REACTION OF 10-FORMYL-3-METHYL-1,2,3,4-TETRAHYDROPYRIMIDO[1,2-a]INDOLE AND ITS DIMETHYLIMINIIUNIUM SALT WITH NUCLEOPHILIC AGENTS

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The reaction of 10-dimethyliminium-3-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole chloride and the protonated form of 10-formyl-3-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole with some N- and C-nucleophiles leads to the formation of products of condensation at the carbonyl carbon atom. Condensation with the potassium enolate of cyanoacetic ester is accompanied by subsequent cyclization to give compounds of the α-carboline series. Acidic hydrolysis of the aldehyde gives 3-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole hydrochloride.

We have previously shown [1] that the reaction of 1-acetyl-2-phenyl-4-methylpyrazolidine with iminium salts leads to 10-methylenedimethyliminium-3-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole chloride (I) in high yield; alkaline hydrolysis of I gives 10-formyl-3-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole (II). The virtually complete lack of data on the synthesis and properties of such compounds compelled us to investigate the reactivities of these bifunctional indole derivatives.

It is known that 3-indolyldimethyliminium chloride (III), which is formed in the formylation of indole under the conditions of the Vilsmeier reaction, in the presence of bases (pyridine, triethylamine) gives enamine IV, which reacts readily with nucleophilic agents [2, 3]:

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\text{III} \quad \text{IV}
\]

We have shown that iminium salt I reacts with p-toluidine in pyridine to give azomethine Va. Azomethine Vb was similarly obtained even with a weak nucleophile such as p-nitroaniline. The reaction of I with hydroxylamine leads to the formation of nitrile VI as a consequence of dehydration of the initially formed oxime, which also takes place readily in the case of oximes of 3-formylindoles themselves [4, 5]. Intense absorption at 2210 cm\(^{-1}\), which corresponds to the cyano group, is observed in the IR spectrum of VI; the PMR spectrum does not contain the weak-field signals of azomethine and hydroxy protons that are characteristic for oximes.

For iminium salt I we also found that the reaction with active C-nucleophiles, viz., nitromethane in the presence of sodium ethoxide and the potassium enolate of cyanoacetic
ester, was possible. In the first case nitrovinyl derivative VII was obtained in good yield. A long-wave maximum at 476 nm ($\lambda_{\text{max}}$ 400 nm for the analogous derivatives of 3-formylindoles [6]) is observed in the UV spectrum of this compound. The bathochromic shift in the UV spectrum of VII is evidently explained by participation of the amidine fragment of 2-aminoindole in the overall conjugation chain. The PMR spectrum of VII contains an AX system of vinyl protons with $J = 12$ Hz at 7.56 and 8.48 ppm, which indicates that the vinyl fragment exists in the trans form [6].

The reaction of salt I with the potassium enolate of cyanoacetic ester leads to VIII. Absorption bands at 1690, 2190, and 3350 cm$^{-1}$, which correspond to the vibrations of ester, cyano, and amino groups, are observed in the IR spectrum of VIII. Signals of protons of an ethoxy group and a weak-field singlet of a vinyl proton at 8.35 ppm are present in the PMR spectrum. Intramolecular acylation of the amino group to give $\alpha$-carbolinone IX, which was isolated in quantitative yield, occurs at room temperature (and more rapidly upon heating of the reaction components). The IR spectrum of IX did not contain the signals of an ethoxy group that were observed for noncyclic condensation product VIII.

It is known [7, 8] that the carbonyl group in 3-formylindoles loses its reactivity with respect to nucleophilic agents; this was due to its significant conjugation with the pyrrole fragment of the indole molecule. One might have expected that the formyl group in aminoformylindole II would prove to be even less active in view of additional conjugation with the amino group in the 2 position of the indole ring.

In fact, attempts to carry out the reaction of aminoformylindole II with the nucleophilic agents that we previously used in reactions with iminium salt I were unsuccessful, although these transformations are known for 3-formylindole itself [6, 9, 10]. On the basis of the spectral characteristics and some anomalous chemical properties of 3-acylindoles Thesing [7] and Szmuszkowich [8] regard these compounds as vinylogs of amides. Thus, for example, it has been shown [11, 12] that deformylation of 3-formylindoles, which can be compared with the hydrolysis of amides, occurs in acidic and basic media. An analogy with amides should be observed to an even greater extent for aminoformylindole II, the protonation of which at both the oxygen atom and the amino group should lead to an increase in the activity of the carbonyl carbon atom with respect to attack by nucleophiles. Quantitative deformylation of II to give 3-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole hydrochloride (X), which was previously described in [13], occurs when it is refluxed in 20% hydrochloric acid.

We were also able to carry out the reaction of aminoformylindole II with some nucleophiles under conditions for which the formation of the protonated form of this compound is