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TRANSFER OF OXYGEN FROM NICOTINIC ACID N-OXIDE TO PYRIDINE

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Reversible transfer of oxygen from nicotinic acid N-oxide to pyridine has been observed in a sealed ampul at 190-260°C.

Deoxygenation is an important reaction of heterocyclic N-oxides. The reduction of N-oxides is usually carried out with phosphorus(III) compounds or with hydrogen in the presence of a catalyst [1]. Some N-oxides lose their oxygen on heating with oxidants, for example a mixture of sulfuric acid and selenium dioxide [2]. The N-oxides of pyridine, quinoline, and their derivatives are also known to decompose on heating with the liberation of oxygen and the formation of the corresponding bases [3-5], enabling these oxides to be used as oxidants [6, 7].

We have now found that it is possible to oxidize nitrogenous heterocycles with N-oxides in a closed system, as exemplified by the reaction between nicotinic acid N-oxide and pyridine:

I II III IV

It has been shown that prolonged boiling of a mixture of these compounds, either without a solvent or in the presence of acetic acid or acetic anhydride, results in quantitative deoxygenation of the nicotinic acid N-oxide without the formation of pyridine N-oxide. In order to reduce the duration of deoxygenation and prevent the loss from the reaction mixture of the oxygen formed, the reactants were heated at higher temperatures in sealed ampuls. When the reaction was carried out with equimolar amounts of the reactants, reaction was 90% complete at 170-180°C. When a threefold excess of pyridine was used, the conversion was quantitative. Increasing the temperature considerably shortened the reaction time. The reverse transfer of oxygen from pyridine N-oxide to nicotinic acid is also possible in principle, but even when a fivefold excess of pyridine N-oxide was used, the reaction occurred to the extent of 25% only. By using acetic acid as solvent, it is possible to shorten the reaction time by a factor of nearly two, the position of the equilibrium remaining unchanged (Table 1). In this reaction, the equilibrium is strongly shifted toward the formation of the N-oxide of the more basic heterocycle, namely pyridine. This is in accordance with the known fact that the formation of the N-oxides of pyridines with electron-acceptor substituents, which reduce the basicity of the nitrogen, requires more severe conditions [8].

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TABLE 1. Transoxygenation Reaction Conditions

Reactant ratio	Temperature, °C	Reaction time, h	Transoxygenation, %
I : II (1 : 1)	190—200	10	90
I : II (1 : 3)	190—200	10	100
I : II (1 : 3)	100	20	0
I : II (1 : 3)	170—180	20	100
I : II (1 : 3)	250—260	4	100
I : II (1 : 3)*	190—200	6	100
III : IV (1 : 2)	190—200	10	6
III : IV (1 : 5)	190—200	10	23

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*The solvent used was glacial acetic acid.

EXPERIMENTAL

The IR spectra of pyridine N-oxide (2% solution in chloroform) were obtained on a UR-20 instrument. The N-oxides of nicotinic acid (I) and pyridine (IV) were synthesized by standard methods, using hydrogen peroxide [9, 10]. Pyridine was dried over KOH and distilled.

Deoxygenation of Nicotinic Acid N-Oxide (I). A. A mixture of 0.139 g (1 mmole) of the N-oxide (I) and 2.41 ml (10 mmole) of pyridine was boiled for 30 h under reflux. The progress of the reaction was monitored by TLC on Silufol (eluent ethanol—chloroform—25% aqueous ammonia, 3:2:0.8). Pyridine was removed under reduced pressure. The residue was recrystallized from water, to give 0.103 g (85%) of nicotinic acid, mp 235°C.

B. The mixture of compounds as above and 2.4 ml of acetic anhydride were boiled for 22 h under reflux, to give 0.097 g (80%) of nicotinic acid.

Reaction of N-Oxide (I) with Pyridine. A mixture of 0.139 g (1 mmole) of the N-oxide (I) and 0.237 g (3 mmole) of pyridine was heated in a sealed ampul for 10 h at 190-200°C. After cooling, the ampul was opened, the contents evaporated under reduced pressure, and the pyridine N-oxide extracted with three 0.5-ml portions of a mixture of diethyl ether and chloroform (4:1). The residue was recrystallized from hot water and air-dried to give 0.106 g (86%) of nicotinic acid (mp 235-236°C). The ethereal chloroform solution was diluted with 10 ml of chloroform, heated with a small amount of activated charcoal, filtered, and the chloroform removed under reduced pressure. The residue was recrystallized from dry diethyl ether to give 0.076 g (80%) of pyridine N-oxide (mp 65-67°C).

Reaction of Pyridine N-Oxide (IV) with Nicotinic Acid (III). A mixture of 0.062 g (0.5 mmole) of the acid (III) and 0.237 g (2.5 mmole) of the N-oxide (IV) was heated in a sealed ampul for 10 h at 190-200°C. Unreacted (IV) was extracted with a mixture of ether and chloroform, as described above. To the residue [a mixture of the acid (III) and its N-oxide] was added 1 ml of water, and the pH of the mixture adjusted to 7.0 with a 10% solution of ammonia. The acid (III) was precipitated by adding a solution of 0.119 g (0.7 mmole) of silver nitrate in 0.5 ml of water. The solid was separated by centrifugation, washed twice with small amounts of cold water, and air-dried to give 0.089 g (77%) of the silver salt of the acid (III).

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CO-CONDENSATION OF 2-AMINOPYRIDINE, AROMATIC ALDEHYDES, AND KETONES

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The co-condensation of 2-aminopyridine with aromatic aldehydes and ketones proceeds via the initial formation from the amine and the benzaldehydes of (2-pyridylamino)aryl carbinols, which then react with p-nitroacetophenone to give 3-aryl-1-(4-nitrophenyl)-3-(2-pyridylamino)-1-propanones and 3-aryl-1-nitrophenylprop-2-en-1-ones, or with antipyrine to give (2-pyridylamino)aryl-(4-antipyryl)methanes and aryl(diantipyryl)methanes.

The co-condensation of amines, aldehydes, and ketones (the Bayer—Döbner—Mannich reaction [1]) has been used extensively for the synthesis of heterocyclic compounds and aminoketones, but the mechanism of these reactions has been little studied. The Mannich reaction is said to occur via the intermediate formation of the Schiff base [2]. We, too, have observed the intermediate formation of Schiff bases in the synthesis of benzo[f]quinolines from 2-amino-8-naphthol-6-sulfonic acid, aromatic aldehydes, and ketones [3].

We have now examined the behavior of 2-aminopyridine (I) on co-condensation with aldehydes and ketones. It was of interest to investigate the reactions taking place, since the formation of Schiff bases by reaction of the amine (I) with aldehydes in solution has been disputed by many workers [4-6]. For example, the products of the reaction of 2-aminopyridine with aromatic aldehydes in alcohol, toluene, or xylene have been assigned [4, 5], without clear proof, the arylidenepyridylimine structure. With this in mind, we set ourselves the initial task of examining the reaction of the amine (I) with benzaldehydes (IIa-c) and establishing the precise structure of the products, which we required as reference samples in the study of the co-condensation of 2-aminopyridine, benzaldehydes, and ketones.

It was found that brief heating of equimolar amounts of (I) and (II) in alcohol gave the 2-pyridylaminoaryl carbinols (IIIa-c). The UV spectra of these compounds show the absence of a highly conjugated chromophore (Fig. 1). The IR spectra show a narrow absorption band of medium intensity at 3400-3410, and a broad band at 3200-3300 cm^{-1} attributed to absorption of the secondary amino group and the intramolecularly hydrogen-bonded hydroxyl group. Absorption at 1600-1670 cm^{-1}, which would indicate the presence of the azomethine group, was absent. In the PMR spectrum, the signal for the methine proton was seen at 6.12-6.16 ppm. Stability is probably conferred on these compounds by the presence of a strong hydrogen bond between the heteroatom of the pyridine ring and the hydroxyl group.

When the amine (I) was reacted with the aldehyde (IIa) in benzene with azeotropic removal of the water formed by the solvent, a product was obtained which had a higher melting point than (IIIa). From its UV, IR, and PMR spectra, this compound is assigned the structure represented by formula (IV).

This compound (IV) is quite stable, crystallizing from benzene without any changes in its physicochemical constants. Cryoscopic measurement of its molecular mass gave a value close to theoretical. The UV spectrum indicates the presence of a chromophore with a longer conjugated chain than in (IIIa). In the IR spectrum, the absorption at 3200-3500 cm^{-1} was still present, and in addition a weak band at 1670 and a medium band at 1700 cm^{-1} appeared,

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