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RECYCLIZATION OF 5-ETHOXYCARBONYL-PYRIMIDINES OCCURRING WITH SUBSTITUTION OF A CARBON ATOM IN THE HETEROCYCLE BY AN EXOCYCLIC CARBON ATOM

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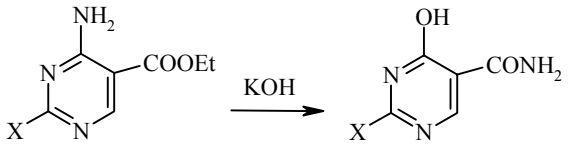
Keywords: potassium hydroxide, 5-carbamoyl-4-hydroxypyrimidines, 5-ethoxycarbonylpyrimidines, nucleophilic rearrangement, recyclization.

Among isomerization recyclizations of pyrimidines, the best studied have been the Dimroth [1] and Kost–Sagitullin [2-4] rearrangements. They occur as a result of substitution of the ring nitrogen atom in the α-position of the pyrimidine by an exocyclic nitrogen atom (in the first case) or carbon atom (in the second case), which leads to formation of a pyrimidine or pyridine ring respectively. This report is devoted to study of yet another recyclization transformation of a pyrimidine ring accompanied by substitution of a carbon atom in the heterocycle by a non-ring carbon atom, which from the type of substitution that occurs can be called C–C recyclization.

We have shown that upon brief boiling in aqueous solution of base, the substituted 4-amino-5-ethoxycarbonylpyrimidines **1a-c** rearrange to form the 5-carbamoyl-4-hydroxypyrimidine derivatives **2a-c**. The recyclization described proceeds *via* substitution of the $C_{(4)}$ atom of the ring by a non-ring carbon atom of the ester group.



1 **2**

a X = OH, **b** X = SH, **c** X = Bn

Probably the reaction occurs as a result of attack by the hydroxyl group on position 4 of the pyrimidine, followed by opening of the ring and cyclization, with attack by the nitrogen atom on the carbon atom of the ester group (route **A**). We thought that the preferred direction of attack by the nucleophile might be the unsubstituted position 6 of the pyrimidine ring and consequently that the expected recyclization would be formation of the 5-formylpyrimidine derivative **3** (route **B**). However, for such a direction of attack and opening of the pyrimidine ring, the likely formation as an intermediate of a more electrophilic (and thus a more reactive) formyl group in the cyclization step probably should exclude the possibility of concurrent attack on the ester

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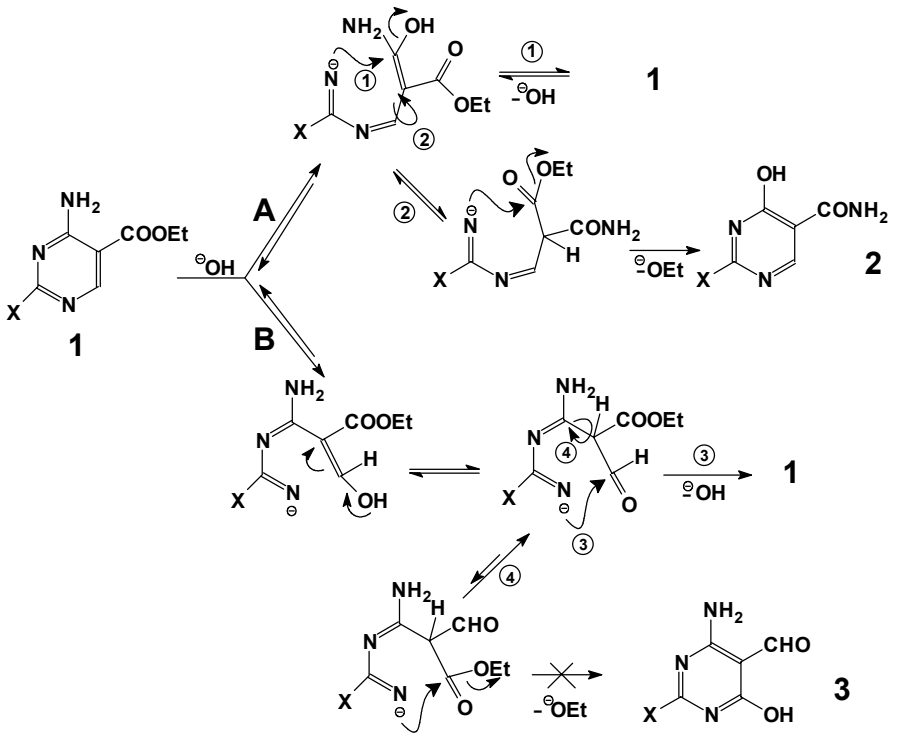
carbon atom, which as a result would lead to reversible formation of the starting molecule. Conversely, attack on the position 4 would irreversibly lead to obtaining the thermodynamically more favorable structure of the 5-carbamoylpyrimidine derivative **2**.



2-Substituted 5-Carbamoyl-4-hydroxypyrimidines 2a,b. 5-Ethoxycarbonylpyrimidine **1a,b** (0.025 mol) was boiled in a 10% solution of potassium hydroxide (100 g) prepared from water (90 ml) and KOH (10 g, 0.179 mol). After 10 min the crystals had dissolved, the solution was acidified with 32% hydrochloric acid (25 ml, 0.24 mol) and then all the water was evaporated off. Cold water (20 ml) was added to the residue and the mixture was stirred for several minutes; the precipitate was filtered out and dried in air. Obtained were:

5-Carbamoyluracil (2a), yield 2.3 g (59%); mp >300°C, R_f 0.54 (Silufol UV-254, acetone–toluene, 2:1). ^{1}H NMR spectrum (DMSO-d_6, 300 MHz), δ, ppm: 7.53 (1H, br. s, NH); 8.03 (1H, s, 6-H); 8.38 (1H, br. s, NH); 10.7-11.2 [2H, s, OH (NH)]. Found, %: N 27.34. $C_5H_5N_3O_3$. Calculated, %: N 27.09.

5-Carbamoyl-4-hydroxy-2-mercaptopyrimidine (2b), yield 2.25 g (53%); mp >300°C, R_f 0.48 (acetone–toluene, 2:1). ^{1}H NMR spectrum (DMSO-d_6, 300 MHz), δ, ppm: 2.9-3.5 (1H, br. s, SH); 8.0 (1H, s, 6-H); 8.02 (1H, s, NH); 8.53 (1H, s, NH); 11.8-13.2 (1H, br. s, OH). Mass spectrum, *m*/*z* (I_{rel}, %): 171 (100), 127 (42), 113 (12), 95 (14), 85 (20), 71 (10), 70 (21), 69 (28), 68 (28), 67 (14), 53 (13), 52 (11), 44 (18). Found, %: N 24.78; S 18.89. $C_5H_5N_3O_2S$. Calculated, %: N 24.55; S 18.73.

2-Benzyl-6-carbamoyl-4-hydroxypyrimidine (2c). 4-Amino-2-benzyl-5-ethoxycarbonylpyrimidine (0.5 g, 2 mmol) was refluxed for 1 h in a 5% KOH solution (60 ml). Then the mixture was acidified with a 10% hydrochloric acid solution to pH 6 and the water was evaporated down to a volume of 20 ml. This was cooled with stirring for several minutes, then the precipitate was filtered out and dried in air. Obtained 0.28 g (62%) of compound **2c**; mp 240-241°C, R_f 0.54 (Silufol UV-254, 2-propanol–ammonia–water, 7:0.5:1). ^{1}H NMR spectrum (DMSO-d_6, 300 MHz), δ, ppm: 3.95 (2H, s, CH_2); 7.1-7.35 (5H, m, C_6H_5); 7.43 (1H, br. s, NH); 7.71 (1H, br. s, NH); 8.64 (1H, s, 6-H), 10.6-12.4 (1H, br. s, OH), Found, %: N 18.57. $C_{12}H_{11}N_3O_2$. Calculated, %: N 18.33.

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