MECHANISM OF MIGRATION OF AN ACYL GROUP IN THE PYRROLE RING OF INDOLE

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UDC 547.756.07:543.422.4

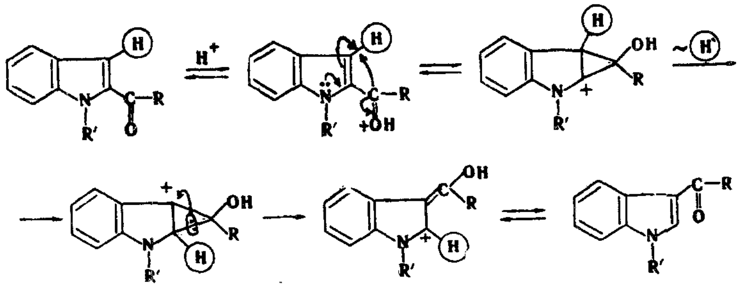
The isomerization of deuterium-labeled (in position 3) 2-acylindoles in polyphosphoric and trifluoroacetic acids was studied. It is shown that migration of the acyl group from position 2 to position 3 is accompanied by an intramolecular hydride shift.

We have previously shown that 2-acylindoles are readily converted to the 3-acyl isomers by heating in polyphosphoric or trifluoroacetic acid and expressed an assumption regarding the isomerization mechanism [1]. We assumed that the first act in the process is the addition of a proton to the carbonyl oxygen atom — the site of the highest electron density of the molecule. In this connection we studied the PMR spectra of 2- and 3-acylindoles in acids. The aliphatic part of the spectrum of 1-methyl-3-acetylindole recorded at −55°C in a mixture of fluorosulfonic acid and liquid sulfur dioxide contains two singlet signals (1.95 and 3.35 ppm) of methyl groups. The absence of other signals in this region confirms that a proton is not added to any carbon atom or to the nitrogen atom. The indole 2-H signals lies at 9.1 ppm, while the signal of the hydrogen atom added to the carbonyl oxygen atom lies at 10.81 ppm. The position of the signal of the proton bonded to the oxygen corresponds to the literature data on the protonation of ketones under similar conditions [2].

In the analogous spectrum of 3-formylindole the signal of the proton added to the carbonyl oxygen atom lies at 10.7 ppm, and, in addition, one sees a broad signal of a hydrogen atom bonded to the nitrogen atom. The singlet of the formyl hydrogen atom is shifted to stronger field (8.8 ppm) as compared with the netural solvent as a consequence of a change in the magnetic anisotropy of the C=O bond in the case of protonation. Synchronous broadening of the signals of the aldehyde proton and the proton of the OH group is observed as the temperature is lowered.

Rapid isomerization was observed during recording of the PMR spectra of 2-acylindoles under these conditions, and only the spectra of the protonated 3-acyl isomers were seen. In the case of trifluoroacetic acid, in which the rearrangement proceeds more slowly, the spectra of both 2- and 3-acylindoles do not display additional splitting of the aliphatic protons, but an oxonium proton does not appear in the spectra because of rapid exchange with the solvent.

Thus the isomerization of 2-acylindoles to the 3-acyl isomers includes initial protonation of the keto group and subsequent intramolecular electrophilic attack of the resulting carbonium ion on the C_3 atom.



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Calculation of the protonated 2-acetylindole molecule by the LCAO MO method [1] shows that rather high electron density on the upper occupied orbital is retained, despite an increase in the positive charge. It is precisely this electron density that determines the site of electrophilic attack in protonated indoles [3].

After electrophilic attack or simultaneously with it, a hydride shift takes place and is followed by a rearrangement of the Wagner—Merrwein type, as a result of which a protonated 3-acylindole is formed. The cycle of transformations ends with detachment of a proton. The high yield of the final product (up to 100%) confirms the intramolecular character of the rearrangement.

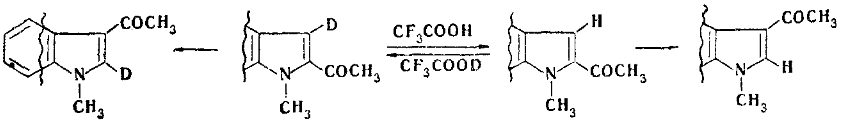
The hydrogen atom in the α position of the final molecule (encircled in the scheme) does not "come" from the medium but rather migrates intramolecularly from position 3 to position 2 of the acylindole.

To prove this, we carried out the rearrangement of 1-methyl-2-acetylindole to deuterotrifluoroacetic acid. The reaction stopped at different degrees of conversion (30, 40, and 50%), and both isomers were isolated. It was observed by PMR spectroscopy that 45-55% hydrogen (protium) is retained for all degrees of conversion of one isomer to the other. It follows from this that at least 45-55% intramolecular hydride shift from position 3 to the C_2 atom is observed in the rearrangement. However, a mass-spectral analysis of the reaction products was hindered by the fact that deuterium exchange in the other positions of the indole molecule occurs under these conditions.*

To avoid this deuterium exchange we carried out the rearrangement of 1-methyl-2-acetyl-3-deuteroindole in trifluoroacetic acid; the process was stopped at degrees of conversion of 40 and 80%, and the substances were isolated. According to the data from the mass and PMR spectra, this rearrangement led to 2- and 3-acylindoles containing identical amounts of deuterium, viz., 28-30% at a molecular ratio of the deuteroindole and the acid of 1:10, or 2-4% at a ratio of 1:100. It is apparent that the reaction is accompanied by deuterium ex- and that the rate of deuterium exchange evidently increases more than the rate of rearrangement as the acid concentration is increased.

We simultaneously demonstrated that deuterium in position 2 of 1-methyl-3-acetylindole does not undergo exchange under these conditions. For this, 1-methyl-3-acetyl-2-deuteroindole was sealed in an ampul containing trifluoroacetic acid and allowed to stand for several days with periodic recording of the PMR spectrum. The intensity of the peak corresponding to the 2-H signal (8.4 ppm) did not change. After 10 days, the ampul was opened, the indole was isolated, and its mass spectrum was recorded. The percentages of deuterium in 1-methyl-3-acetyl-2-deuteroindole were the same before and after the experiment.

On the basis of the information stated above, one might assume that processes that can be described by the following scheme take place in the rearrangement of 1-methyl-2-acetyl-3-deuteroindole:



In other words, under the reaction conditions deuterium exchange occurs only in the starting 1-methyl-2-acetylindole, since otherwise 1-methyl-3-acetylindole should have contained less deuterium than 1-methyl-2-acetylindole. The same percentage of deuterium was also obtained in the rearrangement of 1-methyl-2-benzoyl-3-deuteroindole. Migration of the acetyl group is consequently accompanied by an intramolecular hydride shift.

As pointed out above, the percentage of deuterium was determined by a mass-spectral method in all cases, whereas the position of the label was determined by PMR spectroscopy. The PMR spectrum of 1-methyl-2-acetylindole with added europium tris(dipivaloylmethanate) makes it possible to readily identify the 3-H signal [4]. It lies at 7.61 ppm, while the 2-H signal of 1-methyl-3-acetylindole is shifted to 8.04 ppm. These signals are absent in the case of introduction of labels in positions 3 and 2.

The study of the rearrangement of labeled acylindoles required the development of a method for the synthesis of these compounds. The accessibility of acyl(chloromercuri)in-

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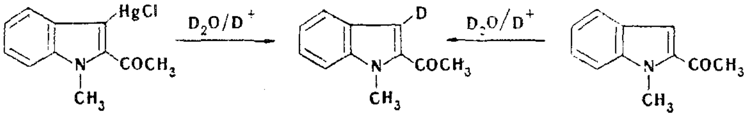
*Mass-spectral studies of 2- and 3-acylindoles will be published separately.

doles and the possibility of their protodemercuration [5] made it possible to obtain 1-methyl-2-acetyl-3-deuteroindole by deuterolysis of 1-methyl-2-acetyl-3-chloromercuriindole.



The same compound is obtained by heating 1-methyl-2-acetylindole in D_2O with the addition of catalytic amounts of deuterosulfuric acid.

EXPERIMENTAL

The spectral characteristics of the compounds were obtained with RS-60 (PMR), NA-100 (PMR), and MKh-1303 spectrometers.

Rearrangement of 1-Methyl-2-acetylindole in Deuterotrifluoroacetic Acid. A 0.2-g (1 mmole) sample of 1-methyl-2-acetylindole and 2 ml of deuterotrifluoroacetic acid were placed in an ampul, and the ampul was sealed and allowed to stand at room temperature. The process was monitored by PMR spectroscopy. After 9 days (40% conversion), the ampul was opened, the acid was evaporated in vacuo, and D_2O was added to the residue. The resulting mixture was extracted with absolute ether, and the extract was washed with water and dried with magnesium sulfate. The solvent was evaporated in vacuo to give a mixture of the 2- and 3-acyl isomers, which was separated by preparative TLC on neutral aluminum oxide in benzene. The yield of 1-methyl-2-acetylindole was 0.12 g (60%), and the yield of 1-methyl-3-acetylindole was 0.074 g (37%).

The isomerization of 1-methyl-2-acetyl-3-deuteroindole in trifluoroacetic acid was carried out similarly.

Study of Deuterium Exchange of 1-Methyl-3-acetyl-2-deuteroindole. The 1-methyl-3-acetyl-2-deuteroindole obtained by isomerization, which, according to the mass-spectral data, contained 27% deuterium was sealed in an ampul with trifluoroacetic acid (the ratio of the indole to the acid was 1:100). After several days, the ampul was opened, and the acid was evaporated in vacuo. The residue was worked up as described above to give 1-methyl-3-acetyl-2-deuteroindole containing 27% deuterium according to the mass-spectral data.

1-Methyl-2-acetyl-3-deuteroindole. A) Two drops of concentrated H_2SO_4 were added to a mixture of 0.1 g (0.5 mmole) of 1-methyl-2-acetylindole in 10 ml of D_2O, and the mixture was refluxed in an argon atmosphere for 4 h, after which it was allowed to stand at 20°C for 10 h. It was then extracted with absolute benzene, and the extract was washed with D_2O and dried with magnesium sulfate. Evaporation of the solvent in vacuo gave 0.095 g of 1-methyl-2-acetyl-3-deuteroindole.

B) A catalytic amount of sulfur trioxide was added to a mixture of 1 g (2.5 mmole) of 1-methyl-2-acetyl-3-chloromercuriindole in 50 ml of D_2O and 20 ml of absolute dioxane, and the mixture was allowed to stand at 20°C for 18 days. The solution was then filtered, and the solvent was evaporated in vacuo. The residue was dissolved in ether, and the ether solution was washed with water and dried with magnesium sulfate. Evaporation of the solvent gave 0.35 g (82%) of 1-methyl-2-acetyl-3-deuteroindole.

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