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DIRECT PHENYLATION OF PIRIDINE DERIVATIVES BY NUCLEOGENIC PHENYL CATIONS

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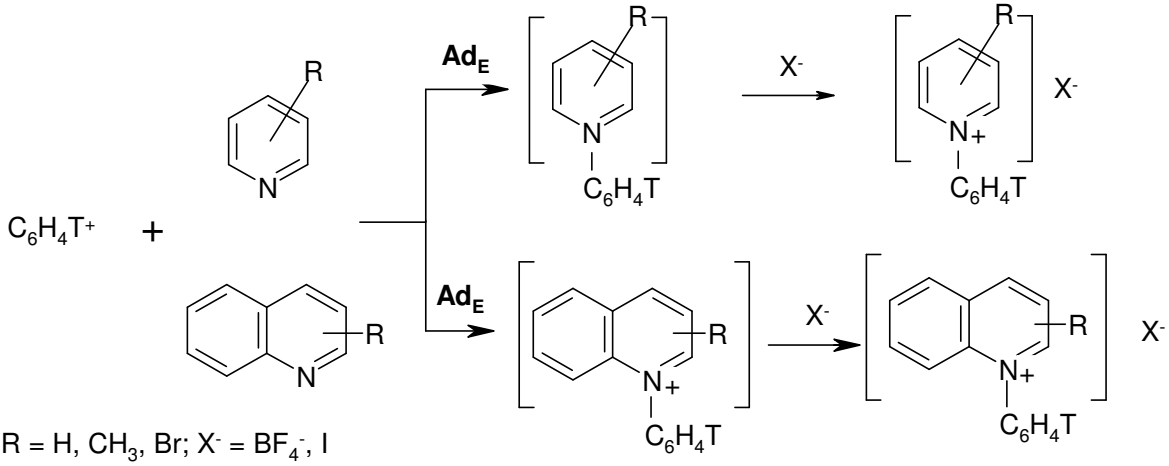
Abstract

By nuclear-chemical method several unknown tritium labeled N-phenylpyridinium derivatives have been synthesized.

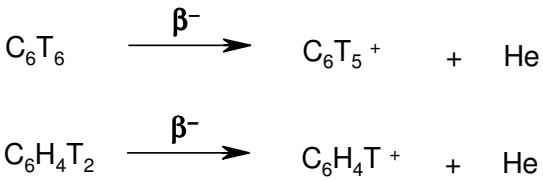


Introduction

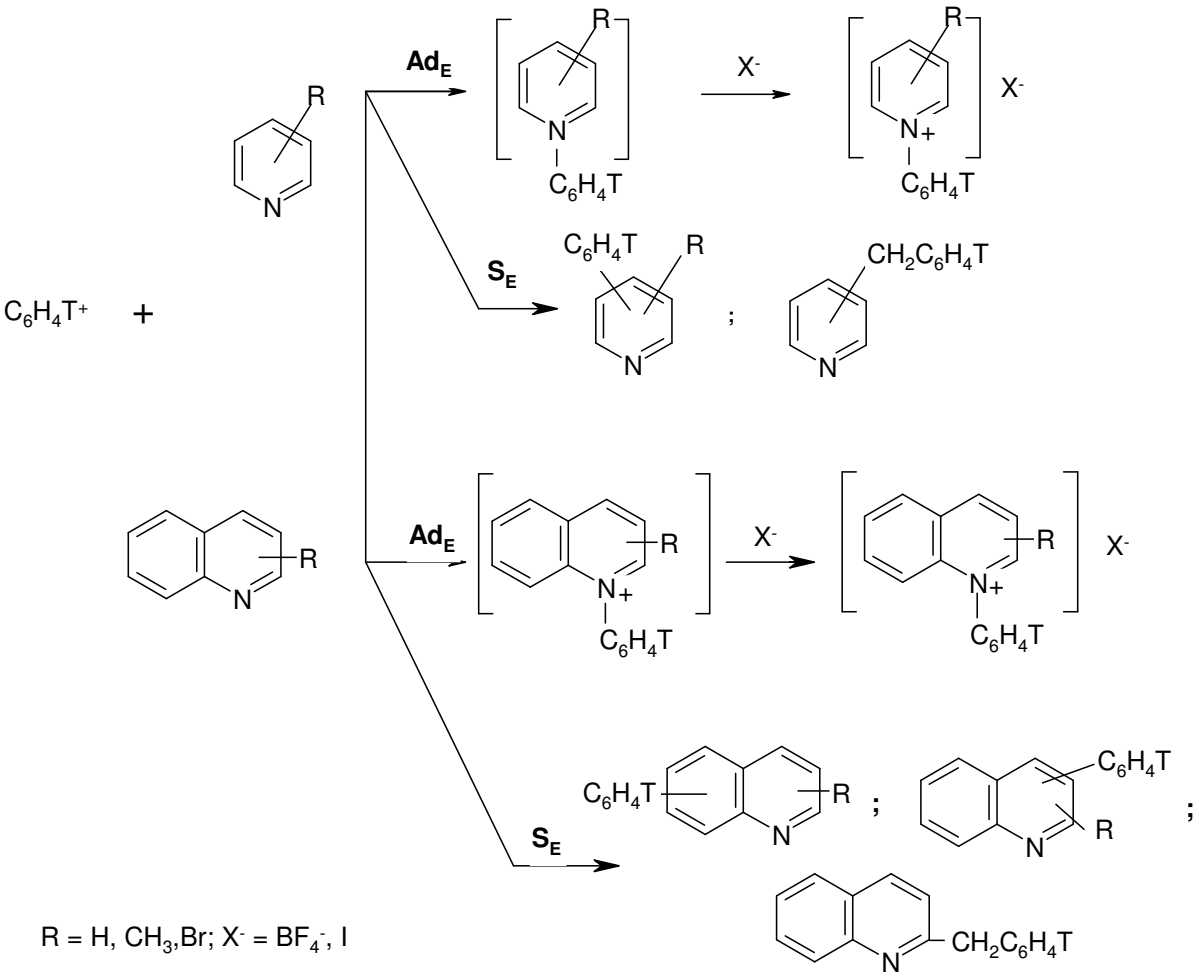
It is well-known that by Nesmeyanov reaction (formation of phenyl cations from iodonioum tetrafluoroborates) nitrogen phenylation undergoes only for unsubstituted pyridine [1]. For other derivatives direct synthesis of quaternary pyridinium compounds is impossible. Previously we have achieved success in application of nuclear-chemical method for synthesis of unknown fluoronium and ammonium derivatives [2-4]. Further investigations were turned to the formation of N-phenyl substituted pyridinium salts [5]. Six-member ring nitrogen heterocyclic compounds particularly derivatives of pyridine are extremely important objects for biological investigations. There are natural objects: enzymes and vitamins, together with a long list of artificial drugs: pyroxicam with untinflammatory activity, nifedipine and amlodipine used for treatment of heart diseases, pynaxidil – drug for hypersonic disease and also different quinolone derivatives with high antimicrobial activity [5-11]. It was shown that obtained only in the mid of the 20th century N-phenyl pyridinium derivatives in many cases exceed their aliphatic analogues in biological action. Taking into account extraordinary usefulness of quaternary nitrogen derivatives one can understand great importance of detail investigations of mechanisms of drug action and also metabolism processes in organism. For this purpose method of isotopic labeling is highly applicable, especially of tritium labeling, which allows carrying out quite sensitive investigations of bioorganic molecules and pharmaceuticals [12-14]. But the main obstacle in the wide application of N-phenyl pyridinium derivatives remains to be the complexity of their methods of synthesis. Great horizons for the detail investigations of biological processes with the help of labeled building blocks of drugs are opened by elaboration of nuclear-chemical method of synthesis.

Results and discussion

The nuclear-chemical method gives unique opportunity for generation of free carbenium ions by tritium β-decay. Among other carbenium ions phenyl cations have essential advantage: hence it's aromasity it is more stable and the label is fixed. As a source of plenyllium ions polytritiated benzene has been used:



Since in order to perform investigations of ion-molecular reactions with phenyl cations generated by nuclear-chemical method it is necessary to have in the benzene ring not less than two tritium atoms we have switched to the easier synthesis of double labeled benzene. The scheme of the investigated ion-molecular reactions may be represented in the following way:



Nuclear-chemical synthesis was undertaken by the elaborated procedure [2] in the sealed glass ampoules containing tritiated benzene (the source of phenyl cations) and substrates (different pyridine derivatives), which were placed on the crystals of stabilizing salt (KBF_4, KI). Ampoules with the reaction mixture were kept for the accumulation of the reaction products in amounts enough for its reliable radioactive determination (not less than 1 month) and then isolation and

identification of the synthesized labeled products were carried out. The yields of tritium labeled quaternary pyridinium derivatives have been presented in the table 1.

Table 1.

Yields of tritium labeled quaternary pyridinium derivatives obtained by nuclear-chemical synthesis

Substrate	**Yield of onium salt (Ad_E), %**
Pyridine	66±2
2-Methylpyridine	35±3
3-Methylpyridine	36±2
4-Methylpyridine	25±1
2-Bromopyridine	25±1
Quinoline	21±3
2-Methylquinoline	18±3
3-Bromoquinoline	16±1

It is necessary to mention that in spite of some cases when the yields of onium salts don't exceed 16% the nuclear-chemical method allows to carry out simple and one-step synthesis of hardly available tritium labeled compounds together with their application in biological and medical investigations. Unlabeled carries – N-phenylpyridinium, picolinium, quinolinium and quinaldinium salts have been investigated in order to testify antimicrobial activity. The results were extremely encouraging since all of them showed high antimicrobial effect towards gram-positive and gram-negative bacteria. Application of tritium labeled quaternary pyridinium compounds clears up the way for more detail investigations of cationic biocides interaction mechanisms together with purposeful search for new syntheses of pyridine derivatives with perfected antimicrobial features.

General experimental procedure

The reaction of catalytic substitution of halogen atoms by tritium in a molecule of *p*-dibromobenzene serves as a basis for synthesis of tritium double labeled benzene:

$$C_6H_4Br_2 + T_2 \xrightarrow[t=25^oC]{5\%\ Pd/BaSO_4} C_6H_4T_2$$

From 5 mg of dibromobenzene, 6.5 μL thriethylamine diluted in 0.5 mL of hexane (addition of triethylamine is necessary for binding of the formed hydrogen bromide) and 5 Cu of gaseous tritium by hydrogenation at room temperature on 5% $Pd/BaSO_4$ catalyst during 1 hour the solution of tritium double labeled benzene has been obtained. The chemical purity was not less than 99%. The volume specific activity of the synthesized benzene came to 4 Cu/cm^3. All ion-molecular reactions were carried out in sealed glass ampoules containing the source of phenyl cations (tritiated benzene), the investigated nucleophile (pyridine, α-, β- and γ-picolines, 2-bromopyridine, benzopyridine, quinaldine and 3-bromoquinoline) in ~1:1000 ratio (1 μL of hexane solution of $C_6H_4T_2$ and 5 μmol of substrate)) and an inorganic salt with the desired stabilizing anion (KBF_4 or KI). The ampoules were sealed cold and kept at 0-5 ^oC during the accumulation time (about 1 month). After this period, the radioactivity of the obtained products is enough for detection. The ampoules were opened, solvent added (acetone) and the mixture subjected to TLC. Radiochromatography of the obtained tritiated compounds was accomplished on glass plates Reverse Phase C18 silica gel (Fluorescent Indicator) with the use of acetonitrile eluent. Parts of the chromatographic adsorption layer in 1 cm were scraped off and put into dioxane scintillator and their radioactivity was measured with the liquid scintillation detector by scintillation spectrometer RackBeta 1215 (LKB Wallac, Finland).

Acknowledgement

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