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Reductive Amination of Quinoline N-Oxide with Aminopyridines and Their N-Tozyl Derivatives

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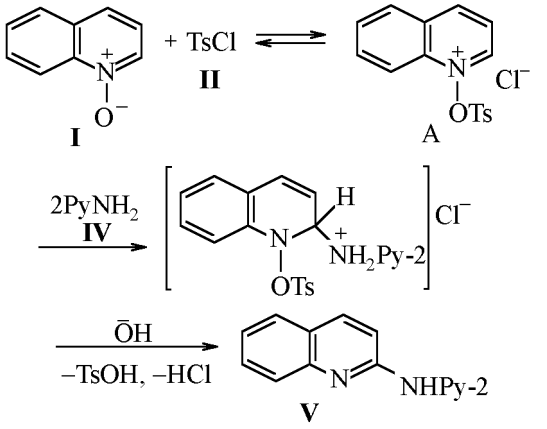
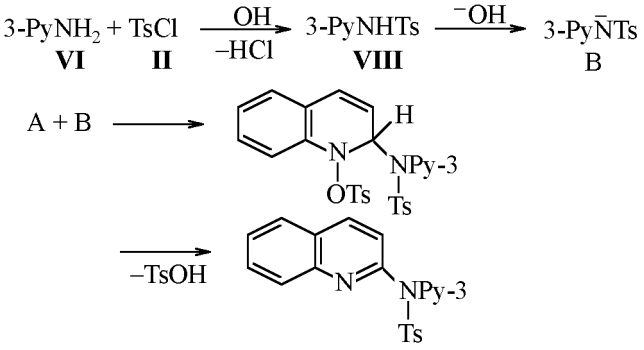
Abstract—In reaction of quinoline N-oxide with 2-aminopyridine in the presence of tosyl chloride the substrate undergoes reductive amination into 2-pyridyl(2-quinolyl)amine, and with 3- and 4-aminopyridines reductive tosylamination occurs to furnish N-tosyl derivatives of the corresponding 3- and 4-pyridyl(2-quinolyl)amines. N-tosyl derivatives of aminopyridines also react along reductive tosylamination pathway.

In reaction of quinoline N-oxide (**I**) with ammonia in the presence of tosyl chloride (**II**) that activates the substrate molecule by its *in situ* transformation into an N-acyloxy cation a reductive amination occurs resulting in a high yield of 2-aminoquinoline [1]. Unlike that the pyridine N-oxide under similar conditions undergoes acylamination furnishing as main products *N*-tosyl-2-aminopyridine (**III**) and tosyldi-(2-pyridyl)amine, and amination occurs only as side process [2]. The direction of reaction depends on the activity of the heterocyclic system in the nucleophilic substitution, on the nucleophilicity of the reagent (respectively ammonia and the secondary arising anion), on the ease of amide formation and its ionization effected by basic agent, and on the side processes that remove the reagents from the reach of the main process.Among the latter the most important is the alkaline hydrolysis of sulfonyl chloride. Therefore in performing this type of reactions it cannot be unambiguously predicted which among them will prevail.

Proceeding from the above mentioned results of the previously studied reaction of oxide **I** amination with ammonia [1], acylamination of pyridine N-oxide [2] and also of oxide **I** with *N*-tosylanilide [3] we report here on investigation of reaction between oxide **I** and isomeric aminopyridines and N-tosyl derivatives thereof. As we described before [4] oxide **I** with 2-aminopyridine (**IV**) in the presence of compound **II** under phase-transfer conditions (chloroform–water) in alkaline medium (sodium hydroxide or carbonate solution) underwent amination to afford 2-pyridyl(2-quinolyl)amine (**V**) in 80% yield.





Reaction of oxide **I** and 3-aminopyridine (**VI**) under similar conditions gives rise to 3-pyridyl(tosyl)-(2-quinolyl)amine (**VII**) but in significantly lower yield (10–15%), and the main part of amine **VI** remained unreacted.

Similarly oxide **I** reacts with 4-aminopyridine (**IX**). Therewith as the main product arises 4-pyridyl-(tosyl)(2-quinolyl)amine (**X**) in up to 53% yield, and as a side reaction occurs acylation of amine **IX**.

In the acylamination reactions under study the reactive form is presumably the secondary formed *N*-tosylimide ions [5]. Therefore it was logical to try as reagents monotosyl aminopyridine derivatives.

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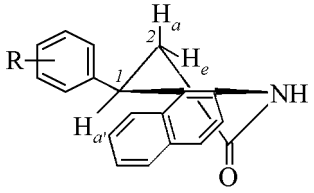
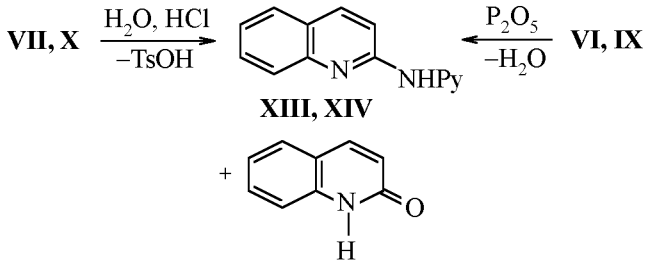
Actually, the reaction of oxide **I** with N-tosyl derivatives of 2- (**III**), 3- (**VIII**), and 4-aminopyridine (**XI**) under analogous conditions furnished the corresponding 2-tosylamino quinoline derivatives **VII, X, XII** in considerably higher yield.



XVI–XXVII

2-Py (**III, XII**), 3-Py (**VII, VIII**), 4-Py (**X, XI**).

The structure of amide **XII** was proved by acid hydrolysis to amine **V**, and the structures of isomeric



XIII, XIV

3-Py (**VI, VII, XIII**), 4-Py (**IX, X, XIV**).

amides **VII** and **X** was confirmed by acid hydrolysis to the corresponding amines **XIV, XV** and by independent synthesis of the latter by condensation of carbostyril with amines [6].

In reaction of compound **XI** was obtained as side product *N*,*N*-ditosyl-4-aminopyridine **XV**; its structure was confirmed by hydrolysis to monotosyl derivative **XI** and further to amine **IX**.

The reactions described are of interest for the synthesis of sulfonylamides of quinoline and pyridine series, and also for preparation of the corresponding amines. All these substances are potential biologically active compounds.

EXPERIMENTAL

The reaction progress was monitored and homogeneity of compounds obtained was checked by paper chromatography (no. 2, fast) in the system 1-butanol–hydrochloric acid–water (50 : 7 : 14), development with Dragendorff reagent [7]. All the known compounds were identified by melting point determination in a mixed probe with authentic samples.

Amination of quinoline N-oxide (I) with amine IV. A solution of 11 mmol of oxide **I** dihydrate, 13 mmol of amine **IV**, and 11 mmol of sulfonyl chloride **II** in 100 ml of chloroform was stirred with 40 ml of 10% water solution of sodium hydroxide for 2 h at 20°C. The water layer was separated, several times extracted with chloroform, combined chloroform solutions were dried with Na_2SO_4, the solvent was distilled off, and the oily residue was several times washed with hot water. The cooled water solution was extracted with ethyl ether, the extract was dried on Na_2SO_4, the solvent was removed, and 0.3 g (25%) of unreacted amine **IV** was thus recovered. The crystalline residue after washing with water was amine **V**, R_f 0.7, yield 2 g (80%), mp 110°C (from hexane) (mp 108°C [8]), mp of picrate 240°C (mp 242–244°C [8]), mp of hydrochloride 114°C (mp 115–116°C [8]).

Amination of quinoline N-oxide (**I**) with compounds **III, VI, XIII, IX, XI**. A solution of 5.5 mmol of oxide **I**, 5.5 mmol of compound **III, VI, XIII, IX, XI**, and 5.5 mmol of sulfonyl chloride **II** in 50 ml of chloroform was stirred with 20% solution of sodium hydroxide (in reaction with compound **XI** was used 20% solution of sodium carbonate). The stirring at 20°C was carried out for 2 h. The water layer was separated, several times extracted with chloroform, combined chloroform solutions were dried with Na_2SO_4, the solvent was distilled off. The remaining crystalline residue was washed with 5% solution of $NaHCO_3$ to obtained reaction products **VII, X, XII**. Below are given the amine number, its yield (%), mp (°C), R_f respectively: (**VII**) – 10, 127–128 (from ethanol), 0.8; (**X**) – 53, 225–226 (from ethanol), 0.9; (**XII**) – 58.4, 186 (from ethanol), 0.96; (**VII**) – 85.8, 127–128 (from ethanol), 0.9; (**X**) – 36.7, 224–226 (from ethanol), 0.9.

Unreacted compounds **III, VI, XI** were recovered from water solutions. From reaction with compound **XI** was isolated a side product, *N*,*N*-ditosyl-4-aminopyridine **XV**, R_f 0.7, mp 204–205°C (from ethanol). Found, %: N 8.5. $C_{19}H_{18}N_2O_4S$. Calculated, %: N 9.0.

Hydrolysis of amides VII, X, XII. In 5 ml of concn. HCl was dissolved 2.7 g of amide **VII, X, XII**, and the solution was boiled for 18 h. The reaction mixture was evaporated to dryness, the residue was washed with ethyl ether, dissolved in water, the solution was alkalized with potassium carbonate and extracted with chloroform. On removing the solvent amines **V, XIII, XIV** were obtained. Below are given

the amine number, its yield (%), mp (°C): (°C): (**V**) – 55, 108 (from hexane) (mp 108°C [8]); (**XIII**) – 87, 168–170 (from ethanol). Found, %: N 18.75. $C_{14}H_{11}N_3$. Calculated, %: N 19.0. (**XIV**) – 65, 140–141 (from petroleum ether, bp 40–60°C). Found, %: N 18.8. $C_{14}H_{11}N_3$. Calculated, %: N 19.0.

Hydrolysis of amide XI. A solution of 1.5 mmol of amide **XI** in 5 ml of concn. HCl was boiled for 10 h. The reaction mixture was evaporated to dryness, the residue was washed with ethyl ether, the solvent was evaporated to obtain 0.2 g (80%) of *p*-toluenesulfonic acid, mp 90–92°C (mp 92°C [9]). The dry residue was dissolved in a minimal volume of water, alkalized with sodium carbonate, extracted with ethyl ether to isolate 0.1 g (70%) of amine **IX**, mp 156–157°C (mp 158°C [9]).

Synthesis of amines XIII and XIV. A mixture of 5 mmol of carbostyril, 5 mmol of amine **VI** or **IX**, and 20 mmol of P_2O_5 was heated to 200°C for 19–24 h. The reaction mixture was dissolved in 10% HCl, alkalized with potassium carbonate, the separated precipitate was filtered off, mixed with alumina, extracted with petroleum ether, and on removing the solvent amine **XIII** or **XIV** was obtained. Below are given the amine number, R_f, its yield (%), mp (°C): (**XIII**) – 0.25, 9, 168–170; (**XIV**) – 0.3, 18, 140–141.

Hydrolysis of amide XV. In 5 ml of 95% ethanol was dissolved 5 mmol of amide **XV**, and the solution was boiled for 5 h. The reaction mixture was cooled, the separated crystals were filtered off to obtain 67% of amide **XI**, mp 280°C (subl.) (mp 280°C (subl.) [10]).

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