THE SYNTHESIS OF VIRANTMYCIN ANALOGUES

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CONTENTS

Abstract

A general synthesis of analogues of the antiviral drug virantmycin (1) is described. The key reaction in the sequence is the cyclization of an N-(1,1-disubstitutedpropargyl)aniline system to the corresponding 2,2-disubstituted-1,2-dihydroquinoline system, using cuprous chloride in refluxing toluene. For 2,2-dimethyl substituted systems, the rate of cyclization was found to be mainly dependent on the electronic nature of the *para*-aromatic substituent. Electron donating substituents, such as a methoxy group, accelerate the reaction, while electron withdrawing substituents, such an ester group, cause a decrease in the rate of cyclization. When the cyclization conditions were applied to N-propargyl anilines with methoxymethyl and *n*-butyl side chains α- to the nitrogen atom, cyclization to the dihydroquinoline was followed by spontaneous loss of dimethyl ether to give the corresponding 2-*n*-butylquinoline systems. This aromatization could be avoided by trapping the NH group of the dihydroquinoline as a trifluoroacetamide. N-propargylaniline systems with both the larger side chains and electron withdrawing *para*-substituents could not be cyclized to the corresponding dihydroquinolines. Attempted preparation of an N-(1,1-di-*n*-butylpropargyl)aniline system was unsuccessful, presumably due to the steric hindrance of the bulky butyl groups.

N-trifluoroacetyl protected dihydroquinolines were chlorinated to give 2,2-disubstituted-*cis*-3,4-dichlorotetrahydroquinolines. The mechanism of this reaction is discussed. Selective dechlorination of these dichloro compounds at the benzylic position provided the corresponding 3-chloro systems. The analogous 3,4-dibromo compound was also synthesized, but was found to be very unstable.

Other reactions of the N-acyldihydroquinoline system were investigated. *Trans*-chlorohydrins were formed from N-acyldihydroquinolines. The stereochemistry and mechanism of this transformation is discussed. Epoxidation of the dihydroquinoline double bond provided a 3,4-epoxy system, which was hydrogenolyzed at the benzylic position to give a 3-hydroxytetrahydroquinoline. Subjection of this alcohol to Mitsunobu conditions did not result in the formation of the expected 3-chloro derivative, but rather the 3-trifluoroacetate, formed by intramolecular transfer of the trifluoroacetyl group from the nitrogen atom to the oxygen atom. This trifluoroacetate was converted to the corresponding 3-chloro system by S_N2 displacement of the trifluoroacetate moiety with chloride ion.

The copper-catalyzed cyclization reaction was extended to N-(1,1-dimethylpropargyl)-2-aminoanthracene and several N-(1,1-dimethylpropargyl)aminoquinolines. Also cyclized using the same conditions were *meta*- and *ortho*-substituted N-(1,1-dimethylpropargyl)aniline systems. N-methyl-N-(1,1-dimethylpropargyl)aniline did not cyclize to the corresponding dihydroquinoline, supporting the proposed mechanism for the cyclization. An N-propargyl aniline system possessing a hydrogen atom α- to the nitrogen atom cyclized to give the corresponding quinoline.