SYNTHESIS OF NATURAL PRODUCTS VIA ISOXAZOLIDINES AND ISOXAZOLINES

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Synthesis of natural products by 1,3-dipolar addition reaction of nitrones, nitroesters, and nitrile oxides to olefins was examined.

As model compounds 5-formylmethyl- (1) and 5-(2-formylethyl)cholestan-3-enes (2) were prepared and allowed to react with phenylhydroxylamine. The compound (1) produced the nitrone which on heating in xylene gave an intramolecular 1,3-dipolar adduct, in which the newly formed carbon ring was four membered (50% yield) besides a dimer. On the other hand, the nitrone group on the side chain at C-5 of 2 reacted with the intramolecular olefinic bond (Δ^3) in such a manner as to form exclusively a cyclopentane ring (70% yield). Similarly, intramolecular cyclization of the nitrone obtained from 2-butenylcyclohexanone and N-methylhydroxylamine yielded a perhydroindane derivative in a good yield, and the nitrone from 2-pentenylcyclohexanone and N-methylhydroxylamine afforded a 1:1 mixture of perhydronaphthalene and perhydrohomonaphtalene derivatives.

Methyl ester of methyl nitroacetate did not react with 1,4-quinones in the absence of Lewis acids. Addition of boron trifluoride etherate to the reaction mixture catalyzed the reaction giving mainly isoxazoles resulted from elimination of methanol from the 1:1 adduct of the nitroester and quionones. Ethyl ester of nitromethane smoothly reacted with methyl acrylate, giving 2-methoxy-5-methoxycarbonylisoxazolidine, and the adduct was converted to 4-amino-2-hydroxybutyric acid, which was known to activate antibiotics such as kanamycin.

Reaction of ethyl cyanoformate oxide (3) with methyl acrylate afforded 3-ethoxycarbonyl-5-methoxycarbonyl-2-isoxazoline which was converted into γ-hydroxyglutamic acid through hydrogenation and hydrolysis. The nitrile oxide (3) also reacted with isobutene and styrene giving rise to 5,5-dimethyl- and 5-phenyl-3-ethoxycarbonyl-2-isoxazolines, respectively. The former was converted to γ-hydroxyleucine.