

SYNTHESIS OF 4(5)-[2-BICYCLO(2.2.2)OCTYL]IMIDAZOLE DERIVATIVES

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The synthesis and separation of endo-5-(4(5)-imidazolyl)bicyclo[2.2.2]oct-endo- and -exo-2-yl trans-cinnamates via endo-5-(1-keto-2-hydroxyethyl)bicyclo[2.2.2]oct-2-ene are described. The imidazolyl derivatives have a rigid bicyclo[2.2.2]octane skeleton; the endo, endo compound was synthesized as a model for acyl-g-chymotrypsin and the endo, exo compound was synthesized for purposes of comparison.

The mode of 2,5 disubstitution of bicyclo[2.2.2]octane was determined by ^{13}C NMR spectroscopy. The synthesis and structural determination were carried out in comparison with those for the corresponding bicyclo[2.2.1]heptane derivatives which were described earlier (J. Org. Chem., 39, 3772 (1974)).

A 3 : 1 mixture of endo- and exo-5-(4(5)-imidazolyl)bicyclo[2.2.2]oct-2-enes was obtained from a 9 : 1 mixture of endo- and exo-5-(1-keto-2-hydroxyethyl)bicyclo[2.2.2]oct-2-enes by the Weidenhagen method in 60-70% yield. Hydrogenation using Pd/C of the mixture of the endo- and exo-imidazolyl derivatives gave 4(5)-[2-bicyclo[2.2.2]octyl]imidazole nearly quantitatively. Oxidation of the mixture of the endo- and exo-imidazolyl derivatives yielded only endo-5-(4(5)-imidazolyl)bicyclo[2.2.2]octan-2-one in a 43% yield based on the endo-imidazolyl derivative. This stereo- and regiospecific oxidation was attributed to the presence of the endo-5-imidazolyl group. The ketone was reduced with LiAlH_4 to give the corresponding endo and exo alcohols, which were separated by means of preparative layer chromatography using alumina. Acylation of the alcohols with trans-cinnamoyl chloride gave the O- and N-diacylated intermediates, which were converted into endo-5-(4(5)-imidazolyl)bicyclo[2.2.2]oct-endo- and -exo-2-yl trans-cinnamates by partial hydrolysis.