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REACTION OF ESTERS OF 2-SUBSTITUTED 5-PYRIMIDINECARBOXYLIC ACIDS WITH HYDRAZINE HYDRATE

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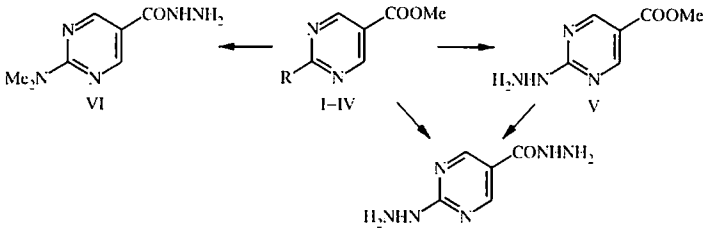
The reaction of methyl esters of 2-substituted 5-pyrimidinecarboxylic acids with hydrazine hydrate at 0-5°C results in the nucleophilic substitution of readily eliminating groups (Cl, CH_3O, CH_3S) at the position 2 of the pyrimidine ring, and, on the boiling with the 80% aqueous solution of hydrazine hydrate, the reaction is accompanied by the formation of hydrazides. The dimethylamino group at the position 2 of the pyrimidine ring is not substituted by hydrazine.

Hydrazides of pyrimidinecarboxylic acids and their derivatives, possessing interesting biological properties [1-6], are utilized in organic synthesis [7-11]. The most common method for the synthesis of hydrazides is the acylation of hydrazine by esters [12]. The majority of known hydrazides of 5-pyrimidinecarboxylic acids were synthesized by this method [1, 8, 13-16]. According to the data of the works [8, 17, 18], readily removable groups at the electrophilic carbon atom at the position 2 of the pyrimidine ring can cause competitive nucleophilic attack by hydrazine molecule and the very formation of hydrazinopyrimidines or the mixture of hydrazinopyrimidines and the corresponding 5-pyrimidinecarboxylic acid hydrazides. No more detailed investigations in this regard were found in the literature.

With the object of a qualitative evaluation of the relative reactivity of the ester group and groups situated at the position 2 of the pyrimidine ring, we studied the reaction of the methyl esters of 2-substituted 5-pyrimidinecarboxylic acids I-IV with hydrazine hydrate.



I R = Cl, II R = MeO, III R = MeS, IV R = Me_2N

Under mild conditions (0-5°C), the esters I-III only undergo nucleophilic attack by hydrazine molecule at the position 2 of the pyrimidine ring, whereby the eliminating groups are ranged in the following order according to mobility: Cl > CH_3S > CH_3O. The ester group does not react with hydrazine hydrate under these conditions. Methyl 2-hydrazino-5-pyrimidinecarboxylate (V) is formed as a result of the reactions. The compound IV is unchanged under these conditions. The ester groups of the compounds IV and V enter into the reaction with hydrazine hydrate with difficulty. The formation of hydrazides was not even noted during the prolonged boiling of the reaction mixture in solutions of methanol or ethanol. The corresponding hydrazides VI and VII were only

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obtained successfully by the boiling with large excess of the 80% aqueous solution of hydrazine hydrate. The relatively low reactivity of the ester group in the compounds IV and V to hydrazine hydrate can be explained by the +M-effect of the dimethylamino and hydrazino groups.

The compounds V and VII probably have the hydrazine structure since their UV spectra are similar to the UV spectra of the compounds IV and VI. The PMR spectra of the compounds I-VII contain signals of the 4-H and 6-H protons of the pyrimidine ring at 8.69-9.46 ppm. The PMR spectra of the methyl esters I-V have signals of the methyl protons of the ester group (3.68-4.06 ppm) which are absent from the spectra of the compounds VI and VII. This indicates the conversion of the ester group. The PMR spectra of the compounds II and III contain signals of protons of the methoxy group (3.69 ppm) and the methylthio group (2.51 ppm), the absence of which from the spectra of compounds V and VII indicates their nucleophilic substitution.

EXPERIMENTAL

The monitoring of the course of reactions and the purity of the compounds was performed on plates of Silufol. The UV spectra were obtained on in Specord UV-VIS spectrometer in ethanol. The PMR spectra were taken on a Tesla BS-487C instrument (80 MHz) in CF_3COOH, and the internal standard was HMDS.

Methyl 2-Chloro-5-pyrimidinecarboxylate (I). This compound is synthesized by analogy with the ethyl ester [19]. The yield is 52%, and the mp is 72.5-73°C (from hexane). UV spectrum, λ_{max}, nm (log ε): 226 (4.09), 254 (3.35, shoulder). PMR spectrum: 4.06 (3H, s, CH_3OCO); 9.46 (2H, s, 4-,6-H). Found, %: C 41.51; H 2.98; N 16.19. $C_6H_5ClN_2O_2$. Calculated, %: C 41.74; H 2.92; N 16.24.

Methyl 2-Methoxy-5-pyrimidinecarboxylate (II). To the solution of 2.0 g (12 mmol) of compound I in 20 ml of methanol, the solution of 0.65 g (12 mmol) of sodium methoxide in 10 ml of methanol is added, dropwise. The reaction mixture is boiled for 2 h on a water bath, and methanol is distilled off in vacuum. To the residue 10 ml of water are added, and the precipitate is filtered off and recrystallized from methanol. The yield is 1.3 g (65%), mp 127-128°C. UV spectrum, λ_{max}, nm (log ε): 233 (4.14), 263 (3.62, shoulder). PMR spectrum: 3.69 (3H, s, CH_3O); 4.05 (3H, s, CH_3OCO); 9.09 ppm (2H, s, 4-,6-H). Found, %: C 49.62; H 4.87; N 16.90. $C_7H_8N_2O_3$. Calculated, %: C 49.98; H 4.80; N 16.67. The published data [20]: mp 128-129°C.

Methyl 2-Methylthio-5-pyrimidinecarboxylate (III). This compound is synthesized by analogy with methyl 2-methoxy-5-pyrimidinecarboxylate II, utilizing the equimolar amount of sodium methylmercaptide. The yield is 90%, mp 95-96°C (from methanol). UV spectrum, λ_{max}, nm (log ε): 232 (3.82), 285 (4.25). PMR spectrum: 2.51 (3H, s, CH_3S); 3.71 (3H, s, CH_3OCO); 9.03 ppm (2H, s, 4-,6-H). Found, %: C 45.50; H 4.61; N 15.14. $C_7H_8N_2O_2S$. Calculated, %: C 45.62; H 4.38; N 15.21. The published data [20]: mp 95-96°C.

Methyl 2-Dimethylamino-5-pyrimidinecarboxylate (IV). To the solution of 2.0 g (12 mmol) of compound I in 20 ml of methanol 3.8 g (36 mmol) of anhydrous Na_2CO_3 are added. To the resulting suspension the solution of 1.6 g (36 mmol) of dimethylamine in 6 ml of methanol is added slowly on stirring, maintaining the temperature below 30°C. The reaction mixture is stirred for 2 h more at 30°C. The precipitate is filtered off, and the filtrate is evaporated in vacuum. The substance obtained is added to the previously precipitated solid, and recrystallization is performed from hexane. The yield is 1.1 g (51%), mp 130.5-131°C. UV spectrum, λ_{max}, nm (log ε): 203 (3.46); 281 (4.47). PMR spectrum: 3.1 (6H, s, CH_3N); 3.68 (3H, s, CH_3OCO); 8.73 ppm (2H, s, 4-,6-H). Found, %: C 52.85; H 6.02; N 23.41. $C_8H_{11}N_3O_2$. Calculated, %: C 53.01; H 6.12; N 23.20.

Methyl 2-Hydrazino-5-pyrimidinecarboxylate (V). To the solution of 0.5 g (2.9 mmol) of compound I in 12 ml of methanol, cooled to 5 °C, 0.25 g (5.8 mmol) of 95% hydrazine hydrate are added, dropwise at the same temperature. The reaction mixture is stirred at 0-5 °C for 40 min. The precipitate formed is filtered off and recrystallized from 50% aqueous methanol. The yield is 0.49 g (82%), mp 223-224 °C. Compound V is synthesized analogously from compound II with the yield of 79%, and the reaction time being 4 h, and from compound III with the yield of 70%, the reaction time being 2.5 h. UV spectrum, λ_{max}, nm (log ε): 273 (4.19). PMR spectrum: 4.05 (3H, s, CH_3OCO); 9.26 ppm (2H, s, 4-,6-H). Found, %: C 42.52; H 4.70; N 33.51. $C_6H_8N_4O_2$. Calculated, %: C 42.84; H 4.80; N 33.33.

2-Dimethylamino-5-pyrimidinecarboxylic Acid Hydrazide (VI). The mixture of 0.8 g (4.4 mmol) of compound IV and 6.7 g (0.11 mol) of 80% hydrazine hydrate is boiled for 1.5 h. The mixture is cooled, and the formed precipitate filtered off and recrystallized from ethanol. The yield is 0.6 g (75%), mp 194-195 °C. UV

spectrum, λ_{max}, nm (log ε): 206 (3.57), 278 (4.23). PMR spectrum: 3.05 (6H, s, CH_3N) ;8.69 ppm (2H, s, 4-,6-H). Found, %: C 46.21; H 6.40; N 38.93. $C_7H_{11}N_5O$. Calculated, %: C 46.38; H 6.12; N 38.67.

2-Hydrazino-5-pyrimidinecarboxylic Acid Hydrazide (VII). This compound is synthesized by analogy with the hydrazide VI from the methyl esters I-III and V. The reaction time is 2-2.5 h. The yield is 60-65%, mp 226-227°C (from 50% aqueous methanol). UV spectrum, λ_{max}, nm (log ε), 264 (4.00). PMR spectrum: 9.14 ppm (s, 4-,6-H). Found, %: C 35.82; H 4.61; N 50.10. $C_5H_8N_6O$. Calculated, %: C 35.69; H 4.80; N 49.99.

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