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PECULIARITIES OF NUCLEOPHILIC SUBSTITUTION IN INDOLYLIDONIUM SALTS

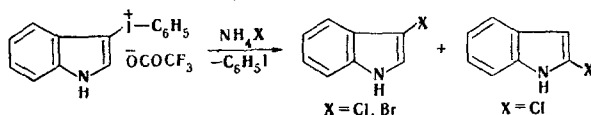
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3-Indolylphenyliodonium trifluoroacetate reacts with ammonium bromide and lithium chloride and bromide to give 3-haloindoles. The reaction with ammonium chloride and tetrabutylammonium chloride leads to a mixture of 2- and 3-chloroindoles. The same mixture of chloroindoles is also formed by the action of lithium chloride but in the presence of 15-crown-5 ether. The course of the reaction is explained by ambident reaction of the cation of the iodonium salt.

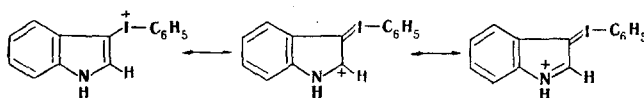
We have previously shown [1] that the phenyliodonium grouping is replaced in the reaction of alkali metal halides with 3-indolylphenyliodonium tosylate to give 3-haloindoles; it was also established that substitution occurs only in the indole ring.

Continuing our research, we studied the nucleophilic substitution by halide ions in 3-indolylphenyliodonium trifluoroacetate. We found that lithium chloride and bromide react with the trifluoroacetate in precisely the same way as with the tosylate, i.e., exclusively 3-haloindoles and iodobenzene are formed. However, the reaction pathway changes somewhat when the alkali metal salt is replaced by an ammonium salt. Whereas the iodonium salt reacts with ammonium bromide exclusively to give 3-bromoindole, a mixture of 3- and 2-chloroindoles, with preponderance of the former, is formed in the case of ammonium chloride.



It is known [2, 3] that 2- and 3-isomeric indoles undergo acid-catalyzed interconversion under the influence of acids. We demonstrated by special experiments that 2- and 3-chloroindoles do not undergo isomerization to one another under the reaction conditions [dimethyl sulfoxide (DMSO), 2 h, 100°C]. In addition, we found that replacement of ammonium chloride, which is capable of undergoing decomposition to hydrogen chloride and ammonia when it is heated, by tetrabutylammonium chloride does not change the reaction pathway, and the chloroindoles are formed in approximately the same ratio. The difference in the reactions is explained by the fact that lithium halides are dissociated to a lesser extent in solution than the corresponding ammonium halides [4]. In fact, a mixture of chloroindoles is also formed in the reaction of 3-indolylphenyliodonium trifluoroacetate with lithium chloride in the presence of 15-crown-5 ether, which complexes lithium ions.

The iodonium salt is an ambident electrophile that permits nucleophilic attack at the iodine atom and at the α -carbon atom of the indole ring.



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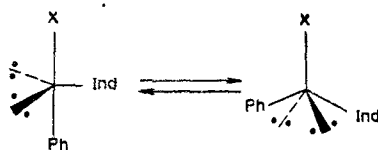
TABLE 1. Yields of 2- and 3-Haloindoles

Compound	Yield, %					
	LiBr	NH ₄ Br	LiCl	NH ₄ Cl	Bu ₄ NCl	LiCl ₄
2-Haloindole	— ^c	— ^c	— ^d	20 ^b	25 ^b	24 ^b
3-Haloindole	75 ^c	70 ^c	80 ^d	62 ^d	64 ^d	50 ^d

^aIn the presence of an equimolar amount of 15-crown-5 ether.

^bThis compound had mp 73-74°C (mp 72-76°C [10]). ^cThis compound had mp 66-67°C (dec.) (mp 67°C [9]). ^dThis compound had mp 90-91°C (mp 91.5°C [9]).

The positively charged iodine atom has lower orbital electronegativity (Klopman) as compared with the positively charged carbon atom or, in terms of the theory of hard and soft acids and bases (HSAB) (Pearson), it is a "softer" acid center. In this case [5] nucleophilic attack on positively charged iodine is an orbitally-controlled reaction (the covalent term of the general equation of perturbation theory), whereas attack on carbon is controlled to a large extent by the charge (the electrostatic term of the equation). In terms of the Pearson concept, the "softer" the nucleophile, the greater the force of its attack on the iodine atom. With respect to their ability to attack the "soft" center of the iodine atom, halide ions can be arranged in the order $I > Br > Cl > F$. This order is reversed in the case of attack on the carbon atom. All other conditions being equal, the higher the charge on the nucleophile, the more its attack will be controlled by the electrostatic term of the equation, i.e., the greater the force of its attack on the "harder" center (the carbon center). Thus iodide and bromide ions, which are "soft" nucleophiles, should attack the iodine atom; the transition state or the intermediate will have a structure close to that of a trigonal bipyramid. The decomposition of this reaction complex takes place with the ejection of iodobenzene via a reaction mechanism dubbed "cheletropic" by Woodward and Hoffmann [6]. Proceeding from the general rules of the construction of a trigonal bipyramid [7] it should be assumed that in the case of indolyliodonium salts the two unshared pairs of electrons of iodine are located together with indole in the equatorial region of the bipyramid, while the phenyl residue and the attacking nucleophile are situated in the apical region; the two unshared



pairs in this case should stabilize the bipyramid with respect to permutation processes.

It is possible that in this case the trigonal bipyramid undergoes decomposition to the products through a tetragonal pyramidal transition state [8].

Thus attack by a "mild" nucleophile should lead to 3-substituted indoles. In fact, lithium bromide, ammonium bromide, and tetrabutylammonium iodide [1] react with 3-indolyliodonium salts exclusively with the formation of 3-haloindoles.

The chloride ion is intermediate in the order of "hardnesses" of halide ions. Lithium chloride, which exists in solution primarily in the form of ion pairs, reacts with 3-indolyliodonium salts only at the iodine atom. At the same time, ammonium chloride, which is dissociated to a significantly greater degree, reacts at both the iodine atom and at the carbon atom. Bonding of the lithium ion with the crown ether leads to the same result.

Thus 3-indolyliodonium salts are ambident electrophiles and, depending on the nature of the nucleophile, can react to give 3- or 2-substituted indoles.

EXPERIMENTAL

Reaction of 3-Indolylphenyliodonium Trifluoroacetate with Lithium or Ammonium Halides.

A solution of 2-3 mmole of 3-indolylphenyliodonium trifluoroacetate and 4-6 mmole of dried lithium or ammonium halide in 10 ml of dry DMSO was heated at 100°C for 2 h, after which it was cooled and poured into water. The aqueous mixture was extracted with benzene, and the

extract was dried with anhydrous $MgSO_4$. The solvent was removed *in vacuo*, and the residue was chromatographed with a column filled with silica gel [elution with chloroform-carbon tetrachloride (1:2)]. The yields are indicated in Table 1.

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UNUSUAL FISCHER REACTION IN THE 1-AMINOBENZIMIDAZOLE SERIES.

SYNTHESIS OF PYRIDO[1,2-a]BENZIMIDAZOLE DERIVATIVES

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The reaction of N-aminobenzimidazoles with ketones under the conditions of the Fischer reaction, as a result of which derivatives of 1,3-disubstituted pyrido-[1,2-a]benzimidazoles are unexpectedly formed, was investigated. The structure of the latter was established on the basis of data from IR, PMR, and mass spectroscopy, as well as by an independent method based on 2-cyanomethylbenzimidazole and β -diketones.

The formal similarity between N,N-disubstituted hydrazines and N-amino derivatives of nitrogen heterocycles compelled us to study the Fischer reaction in the 1-aminobenzimidazole series.

It is known that 1-aminobenzimidazoles (I) readily react with aldehydes to give Schiff bases [1]. At the same time, the corresponding ketimines II cannot be obtained under the ordinary conditions for the synthesis of hydrazones. The latter were isolated only after heating solutions of the starting components in the presence of catalytic amounts of anhydrous zinc chloride with the simultaneous removal of water by distillation and excess ketone. The resulting compounds are quite labile and are readily hydrolyzed not only by dilute mineral acids but also during chromatography on aluminum oxide.

Ammonia is evolved in conformity with the classical scheme of the reaction when ketimines II are heated under the conditions of the Fischer reaction (at 200-250°C with an equivalent amount of $ZnCl_2$). However, judging from the results of elementary analysis, two molecules of the ketone are included in the composition of the resulting III (in 20% yield). The yields of the reaction products increase substantially in the reaction of 1-aminobenzimidazole with excess ketone. We subsequently established that α,β -unsaturated ketones, viz., mesityl oxide and dypnone, react with 1-aminobenzimidazoles similarly but under milder conditions.

Since the formation of indoles via the Fischer route is an electrophilic reaction [2],

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