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INTERACTION OF ENAMINES OF TETRAHYDROPYRIDIN-4-ONE AND α,β-UNSATURATED ACID CHLORIDES

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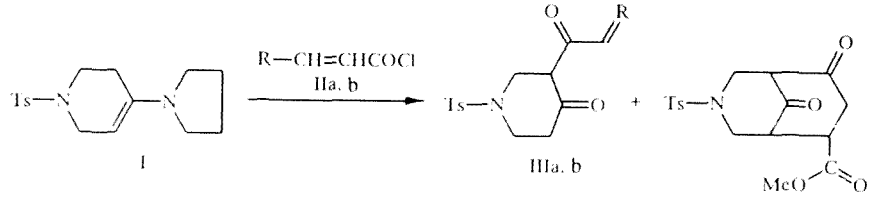
The interaction of N-tosyl-4-pyrrolidinyl-1,2,4,5-tetrahydropyridine with acryloyl chloride and the methyl ester of 3-chloroformylacrylic acid was investigated. In addition to acylated derivatives of tetrahydropyridin-4-one, the methyl ester of 3-N-tosyl-3-acrylate-8,9-1[3.1.1]nonane-6-carboxylic acid was obtained.

Enamines of tetrahydropyridin-4-one are used in heterocyclization reactions for the synthesis of the most varied structures [1, 2]. Earlier we reported on the cyclization of enamines of cyclohexanone to polyfunctional derivatives of bicyclo[3.3.1]nonanes by the reaction with esters of chloroformylacrylic acid [3]. The use of this reaction in the case of nitrogen-containing enamines may lead to a 3-azabicyclononane structure, which is contained in many alkaloids and other natural compounds [4, 5], and is also a convenient model for stereochemical investigations [6, 7]. However, it is evident that in the reaction of a heterocyclic enamine and electrophilic reagents, such as derivatives of α,β-unsaturated acids, the cyclization may be complicated by the presence of the heteroatom. Chlorides of unsaturated acids are reactive but unselective electrophiles, and therefore the reaction may proceed in several directions. Moreover, heterocyclic enamines are very readily hydrolyzed, and their isolation and purification presents definite difficulties, whereas the annelation reactions are very sensitive to impurities. We investigated the reaction of a pyrrolidine enamine of tetrahydropyridin-4-one I with acryloyl chloride (IIa) and the methyl ester of chloroformylacrylic acid (IIb).



II, III a R=H, b R=COOMe

The reaction of the enamine I with the acid chloride IIa under various conditions leads to an acylated oxopiperidine IIIa with a yield of 40%. The interaction of compound I with the ester IIb has a more complex course, and a mixture of compounds is formed; it is separated by repeated chromatography on a column with silica gel (eluent carbon tetrachloride-acetone, 6:5). In the IR spectrum of the basic compound, absorption bands of the C≡O groups (1710 cm^{-1}) and the conjugated fragment C≡O–C≡C (1620 cm^{-1}) and OH (3350 cm^{-1}) are observed. In the ^{13}C NMR spectrum signals are observed in the region of 143.9...127.0 ppm, characteristic of carbon atoms at a double bond. The structure of IIIb may be in several tautomeric forms, and, consequently, this structure can be ascribed to the major component.

On the basis of the IR and ^1H NMR spectral data a 3-azabicyclononane structure IV was assigned to the other component of the mixture. It can be noted that the two compounds has the same molecular formula. In the IR spectrum of compound IV an absorption band of the C≡O group (1720 cm^{-1}) is observed: there is no absorption in the region of 3100...3600 cm^{-1}. In the ^1H NMR spectrum the signal at 4.1 ppm (half-width ~12 Hz) is characteristic of a proton at C_6 with an endo-configuration of the ester group in the cyclohexanone ring. The conformation of the cyclohexanone ring and the configuration of the ester group also follow from the mechanism of the cyclization reaction and calculations of the analogous carbocyclic derivative according to the MM method [7].

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EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 instrument in liquid petrolatum. The ^1H NMR spectra (in CD_2Cl_2) and ^{13}C NMR spectra (in $CDCl_3$) were recorded on a BS-587A spectrometer with working frequency 80 MHz for protons and 20 MHz for carbon, internal standard TMS. Column chromatography was conducted on silica gel L40/100 μ (Chechia).

The data of elementary analysis of the compounds synthesized for C, H, N, and S and correspond to the calculated values.

The enamine I was synthesized according to the procedure described in [8] and used directly in the reaction with acid chlorides.

Interaction of the Enamines I with Acryloyl Chloride IIa. To a solution of 0.32 g (1.0 mmole) of the enamine I in 15 ml of benzene at room temperature we added 0.09 g (1.0 mmole) of freshly redistilled acryloyl chloride in 2 ml of benzene. Then the reaction mixture was boiled for 6 h, cooled, and the precipitate was filtered and washed with hexane. The crystals were dissolved in ice water and mixed for 1 h. The aqueous solution was extracted with ether, dried with $MgSO_4$, and after distilling off the solvent, the residue was purified by column chromatography. We obtained 0.1 g (40%) 2-propenoyl-N-tosylpiperidin-4-one (IIIa). IR spectrum, cm^{-1}: 1707, 1703, 1647, 1595, 1447, 1153. NMR spectrum: 8.25...7.2 (6 H, m, H_{arom}, and $\equiv CH_2$), 4..1...3.8 (3 H, m, $CH_2COCHCO$), 3.0...2.1 (4 H, m), 2.3 ppm (3 H, s, CH_3).

Interaction of the Enamine I with the Ester IIb. A 3.6 g (12 mmoles) portion of freshly prepared enamine I was dissolved in 120 ml of absolute benzene and heated to 45°C in an atmospheric of nitrogen. To the solution we added 1.8 g (12 mmoles) of the acid chloride IIb in 6 ml of benzene after 45 min. The reaction mixture was heated for 6 h at 45...50°C. The precipitate formed was filtered, washed twice with benzene, dissolved in 50 ml of cold water, and left overnight. The precipitate was filtered, and 3.6 g of the substance was obtained. A 0.3 g portion of the mixture was separated by chromatography on a column with silica gel (eluent chloroform-acetone, 9:1). Repeated chromatography (eluent carbon tetrachloride–acetone, 6:5) yielded 0.14 g (47% yield) of compound IIIb and 0.05 g (17%) of compound IV. Methyl ester of 4-oxo-4-(N-tosyl-4'-oxopiperidin-3'-yl)butenecarboxylic acid (IIIb), T_m 95°C (from 2-propanol). IR spectrum, cm^{-1}: 3350 (broad, OH), 1710 (CO), 1620 (C=C–C=O), 1330 and 1160 (SO_2Ph). NMR spectrum: 8.5...7.3 (6 H, m, H_{arom}, and COCH=CHCOO), 3.6 (3 H, s, OCH_3), 3.4...2.5 (2 H, m), 2.5...2.3 (4 H, m), 2.25 ppm (3 H, s, CH_3). ^{13}C NMR spectrum: 206.9, 198.6, 177.1, 174.2, 144.1, 143.9, 133.5, 133.2, 129.7, 129.4, 127.3, 127.0, 51.0, 45.6, 45.4, 43.8, 42.6, 40.4, 36.9. Methyl ester of N-tosyl-3-acrylate-8,9-dioxobicyclo[3.3.1]nonane-6-carboxylic acid (IV), mp 55°C. IR spectrum (KBr), cm^{-1}: 1720, 1330, and 1160 (SO_2Ph). NMR spectrum: 8.25...7.3 (4 H, two d, H_{arom} protons), 4.1 (1 H, m, C_6–H), 4.0 (1 H, m, COCHCO), 3.6 (3 H, s, OCH_3), 3.5...2.35 (7 H, m, $H_{alicycl}$), 2.35 ppm (3 H, s, CH_3Ar).

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