NUCLEOPHILIC SUBSTITUTION IN IODONIUM DERIVATIVES OF INDOLE

M. S. Ermolenko, V. A. Budylin,
and A. N. Kost

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3-Indolylphenyliodonium 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.

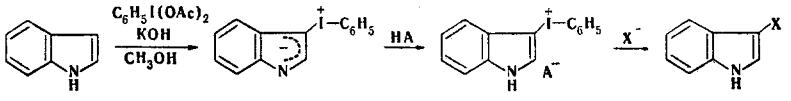
Electrophilic substitution in the indole series has been quite adequately studied; however, the set of electrophiles is limited, the reaction conditions are often rather severe, and synthetic difficulties are consequently created. Nucleophilic substitution could serve as a natural supplement to electrophilic 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 hetaryne 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-indolylphenyliodonium 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 (β-indolyl)phenyliodonium 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 (β-indolyl)phenyliodonium salts for the synthesis of haloindoles.

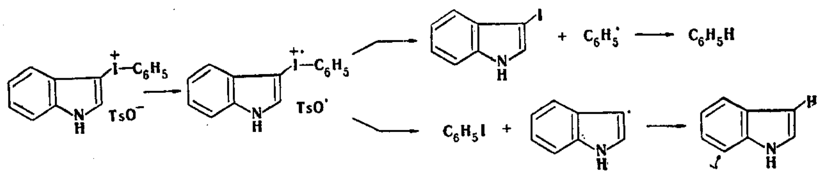
(β-Indolyl)phenyliodonium tosylate [2] and trifluoroacetate were used as the starting compounds (the latter salt was quite soluble in many organic solvents).



I II, III IVa-d

II A=TsO; III A=CF_3COO; IVa X=F; b X=Cl; c X=Br; d X=I

A substance that was characterized as fluoroindole by mass spectrometry was obtained in the reaction of iodonium salt II with potassium fluoride in N-methylpyrrolidone. 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

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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 μ) in a petroleum ether–ether system (2 : 1) to give 180 mg (16%) of indole [mp 60-62°C and R_f 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 R_f 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 CCl_4 to give 500 mg (66%) of 3-chloroindole with mp 91-92°C (mp 91.5°C [4]) and R_f 0.18. Mass spectrum: 151 (100), 150 (5.4), 124 (7.5), 116 (18.5), 89 (39).

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 R_f 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 tetrabutylammonium 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 CCl_4 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).

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

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INDOLE DERIVATIVES

CXV.* SYNTHESIS AND SOME TRANSFORMATIONS OF 5-(3-INDOLYL)ISOXAZOLE-3-CARBOXYLIC ACID

V. P. Gorbunova and N. N. Suvorov

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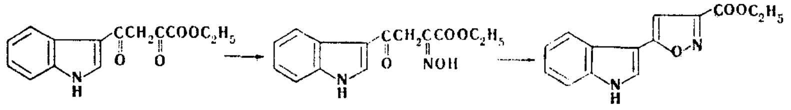
5-(3-Indolyl)isoxazole-3-carboxylic acid and its amide and hydrazide were obtained from ethyl 5-(3-indolyl)isoxazole-3-carboxylate. When 5-(3-indolyl)isoxazole-3-carboxylate is heated, it undergoes decarboxylation with isomerization to 3-(ω-cyanoacetyl)indole; when it is heated in alcohol with hydrazine and phenylhydrazine in the presence of copper, it undergoes isomerization to 5-(3-indolyl)pyrazole-3-carboxylic and 1-phenyl-5-(3-indolyl)-pyrazole-3-carboxylic acids. 5-(3-Indolyl)pyrazole-3-carboxylic acid hydrazide is formed when a solution of ethyl 5-(3-indolyl)isoxazole-3-carboxylate is refluxed with hydrazine in 96% alcohol.

Very interesting physiologically active compounds have been found among indolylazoles [2]. Least study has been devoted to indolyloxazoles. To obtain the latter we used ethyl 4-(3-indolyl)butane-2,4-dioate (I) [3].

Monooxime II was obtained by the action of hydroxylamine on ester I in the presence of acetic acid. Its IR spectrum contains a broad band at 3200-3230 cm^{-1}, which merges with a narrow band at 3310 cm^{-1} (NH and OH stretching vibrations). There is also a carbonyl band of an ester group at 1620 cm^{-1}. It can be assigned to the vibrations of a carbonyl group attached to an indole ring [4] and is superimposed on the band of the C=N bond.

The PMR spectrum of monooxime II contains a singlet of the two equivalent protons of the side chain at 4.24 ppm. As in the case of I, the indole ring 2-H proton gives a singlet at 8.27 ppm. This indicates rapid exchange of the protons of the NH group, which is characteristic for compounds with a carbonyl group attached to the indole ring [5].

Ethyl 5-(3-indolyl)isoxazole-3-carboxylate (III) was obtained by the action of hydroxylamine on I in the presence of pyridine. It was shown by thin-layer chromatography (TLC) that the initial product is oxime II, which slowly undergoes cyclization to III.



I

II

III

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[*] See [1] for communication CXIV.

D. I. Mendeleev Moscow Chemical-Technological Institute, Moscow 125047. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 936-938, July, 1978. Original article submitted July 14, 1977.

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