NITRATION OF 2- AND 5-BENZYL-3-HYDROXYPYRIDINES AND THEIR N-OXIDES

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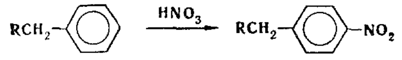
The nitration of 2- and 5-benzyl-3-hydroxpyridines and their N-oxides takes place in the para position of the phenyl ring. The introduction of an N-oxide group into the β-pyridol ring does not affect the orientation of substitution.

The orientation principles in the nitration of isomeric phenyl- and benzylpyridines and their derivatives [1-4] are extremely complex. Thus, a mixture of o- (5%), m- (35%), and p- (42%) nitro isomers is formed in the nitration of 2-phenylpyridine [2, 3], while 3-phenylpyridine [2] is nitrated exclusively in the para position. However, according to the general principles of electrophilic substitution of mononuclear aromatic systems, the predominant formation of m-nitro derivatives should have been expected in both cases. The experimental data attested that weakening of the electronegative effect of the ring nitrogen is accompanied by predominant formation of the para isomer, while strengthening of this effect leads to meta orientation [2]. For example, p-nitro derivatives are exclusively formed on passing from 2-phenyl- to 2-benzyl- [1, 2] or 2-phenyl-3-hydroxypyridine [5].

In the light of the results set forth above, it seemed of interest to investigate the nitration of 2- and 5-benzyl-3-hydroxypyridines and their N-oxides (Ia-d). Nitration of Ia and Ib under conditions similar to those described in [5] occurred in the para position of the phenyl ring.

In the case of 2-(4'-nitrobenzyl)-3-hydroxypyridine (IIa), the character of the PMR spectrum of the protons of the phenyl ring – two groups of symmetrical multiplets centered at 6.8 and 7.5 ppm (A_2B_2 type) – attests to the para position of the nitro group. The protons of the C_4, C_5, and C_6 atoms of the hydroxypyridine ring give signals at 7.03 and 6.5 ppm. The ratio of the integral intensities of the signals is in agreement with the proposed structure – IIa.

The character of the spectrum of 2-(4'-nitrobenzyl)-3-hydroxy-1-pyridine 1-oxide (IIb) is similar (signals of the protons of the hydroxypyridine ring at 7.17 and 6.95 ppm with an intensity ratio of 1 : 2, and two groups of symmetrical signals of phenyl ring protons at 6.97 and 7.78 ppm).



I II

a R= 3-hydroxy-2-pyridyl, b R= 3-hydroxy-N-oxido-2-pyridyl, c R= 3-hydroxy-5-pyridyl, d R= 3-hydroxy-N-oxido-5-pyridyl

Only the nitrates of Ia, b were obtained from the reaction of Ia, b with a mixture of concentrated nitric acid and glacial acetic acid.

The nitration of pyridines Ic, d is of special interest, inasmuch as here it is possible to compare the reactivities of the phenyl ring in the β-position (with a minimal electron-acceptor effect of the heteroatom) with the activity of the 2-position of the β-pyridol ring, occupied by a benzyl group in the case of Ia, b. Analysis of the PMR spectra of the synthesized nitro compounds (IIc, d) indicates that nitration in this case also is directed to the para position of the phenyl ring. Thus, two groups of symmetrical multiplets cen-

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TABLE 1. Nitro Compounds II

Compound	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
			C	H	C	H	
IIa	223—224	$C_{12}H_{10}N_2O_3$	62,8	4,4	62,6	4,4	85
IIb	250—252 (dec.)	$C_{12}H_{10}N_2O_4$	58,7	4,1	58,6	4,1	85
IIc	235—236	$C_{12}H_{10}N_2O_3$	62,8	4,5	62,6	4,4	90
IId	163—164	$C_{12}H_{10}N_2O_4$	58,6	4,1	58,6	4,1	80

tered at 6.5 and 7.2 ppm (as in the PMR spectrum of IIa) are present in the spectrum of 5-(4'-nitrobenzyl)-3-hydroxypyridine (IIc). The signals of the protons attached to the C_6, C_2, and C_4 atoms of the hydroxypyridine ring and of the CH_2 groups are found at 7.18, 6.91, 6.33, and 3.10 ppm.

Thus, the results obtained in this investigation attest to higher reactivity of the para position of the phenyl ring as compared with the 2-, 6-, and 4-positions of the β-pyridol ring. The introduction of an N-oxide group is not reflected in the orientation of substitution. The predominance of para substitution over ortho substitution in the nitration of 2- and 4-benzylpyridines has been explained [4] by pronounced deactivation of the phenyl ring of the protonated pyridyl group due to the effect of the field of positive charge, which weakens with distance and, by virtue of this, affects the para position to a lesser degree than the ortho and meta positions. Our results can apparently also be explained by this rationale.

EXPERIMENTAL

The PMR spectra of solutions in 1 N NaOD (IIa-c) and dimethyl sulfoxide (DMSO) (IId) were recorded with a Varian HA-100 spectrometer at 29° (on the δ scale relative to tetramethylsilane). The purity of the products was monitored by thin-layer chromatography (TLC) on Al_2O_3 in methanol–benzene (1 : 9).

Compounds IIa-d. A 0.01-mole sample of concentrated HNO_3 was added to 0.01 mole of I in 5 ml of concentrated H_2SO_4 at 0°, and the mixture was allowed to stand for 24 h at room temperature. It was then poured into 10 ml of ice water, and the aqueous mixture was filtered. The solid product was recrystallized from ethanol. Data on II are presented in Table 1.

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