NUCLEOPHILIC SUBSTITUTION IN IODONIUM DERIVATIVES OF INDOLE

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3-Indolyphenyliodonium tosylate and trifluoroacetate were synthesized, and their reaction with halide anions was investigated. It is shown that the iodonium grouping is replaced by halogen in all cases. 3-Fluoroindole was synthesized for the first time. The mechanism of the reaction is discussed, and data from the mass spectra of the 3-haloindoles obtained are presented.

Electrophilic substitution in the indole series has been quite adequately studied; however, the set of electrophiles is limited, the reaction conditions are often rather severe, and synthetic difficulties are consequently created. Nucleophilic substitution could serve as a natural supplement to electrophilic substitution, but little study has been devoted to such reactions in the indole series. The available data involve mostly replacement of halogens, and the reactions proceed under rather severe conditions and often via a heteroaryne mechanism [1] to give a mixture of isomeric compounds.

Onium and particularly iodonium compounds are of much greater interest for nucleophilic substitution, but derivatives of this sort have not been known in the indole series until recently. The 3-indolyphenyliodonium system (I, II) was obtained only recently [2], and some of its reactions were studied.

The high yields of substitution products in the reactions of 3-indolyphenyliodonium salts make it possible to hope that expansion of the method would make it possible to obtain various functionally substituted (in the 3 position) indoles.

In the present paper we present some results that demonstrate the prospects for nucleophilic substitution in 3-indolyphenyliodonium salts for the synthesis of haloindoles.

β-Indolyphenyliodonium tosylate [2] and trifluoroacetate were used as the starting compounds (the latter salt was quite soluble in many organic solvents).

A substance that was characterized as fluor indole by mass spectrometry was obtained in the reaction of iodonium salt II with potassium fluoride in N-methylpyrroloidine. The other reaction products were indole and trace amounts of 3-iodoindole, the formation of which can be explained by competitive (at high temperatures) homolytic cleavage of the iodonium salt.

When a solution of iodonium salt II in DMSO was heated with lithium chloride and bromide, the reaction
products were, respectively, 3-chloro- and 3-bromoindoles. The formation of indole and 3-iodoindole was not observed in these cases.

The course of the reaction of (3-indolyl)phenyliodonium salts with iodide ion depends markedly on the solvent. Thus individual compounds were not identified when the reaction of iodonium salt II with ammonium iodide was carried out in DMSO at 80°C. A mixture of indole and 3-iodoindole is formed in the reaction of iodonium salt III with tetrabutyl ammonium iodide in benzene. In this case the reaction evidently proceeds via a homolytic mechanism; this can be explained by the strong reductive effect of iodide ion.

Thus the reaction of (3-indolyl)phenyliodonium salts with halide ions proceeds at moderate temperatures via a mechanism of the nucleophilic substitution type, except in those cases in which the facile oxidizability of the anion present in the reaction medium shifts the reaction to favor radical substitution.

The exclusive occurrence of nucleophilic attack at the pyrrole ring of indole can be explained by the decreased aromatic character of the pyrrole ring as compared with the phenyl ring. This should decrease the localization energy of both the cationic form (which is well known for electrophilic substitution in indoles [3]) and anionic form and in the case of reaction through a "later" transition state should ensure primary substitution in the pyrrole ring.

**EXPERIMENTAL**

The mass spectra were recorded with an MKh-1303 mass spectrometer with a modified system for introduction of the samples into the ion source at an ionizing-electron energy of 50 eV. The reactions were monitored by chromatography on Silufol UV-254 plates in a hexane–ether system (2:1).

(3-Indolyl)phenyliodonium Tosylate (II). This salt was obtained by the method in [2].

(3-Indolyl)phenyliodonium Trifluoroacetate (III). A 6-g (3.9 ml [52 mmole]) sample of trifluoroacetic acid was added slowly with stirring to a cooled (to −10−0°C) suspension of 16.7 g (52 mmole) of (3-indolyl)-phenyliodonium betaine (I) [2] in 20 ml of ethanol, and the mixture was diluted with 200 ml of ether and allowed to stand overnight in a refrigerator. The resulting precipitate was removed by filtration, washed with ether, and dried in a vacuum desiccator to give 16.4 g (74%) of a product with mp 129-130°C (reprecipitation from methanol by the addition of ether).

3-Fluoroindole (IVa). A 1.16-g (20 mmole) sample of anhydrous KF was added to a solution of 4.91 g (10 mmole) of iodonium salt II in 20 ml of N-methyl-2-pyrrolidone, and the mixture was heated at 135-140°C for 15 min, after which it was poured into water. The aqueous mixture was extracted with benzene, and the benzene layer was dried and evaporated to a minimal volume. The concentrated solution was chromatographed with a column filled with silica gel L (40-100 #) in a petroleum ether–ether system (2:1) to give 180 mg (16%) of indole [mp 60-62°C and Rf 0.37. Mass spectrum: 117 (39),* 116 (3), 90 (13), 89 (8) and 630 mg (46%) of 3-fluoroindole with mp 72-73°C and Rf 0.36. Mass spectrum: 135 (100), 134 (60), 116 (10), 108 (29).

3-Chloroindole (IVb). A solution of 2.46 g (5 mmole) of iodonium salt II and 0.43 g (10 mmole) of calcined lithium chloride in 20 ml of dry DMSO was heated at 100°C for 20 min, after which it was poured into water, and the aqueous mixture was extracted with benzene. The benzene layer was dried and evaporated to a minimal volume, and the concentrated solution was chromatographed with a column filled with silica gel L (40-100 μ) in CCl4 to give 500 mg (66%) of 3-chloroindole with mp 91-92°C (mp 91.5°C [4]) and Rf 0.18. Mass spectrum: 151 (100), 150 (5.4), 124 (7.5), 116 (18.5), 89 (89).

3-Bromoindole (IVc). A solution of 2.46 g (5 mmole) of iodonium salt II and 0.87 g (10 mmole) of anhydrous lithium bromide in 20 ml of dry DMSO was heated at 100°C for 2 h, after which the mixture was poured into water, and the aqueous mixture was extracted with benzene. The benzene layer was dried and evaporated, and the residue was recrystallized from hexane to give 780 mg (80%) of 3-bromoindole with mp 67-68°C (dec.) [mp 67°C (dec.) [5]] and Rf 0.20. Mass spectrum: 195 + 197 (100), 194 + 196 (2.2), 167 + 169 (1.2), 116 (49.8).

3-Iodoindole (IVd). A mixture of 2.16 g (5 mmole) of iodonium salt III, 3.69 g (10 mmole) of tetrabutyl ammonium iodide, and 20 ml of benzene was refluxed for 20 min, after which it was washed with water, dried, and evaporated. The residue was chromatographed on silica gel L (40-100 μ) in CCl4 to give 140 mg (24%) of indole, with mp 60-63°C, and 720 mg (59%) of 3-iodoindole with mp 72-73°C (dec.) [mp 72°C (dec.) [5]]. Mass spectrum: 243 (100), 242 (4.3), 216 (5.3), 116 (23).

* Here and subsequently, the m/e values (and intensities in percent of the maximum ion peak) are presented for the ion peaks.