STERIC REQUIREMENTS AND HIGH PRESSURE INFLUENCE ON THE THERMAL DEOXYGENATION OF *N*-OXIDES OF ORELLANINE-LIKE STRUCTURE

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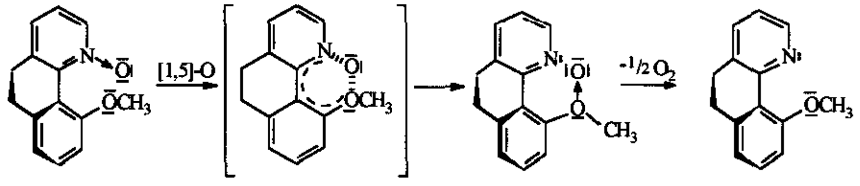
This paper is dedicated to Dr.Arnold Brossi on the occasion of his 70th birthday.

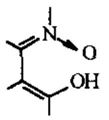
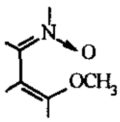
Abstract - 5-Hydroxy-9,10-dihydro-4-azaphenanthrene-*N*-oxide (**1**) and its methyl ether (**2**) were found to undergo the facile thermally induced *N*-oxide oxygen elimination characteristic for the orellanine-like structures. The relationship between the conformation of the *N*-oxides, the functional group being part of an oximinopropenoxy system, and the deoxygenation temperature requirements is discussed. The significant decrease of the deoxygenation temperature caused by the pressure of 12 kbar in the case of **2** is supposed to indicate the concerted character of the transformation.

Contrary to the generally observed stability of the *N*-oxide function of bipyridine derivatives[1] the mushroom alkaloid orellanine[2,3] was found to decompose easily to the corresponding *tert.* base orelline under the influence of an elevated temperature or uv light [4] Using a suitable model compound it was demonstrated[5] that the oximinopropenoxy system composing the bay-fragment of the orellanine molecule is responsible for the facile deoxygenation process. In agreement with these observations we have now found the 5-hydroxy-9,10-dihydro-4-azaphenanthrene-*N*-oxide (**1**)[6] to be similarly sensitive to an elevated temperature or uv irradiation. Moreover, it appeared that its methyl ether, 5-methoxy-9,10-dihydro-4-azaphenanthrene-*N*-oxide (**2**),[6] underwent the deoxygenation to the *tert.* base (accompanied by a small amount of the further demethylated product **1-a**) even at a lower temperature than the parent phenol (**1**) (see Table).

According to our previously suggested mechanism[5] the *N*-oxide oxygen elimination from molecules containing *the oximinopropenoxy system as the structure unit is supposed to proceed via a sigmatropic [1,5]-oxygen shift* from nitrogen to the phenolic (anisolic) oxygen with the formation of an unstable peroxide intermediate. Such an interpretation requires a coplanar cyclic transition state which would have to be reached by the molecules being in the ground state in different conformations with the aromatic rings twisted out of the mutual plane in the case of the investigated compounds (see Table) To reach the more crowded and, thus, unfavourable planar conformation in the transition state the molecules have to gain some energy, the quantity of which should be smaller (and, thus, the lower temperature required for deoxygenation) if the more planar is the conformation of the starting *N*-oxide.[7]



or/and products of the subsequent OCH_3 or solvent oxidation

Compound		Dihedral angle between the aromatic rings (crystalline state)	Deoxygenation temperature (under atmospheric pressure) neat sample
	**1**	27.0-29.9°[8]	180°C
	3	38.2°[9]	220°C
	5	-	277°C
	**2**	39.0-41.5°	105°C[10]
	4	67.0°	170°C
	6	74.7°	225°C

The dependence of the susceptibility to deoxygenation of the *N*-oxides upon their ground state conformations of different dihedral angles can be observed when we compare the temperature of the deoxygenation of **1** with that of the not annelated 2-(2-hydroxyphenyl)pyridine-1-oxide (**3**),[5] or its homologue 2-(2-hydroxyphenyl)-3-methylpyridine-*N*-oxide (**5**),[11] revealing an increased steric hindrance due to the presence of the methyl group in the "bay-region". A similar relationship could be found for the methyl ethers of **1**, **3** and **5** (**2**, **4**[5] and **6**,[11] respectively) not stabilized by hydrogen bonding in the ground state but still differentiated by the steric ability to reach the coplanar transition state. In spite of the larger values of the dihedral angle the methyl ethers decompose at a lower temperature than the corresponding phenolic analogues. In contrast to the methyl ethers the phenolic derivatives need energy to overcome not only the steric strain but also the additional tightness resulting from hydrogen bond annelation for reaching the planar transition state.

The *N*-oxides listed in the Table (additionally including orellanine and its tetramethyl ether) in CH_2Cl_2 solutions were subjected to the pressure of 12 kbar for 15 h.[12] At the temperature of 50°C all of the investigated methyl ethers were found to undergo decompositions but with a different amount of the consumed *N*-oxide in each case. The reaction of **2** was completed under these conditions but also when the solution was kept at room temperature (20°C, 12 kbar) for 8 days. A compound **2-a** crystallized from the resulting solution in about a 60% yield for which the combustion analysis and spectroscopic data[13] showed an *N*-protonated salt structure of hypochlorous acid and the base resulted from the deoxygenation of **2** (the free base could be liberated when the product was digested with 5% aqueous NaOH). The presence of the hypochlorite ion (or at least of an active oxygen) also followed from the positive iodide-starch test, however, evidently it was not stable enough to be observed in the negative ion ms and only Cl^- at m/z 35 (16%), accompanied by m/z 37 (5%), could be seen. In the crystal form the product (**2-a**)[14] was found to be stable when refrigerated for several months, however, it quickly decomposed on a silica gel column or under uv irradiation . The appearance of chlorine in the product (**2-a**) proved the solvent oxidation to occur under high pressure which was not observed when **2** in CH_2Cl_2 was kept in a sealed test-tube at 65°C for 15 h. Apart from the salt (**2-a**), **1** (less reactive towards deoxygenation than **2** under atmospheric pressure) was additionally found[15] in a fair yield of 40% in the high pressure post-reaction mixture . The demethylation of **2** was also observed as a by-process in the experiment carried out under atmospheric pressure without the use of CH_2Cl_2 as a solvent; however, in that case the demethylation was accompanied by deoxygenation to the hydroxy *tert.* amine (**1-a**). The ^{1}H-nmr absorption pattern of the crude solution obtained as a result of the reaction of **2** carried out in CD_2Cl_2 instead of CH_2Cl_2 (12 kbar, room temperature) appeared to be mainly a sum of the superimposed spectra of **2-a** and **1** (both revealing separate signals of the protons entrapped by strong intramolecular hydrogen bonds at 15.6 ppm and 12.2 ppm, respectively) and can be accompanied by a trace amount of the starting **2**, only.[16]

The lowering of the energetic requirements for deoxygenation of the investigated methyl ether *N*-oxides, which made possible the reaction to occur under high pressure at room temperature instead of about 100°C (for atmospheric pressure) in the particular case of **2**, indicates the negative volume of activation of this transformation. The observed effect of high pressure on the contraction of the transition state volume is in agreement with the concerted character[17] of the assumed sigmatropic [1,5]-O migration with the formation of an unstable peroxide intermediate, the final oxygen elimination being a separate process.

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7. This assumption seems to be supported by the stereopopulation control theory (S.Milstien and L.A.Cohen, *J. Am. Chem. Soc.*, 1972, **94**, 9158, K.L.Amsberry and R.T.Borchardt, *J. Org. Chem.*, 1990, **55**, 5867). In the case of the natural orellanine hydrate crystals the dihedral angle of 90° was found (M.Kubicki, T.Borowiak,and W.Z.Antkowiak, *J. Cryst. Spectr. Res*, 1991, **21**, 401). The toxic properties of this alkaloid could be the result of the oxygen eliminated (due to the well-known cytotoxic properties of the simple oxygen containing radicals, e.g.D.S.Davies, G.M.Hawksworth and P.N.Bennett, *Proc. Eur. Soc. Toxicol.*, 1977, **18**, 21) and the energy in this case would be supplied by the bonding of the alkaloid with an enzyme. On the other hand, the unsuccessful efforts made in the *N,N'*-dioxide preparation (e.g. ref.1) from 1,10-phenanthroline-*N*-oxide (the molecules of which already exist in the ground state in a planar conformation) could be the result of a immediate [1,5]-O migration to the oxygen of the second *N*-oxide group after it was formed. This assumption is in agreement with the observed degradation of MCPBA to MCBA when the former was kept in $CHCl_3$ solution in the presence of 1,10-phenanthroline-*N*-oxide at room temperature.
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9. M.Kubicki, T.Borowiak, R.Antkowiak,and W.Z.Antkowiak, *J. Cryst. Spectr. Res.*, 1990, **20**, 381.
10. The deoxygenation temperature was found to be lower by about 15°C when the crystals were dissolved in diethylene glycol di-*n*-butyl ether.
11. The synthesis of **5** and **6** was accomplished following the procedure described for **3** and **4**, respectively (ref. 5), using 3-methyl-2-nitropyridine-1-oxide (E.V.Brown, *J. Am. Chem. Soc.*, 1957, **79**, 3565) as the starting material. **5**, mp 215-217°C, ^{1}H-nmr (300 MHz, $CDCl_3$) δ: 2.36 (d, 3H, J=0.7, CH_3), 6.98

(ddd, 1H, J=7.9, 7.2, 1.2, H-8), 7.15 (dd, 1H, J=8.2, 1.2, H-6), 7.24 (dd, 1H, J=7.9, 1.7, H-9), 7.29 (dd, 1H, J=7.8, 6.4, H-3), 7.40 (ddq, 1H, J=7.8, 1.4, 0.7, H-2), 7.45 (ddd, 1H, J=8.2, 7.2, 1.7, H-7), 8.32 (dd, 1H, J=6.4, 1.4, H-4), 10.25 (s, 1H, OH); ^{13}C-nmr (75 MHz, $CDCl_3$) δ: 21.39 (q, CH_3), 119.23 (d, C-8), 119.64 (s), 120.39 (d, C-6), 123.35 (d, C-3), 131.42 (d, C-2), 131.56 (d, C-9), 131.59 (d, C-7), 137.31 (s), 137.42 (d, C-4), 150.26 (s), 158.55 (s). EIms, m/z: 201 (23%, M^+), 185 (17%, M-O), 184 (100%, M-OH), 169 (7%), 156 (9%), 154 (10%). HRms, found: m/z 201.07872, calcd for $C_{12}H_{11}NO_2$: 201.07898. **6**, mp 134-135°C, ^{1}H-nmr (300 MHz, $CDCl_3$) δ: 2.06 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 7.03 (d, 1H, J=8.3, H-6), 7.08 (dd, 1H, J=7.4, 7.2, H-8), 7.12-7.16 (m, 2H, AB of ABX, H-2, H-3), 7.20 (dd, 1H, J=7.4, 1.7, H-9), 7.44 (ddd, 1H, J=8.3, 7.2, 1.7, H-7), 8.22 (m, 1H, H-4); ^{13}C-nmr (75 MHz, $CDCl_3$) δ: 19.36 (q, CH_3), 55.70 (q, OCH_3), 111.30 (d, C-6), 120.91 (d, C-8), 121.27 (s), 123.60 (d, C-3), 126.65 (d, C-2), 130.05 (d, C-9), 130.49 (d, C-7), 136.58 (s), 137.34 (d, C-4), 147.45 (s), 156.60 (s). EIms, m/z: 215 (5%, M^+), 199 (3%, M-O), 198 (8%, M-OH), 184 (100%, M-OCH_3), 183 (7%), 168 (5%), 156(5%). HRms, found: m/z 215.09467, calcd for $C_{13}H_{13}NO_2$: 215.09463.

12 For the high-pressure experiments we used the piston-cylinder type apparatus described earlier by J. Jurczak, M. Chmielewski, and S. Filipek, *Synthesis*, 1979, 41.

13. Mp 202°C. The nmr signal assignments were based on the ^{1}H-^{1}H COSY, ^{1}H-^{13}C 2D-HETCOR and DEPT experiments. ^{1}H-Nmr (300 MHz, CD_2Cl_2) δ: 2.9-3.1 (m, 4H, H-9, H-10), 4.23 (s, 3H, OCH_3), 6.98 (d, 1H, J=7.5, H-8), 7.06 (d, 1H, J=8.4, H-6), 7.50 (dd, 1H, J=8.4, 7.5, H-7), 7.61 (dd, 1H, J=7.6, 5.9, H-2), 8.13 (dd, 1H, J=7.6, 1.2, H-1), 9.36 (dd, 1H, J=5.9, 1.2, H-3), 15.6 (s, 1H, $^+$N-H); ^{13}C-nmr (125 MHz, $CDCl_3$, ^{1}J shown only) δ: 27.73 (t, J=131.0, C-10), 27.79 (t, J=132.0, C-9), 57.00 (q, J=146.5, CH_3), 110.63 (d, J=161.5, C-6), 113.74 (s, C-4b), 120.96(d, J=162.6, C-8), 122.98 (d, J=172.8, C-2), 134.74 (d, J=161.0, C-7), 136.52 (s, C-8a), 141.10 (d, J=191.9, C-3), 141.72 (s, C-4a), 143.27 (d, J=165.2, C-1), 145.92 (s, C-10a), 158.64 (s, C-5); ^{14}N-nmr (36 MHz, $CDCl_3$) δ: -183.646 ppm ($^+$N-H).
EIms m/z: 212 (17%), 211 (100%, $C_{14}H_{13}NO$ by HRms), 210 (90%, $C_{14}H_{12}NO$ by HRms), 183 (12%), 182 (75%), 181 (37%), 180 (92%), 167 (14%), 152 (10%), 90 (14%); the additional peak at m/z 227 ($C_{14}H_{13}NO_2$ by HRms) of r.i. 0.3% (as well as that at 245 of similar r.i.) probably appeared as the result of a preliminary reoxidation of the cationic fragment by the hypochlorite ion.
*Anal.*Calcd for $C_{14}H_{14}NO_2Cl\cdot 1/2\ H_20$: C, 61.64; H, 5.54, N, 5.14; Cl, 13.01. Found: C, 61.65; H, 5.39, N, 4.90; Cl, 13.38.

14 The X-ray diffraction of **2-a** is currently investigated by M. Kubicki and T. Borowiak and the results will be

published separately as they are completed.

15. **1** can be best isolated and purified without any observable decomposition by column chromatography when eluted by CH_2Cl_2 from a starch-SiO_2 (6:1) packing used in 70-fold excess. The crystals of **1** obtained from a pale-straw coloured C_6H_6-CH_2Cl_2 solution quickly changed into deep-green characteristic for such a hydroxy-*N*-oxide system (ref. 3).
16. The reaction mixture composition could suggest the demethylation to proceed by a mechanism of a chain reaction initiated by the liberated oxygen.
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