is the Michael addition of the 1,3-ambident nucleophile to C_6 of the dimethyluracils. The resulting adduct then undergoes cleavage of the N_1–C_6 bond followed by cyclization on C_4 with elimination of 1,3-dimethylurea.

The C_6 position of 1,3-dimethyl-*s*-triazine-2,4(1*H*,3*H*)-dione[11] (1,3-dimethyl-5-azauracil, 1, Scheme I) should be much more susceptible to nucleophilic attack than that of 1,3-dimethyluracil because of the presence of the 5-azomethine structure. Replacement of the 1,3-dimethylurea (N_1–C_2–N_3) portion of 1 by a 1,3-ambident nucleophile, therefore, should occur readily. Actually, when 1 was treated with guanidine or urea under basic conditions, the ring transformation reaction occurred smoothly, and 4-amino-*s*-triazine-2(1*H*)-one (5-azacytosine, **2a**) or *s*-triazine-2,4(1*H*,3*H*)-dione (5-azauracil, **2b**) was obtained. A plausible mechanism for these *s*-triazine to *s*-triazine reactions is similar to that proposed[7] for the pyrimidine to pyrimidine transformation, except that in the present cases the adduct is not of the Michael type. Thus, attack by the nitrogen nucleophile forms the 1,2-adduct A followed by cleavage of the N_1–C_6 bond to give the open-chain intermediate B. Ring closure by attack of the terminal nitrogen of B on C_4 with concomitant elimination of 1,3-dimethylurea affords the *s*-triazine **2**.

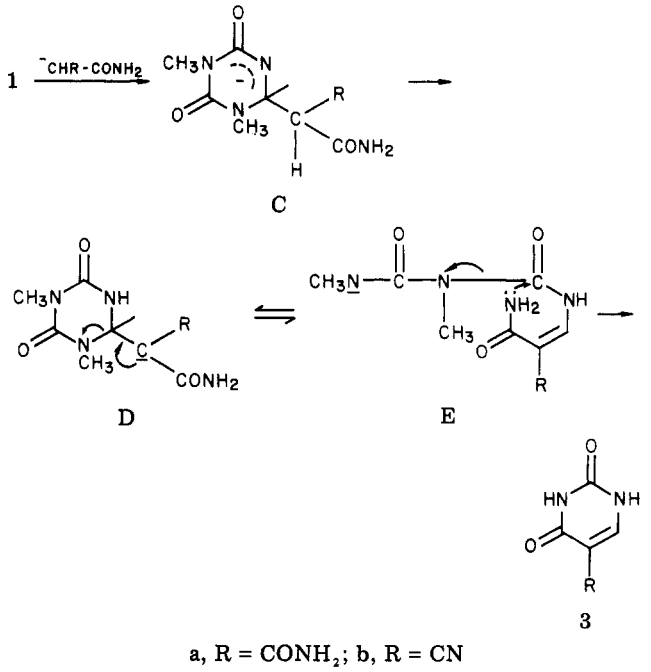
When compound 1 was treated with malonamide, the dimethylurea (N_1–C_2–N_3) portion of 1 was replaced by the C–C–N fragment of the nucleophile and uracil-5-carboxamide (**3a**, Scheme II) was obtained. The UV and IR spectra of the product were identical with those of an authentic sample. The structure of the product was confirmed further by its conversion into uracil by hydrolytic decarboxylation. Similarly, treatment of 1 with cyanoacetamide under basic conditions afforded 5-cyanouracil (**3b**).

Scheme I



a, X = NH; b, X = O

Scheme II



a, R = $CONH_2$; b, R = CN

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(11) 1,3-Dimethyl-5-azauracil was obtained by treatment of 5-azauracil with dimethylformamide dimethyl acetal. This method was found to be superior to the reported procedure.[13] Methylation with a new agent, trimethylsulfoxonium hydroxide [K. Yamaguchi et al., *J. Org. Chem.*, 43, 1593 (1978)], did not give a satisfactory yield of 1,3-dimethyl-5-azauracil.

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These *s*-triazine to pyrimidine transformation reactions probably proceed, as shown in Scheme II, by a somewhat different mechanism than that proposed for other ring transformations.[7,8] Attack of a carbon nucleophile at C_6 would occur to form σ complex C. Proton transfer from the exocyclic α-position of structure C to N_5 would give rise to carbanion D which could then undergo scission of the N_1–C_6 bond to give the open-chain intermediate E. Intramolecular nucleophilic attack of the terminal nitrogen on C_4 with simultaneous elimination of 1,3-dimethylurea results in the formation of pyrimidine **3**.

Experimental Section

General Methods. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Melting points were determined on a Thomas-Hoover capillary apparatus. UV spectra were recorded on a Unicam SP800 spectrophotometer and IR spectra on a Perkin-Elmer Infracord Model 221.

1,3-Dimethyl-*s*-triazine-2,4(1*H*,3*H*)-dione (1; 1,3-Dimethyl-5-azauracil). A mixture of 5-azauracil[12] (5.6 g, 0.05 mol) and dimethylformamide dimethyl acetal (70 mL) was refluxed gently for 1 h and stirred overnight at room temperature. The product was collected by filtration and recrystallized from ethyl acetate: 3.38 g (48%), mp 162–164 °C (lit.[13] mp 164 °C).

Conversion of 1 into 5-Azacytosine (2a). Guanidine monohydrochloride (1.9 g, 0.02 mol) was stirred in 0.7 M ethanolic sodium ethoxide (30 mL) for 10 min, and insoluble NaCl was removed by filtration. To the filtrate was added **1** (1.4 g, 0.01 mol), and the mixture was refluxed for 2 h. The mixture was concentrated to dryness in vacuo. The residue was dissolved in water (10 mL) and neutralized with acetic acid. The crystals were collected by filtration and recrystallized from water: 667 mg (59%), mp >350 °C dec. The IR spectrum of this sample was identical with that of an authentic sample.[14]

Conversion of 1 into 5-Azauracil (2b). To a solution of ethanolic sodium ethoxide (prepared by dissolving 230 mg of Na in 30 mL of ethanol) was added **1** (700 mg, 0.005 mol) and urea (600 mg, 0.01 mol). The mixture was refluxed for 2 h and then concentrated to dryness in vacuo. The residue was dissolved in water (10 mL), and the solution was neutralized with acetic acid to precipitate 5-azauracil (**2b**) which was recrystallized from water: 270 mg (48%), mp 270–272 °C dec (lit. mp 268–270 °C dec[12a], 284–285 °C dec[12b]). The IR spectrum of this sample was identical with that of an authentic sample.[12]

Uracil-5-carboxamide (3a). A solution of malonamide (1.02 g, 0.01 mol) in 0.33 M ethanolic sodium ethoxide was treated with **1** (700 g, 0.005 mol), and the mixture was refluxed for 3 h. The solvent was removed by evaporation in vacuo. The residue was dissolved in water (10 mL), and the solution was neutralized with acetic acid. Crystals were collected by filtration and recrystallized from water: 325 mg (42%), mp >300 °C (lit.[15] mp >300 °C). The IR spectrum of this sample was identical with that of an authentic sample prepared by ammonolysis of 5-(methoxycarbonyl)uracil.

Compound **3a** (100 mg) was dissolved in concentrated HCl (5 mL), and the solution was refluxed for 20 h and then was evaporated in vacuo. The residue was recrystallized from water to give 21 mg of uracil, mp 320–331 °C dec. The UV and IR spectra of this sample were identical with those of uracil.

5-Cyanouracil (3b). A mixture of cyanoacetamide (840 mg, 0.01 mol) and **1** (700 mg, 0.005 mol) in ethanolic sodium ethoxide (prepared by dissolving 230 mg of Na in 30 mL of ethanol) was stirred at room temperature for 48 h, and then the mixture was concentrated to dryness in vacuo. The residue was dissolved in water (10 mL), and the solution was neutralized with acetic acid. The precipitate, which was collected by filtration, did not absorb UV light and was discarded. The filtrate was concentrated in vacuo, and the residue was crystallized from water: 260 mg (38%), mp 289–296 °C dec (lit.[15] mp 295 °C dec). UV and IR spectral characteristics of this sample were identical with those of an authentic sample.

Registry No. **1**, 824-28-2; **2a**, 931-86-2; **2b**, 71-33-0; **3a**, 1074-97-1; **3b**, 4425-56-3; guanidine monohydrochloride, 50-01-1; sodium ethoxide, 141-52-6; malonamide, 108-13-4; cyanoacetamide, 107-91-5.

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Specific Effect of Micellar Microenvironment on an Intramolecular Nucleophilic Anionic Reaction

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Cationic micelles catalyze many nucleophilic anionic reactions,[1] and the exaltation of reactivity, usually 2–100-fold and very often <10,[2] is anion[3-5]—and reaction mechanism[6,7]—dependent. Usually two types of factors can be distinguished as responsible for this catalysis:[2] (1) the substrate and the anion association with cationic micelles through hydrophobic and electrostatic interactions which bring together the reagents in the micelles and lead to an increase of their local concentration and (2) the specific effect of micellar microenvironment, the physical properties of which differ from the rest of the solution.[2] In particular, the hydrogen bond solvating power,[7] as well as the polarity[9] of the micellar medium, is lower than that in water. Electrostatic interactions between positive cationic micelles and negatively charged species they might meet on the reaction path cannot be excluded.[2,8]

It now appears that one of the important obstacles to the better understanding of micellar catalysis is that it is difficult to evaluate the relative importance of concentration and medium effects. Though the role of micellar microenvironment has been demonstrated through the study of unimolecular[8,11] and bimolecular competitive reactions[7] where the same substrate and reagent react by two different mechanisms, there is at present only very little information concerning the specific effect of this medium.

We wanted to elucidate this point, and so we examined the influence of CTAB cationic micelles on a nucleophilic anionic intramolecular reaction. Our choice was the cyclization reaction of salicylaldoximacetate **2** into benzisoxazole **3** in basic medium (Scheme I). For such a model, the structure of **2** first is rigid and second has both nucleophilic and electrophilic centers, which has the advantage of eliminating the proximity and orientation factors. So any observed catalytic effect will be attributed

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