ISOMERIZATION OF 5,7-DIMETHYLTRIAZOLO[4,3-a]-PYRIMIDINE UNDER THE INFLUENCE OF ALKALINE AGENTS

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5,7-Dimethyl-1,2,4-triazolo[4,3-a]pyrimidine is isomerized in the presence of various nucleophilic agents to 5,7-dimethyl-1,2,4-triazole[1,5-a]pyrimidine via a rearrangement of the Dimroth type. Under the influence of hydrazine hydrate, both triazolopyrimidines are converted to a mixture of 3,5-dimethylpyrazole and 3-amino-1,2,4-triazole.

In acid media some triazole [4,3-a]pyrimidines are converted to the corresponding isomeric triazolo[1,5-a]pyrimidines[1,2]; a similar rearrangement also takes place in aquous alkali [3].

We set up rearrangement experiments for the previously unstudied models 5,7-dimethyltriazolo[4,3-a]pyrimidine (I) and 5,7-dimethyltriazolo[1,5-a]pyrimidine (II) in which the nucleophilicity of the attacking agent was varied. In doing this, we proceeded from the fact that this sort of process should proceed via the scheme of the Dimroth rearrangement [4]. It was found that I is converted completely to the isomeric triazolopyrimidine II when it is heated with aqueous or alcoholic alkali for 2 h. Reconversion does not occur under the same conditions. In fact, calculations of the total energy of the ground state of models of this sort by the CNDO-2 complete neglect of differential overlap method have shown that triazolo [1,5-a]pyrimidines are more stable than the isomeric triazolo[4,3-a]pyrimidines [5].

Water plays an essential role in this process. Thus when the reaction is carried out in aqueous triethylamine for 5 h, 60% rearrangement is observed, whereas the reaction does not proceed at all in anhydrous triethylamine. The reaction proceeds very slowly in alcoholic sodium alkoxide solution, but the addition of water increases the rate of transformation sharply. Thus the hydroxide ion, which has sufficiently high nucleophilicity but low steric requirements, was found to be a reagent for rearrangement.

Enol III, which is evidently formed during ring opening, undergoes a change in conformation to give structure IIIa and again closes the pyrimidine ring with electrophilic attack on the other nitrogen atom of the triazole ring with a simultaneous electron shift. The resulting ketone (IV) is cyclized due to electrophilic attack of the carbonyl group on the negatively charged nitrogen atom. All of the steps of the Dimroth rearrangement are fundamentally reversible, but the thermodynamic stability of isomer II determines the unilateral occurrence of the process. In view of its high nucleophilicity, the alkoxide ion should add readily, but the subsequent steps (configurational rearrangement and elimination) for it are limited by steric factors. The PMR spectra of I and II differ imperceptibly. There is also little information in the mass spectra in view of the identity of the fragmentation of the molecular ions of I and II, but there are some available differences; for example the observable ions in the mass spectra of II [M − 15] (5%) and [M − 39] (77.2%) are absent in the spectra of I. Three intense absorption maxima at 211 (log ε 4.45), 288 (log ε 3.56), and 370 nm (log ε 2.65) are observed in the UV spectrum of 5,7-dimethyltriazolo [4,3-a]pyrimidine (I). The spectrum of II contains absorption maxima at 209 (log ε 4.58) and 270 nm (log ε 3.73) and a weak maximum at 3.45 nm (log ε 0.96). The chromatographic mobilities of these compounds also differ, and this makes it possible to monitor the rearrangement by means of thin-layer chromatography (TLC).

It is known that pyrimidines and condensed structures based on them undergo ring opening under the influence of hydrazine hydrate or hydroxylamine [6,7]. In the case of hydrazine

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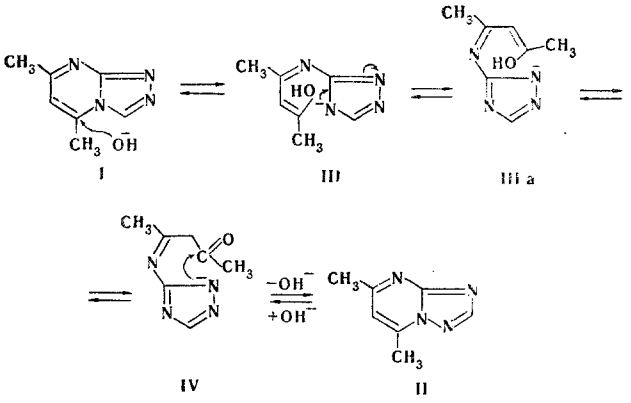
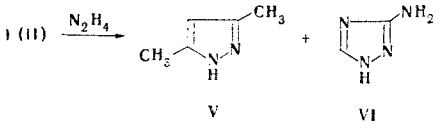


the second amino group of the reagent proves to be the more nucleophilic portion of the molecule, as a result of which the pyrimidine ring undergoes complete cleavage to give pyrazole derivatives [8,9]. However, alternative hydrazinolysis pathways with cleavage of the pyrimidine ring leading, depending on the ring substituents, to pyrazoles or triazoles are also possible [10]. Moreover, β-diketone dihydrazones are isolated as the hydrazinolysis products of pyrimidine [11].

It was found that I and II react with hydrazine hydrate to give a mixture of 3,5-dimethylpyrazole (V) and 3-amino-1,2,4-triazole (VI).



Consequently, opening of the pyrimidine ring also occurs here, but it is not accompanied by recyclization but rather by cleavage of the ketone side chain, which undergoes cyclization to give pyrazole V.

The reaction of hydroxylamine in aqueous media with I and II proceeds in a manner similar to the isomerization in aqueous alkali — I is converted quantitatively to II. We were unable to detect the oxime or a substituted isoxazole.

EXPERIMENTAL

The PMR spectra were recorded with a Varian T-60 spectrometer with tetramethylsilane as the standard. The mass spectra were recorded with an MKh-1303 mass spectrometer with introduction of the substances into the ionization region at 50 eV. The UV spectra of alcohol solutions of the compounds were recorded with a Cary-15 spectrophotometer.

Rearrangement of 5,7-Dimethyltriazole[4,3-*a*]pyrimidine (I) to 5,7-Dimethyltriazolo [1,5-*a*]pyrimidine (II). A) A 0.3-g (2 mmole) sample of I was added to 5 ml of water (or alcohol) containing 0.85 g of potassium hydroxide, and the mixture was refluxed for 2 h. The course of the reaction was monitored by chromatography on silica gel (L 100/160 nm) in an ethyl acetate—methanol (3:1) system. After the conversion of I to II was complete, II was extracted with chloroform. The solvent was removed by distillation, and the residue was recrystallized from petroleum ether—benzene (10:1) to give 0.27 g (90%) of a product with mp 134-135°. PMR spectrum (D_2O): singlets at 2.9 and 3.1 ppm (5- and 7-CH); 7.26 (6-H); 8.66 ppm (2-H). The molecular weight (by mass spectrometry) was 148.

B) Similarly, 0.3 g (2 mmole) of I was refluxed in a solution of hydroxylamine obtained by treatment of 0.2 g (3 mmole) of hydroxylamine hydrochloride with an equimolar amount of potassium hydroxide or sodium carbonate dissolved in 5 ml of water. After refluxing for 12-15 h, I was converted quantitatively to II. Workup of the mixture as described above gave 0.27 g (90%) of a product with mp 133-135° and R_f 0.27.

C) A 0.5-g (3.4 mmole) sample of I was refluxed for 5 h in 5 ml of water containing 1 g of triethylamine, after which a mixture of I and II was extracted with chloroform and subjected to preparative separation on a plate. The product was recrystallized from petroleum

ether—benzene (10:1) to give 0.29 g (58%) of II, with mp 132-134° and R_f 0.27, and 0.17 g (34%) of starting I, with mp 164-165° and R_f 0.55. PMR spectrum (D_2O): singlets at 2.7, 2.9 (5- and 7-CH_3), 7.2 (6-H), and 8.8 ppm (2-H).

Hydrazinolysis of I and II. A 0.3-g (2 mmole) sample of I was dissolved in 10 g of hydrazine hydrate, and the mixture was refluxed for 6 h. The hydrazine hydrate was then vacuum evaporated to dryness, and the residue was refluxed with 20 ml of chloroform. The chloroform-insoluble 3-amino-1,2,4-triazole (VI) was separated to give 0.16 g (94%) of a product with mp 157-158° and a molecular weight (by mass spectrometry) of 84 that was chromatographically identical to a genuine sample.

Removal of the chloroform by distillation, and recrystallization of the residue from benzene gave 0.18 g (93%) of 3,5-dimethylpyrazole (V) with mp 103-104° (in agreement with the literature value) and a molecular weight (by mass spectrometry) of 96. As in the preceding experiment, 1 g of II yielded 0.54 g (95%) of VI and 0.6 g (93%) of V.

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SYNTHESIS AND SOME PROPERTIES OF QUINAZOLYLFORMAZANS

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Some previously undescribed N-quinazolylformazans were synthesized, and some of their properties were studied. The absorption spectra of the formazans and their ions are discussed. The compositions of complexes of the formazans with Ni^{2+} and their instability constants were determined.

The properties and structures of N-quinoxalylformazans were previously examined in [1]. It seemed of interest to synthesize and investigate the previously undescribed N-quinazolylformazans I, which contain an isomeric heterocyclic quinazolyl group.

Formazans Ia-e were obtained by diazo coupling of 4-quinazolylhydrazones with benzenediazonium chlorides via the scheme given below. The structure of Ia was confirmed by oxidation with Pb_3O_4 in acetic acid by the method in [2] to a tetrazolium acetate (IIa), which, as in [3], is converted to a 2,5-diphenyltetrazole (IIIa) on treatment with dilute hydrochloric acid at 20°C.

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