THE SYNTHESIS OF NOVEL TETRAHYDROFURAN ANALOGS AS MOLECULAR PROBES FOR CHOLINERGIC RECEPTORS

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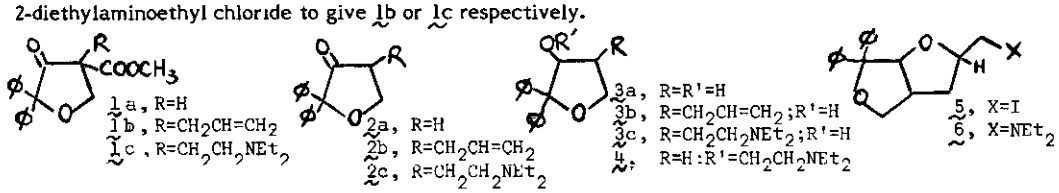
As part of our research effort to synthesize semi-rigid probes for the muscarinic cholinergic receptor, we have prepared a series of novel tetrahydrofuran derivatives using appropriate cyclization and alkylation reactions.

Our general approach has been to synthesize alkylated tetrahydrofuranones by means of a Michael addition-Dieckmann cyclization sequence in DMSO. The intermediate β-keto ester carbanion produced by this process was either treated with dilute acid to obtain 1a or immediately alkylated with allyl bromide or 2-diethylaminoethyl chloride to give 1b or 1c respectively.



The subsequent hydrolysis and decarboxylation of the β-keto esters 1a-c were accomplished under acidic or basic conditions to produce the tetrahydrofuranone intermediates 2a-c.

Reduction of ketone 2a with sodium borohydride afforded a tetrahydrofuranol 3a which was converted to the amino ether 4 by means of a Williamson ether synthesis. Sodium borohydride was also used in the reduction of ketone 2c to yield a mixture of the cis and trans amino alcohols 3c which were separated chromatographically. A stereoselective reduction of ketone 2b was carried out with lithium tri-tert-butoxyaluminohydride to give the cis-3-hydroxy-4-allyl compound 3b and the corresponding trans isomer in a 98:2 ratio. Stereochemical assignments of compounds 3b and 3c were determined from their ^{1}H NMR spectra and from studies on reaction of ketones 2b and 2c with sterically hindered reducing agents.

The cis alcohol 3b underwent an iodoetherification reaction to afford an 85:15 mixture of the exo and endo iodo ethers 5 which were separated by multiple recrystallization. Construction of Dreiding molecular models suggests that the conformation leading to the production of the exo isomer of 5 is favored due to fewer steric interactions during the cyclization process and would be expected to be the major product. Further evidence for the correct assignment of the exo and endo isomers consists of ^{1}H NMR analysis of the two isomers based upon data from appropriate model compounds.

Nucleophilic displacement of the exo and endo iodo ethers 5 with diethylamine was carried out in DMSO. Each resulting crude product was purified chromatographically to obtain the desired exo and endo bicyclic amines 6.