LE II 6

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

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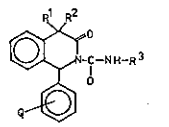
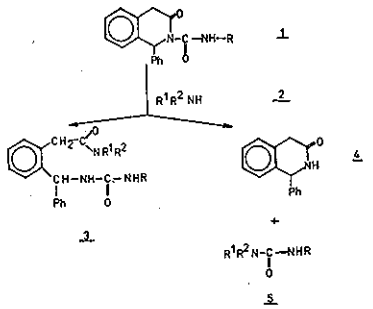
In order to study the influence of the carbamoyl group on biological activity, we have prepared the N-carbamoyl derivatives of the potent anticonvulsant 1-aryl-1,4-dihydro-3(2H)-isoquinolinones synthesized first by us.



I

The compounds of general formula I, in which R^3 is an alkyl or aryl group, have been prepared from the parent compound and the appropriate isocyanate. As the reaction of the N-carbethoxy derivative with ammonia yielded an unexpected product, the compound containing an unsubstituted carbamoyl group (R^3 = H) was prepared by the detritylation of the trityl carbamoyl derivative.

The investigations included kinetic measurements on the formation of the carbamyol 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.

LE II 7

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

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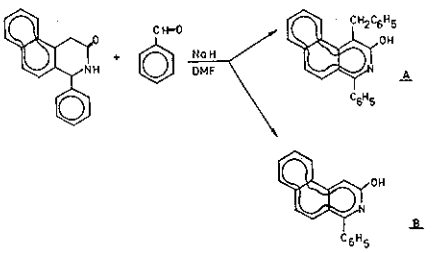
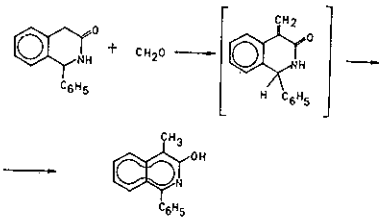
We have recently reported that reaction of 1-aryl-1,4-dihydro-3(2H)-isoquinolinones, synthetized first by us, with aromatic aldehydes in the presence of strong bases yields 1-aryl-4-arylmethyl-3(2H)-isoquinolinone derivatives not known so far. As an extension to condensed isoquinolinone systems, first 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 occured 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.