

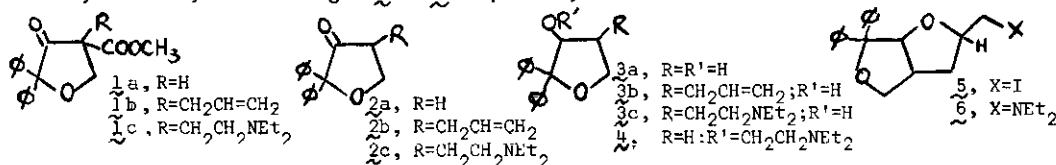
THE SYNTHESIS OF NOVEL TETRAHYDROFURAN ANALOGS AS MOLECULAR PROBES FOR CHOLINERGIC RECEPTORS

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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*-butoxyaluminumhydride 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 ¹H 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 ¹H 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**.