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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-*α*-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 synthsis 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.