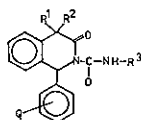


ON THE SYNTHESIS AND REACTIONS OF 1-ARYL-2-CARBAMOYL-1,4-DIHYDRO-3(2H)-ISOQUINOLINONES

E. Zárai-Kaczán*, Gy. Deák and L. Hazai

Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest

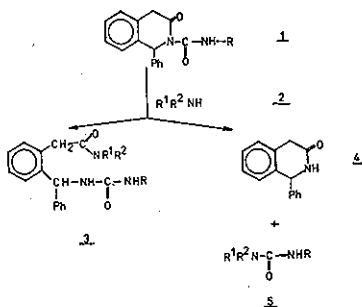
In order to study the influence of the carbamoyl group on biological activity, we have prepared the N-carbamoyl derivatives of the potent anticonvulsant 1-aryl-1,4-dihydro-3(2H)-isoquinolinones synthesized first by us.



I

The compounds of general formula I, in which R³ is an alkyl or aryl group, have been prepared from the parent compound and the appropriate isocyanate. As the reaction of the N-carbomethoxy derivative with ammonia yielded an unexpected product, the compound containing an unsubstituted carbamoyl group (R³ = H) was prepared by the detritylation of the trityl carbamoyl derivative.

The investigations included kinetic measurements on the formation of the carbamoyl derivatives from different isocyanates. The reaction of carbamoyl derivatives 1 (R = H, alkyl, phenyl and substituted phenyl group) with nucleophilic reagents, mainly primary and secondary amines 2 (Fig. 1) has also been studied.



The 2-carbamoyl-1-phenyl-1,4-dihydro-3(2H)-isoquinolinones react with amines in two ways: with primary amines, ring-opening affords urea derivatives 3 in excellent yields, whereas with secondary amines the side chain is split off.

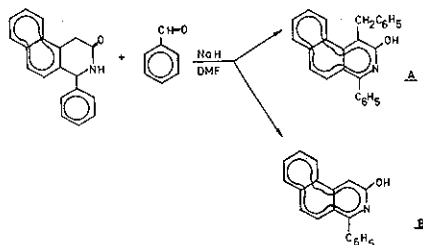
The hitherto unknown urea derivatives 3 can be used as starting materials in the synthesis of new heterocyclic compounds.

CONDENSATION AND AROMATIZATION IN THE REACTION OF BENZOISOQUINOLINONES WITH BENZALDEHYDE IN DMF SOLUTION IN THE PRESENCE OF STRONG BASES

L. Hazai*, Gy. Deák and G. Tóth

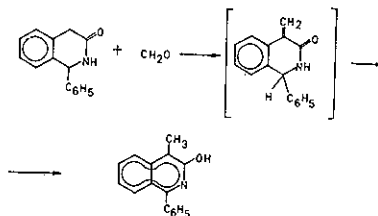
Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest

We have recently reported that reaction of 1-aryl-1,4-dihydro-3(2H)-isoquinolinones, synthesized first by us, with aromatic aldehydes in the presence of strong bases yields 1-aryl-4-aryl-methyl-3(2H)-isoquinolinone derivatives not known so far. As an extension to condensed isoquinolinone systems, first the reaction of 1-phenyl-1,4-dihydro-3(2H)-benzo[f]isoquinolinone with benzaldehyde was investigated and the formation of two products observed: the carbonyl addition type reaction of the active methylene group in position 4, yielding the appropriate 4-benzyl derivative A, was accompanied by aromatization of the starting compound, resulting in the formation of B:



According to NMR spectroscopy, the mole ratio of B to A is 4 : 1 in the product mixture. In the reaction of the benzo[h] derivative no aromatization could be detected, the reaction affording only product A. Assuming the existence of steric hindrance to the formation of product A, the reaction of 1-phenyl-5-methyl-1,4-dihydro-3(2H)-isoquinolinone with benzaldehyde has also been investigated; in this case no carbonyl addition occurred and the aromatized 5-methyl-1-phenyl-3(2H)-isoquinolinone derivative was formed exclusively.

In order to clarify the role of the NaH-DMF system in the aromatization, the reaction was also investigated without benzaldehyde, in the presence of excess NaH. With 1-phenyl-1,4-dihydro-3(2H)-isoquinolinone as model compound the product, however, was 4-methyl-1-phenyl-3(2H)-isoquinolinone rather than the expected aromatized compound:



According to data in the literature, the reaction of NaH with DMF leads to the formation of formaldehyde. Investigations with deuterium-labelled compounds indicate that the condensation of the formaldehyde thus formed with the active methylene group may produce a 4-methylene intermediate, which affords the end product via intramolecular hydrogen migration.