CONVERSIONS OF POLYFUNCTIONAL 3-AMINO-1(2H)ISOQUINOLINES

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The acylation of 3-amino-4-cyano-1(2H)isoquinolines with benzoyl chloride leading to the formation of 1,3-oxazino[4,5-c]isoquinoline-6-ones has been studied. Previously undescribed 1-aminopyrimido[4,5-c]isoquinoline-6-ones have been obtained by the reaction of the appropriate 3-amino-1(2H)isoquinolones with formamide. Nucleophilic replacement has been carried out with 3-amino-1-chloroisooquinoline by the action of sodium hydroxide, primary alcohols, hydrazine hydrate, and various amines. 1,2,4-Triazino[2,3-b]isoquinolone has been synthesized by condensing 2,3-diamino-1(2H)isoquinolone with mesoxalic acid ethyl ester.

Many isoquinoline derivatives are used widely as highly effective drugs [1]. The synthesis and study of the properties of new compounds of this series is therefore a timely problem.

We synthesized previously [2-4] the polyfunctional 3-amino-1(2H)isoquinolones (I)-(III) which possess high biological activity (antimicrobial, analeptic, and sedative). The polyfunctional character of these compounds raises the possibility of further purpose-directed modification of their structure in the search for new substances possessing a set of useful properties.

The reactivity of 3-amino-4-cyano-1(2H)isoquinolones (I) [1] is determined primarily by their basicity, which depends on the electron density on the nitrogen atom of the amino group, its steric accessibility, and is sensitive even to small changes of structure.

It is known [5-7] that 3-aminoisoquinoline (pKₐ = 5.0) is the least basic of the isomeric aminoisoquinolines. The presence of electron-accepting substituents, particularly nitrile and carbonyl groups, in the 3-aminoquinolines (I) studied by us leads to a further reduction in the basic properties of the amino group. In practice, acylation of the amino group occurs under forcing conditions, on boiling the reactants in pyridine for 10-40 h. Only 3-amino-2-benzyl-4-cyano-1(2H)isoquinolone (Ia) gives a benzoylamino derivative (IV) on boiling with an excess of benzoyl chloride in pyridine solution for 10 h.

The stretching vibrations of the amide group are represented by bands at 3200 and 1680 cm⁻¹, the band near 2210 cm⁻¹ belongs to the nitrile group. In the PMR spectrum in DMSO-D₆ the signal for the amide group proton is observed at low field at 11.45 ppm. Addition of deuterated water to the sample leads to disappearance of this singlet. The signals of the amino group protons in the initial 3-aminoisoquinol-1-one are displayed at 8.05 ppm.

The proximity of the amino and nitrile groups leads to the acylation reaction continuing after the first step. The excess of acylating agent in the reaction mixture provokes further acylation of the amine and the formation of derivatives of a new
heterocyclic system, viz. 1,3-oxazino[4,5-c]isoquinoline. In reality the 3-amino-1(2H)isoquinolones (Ia-c) form the 1,3-oxazino-
[4,5-c]isoquinol-6-ones (Va-c) under these conditions.

There is no absorption characteristic of the stretching vibrations of a nitrile group in the IR spectra of compounds (Va-c). The following signals were present in the PMR spectrum of compound (Vc) in CF₃CO₂D: a weak doublet at 9.41 for the 7-H proton, the signal at 8.7 belongs to the 9-H and 10-H protons, the doublet of the methyl groups of the isopropyl substituent is observed at 1.92 (J = 6.84 Hz), and the methine proton gives a heptet at 6.18 ppm.

Compounds (I) are, in essence, heterocyclic enaminnitriles. 1-Aminopyrimido[4,5-c]isoquinolin-6-ones are formed readily and in good yield on brief boiling of compounds (Ia, d, e) in formamide. Two pathways are possible for the conversion leading to the same compounds (VI)-(VIII) (see below).

This reaction is fine for vicinal aminonitriles and has been well studied previously for many structurally related azines [8]. The following data point in favor of the formation of compounds (VI)-(VIII). In the IR spectra there is a band near 3300 cm⁻¹ for the stretching vibration of the N–H bond of a primary amino group and the band for the nitrile group vibration is absent. Study of the PMR spectra showed that the amino group protons are displayed as two signals at 7.49-7.51 and 10.61-10.63 ppm which disappear on addition of heavy water. A singlet for the 3-H proton at 8.29-8.32 ppm is a characteristic of these products.