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The products of reductive cleavage of the isoxazoline ring of α-oxo-4,5-cyclohexano-Δ²-isonoxazolines by catalytic hydrogenation were studied.

Isoxazole derivatives are used for the preparation of complex poly- and heterocyclic structures [1-3]. We recently proposed a new method for the synthesis of 2-acylcyclohexane-1,3-diones from α-oxocyclohexano-isonoxazolines that makes it possible to obtain diverse cyclic tricarbamethanes [4, 5]. The reductive cleavage of the intermediate 4,5-cyclohexanoisonoxazolines, which are potential β-trifunctional derivatives of cyclohexane, is also of interest in addition to the preparative value of this method. The β-trifunctional derivatives of cyclohexane are linked by one step of the transformation with β-triketones and can be used as intermediates in the synthesis of natural and related polycyclic compounds.

Simple Δ²-isonoxazolines undergo reductive cleavage of the N-O bond to give the corresponding β-imino alcohols on catalytic hydrogenation and under the influence of alkali metals [6, 7]. Condensed α-oxocycloalkanoisonoxazolines [4, 5, 8] have not been investigated in this respect. In the present research we have studied the behavior of cyclohexanoisonoxazoline I [4] under catalytic hydrogenation conditions.

Isoxazoline I is more stable than the corresponding isoxazole (V), despite the prevailing concept of the relatively high lability of isoxazoline structures [9]. Thus isoxazoline I does not undergo change during hydrogenation by means of 5% Pd/BaSO₄, at the same time that isoxazole V under these conditions is readily converted to enamino diketone II [10] in the absence of base, in contrast to other isoxazoles [11]. The lability of the isoxazoline ring as compared with the Δ²-isoxazoline ring is apparently due to the activating effect of the conjugated α-carbonyl group on the aromatic system of isoxazole. In fact, in the case of hydroxyisoxazole VI [12], which does have this sort of activating effect, ring cleavage does not occur under the influence of the low-activity 5% Pd catalyst. Isoxazoline I and hydroxyisoxazole VI undergo ring opening when 30% Pd/S₂CO₃ or Ni/Re are used, and one observed a complete analogy in the behavior of these compounds. Various enamino derivatives (II-IV) can be obtained, depending on the conditions. The formation of enamino diketone II observed during the hydrogenation of isoxazoline I on 5% Pd/BaSO₄ in the presence of triethylamine is evidently due to intermediate catalytic dehydrogenation of I to isoxazole V and its subsequent reductive cleavage. In addition to this, one cannot exclude the possibility of the formation of II from I by disproportionation or intramolecular transfer of hydrogen [13]; the formation of a mixture of II-V when a solution of I in triethylamine is refluxed with 5% Pd/BaSO₄ in the absence of hydrogen served as a confirmation of this. Thus the high yield of II in the catalytic hydrogenation of I is due, on the one hand, to the presence of triethylamine, which promotes the formation of isoxazole V, and, on the other, to removal of V from the reaction sphere by means of its reduction on the catalyst, which is ineffective with respect to opening of the isoxazoline ring.

The formation of III and IV under various hydrogenation conditions is associated with cleavages of the N-O bond and evidently proceeds through an intermediate step involving the unstable β-hydroxy enamino ketone (VII), which we were unable to isolate. Compound VII undergoes spontaneous dehydration to give dienamino ketone III, the subsequent reduction of the double bond in which gives enamino ketone IV.

The IR spectrum of III displays the absorption at 1500-1600 cm⁻¹ that is characteristic for β-aminovinyl ketones [14]. The bands at 3120 and 3280 cm⁻¹ correspond to the stretching vibrations of two N-H bonds, indicating inclusion of one of them in a strong intramolecular hydrogen bond of the chelate type; this is also confirmed by the pronounced lowering of the frequency of the carbonyl absorption [15]. Stretching vibrations of C-H bonds of a disubstituted alkene appear in the spectrum of III at 3040 cm⁻¹.

The PMR spectrum of III, in addition to signals of a methyl group, a gem-dimethyl group, and a methylene group adjacent to a carbonyl group in the inspected regions, contains doublets of vinyl protons at 5.25 and 6.15 ppm. The broad lone signals at 5.47 and 10.21 ppm are related to the resonance of the NH protons, and the strong shift of one of these to weak field indicates the presence of a strong intramolecular hydrogen bond in the molecule [16].

A confirmation of the structure of dienamine III is its easy reduction on a Pd catalyst, which proceeds with the absorption of 1 mole of hydrogen and the formation of enamino ketone IV. The latter was also obtained in 95% yield by hydrogenation of I in ethanol over Ni/Re and is the chief product of catalytic hydrogenation on Pd and Rh catalysts of hydroxyisoxazole VI or its acetate. The conversion of VI to IV evidently includes the same sequence of reactions as the hydrogenation of isoxazoline I. However, one cannot exclude the possibility of the formation of enamino ketone IV as a result of hydrogenolysis under the conditions of catalytic hydrogenation of the allylic C-O bond in hydroxyisoxazole VI (or in the corresponding intermediate from opening of the isoxazoline ring).

Dienamino ketone III is the tautomeric form of crossconjugated imino ketone VIII. Compounds of this sort are of interest in connection with the problem of the synthesis of crossconjugated enediones of the IX type and their use in the total synthesis of steroids [17, 18]. Moreover, as in the case of endione IX, which is readily isomerized to ketodienol X, the imino ketone form is evidently thermodynamically less favorable, as a consequence of which only dienamo ketone III or the product of its subsequent reduction—enamino ketone IV—is isolated from the reaction mixture. The structure of IV follows unambiguously from the spectral data and is confirmed by its hydrolysis to the known [19] 2-acetyl-5,5-dimethylcyclohexanone.

EXPERIMENTAL

The melting points were measured with a Kofler block. The IR spectra were recorded with a UR-20 spectrometer. The PMR spectra were recorded with the NMR spectrometer of the HNM-PFT-