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REACTION OF 5-HYDROXY-3,3,5-TRIMETHYLISOXAZOLIDINE WITH ACRYLIC ACID ESTERS

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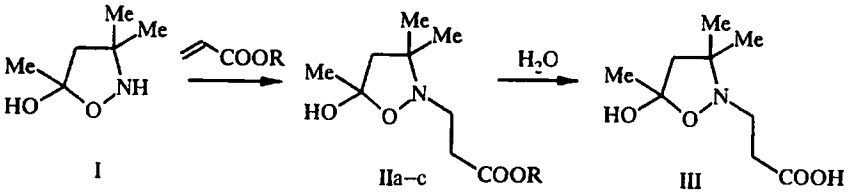
The reaction of 5-hydroxy-3,3,5-trimethylisoxazolidine with methyl, ethyl, and tert-butyl acrylates, proceeds as Michael addition, and produces previously unknown 5-hydroxy-3,3,5-trimethylisoxazolidine-2-propionic acid esters. The structures of the obtained products are proved by ^{1}H and ^{13}C NMR spectroscopy and by their subsequent transformation into 5-hydroxy-3,3,5-trimethylisoxazolidine-2-propionic acid.

We previously have demonstrated [1, 2] that acylation of 5-hydroxy-3,3,5-trimethylisoxazolidine (I) gives, depending on the nature of the acylating agent, both cyclic and linear products, i.e., N-acyl-5-hydroxy-3,3,5-trimethylisoxazolidine and 4-(O-acylhydroximino)-4,4-dimethylbutan-2-one, respectively. Phenyl isothiocyanate reacts with the compound I to give 5-hydroxy-3,3,5-trimethyl-2-(3-phenylthiocarbamoyl)isoxazolidine, which exists in solution as a tautomeric mixture of the isoxazolidine and pyrimidin-2(1H)-thione forms. Its dehydration product has the pyrimidine structure [3].

In continuation of the previous work on functionally substituted isoxazolidine derivatives [1-4], we examined the reaction of 5-hydroxy-3,3,5-trimethylisoxazolidine (I) with acrylic acid esters.



IIa R = Me, bR = Et, cR = *t*-Bu

As it turned out, these compounds react after brief boiling in methanol in the presence of catalytic amounts of NaOH to give the compounds IIa-c in good yields (see Experimental). According to elemental analyses, these compounds correspond to the addition products of 5-hydroxy-3,3,5-trimethylisoxazolidine (I) to the corresponding acrylates (1:1).

The spectral data are consistent with a cyclic isoxazolidine structure for compounds IIa-c. In particular, the PMR spectra contain signals of a typical AB-system at 2.0-2.5 ppm due to diastereotopy of the methylene group protons, and a signal for sp^3-hybridized $C_{(5)}$ atom near 100 ppm in the ^{13}C NMR spectra (see Experimental). Signals in the ^{13}C NMR spectra of series of N-aryl(benzyl)-5-hydroxyisoxazolidines that were previously studied by us [2, 3] and spectral characteristics of derivatives of isoxazolidine-2-propionic acid [5, 6] are consistent with the proposed structure for compounds IIa-c.

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As it turned out, brief heating of compounds IIa,b in 1M NaOH solution at 40-50°C hydrolyzes completely the ester and gives 5-hydroxy-3,3,5-trimethylisoxazolidine-2-propionic acid (III) in good yield.

Thus, we propose another method for synthesizing N-substituted 5-hydroxyisoxazolidines in addition to the method based on hydroxylamine derivatives and α,β-unsaturated carbonyl compounds that we developed previously. The method represents a modification of the isoxazolidine ring itself. It is noteworthy that the studied transformations do not affect the hemiacetal nature of $C_{(5)}$ atom, leaving it available for subsequent interactions with nitrogeneous nucleophiles. This will be the subject of future research.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer at 200 and 50.33 MHz working frequencies, respectively. The course of the reactions and the purity of the products were monitored by TLC on Silufol U-254 plates. Chromatography was performed on a glass column (l = 25 cm, d = 2.5 cm) filled with Chemapol L 100/160 silica gel. The eluent was benzene–acetone (4:1). Compound I was prepared by the literature method [7].

5-Hydroxy-3,3,5-trimethylisoxazolidine-2-propionic Acid Esters (IIa-c). Mixture of compound I (10 g, 0.075 mol), acrylic acid ester (0.1 mol), several drops of 50% NaOH solution, and methanol (50 ml) was boiled for 1 h. The solvent was removed under reduced pressure. The residue was distilled under vacuum or purified on a column.

Methyl 5-Hydroxy-3,3,5-trimethylisoxazolidine-2-propionate (IIa). Yield 70%; bp 92-95°C (1 mm Hg). PMR spectrum ($CDCl_3$): 1.04 (3H, s, 3-CH_3); 1.10 (3H, s, 3-CH_3); 1.21 (3H, s, 5-CH_3); 2.15, 2.30 (2H, AB-system, J_{AB} = 16 Hz, 4-H); 2.62 (2H, m, C$\underline{H}_2$CO); 2.90 (2H, m, CH_2N); 3.63 (3H, s, CH_3O); 5.61 ppm (1H, br. s, OH). ^{13}C NMR spectrum ($CDCl_3$): 23.4 (3-CH_3); 26.7 (3-CH_3); 31.1 (5-CH_3); 35.7 (CH_2–CO); 48.1 (CH_2N); 54.8 (CH_3O); 57.1 ($C_{(4)}$); 63.8 ($C_{(3)}$); 100.9 ($C_{(5)}$); 170.9 ppm (COO). Found, %: C 55.32; H 8.78; N 6.51. $C_{10}H_{19}NO_4$. Calculated, %: C 55.28; H 8.81; N 6.45.

Ethyl 5-Hydroxy-3,3,5-trimethylisoxazolidine-2-propionate (IIb). Yield 75%; bp 98-101°C (1 mm Hg). PMR spectrum (acetone-d_6): 1.03 (3H, s, 3-CH_3); 1.12 (3H, s, 3-CH_3); 1.14 (3H, t, C$\underline{H}_3$CH$_2$); 1.34 (3H, s, 5-CH_3); 2.03, 2.18 (2H, AB-system, J_{AB} = 12 Hz, 4-H); 2.47 (2H, m, C$\underline{H}_2$CO); 2.83 (2H, m, CH_2N); 3.54 (1H, br. s, OH); 4.02 ppm (2H, m, C$\underline{H}_2$CH$_3$). ^{13}C NMR spectrum (acetone-d_6): 13.9 (C$\underline{H}_3$CH$_2$); 23.6 (3-CH_3); 26.1 (3-CH_3); 31.1 (5-CH_3); 33.4 (C$\underline{H}_2$CO); 45.7 (CH_2N); 57.1 ($C_{(4)}$); 59.8 (C$\underline{H}_2$CH$_3$); 63.2 ($C_{(3)}$); 101.6 ($C_{(5)}$); 171.8 ppm (C$\underline{O}$O). Found, %: C 57.08; H 9.20; N 6.10. $C_{11}H_{21}NO_4$. Calculated, %: C 57.12; H 9.15; N 6.06.

***tert*-Butyl 5-Hydroxy-3,3,5-trimethylisoxazolidine-2-propionate (IIc).** Yield 45%; oil, R_f 0.63. PMR spectrum ($CDCl_3$): 1.05 (3H, s, 3-CH_3); 1.16 (3H, s, 3-CH_3); 1.35 [12H, s, $(CH_3)_3C$ and 5-CH_3], 2.05, 2.21 (2H, AB-system, J_{AB} = 14 Hz, 4-H); 2.53 (2H, m, C$\underline{H}_2$CO); 2.87 (2H, m, CH_2N); 8.24 ppm (1H, br. s, OH). ^{13}C NMR spectrum ($CDCl_3$): 23.2 (3-CH_3); 26.3 (3-CH_3); 28.6 [(C$\underline{H}_3$)$_3$C]; 31.5 (5-CH_3); 33.7 (C$\underline{H}_2$CO); 45.3 (CH_2N); 57.5 ($C_{(4)}$); 62.1 ($C_{(3)}$); 79.1 [(CH$_3$)$_3$C]; 100.3 ($C_{(5)}$); 171.2 ppm (C$\underline{O}$O). Found, %: C 60.28; H 9.67; N 5.34. $C_{13}H_{25}NO_4$. Calculated, %: C 60.21; H 9.72; N 5.40.

5-Hydroxy-3,3,5-trimethylisoxazolidine-2-propionic Acid (III). Compounds IIa and IIb (0.05 mol) are held at 50°C in NaOH solution (25 ml, 1 M) for 10 h. The mixture is neutralized with dilute HCl and extracted with ethyl acetate. The solvent is removed under reduced pressure. The residue is purified on a column. Yield 40%; mp 141-144°C. PMR spectrum (DMSO-d_6): 1.07 (3H, s, 3-CH_3); 1.13 (3H, s, 3-CH_3); 1.32 (3H, s, 5-CH_3); 2.32, 2.47 (2H, AB-system, J_{AB} = 14 Hz, 4-H); 2.68 (2H, m, C$\underline{H}_2$CO); 2.85 (2H, m, CH_2N); 6.71 ppm (1H, br. s, OH). ^{13}C NMR spectrum (DMSO-d_6): 24.0 (3-CH_3); 27.6 (3-CH_3); 30.7 (5-CH_3); 33.8 (C$\underline{H}_2$CO); 46.3 (CH_2N); 56.6 ($C_{(4)}$); 63.5 ($C_{(3)}$); 101.5 ($C_{(5)}$); 174.5 ppm (COOH). Found, %: C 53.23; H 8.37; N 6.95. $C_9H_{17}NO_4$. Calculated, %: C 53.19; H 8.43; N 6.89.

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