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XXXI.* REARRANGEMENT OF 2-ACYLINDOLES TO THE 3-SUBSTITUTED ISOMERS

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When 2-acylindoles are heated in polyphosphoric or trifluoroacetic acids, the acyl groups migrate to form 3-substituted indoles. A mechanism is proposed for the isomerization.

It has been shown [2, 3] that 3-alkyl- and 3-arylindoles in acidic media add a proton to the 3 position to form an indoleninium cation, which is converted to the more basic 2-substituted indole by migration of the substituent in the 2 position (where the strong positive charge is localized) and subsequent deprotonation.

In [4, 5] there are indications that reverse isomerization with migration of the acetyl group to the 3 position was observed on attempts to synthesize 2-acetylindoles via the Fischer method from diacetyl arylhydrazones. For a more systematic study of this phenomenon, we synthesized a number of 2-acylindoles by selecting a route in which the probability of similar cationotropic isomerization was a minimum. According to patent data [6], 2-acylindoles are obtained by the action of organolithium compounds on indole-2-carboxylic acid. We used this route to synthesize 2-benzoyl-, 2-(o-toluyl)-, and 2-(p-toluyl)indoles. We selected repeatedly described methods [7, 8] to obtain 2-formyl- and 2-acetylindoles. The synthesis of 2-acetylindole through the corresponding diazoketone was recently described [9]. The preparation and properties of 2-acetoxyacetylindole will be the subject of one of our subsequent communications. A study of the PMR spectra demonstrated that none of the starting ketones contain the 3-substituted isomer (see Table 1). The substances were also chromatographically homogeneous.†

We found that other acyl groups as well as the acetyl group (including the acyl group of an aromatic ring) are capable of migrating from the 2 position to the 3 position (Table 3): 3-acylindoles are formed in 85-90% yields when 2-acylindoles are heated with polyphosphoric acid (PPA) for 15 min. The presence of an alkyl group of the nitrogen atom of the indole ring does not affect the trend of the process. In the case of formylindoles, the yields are poorer in view of considerable resinification. (It is known that 3-formylindole forms diindolylmethene derivatives in acidic media [10].) The migration of the acyl group proceeds without any isomerization of the acyl radical. The rearrangement is more conveniently carried out in trifluoroacetic acid. In this case, the process is slower, but the yields are higher, and the substances do not require additional purification.

The change in the aliphatic portion that occurs for alkyl- or arylindoles [3] does not occur in the PMR spectra of 2-acylindoles (Table 1) on passing from neutral solutions (CCl_3CN) to acid solutions (CF_3COOH). At the same time, the general form of the spectrum changes, and it hence follows that the 2-

*See [1] for communication XXX.

†By chromatography in a thin layer of aluminum oxide with chloroform as the mobile phase and development by iodine vapors. In all cases, the 2-substituted isomers have larger R_f values than the 3-substituted isomers.

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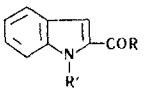
TABLE 1. PMR Spectra of 2-Acylindoles*



R	R′	Aliphatic region		Aromatic region	Solvent
H	H	CHO	9,87	7,30—7,90	CCl_3CN
		CHO	9,20	6,70—7,70	CF_3COOH
H	CH_3	CHO	9,92	7,20—7,80	CCl_3CN
		NCH_3	3,65	6,70—7,70	CF_3COOH
		CHO	9,13		
CH_3	H	CH_3CO	2,78	7,10—8,10	CCl_3CN
		CH_3CO	1,77	6,20—7,00	CF_3COOH
CH_3	CH_3	CH_3CO	2,62	7,20—7,45	CCl_3CN
		NCH_3	4,08		
		CH_3CO	1,93	6,56—7,10	CF_3COOH
CH_2OCOCH_3	H	CH_3	2,40	7,20—8,00	CCl_3CN
		CH_2	5,40		
		CH_3	1,70	6,30—7,20	CF_3COOH
		CH_2	4,64		
C_6H_5	H	—	—	7,20—8,30	CCl_3CN
		—	—	6,70—7,70	CF_3COOH
p-$CH_3C_6H_4$	H	CH_3	2,70	7,10—8,40	CCl_3CN
		CH_3	2,22	6,70—7,70	CF_3COOH
o-$CH_3C_6H_4$	H	CH_3	2,70	7,00—8,00	CCl_3CN
		CH_3	2,17	6,80—7,70	CF_3COOH

*Chemical shifts are given on the δ scale in parts per million. Hexamethyldisiloxane was used as the external standard. No corrections were made for the magnetic susceptibility of the solution.

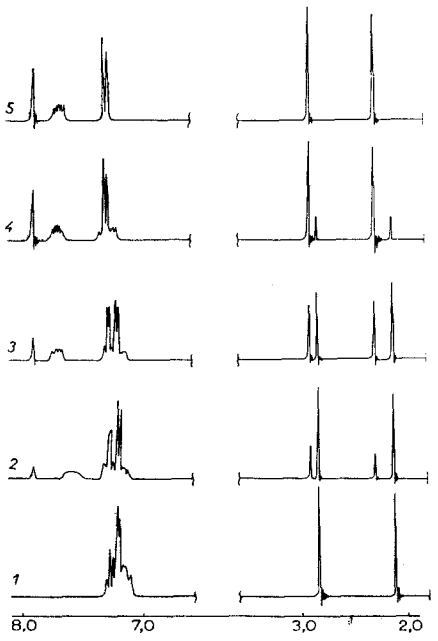
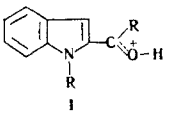


Fig. 1. PMR spectra of 1-methyl-2-acetylindole [1) at the start of the reaction; 2) after 24 h; 3) after 3 days; 4) after 10 days] and of 1-methyl-3-acetylindole (5) in trifluoroacetic acid.

acylindole molecule adds a proton or acid elements (formation of an ion pair) in acidic media but to the carbonyl oxygen atom rather than to the carbon or nitrogen atoms.



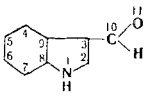
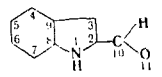
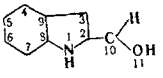
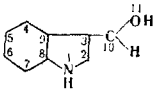
I

Moreover, the protons of the group bonded to the carbonyl carbon atom absorb at stronger fields in acid than in neutral solutions. An oxonium ion (I) rather than a carbonium ion is apparently formed on protonation, and this changes the magnetic anisotropy of the C = O bond and leads to a shift in the signal of the protons of the acyl radical to strong fields.

If 2-acylindoles are allowed to stand in a solution of trifluoroacetic acid for several days, the PMR spectrum gradually changes, and signals corresponding to 3-acylindoles appear. The migration of the acyl group consequently occurs even at room temperature. For example, additional signals of the methyl groups (at 2.70 and 3.77 ppm) and a singlet from the α proton at 8.40 ppm appear in the spectrum of 1-methyl-2-acetylindole after 24 h. In this case, there is 45% conversion after 3 days, and complete transformation occurs after 1.5 weeks (Fig. 1).

It follows from quantum-mechanical calculations (Table 2) that the total electron density on the β carbon atom decreases on protonation of 2-acylindoles, but the density on the boundary orbital remains quite high. At the same time, the density on the car-

TABLE 2. Charges and Electron Densities on the Boundary Orbitals and Bond Multiplicities for 2- and 3-Formylindoles and Their Protonated Forms*

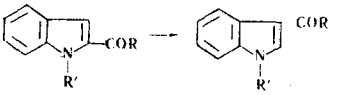
Structure	Atom No.	Total charge	Density on the boundary orbital	Bond multiplicity	
 $E=-173{,}813$ eV	1	+0,3831	0,2098	N—C_2	0,5198
	2	−0,0298	0,2084	C_2—C_3	0,7345
	3	−0,1121	0,4370	C_3—C_9	0,4613
	4	+0,0204	0,3748	C_9—C_4	0,5566
	5	−0,0146	0,0898	C_4—C_5	0,7358
				C_5—C_6	0,5934
	6	−0,0032	0,1836	C_6—C_7	0,7348
	7	−0,0448	0,3324	C_7—C_8	0,5553
	8	−0,0689	0,0102	C_8—C_9	0,5871
	9	−0,0329	0,0142	C_8—N	0,3996
	10	+0,2937	0,0038	C_3—C_{10}	0,3490
	11	−0,3909	0,1352	C_{10}—O_{11}	0,8713
 $E=-174{,}282$ eV	1	+0,4620	0,2208	N—C_2	0,5211
	2	−0,1366	0,1566	C_2—C_3	0,6979
	3	−0,1041	0,3900	C_3—C_9	0,5342
	4	+0,0018	0,4334	C_9—C_4	0,5229
	5	−0,0096	0,1024	C_4—C_5	0,7571
	6	+0,0021	0,2242	C_5—C_6	0,5716
	7	−0,0212	0,3992	C_6—C_7	0,7535
	8	−0,0539	0,0062	C_7—C_8	0,5326
	9	−0,0640	0,0138	C_8—C_9	0,5726
	10	+0,2997	0,0016	C_8—N	0,4825
	11	−0,3762	0,0458	C_2—C_{10}	0,3196
				C_{10}—O_{11}	0,8840
 $E=-190{,}714$ eV	1	+0,3512	0,2874	N—C_2	0,3857
	2	−0,1227	0,0468	C_2—C_3	0,5675
	3	+0,1138	0,1472	C_3—C_9	0,6218
	4	+0,0503	0,4972	C_9—C_4	0,4845
	5	+0,0209	0,2660	C_4—C_5	0,7670
	6	+0,0915	0,0882	C_5—C_6	0,5611
	7	−0,0380	0,5256	C_6—C_7	0,7367
	8	+0,0276	0,0618	C_7—C_8	0,5585
	9	−0,0504	0,0016	C_8—C_9	0,5158
	10	+0,2884	0,0442	C_8—N	0,4895
	11	+0,2674	0,0230	C_2—C_{10}	0,6250
				C_{10}—O_{11}	0,5810
 $E=-190{,}698$ eV	1	+0,4655	0,1070	N—C_2	0,6479
	2	+0,0959	0,0137	C_2—C_3	0,5708
	3	−0,1234	0,1621	C_3—C_9	0,3519
	4	+0,0044	0,5578	C_9—C_4	0,5920
	5	+0,0469	0,1086	C_4—C_5	0,7090
	6	+0,0402	0,2062	C_5—C_6	0,6130
	7	+0,0056	0,5520	C_6—C_7	0,7168
	8	−0,0690	0,0280	C_7—C_8	0,5754
	9	−0,0400	0,0975	C_8—C_9	0,5945
	10	+0,3026	0,1050	C_8—N	0,3996
	11	+0,2712	0,0612	C_3—C_{10}	0,6276
				C_{10}—O_{11}	0,5881

*The calculations were performed by the Pariser−Parr−Pople method. The two-electron coulombic integrals were calculated by the Mataga−Nishimoto method. The principal parameters (ionization potentials and one-electron coulombic integrals) were taken from [11].

bonyl carbon atom not only does not undergo a decrease but even increases somewhat. This is in agreement with the fact that the protons of the radical bonded to this carbon atom absorb at stronger field in acids than in neutral solution in the PMR spectrum. When 3-acylindoles are protonated at the α carbon atom, both the total electron density and the density on the boundary orbital change markedly.

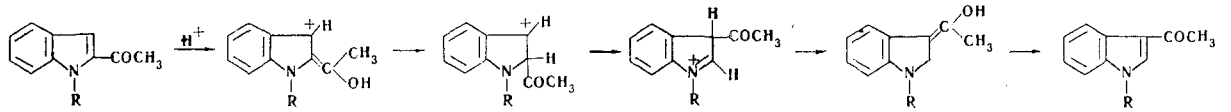
In the course of the development of this research, there appeared a paper by Chastrete [12], who investigated the prototropic isomerization of 2-acetyl-, 1-methyl-2-acetyl-, and 2-phenyl-2-acetylindoles in the process of the Fischer synthesis and under the influence of aluminum chloride, polyphosphoric acid, or trifluoroacetic acid. Just as we did, Chastrete concluded that there is a relatively linear dependence of the

TABLE 3. Acid Isomerization of 2-Acylindoles



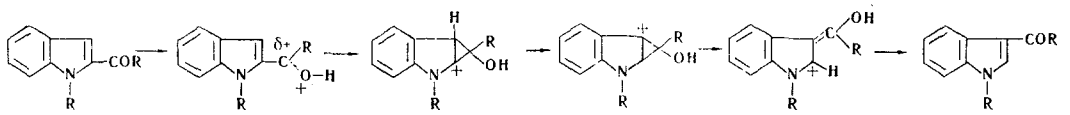
R	R′	Temp., °C (in PPA)	Yield, %		Mp, °C	
			in PAA	in CF_3COOH	found	literature data
H	H	110—115	50	—	192—195	194—196 [14]
H	CH_3	120	50	—	65—66	69—70 [15]
CH_3	H	125—130	100	98	189—191	191 [16]
CH_3	CH_3	115—120	80	98	108—110	108—110 [17]
C_6H_5	H	125	90	96	239	241 [18]
p-$CH_3C_6H_4$	H	125	90	—	178—179	179—181 [19]
o-$CH_3C_6H_4$	H	125	86	—	190	190—192 [19]

direction of the reaction on the ratio of the basicities of the starting and final substances (3-acetylindoles are more basic than the 2-isomers). A study of the PMR spectra enabled her to conclude that 2-acetylindoles are protonated at oxygen. On the basis of all of this, she proposed a mechanism involving an enol-forming step, migration of the charge to the ring, migration of the radical, and again stabilization through the enol form:



However, the first ketone–enol isomerization is equivalent to protonation of the acylindole at the α position, which neither we nor Chastrete observed experimentally, and which contradicts the calculated values presented above.

We suppose that the migration of the acyl group does not require the assumption of a ketone–enol tautomerism.



The proton initially adds to the carbonyl oxygen, which is the site of the highest electron density. Intramolecular attack by the carbonyl carbon atom at the 3 position occurs in the resulting cation. Moreover, as in the usual electrophilic substitution [13], the site with the highest electron density in the boundary orbital undergos attack. Migration of the Wagner–Meerwein rearrangement type then occurs along with a hydride shift, and the resulting ion loses a proton to give 3-phenacylindole. Reverse migration of the substituent does not occur, since the low density on the boundary orbital in the protonated 3-acylindole hinders successful electrophilic attack at this position.

EXPERIMENTAL

2-Benzoylindole. Helium was bubbled into a mixture of 1.2 g (0.17 g-atom) of finely cut lithium and 40 ml of absolute ether, and 12 g (75 mmole) of bromobenzene in 15 ml of absolute ether was added dropwise to the mixture at such a rate that the ether boiled evenly. The mixture was refluxed for 1 h, cooled, and filtered through glass wool into another flask that had previously been flushed with helium. A solution of 2.2 g (14 mmole) of indole-2-carboxylic acid in 40 ml of absolute ether was added dropwise with stirring to the cooled (to room temperature) phenyllithium solution. The mixture was stirred at room temperature for 4 h and refluxed for 30 min. It was then decomposed with 10 ml of water, and the precipitated LiOH was removed by filtration and washed with ether. The ether was dried with magnesium sulfate, and then was evaporated. The residue was recrystallized from aqueous alcohol to give 3 g (79%) of 2-benzoylindole with mp 144-145° [6]. Similar conditions were used to obtain 50% 2-(o-toluyl)indole with mp 123-124° [6] and 70% 2-(p-toluyl)indole with mp 185-186° [6].

Rearrangement of 2-Acylindoles. A) A mixture of 1 mmole of 2-acetylindole was heated with polyphosphoric acid (from 5 ml of 85% orthophosphoric acid and 10 g of phosphorus pentoxide) with constant stirring for 15 min. The mixture was then poured over ice and extracted with a small amount of chloroform. The chloroform extract was washed with sodium bicarbonate solution and water and dried with magnesium sulfate. The solvent was removed to give the pure 3-isomer. The yields and reaction conditions are presented in Table 3.

B) A mixture of 0.01 mole of 2-acetylindole and 10 ml of trifluoroacetic acid was refluxed. The completion of the reaction was determined by thin-layer chromatography on aluminum oxide. The acid was vacuum evaporated, water was added to the residue, and the mixture was extracted with chloroform. The chloroform extract was washed with water and dried with magnesium sulfate. The solvent was vacuum evaporated to give the pure 3-acylindole, which according to PMR spectroscopy and chromatography, did not contain the 2-isomer.

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