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CHEMISTRY OF HETEROCYCLIC N-OXIDES AND RELATED COMPOUNDS. VI.* REACTION OF PYRIDINE, DIPYRIDYL, AND QUINOLINE N-OXIDES WITH AMMONIA AND AMMONIUM SALTS

M. A. Solekhova, Yu. V. Kurbatov, O. S. Otroshchenko, and A. S. Sadykov

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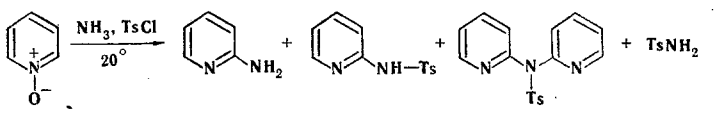
The amination of pyridine, quinoline, and 2,3'- and 4,4'-dipyridyl N-oxides with ammonia and ammonium salts in the presence of p-toluenesulfonyl chloride was studied. 2-Aminopyridine, N-(p-tosyl)-2-aminopyridine, and N-(p-tosyl)-2,2'-dipyridyls were obtained in reactions with pyridine N-oxide. 2-Aminoquinoline was obtained in the amination of quinoline N-oxide. Dipyridyl N-oxides do not undergo amination.

The nucleophilic amination of heteroaromatic N-oxides, which is realizable by the action of ammonia or amines in the presence of acyl halides [2], opens up extensive possibilities for the synthesis of hard-to-obtain α- and γ-amino derivatives of N-heterocycles.

Up until now, amination with ammonia has been investigated only in the case of the reaction with quinoline N-oxide [2]. In the present research we have studied the amination of pyridine, quinoline, and dipyridyl N-oxides with ammonia and ammonium salts in the presence of p-toluenesulfonyl chloride.

According to the data in [2] and our results, the amination of quinoline N-oxide (I) can be achieved by the action of various aminating agents (see Table 1). The utilization of ammonia and ammonium phosphate, which makes it possible to carry out the amination rapidly to give 2-aminoquinoline in high yield (82%), is the most effective procedure. The reaction can be used as a preparative method for the synthesis of aminoquinoline.

In the case of pyridine N-oxide (II), the amination proceeds in a more complex manner: In addition to the expected 2-aminopyridine (III), N-tosyl-2-aminopyridine (IV), N-tosyl-2,2'-dipyridylamine (V) (the chief reaction product), and p-toluenesulfonamide (VI) are formed.



II III IV V VI

In analogy with the scheme for the formation of III, it might have been assumed that the chief reaction product (V) is obtained as a result of amination of N-oxide II by amine III, formed as a result of the reaction, and subsequent tosylation of 2,2'-dipyridylamine (VII).

*See [1] for communication V.

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TABLE 1. Amination of N-Oxides of Pyridine Bases

N-Oxide	Aminating agent	N-Oxide: aminating agent: TsCl molar ratio	Reaction time, h	Yields of reaction products, %			
				2-amino derivative	IV	V	VI
II	NH_4OH	1 : 17 : 1	2	11	5	34	39
II	$(NH_4)_2CO_3$	1 : 1 : 1	2	8	—	24	62
II	$(NH_4)_3PO_4$	1 : 1 : 1	2	19	—	57	18
II	III	1 : 1 : 1	2	35	6	25	
II	III, K_2CO_3	1 : 1 : 1	2	42	22	34	
II	VI	1 : 1 : 1	2		—	—	
II	VI, K_2CO_3	1 : 1 : 1	2	—	11	32	
II	IV, K_2CO_3	1 : 1 : 1	2		30	15	
I	NH_4OH	1 : 17 : 1	1	70			
I	NH_4OH, $(NH_4)_3PO_4$	1 : 20 : 1	1	80—84			
I	$(NH_4)_2CO_3$	1 : 7 : 1	2	40—44			
I	NH_4OH, $(NH_4)_2CO_3$	1 : 20 : 1	1	80			
I	NH_4HCO_3	1 : 17 : 1	2	62			
VIII	NH_4OH, $(NH_4)_3PO_4$	1 : 20 : 1	8	—			
IX	NH_4OH, $(NH_4)_3PO_4$	1 : 20 : 1	24	—			

In a model experiment involving the reaction of II and III we obtained amide V, but the hypothetical intermediate dipyridylamine (VII) was not detected in the reaction products. Moreover, an authentic sample of amine VII, added to the reaction mixture, was not acylated and was isolated unchanged at the end of the reaction. Thus amide V is most likely obtained as a result of acylamination of N-oxide II by N-tosyl-2-aminopyridine (IV), which, under the reaction conditions, may be formed not only as a result of tosylation of amine III, but also by direct acylamination of oxide II by tosylamide VI.

The possibility of acylamination of pyridine N-oxide by less basic amides under the reaction conditions can be explained by their participation in the form of N-anions, which are active nucleophiles [3]. The structure of product V was proven by acid hydrolysis to dipyridylamine VII and by alkaline cleavage to amine III.

In contrast to pyridine and quinoline N-oxides, 4,4'- (VIII) and 2,3'-dipyridyl (IX) N,N'-dioxides are not aminated under similar conditions. This is probably explained by delocalization of the π-electron density in the ring [4], which leads to a decrease in the basicity and the impossibility of creation of a sufficient concentration of the reactive form of the O-acylium cation.

EXPERIMENTAL

The isolation of the reaction products was monitored by means of thin-layer chromatography (TLC) on activity-II aluminum oxide in a chloroform–benzene–alcohol system (22:8:2, system A) with development by iodine vapors and by paper chromatography in a butanol–hydrochloric acid–water system (50:7:14, system B) with development by Dragendorf's reagent.

Amination of Quinoline N-Oxide (I) (General Method). A solution of equimolecular amounts of N-oxide I and p-toluenesulfonyl chloride in 40 ml of chloroform and 20 ml of 10% ammonium hydroxide (or the corresponding ammonium salt) was shaken at 20° for 1-2 h, after which the aqueous layer was separated from the chloroform layer and extracted with chloroform. The combined chloroform solutions were treated with 10% HCl, and the hydrochloric acid solution was made alkaline to pH 8-9 with potassium carbonate and extracted with ether to give 2-aminoquinoline. The results are given in Table 1.

Amination of Pyridine N-Oxide (II) with Ammonia. A solution of 5 g (52 mmole) of II and 10 g (52 mmole) of p-toluenesulfonyl chloride in 300 ml of chloroform and 150 ml of 10% ammonium hydroxide was shaken at 20° for 2 h, after which the aqueous layer was extracted with chloroform. The combined chloroform solutions were washed with 10% HCl and dried with sodium sulfate, and the solvent was removed by distillation. The residue was washed with ether to give 1.91 g (34%) of N-tosyl-2,2'-dipyridylamine (V) with mp 150-151° (from acetonitrile), R_f 0.68 (system A), and R_f 0.97 (system B). Found, %: C 62.8; H 4.6; N 12.8. $C_{17}H_{15}N_3O_2S$. Calculated, %: C 62.8; H 4.6; N 12.9.

The ether solution was evaporated to a small volume to give 0.19 g of N-tosyl-2-aminopyridine (IV) with mp 210-211° (from alcohol) and R_f 0.11 (system A). No melting-point depression was observed for a mixture of this product with a sample synthesized by the method in [5]. Workup of the residual ether solution yielded 1.95 g (33%) of p-toluenesulfonamide (VI) with mp 135-136° (from water) and R_f 0.35 (system A), in agreement with the data for authentic samples. The hydrochloric acid solution was extracted with ether and chloroform, and the ether extract was worked up to give 0.26 g (4%) of amide VI; the chloroform extract yielded 0.03 g of amide IV. The residual acidic solution was made alkaline to pH 8-9 and extracted with ether to give 0.53 g (11%) of 2-aminopyridine (III), which was identical to an authentic sample and had mp 55-56° and R_f 0.52 (system A). The ammoniacal aqueous layer of the reaction mixture was acidified to pH 1-2 with hydrochloric acid and extracted with chloroform. The solvent was removed by distillation, and the residue was washed with ether to give 0.09 g of amide IV. The overall yield of IV was 0.31 g (5%). Workup of the ether solution yielded 0.12 g of sulfonamide VI. The overall yield of tosylamide VI was 2.33 g (39%).

Amination of Pyridine N-Oxide (II) by Ammonium Salts. The reaction was carried out by the method described above for amination with ammonia. See Table 1 for the results.

Amination of Pyridine N-Oxide (II) with 2-Aminopyridine (III), N-Tosylaminopyridine (IV), and p-Toluenesulfonamide (VI). A mixture of equimolecular amounts of N-oxide II, amine III (or amides IV or VI), and p-toluenesulfonyl chloride in chloroform and a twofold quantity of 10% K_2CO_3 was shaken at 20° for 2 h. The reaction products were separated by the method described for the amination of N-oxide II with ammonia. The results are presented in Table 1.

Tosylation of 2-Aminopyridine (III) in the Presence of Ammonia. A mixture of 0.15 g (1.6 mmole) of amine III and 0.61 g (3.2 mmole) of p-toluenesulfonyl chloride in 10 ml of chloroform and 5 ml of 10% ammonium hydroxide was shaken at 20° for 2 h, after which the aqueous layer was separated from the chloroform layer and extracted with chloroform. The chloroform solutions were washed with 10% HCl, the solvent was removed by distillation, and the residue was washed with ether to give 0.02 g (5.1%) of amide IV with mp 210-211°. Workup of the ether mother liquor yielded 0.40 g (74%) of tosylamide VI. The hydrochloric acid solution was extracted with chloroform, and the extract was worked up to give an additional 0.14 g (26%) of VI. The mother liquor was made alkaline to pH 8-9 with potassium carbonate and extracted with chloroform to give 0.08 g (53.0%) of unchanged aminopyridine.

Alkaline Cleavage of N-Tosyl-2,2'-dipyridylamine (V). A mixture of 0.25 g (7.7 mmole) of V and 5 ml of 20% NaOH was refluxed for 16 h, after which it was cooled and extracted with chloroform to give 0.07 g (96%) of amine III with mp 55-56° (from petroleum ether). The mother liquor was acidified to pH 1-2 with hydrochloric acid and extracted with ether to give 0.12 g (92%) of p-toluenesulfonic acid.

Acid Hydrolysis of N-Tosyl-2,2'-dipyridylamine (V). A 1.38-g (4.2 mmole) sample of V was refluxed in 20 ml of concentrated HCl for 12 h, after which the mixture was diluted to twice its volume with water and extracted with ether. Workup of the ether extract gave 0.17 g (26%) of p-toluenesulfonic acid. Extraction of the aqueous mixture with chloroform yielded 0.35 g (25%) of starting V. The mother liquor was made alkaline to pH 8-9 with potassium carbonate and extracted with chloroform. The solvent was removed from the extract by distillation, and the residue was extracted with petroleum ether (bp 40-60°) to give 0.2 g (28%) of dipyridylamine VII with mp 84-85° and R_f 0.9 (system A). The product was identical to the compound obtained by the method in [6].

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