REACTION OF 2-AMINOPYRIMIDINES WITH α-HALOCARBOXYLIC ACIDS AND THEIR ESTERS

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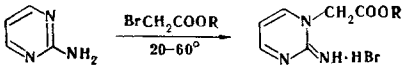
N-Pyrimidylcarboxylic acids and their esters, which can be cyclized to tetrahydromidazo-[1,2-*a*]pyrimidine-2,5-diones, are formed from 2-aminopyrimidine and its C-substituted derivatives by reaction with α-halo acids and their esters under mild conditions. Alkylation proceeds at the N_1 and N_3 atoms of the pyrimidine ring during the action of unsymmetrical 2-aminopyrimidines with α-halo acids.

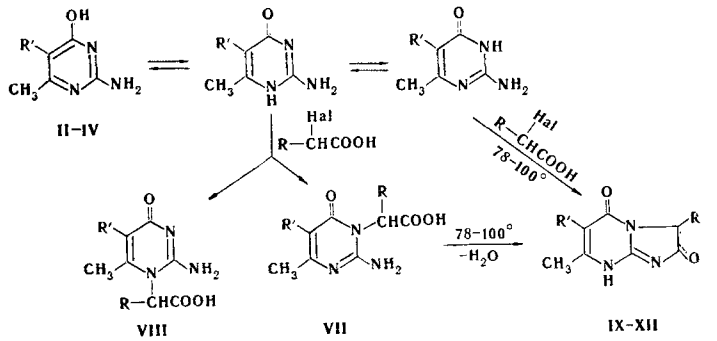
In order to search for biologically active compounds in a number of condensed imidazole systems, we accomplished the previously uninvestigated reaction of 2-aminopyrimidines (I-IV) with α-halo acids and their esters. 1,2-Dihydro-2-imino-1-pyrimidylacetic acid ester hydrobromides (V, VI) are formed in the reaction of amine I with bromoacetic acid esters. As in the case of the cyclization of N-(4-pyrimidyl)



I V R=CH3, VI R=C2H5

aminoacetic acid [1], colored products of unknown structure are formed during attempts to isolate the bases of esters V and VI or to obtain 1,2-dihydro-2-imino-1-pyrimidylacetic acid by alkaline hydrolysis of hydrobromides V-VI.

The alkylation of unsymmetrical 2-aminopyrimidines with α-halo acids proceeds at the N_1 and N_3 atoms of the pyrimidine ring. Thus, 2-amino-4-methyl-6-oxo-1,6- and 1,4-dihydro-1-pyrimidylacetic acids (VII and VIII) are isolated in a ratio of 4:1 when amine II is heated with haloacetic acids in water in the presence of two equivalents of alkali. The structure of acid VII was confirmed by alternative synthesis from guanidoacetic acid and acetoacetic ester [2]. The structure of acid VIII also does not raise



II R′=H; III R′=NO2; IV R′=Br; VII, VIII R=R′=H; IX-XII R=H, Al, R′=H, Br, NO2

any doubts, inasmuch as it differs from both acid VII and N-(4-methyl-6-hydroxy-2-pyrimidyl)aminoacetic acid obtained by the method in [3].

When acid VII is heated in an aqueous or alcohol solution of alkali, in glacial acetic acid in the presence of anhydrous sodium acetate, or treated with cold concentrated sulfuric acid, it is readily cyclized

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to give 7-methyl-2,3,5,8(1)-tetrahydroimidazo[1,2-*a*]pyrimidine-2,5-dione (IX). 2,3,5,8(1)-Tetrahydroimidazo[1,2-*a*]pyrimidine-2,5-diones (IX-XII) are formed immediately when amines II-IV are refluxed with α-halo acids in water or alcohol in the presence of two equivalents of alkali.

EXPERIMENTAL

The IR spectra of mineral-oil suspensions of the compounds were recorded with a UR-20 spectrometer.

Methyl 1,2-Dihydro-2-imino-1-pyrimidylacetate Hydrobromide (V). A) A 1.75-g (11 mmole) sample of methyl bromoacetate was added to a solution of 0.95 g (10 mmole) of amine I in 5 ml of anhydrous methanol, and the mixture was refluxed for 1 h (with activated charcoal for the last 5 min). It was then filtered, and 30 ml of ether was added to the filtrate. The precipitated hydrobromide (V) was removed by filtration and washed with ether to give 1.25 g (50%) of a product with mp > 280° (dec., reprecipitation from methanol by the addition of ether). Found: C 33.5; H 4.3; Br 31.0; N 16.6%. $C_7H_9N_3O_2$. Calculated: C 33.8; H 4.1; Br 31.2; N 16.9%.

B) A 3.5-g (22 mmole) sample of methyl bromoacetate was added to a solution of 1.9 g (20 mmole) of amine I in 6 ml of dimethylformamide (DMFA), and the mixture was allowed to stand at room temperature for 24 h. Ether (50 ml) was then added, and the precipitated hydrobromide (V) was removed by filtration, washed with ether, and dried to give 3.9 g (80%) of product.

Ethyl 1,2-Dihydro-2-imino-1-pyrimidylacetate Hydrobromide (VI). Under the conditions of the preceding experiment, 30 mmole of amine I and 5.5 g (33 mmole) of ethyl bromoacetate gave 4.5 g (57%) of salt VI with mp > 280° (dec., by reprecipitation from ethanol by the addition of ether). IR spectrum, cm^{-1}: 1665, 1750, (CO); 3080, 3220, and 3260 (NH or OH). Found: C 36.4; H 4.8; Br 30.6; N 15.6%. $C_8H_{11}N_3O_2 \cdot HBr$. Calculated: C 36.6; H 4.6; Br 30.5; N 16.0%.

2-Amino-4-methyl-6-oxo-1,6-dihydro-1-pyrimidylacetic Acid (VII) and 2-Amino-4-oxo-6-methyl-1,4-dihydro-1-pyrimidylacetic Acid (VIII). A 2.5-g (20 mmole) sample of amine II and 22 mmole of chloro-, bromo-, or iodacetic acid were added to a solution of 40 mmole of sodium hydroxide in 10 ml of water, and the mixture was heated on a boiling-water bath for 2 h (until the medium was neutral). It was then cooled and acidified to pH 4-5 with acetic acid, and the precipitate was removed by filtration and washed with a small amount of water. The yield of acid VII with mp 240-241° (dec., from water) was 2.6 g (70%). IR spectrum, cm^{-1}: 1710, 1760 (CO); 3090, 3300 (NH). According to [2], this compound has mp 240-241° (dec.). The solution remaining after separation of acid VII was evaporated to dryness, and the residue was washed with cold water and crystallized from a small amount of water (with activated charcoal). The yield of acid VIII with mp 228-230° (from water) was 0.7 g (18%). IR spectrum, cm^{-1}: 1670, 1765 (CO); 3090, 3300 (NH). Found: C 45.7; H 4.8; N 23.3%. $C_7H_9N_3O_3$. Calculated: C 45.7; H 4.8; N 22.9%.

7-Methyl-2,3,5,8(1)-tetrahydroimidazo[1,2-*a*]pyrimidine-2,5-dione (IX). A) A 1.83-g (10 mmole) sample of VII was refluxed for 1-2 h in 10 ml of glacial acetic acid in the presence of 2.0 g of anhydrous sodium acid or in 10 ml of a 4% alcohol or water solution of sodium hydroxide, after which the solvent was evaporated, and a 5% solution of HCl was added to the residue to bring the pH to 2-3. The resulting precipitate was removed by filtration to give IX with mp 281-283° [dec., from water (mp 310° (dec.) [2]] in 75% yield.

B) A 1.83-g (10 mmole) sample of acid VII was added to 10 ml of 96% sulfuric acid, the mixture was allowed to stand for 10-12 h, after which it was poured over ice. A 20% solution of sodium hydroxide was added to the aqueous mixture to bring the pH to 2-3, and the precipitate was removed by filtration to give 1.2 g (73%) of IX.

C) A 2.5-g (20 mmole) sample of II and 2.78 g (22 mmole) of bromacetic acid were added to a solution of 40 mmole of sodium hydroxide in 40 ml of ethanol, and the mixture was refluxed for 9 h. The solvent was then removed by vacuum evaporation to dryness, and 15 ml of water and 5% HCl were added to the dry residue to pH 2. The resulting precipitate was removed by filtration and washed with a small amount of water to give 2.6 g (80%) of IX.

6-Nitro-7-methyl-2,3,5,8(1)-tetrahydroimidazo[1,2-*a*]pyrimidine-2,5-dione (X). A 2.38-g (20 mmole) sample of bromoacetic acid was added to a suspension of 3.4 g (20 mmole) of III in a solution of 1.6 g (40 mmole) of sodium hydroxide in 40 ml of water, and the mixture was refluxed for 1 h. Workup of the reaction mixture as in the preceding experiment gave 2.02 g (48%) of X as pale-yellow crystals with mp 238-

240° (dec., from water). IR spectrum, cm^{-1}: 1715, 1790 (CO); 3350 (NH). Found: C 40.3; H 3.1; N 27.0%. $C_7H_6N_4O_4$. Calculated: C 40.0; H 2.9; N 26.7%.

3,7-Dimethyl-2,3,5,8(1)-tetrahydroimidazo[1,2-*a*]pyrimidine-2,5-dione (XI). This compound, with mp 281-283° (dec., from water) [2], was obtained in 60% yield from amine II and α-bromopropionic acid under the conditions of the preceding experiment.

6-Bromo-7-methyl-2,3,5,8(1)-tetrahydroimidazo[1,2-*a*]pyrimidine-2,5-dione (XII). Compound XII [3.2 g (87%)], with mp 242-244° (dec. from water), was obtained under the same conditions from 1.2 g (30 mmole) of sodium hydroxide in 15 ml of water, 3.1 (15 mmole) of amine IV, and 1.98 g (17 mmole) of bromoacetic acid. IR spectrum, cm^{-1}: 1690, 1780 (CO); 3090 (NH). Found: C 34.7; H 2.6; Br 32.6; N 17.4%. $C_7H_6BrN_3O_2$. Calculated: C 34.5; H 2.5; Br 32.7; N 17.2%.

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