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SYNTHESIS OF 2-(2'-HYDROXYPHENYL)PYRIDINE-N-OXIDE AND ITS THERMAL DECOMPOSITION AS A MODEL REACTION OF ORELLANINE DEOXIDATION[§]

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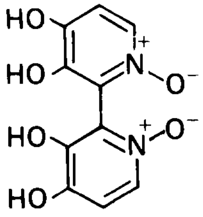
Abstract: 2-Methoxyphenylmagnesium bromide was reacted with 2-nitropyridine-N-oxide and demethylated to give 2-(2'-hydroxyphenyl)pyridine-N-oxide (II) which was found to undergo a thermal deoxidation to the free base (VI); the process is interpreted as a [1.5] oxygen shift followed by decomposition of the hydroperoxide intermediate.

The N-oxide function in pyridine derivatives generally demonstrates great thermal stability, even if the molecule bears electron-donating or -withdrawing substituents.[1] In this respect orellanine, for which the structure of 3,3',4,4'-tetrahydroxy-2,2'bipyridyl-N,N'-dioxide I was proposed by us,[2] behaved abnormally, since it decomposed slowly above 150° and explosively at about 270° with oxygen elimination giving the free base, orelline (3,3',4,4'-tetrahydroxy-2,2'-bipyridyl).[2] To find a reasonable explanation of these contradictory observations, we presumed that with orellanine the decomposition proceeded via a special mechanistic pathway resulting from the structural features of its molecule.

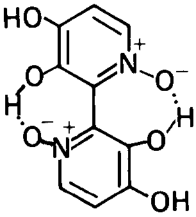
First of all we concluded that the mechanism discussed by Wenkert and Woodward,[1] which postulates the existence of a covalent bond between oxygen atoms of both N-oxide functions prior to oxygen molecule elimination from the bipyridyl system, can not be applied to our case for two reasons. Apart from the dipole-dipole repulsion of the N-oxides, which should destabilize the syn-periplanar conformation Ia, the anti-periplanar system Ib should be especially predominant because it allows hydrogen bonding which should stabilize the molecule. Moreover, the Wenkert-Woodward mechanism does not fit our observation that during pyrolysis (as well as during mass fragmentation) orellanine loses the two oxygens in separate processes, yielding first a mono-N-oxide and finally 3,3',4,4'-tetrahydroxy-2,2'-bipyridyl.[3]

In our search for the reason for facile oxygen elimination from the orellanine molecule, our attention was attracted to the possible coupling between an N-oxide function and an hydroxyl group at C-3 in the second ring of I.

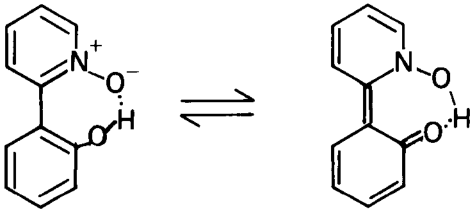
[§] Dedicated to Dr. Arnold Brossi on the occasion of his 60th Birthday.



Ia



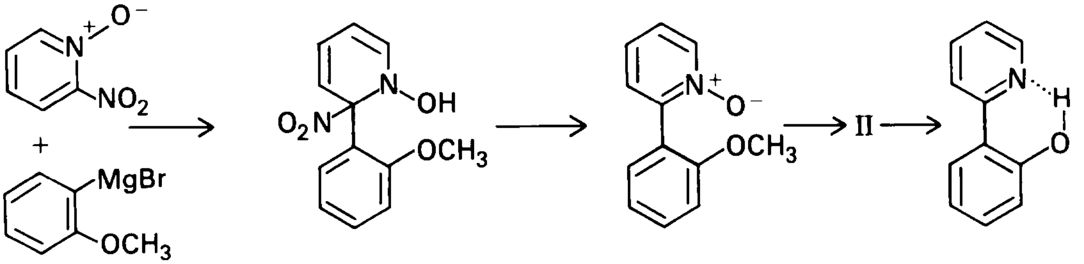
Ib



IIa IIb

Conformer Ib stabilized by hydrogen bonds would be a convenient system for a cyclic transition state in a sigmatropic rearrangement. A [1.5] oxygen shift from nitrogen to oxygen in the hydroxyl moiety in the C-3 position of the second ring can give a hydroperoxide. Elimination of oxygen from the orellanine molecule would then be the result of hydroperoxide decomposition, under the thermal conditions of rearrangement, instead of N-oxide decay. Both the sigmatropic rearrangement and the hydroperoxide decomposition should be relatively low-energy processes.

We decided to attempt to verify the possibility of such a reaction course by using a model compound, 2-(2'-hydroxyphenyl)pyridine-N-oxide (II), which contains all the necessary structural features for this process. Synthesis of the model compound was achieved as follows. The nucleophilic addition of 2-anisylmagnesium bromide to 2-nitropyridine-N-oxide, carried out in THF at -70°C, yielded 2-nitro-2-(2'-methoxyphenyl)-1,2-dihydropyridine -N-oxide III. Because of its tendency to decompose during chromatographic purification, the crude addition product III in the form of its magnesium bromide salt, was refluxed in toluene for 1 hr yielding, after an elimination of brown nitrogen oxides, a crude brown solid which contained up to 65% of 2-(2'-methoxyphenyl)pyridine-N-oxide IV. It was purified by short column chromatography on SiO_2, and crystallized from toluene yielding colorless crystals mp 169-171° for which ^{1}H-NMR, IR, MS spectra (M^+ 201.07699), as well as combustion analysis were fully consistent with the proposed structure IV.

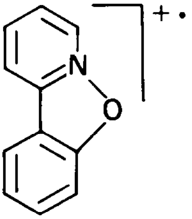


III IV VI

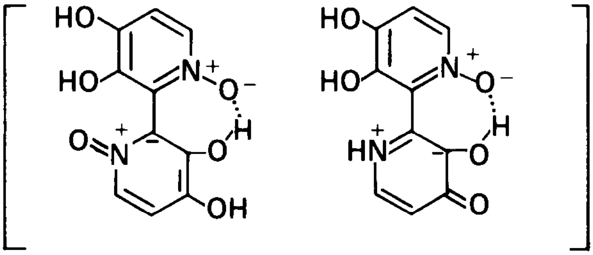
The methoxy group in IV was easily cleaved by BBr_3 in CH_2Cl_2 giving 2-(2'-hydroxyphenyl) pyridine-N-oxide II as colorless needles mp 124-126° (CCl_4), and its structure was proven by ^{1}H-NMR, IR and MS spectra (M^+ 187.06281), as well as by combustion analysis. The crystals thus obtained, when exposed to daylight, turned green-blue. The color disappeared, however, after the compound had been redissolved. The color change was probably due to the interconversion of tautomers IIa$\rightleftharpoons$IIb[4]. Mass fragmentation of II, as in the case of the parent methyl ether IV from which it was obtained, led mainly to an ion of m/e 170.06021, consistent with isoxazolinium cation structure V. Thus, the facile loss of the N-oxide oxygen can be observed in this system.[5]

Compound II, when heated above 220°, undergoes decomposition to form the free base of 2-(2'-hydroxyphenyl)pyridine VI. Because of the volatility of II above 200°, complete reaction was achieved (with 47% yield) when the substance was kept at 250° for 30 min in a sealed evacuated vial, or at 225° in diethylene glycol dibutyl ether solution, followed by purification of the product VI on a SiO$_2$ column). Its structure was confirmed by ^{1}H-NMR, IR and MS spectra (M$^+$ 171.06739), as well as by mp 179.0-179.5°C of its picrate salt (lit.[6] 176-178°C).

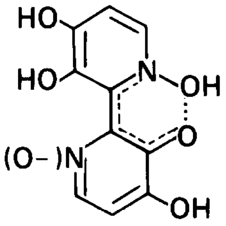
The demonstration of thermal decomposition of 2-(2'-hydroxyphenyl) pyridine-N-oxide II to the free base VI confirmed our supposition of [1.5] oxygen migration in such a system from N-oxide to hydroxyl function preceding oxygen elimination from the molecule. It allows us to presume that, due to its structural similarity, an analogous process can occur during thermal decomposition of orellanine to orelline. The observation, that orellanine (VII) undergoes deoxidation in temperature 50-70°C below the temperature observed for 2-(2'-hydroxyphenyl)-pyridine N-oxide (II) is not unreasonable considering the influence of additional substituentes present in a molecule of orellanine and in that of its monodeoxidized derivative VIII.



V



VII VIII



IX

It seems that reasonance structures VII and VIII have a significant contribution to the hybrid structures of these compounds, and can effectively increase electron density in the cyclic transition state IX, thus lowering the energetic barrier of sigmatropic rearrangement.[7]

ACKNOWLEDGEMENT

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