Tetrahedron Vol. 46, No. 8, pp. 2891-2902, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

IN-SITU RADIOLYSIS ESR STUDIES OF HYDROXYPYRIDONES

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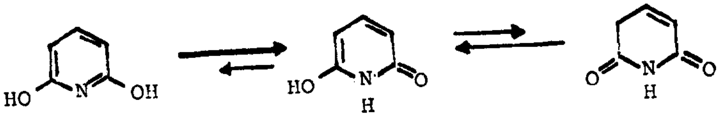
(*Received in UK* 15 *February* 1990)

In situ radiolysis of hydroxypyridones in aqueous solution produces several radicals detected by ESR. These are produced by primary and secondary reactions of hydroxyl radicals. Azaquinoidal structures were detected from 3- and 5-hydroxypyridones.

INTRODUCTION

Dihydroxypyridines would be expected to be different in reactivity towards hydroxyl radical produced by the radiolysis of water (1). Dihydroxypyridones are known to be in hydroxypyridone structures in aqueous solution (2-4,6-12). One may expect also selectivity in the addition reaction of electrophilic OH radical to the ring. Hydroxypyridones appear to be closer models to biologically related compounds like, for example, uracil than are the pyridines and pyridones. It has been suggested that azaquinoid structures, found in bacterial pigments, are formed by the oxidation of hydroxypyridones in nature (3-a,b). Electrophilic reagents are known to attack at the 3-(5-) positions of pyridones. In agreement with this characteristic property 6-hydroxy-2-pyridone undergoes substitution at the 3-(5-) positions and 4-hydroxy-2-pyridone only at the 3-position (4,5). The pattern of electrophilic substitution in 3- or 5-hydroxy 2-pyridones, which exist in different tautomeric forms from 2,4- and 2,6-derivatives, is probably due to the ease of oxidation to azaquinone structures under the reaction conditions (3).

Hydroxypyridones may exist in aqueous solution in diol and/or dione form.



IV - A   IV   IV-B

Studies of the tautomeric structures of the various isomers of hydroxypyridones report the pyridone structure as being dominant (4-10).

Katritzky (11) reported a ratio of 25:60:15, IV-A, IV , IV-B respectively for the tautomers of 6-hydroxypyridone, IV. Spinner (12) found no evidence of the diol form and subsequently reported a 20:80:0 ratio to IV-A, IV, IV-B, respectively.

Analogous to the reactions of phenols (13) and pyridones (2) OH adducts of hydroxypyridones can possibly undergo elimination of water to yield pyridinoxyl radicals in primary processes. However, the high reactivity towards OH radical, which increases in the order of pyridine-pyridone-hydroxypyridone, may lead to the occurence of secondary processes, especially oxidation. This conjecture is supported by the evidence summarised in table 1, i.e., a listing of the hydroxy pyridones studied and an analysis of the structures of identified radicals.

EXPERIMENTAL

The in-situ radiolysis ESR experiments were carried out by the method described by Eiben and Fessenden (14). Analysed solutions contained 2 mM concentrations of substrate saturated with N_2O. Potassium bromide was added at 20 mM concentrations when required.

The flow system photolysis ESR experiments were done in Ar-saturated 1 mM solutions of the substrate with or without 1 % acetone and 1 mM potassiumpersulphate. A Philips Sp 1000 superhigh-pressure mercury lamp and quartz optics for foccusing the light into the ESR cell were used as described(2). The g-factors and the coupling constants of the radicals (accurate to $5x10^{-5}$ and 30 mG, respectively) were determined from simultaneous measurements of field and microwave frequencies, taking into account of the difference in magnetic field between the ESR cell and the NMR probe positions.

For product analysis, 2 mM solutions of methoxypyridine derivatives in triplely distilled water were saturated with N_2O and $^{60}Co_\gamma$ irradiated with dose rates of 6 krd/min as determined by Fricke dosimetry. Samples of irradiated solutions were analysed for only methanol formation with high pressure liquid chromatography, the pH of the solutions was 6.

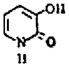
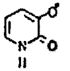
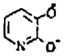
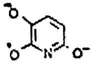
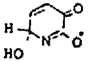
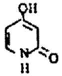
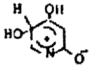
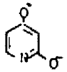
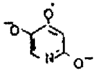
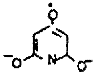
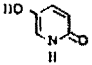
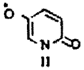
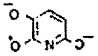
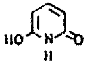
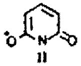
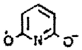
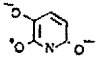
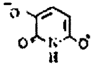
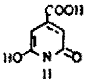
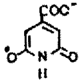
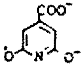
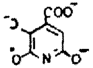
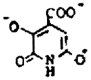
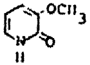
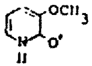
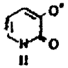
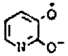
The substrates (excluding III), were obtained from Fluka and EGA and were used as received. The 2,5-dihydroxypyridine, III, was synthesized by hydroxylation of 2-pyridone with potassiumpersulphate in alkaline solution, according to the method of Behrman and Pitt (17).

RESULTS AND DISCUSSIONS

Radicals of Primary Processes

Radicals derived from primary processes were detected by flow rate experiments in-situ radiolysis ESR studies and gave intense signals in comparison with signals from other radicals. At higher flow rates

Table 1 : Hydroxypridones studied by in-situ radiolysis ESR and the structures of identified radicals

		IDENTIFIED RADICALS								
PYRIDONES		**Primary**					**Secondary**			
I		$\mathrm{I_a}$			$\mathrm{I_b}$		$\mathrm{I_{bb}}$		$\mathrm{I_{ba}}$	
II				 $\mathrm{II_{adduct}}$	$\mathrm{II_b}$		$\mathrm{II_{bb}}$		$\mathrm{II'_{bb}}$	
III		$\mathrm{III_a}$			$\mathrm{III_b}$		$\mathrm{III_{bb}}$		$\mathrm{III_{ba}}$	
IV		$\mathrm{IV_a}$			$\mathrm{IV_b}$		$\mathrm{IV_{bb}}$		$\mathrm{IV'_{bb}}$	
V		$\mathrm{V_a}$			$\mathrm{V_b}$		$\mathrm{V_{bb}}$:		$\mathrm{V'_{bb}}$	
VI		$\mathrm{VI_a}$		 $\mathrm{VI'_a}$  $\mathrm{VI_{adduct}}$	$\mathrm{VI_b}$					

a : in acidic medium, · b : in basic medium.

Table 2: The ESR parameters of identified radicals attributed to primary processes in aqueous media (*)

PYR	RAD.	pH-RANGE	g-VALUE	a_N	a_{NH}	a_{3H}	a_{4H}	a_{5H}	a_{6H}	a_{2OH}	a_{6OH}
I	I_a	3.5-8.0	2.00438	1.52	--	--	5.91	0.35	9.14		
	I_b	8.0-13.5	2.00453	0.96	--	--	2.63	2.47	6.31		
II	II_a	NOT	OBSERVED								
	II_b	6.0-10.2	2.00497	1.70	--	0.91	--	4.20	0.45		
	$II_{add.}$	3.0-7.0	2.00318	2.39	--	19.5	--	2.84	13.4	0.25	0.73
III	III_a	3.0-5.0	2.00484	0.20	0.10	1.45	2.00	--	9.85		
	III_b	7.0-13.5	2.00461	0.16	--	0.78	2.63	--	5.90		
IV	IV_a	3.5- 5.0	2.00379	0.99	0.20	12.52	2.91	12.52	--		
	IV_a	7.0-13.5	2.00461	0.63	–	12.24	2.75	12.24	--		
V	V_a	2.5-10.0	2.00381	0.96	3.24	12.27	--	12.27	--		
	V_b	5.5-13.5	2.00372	0.61	--	12.04		12.04	--		

PYR.	RAD.	pH-RANGE	g-VALUE	a_N	a_{NH}	a_{2H}	a_{3H}	a_{4H}	a_{5H}	a_{6H}	a_{OCH_3}
VI	VI_a	3.5-10.0	2.00422	0.56	--	--	--	1.07	7.78	2.96	2.22
	VI'_a	2.5- 3.5	2.00438	1.52	--	--	--	5.91	0.35	9.14	
	VI'_b	8.5-14.0	2.00452	0.96	--	--	--	2.63	2.47	6.31	
	$VI_{add.}$	2.5- 8.0	2.00288	1.72	--	--	--	2.58	11.38	13.96	0.35(**)

a : acidic media, b : basic media, (**) : a_{6OH}

(*) Coupling constants are in Gauss.

these signal intensities remained unchanged or increased. The process for the generation of these radicals is attributed to hydroxyl adduct radical formation on the aromatic ring followed by dehydration leading to the formation of the azasemiquinone radical. The same radicals were observed in photolysis/oxidation scheme.

The radicals assigned to these processes are shown in table 2. Two radicals observed in acidic, (a) and in basic, (b), assigned to pyridones (azasemiquinone) and deprotonated pyridines, respectively. Only in the case of acidic 4-hydroxy-2-pyridone, II, solution was the azasemiquinone type radical not detected, but the intermediate OH-adduct radical was observed. In contrast to the results from pyridone derivatives. The observation of the radicals in acidic and basic media were in general consistent with the p^Ka values of first deprotonation of the parent compound (Table 3). All the radicals included in table 2 -excluding the OH adducts -were also detected in the oxidative phase of N_2O saturated potassium bromide solutions. In some cases oxidations were accomplished by the photolysis of acetone/potassiumpersulphate solutions. The coupling constants and the g-factors of the radicals of table 2 were found to be independent of the source of generation. Signal to noise raios were usually better in the oxidation experiments.

Table 3 : p^Ka values of hydroxypyridones for proton loss .

PYRIDONE	p^Ka	Ref.
2-Pyridone	11.46	(13)
3-Hydroxy(I)	9.0	(15)
4-Hydroxy-2-pyridone (II)	6.50 13	(13)
5-Hydroxy-2-pyridone (III)	8.51	(13)
6-Hydroxy-2-pyridone (IV)	4.5 15	(12,15)
Citrazinic acid (V)	3.00 4.76	(9)

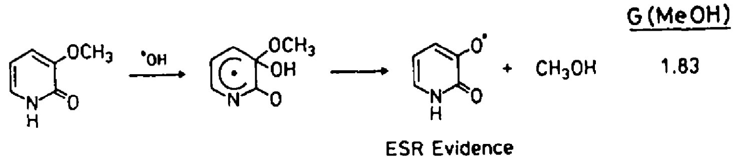
The unpaired electron spin density is considered to be centered on the non-ortho substituted oxygen atom. This assumption is based on the observation that the hydroxyl radical attacks the ortho carbon to give a product which rapidly equilibriates to the keto form and is in agreement with the preference of pyridone structures in aqueous solution. The results were confirmed by comparison analysis of the g-factors and and the coupling constants of radicals generated from 3-(I), 4-(II) and 5-hydroxy-2-pyridone (III) with 6-hydroxy-2-pyridone (IV) and with citrazinic acid (V). The lower g-alues and higher coupling constants of 3- and 5 -aromatic hydrogens of the radicals from IV and V provide evidence that the unpaired electron is localised on the ortho oxygen.

The adduct radical resulting from dehydration was only observed with 4- hydroxy-2-pyridone (II-adduct). The structure of the adduct radical was based on the ESR parameters and the literature evidence of specific electrophilic substitution at 3- position (4,5).

ESR experiments with 3-methoxy-2-pyridone, VI, gave different results. The radicals produced are the same as those from 3-hydroxy-2-pyridone, I, resulting from dehydration. They are observed in both acidic and basic media (I_a and I_b). By comparison to I_a to VI'_a and I_b to VI'_b, the signal intensities were lower and the pH range of observation was narrower in acidic medium, 2.5-3.5 (Table 2). It is theorised that the dominant primary process involves the methanol elimination from the hydroxyl adduct radical.

The product analysis after irradiation indicated the consistent formation of methanol (G-1.83). Similar experiments with the 2,6-dimethoxypyridine is reported to have shown negligible amount of methanol formation (1). The dominant methanol elimination process is in agreement with previous ESR results, i.e., the hydroxyl attack at carbon-3 of compound VI (Table 2).

Reaction of Hydroxyl Radical with Pyridinyl-Methyl Radicals



VI

VI_a

An adduct radical (VI-adduct) was detected in acidic to moderately basic pH ranges, 2.5-8.0, and in a similar range, 3.5-10.0, the radical of the parent compound VI was observed (Table 2).

Radicals of Secondary Processes:

The radicals considered to be generated by secondary processes were identified by the decrease of signal intensities or the complete loss of signals at higher flow rates. In general the signal intensities of these radicals were weak in comparison to the signal intensities from the radicals of primary processes and in some cases g-values were found to be pH dependent. The pH ranges of observations were from neutral to strongly basic solutions (Table 4).

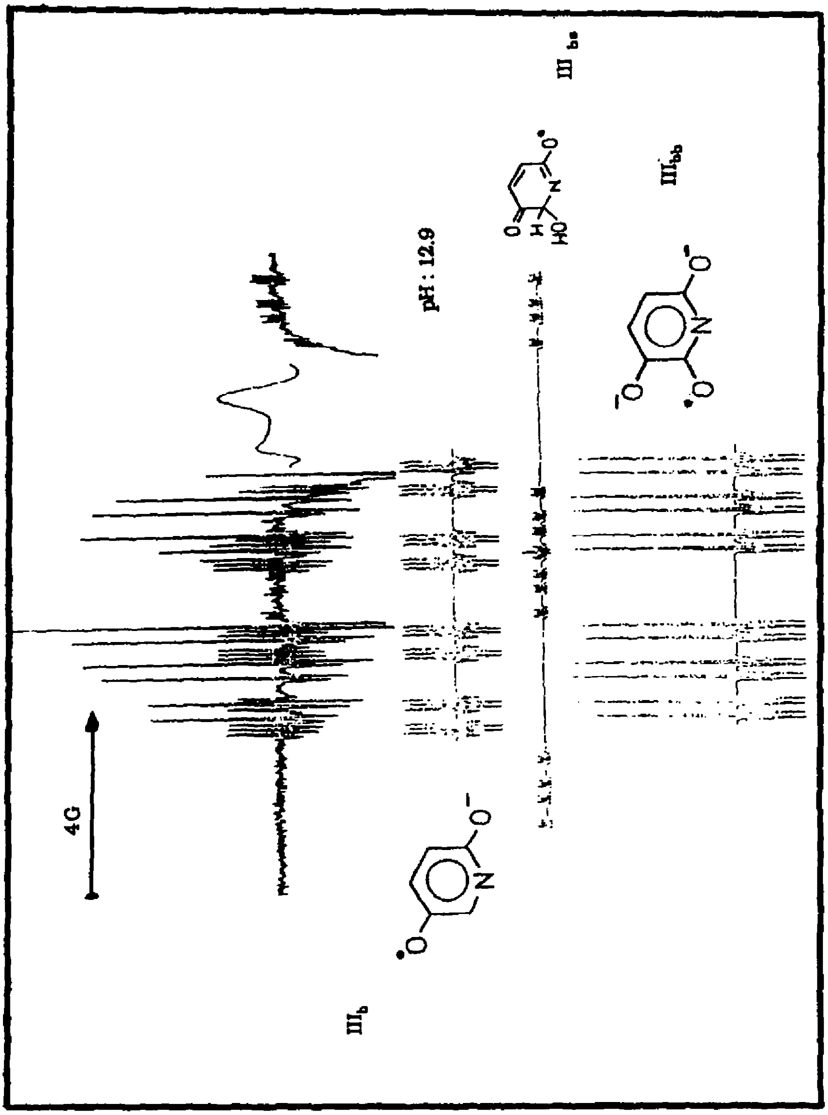
In strongly basic solutions a predominant radical type with a high signal intensity was detected from I,II,III, IV and V compounds (Figure 1).

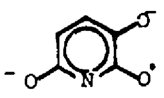
Table 4 : The ESR parameters of identified radicals attributed to secondary processes in aqueous media (*).

PYR	RAD.	pH-RANGE	g-VALUE	a_N	a_{NH}	a_{2H}	a_{3H}	a_{4H}	a_{5H}	a_{6H}	a_{2OH}	a_{6OH}
I	I_{bb}	12.0	2.00443	1.47	--	--	--	0.51	5.95	--		
		13.5	2.00439	1.25	--	--	--	0.51	6.00	--		
	I_{bs}	7.0=9.0	2.00387	0.67	--	--	--	1.95	9.55	9.75	--	0.70
II	II_{bb}	9.5-13.0	2.00460	1.32	--	--	5.91	--	0.28			
	II'_{bb}	12.5-13.5	2.00365	0.67	--	--	11.25	--	11.25	--		
III	III_{bb}	12.9	2.00442	1.35	--	--	6.00	0.51	--	--		
		13.5	2.00439	1.27	--	--	6.00	0.51	--	--		
	III_{bs}	7.0-13.0	2.00373	0.14	--	7.65	1.39	--	9.58	--	--	0.85
IV	$IV_{bb}(I_{bb})$	12.8	2.00042	1.37	--	--	--	0.51	6.00	--	--	
		13.1	2.00439	1.33	--	--	--	0.51	6.00			
	IV'_{bb}	6.0-10.5	2.00456	1.60	0.25	--	--	0.50	5.85			
V	V_{bb}	12.0	2.00442	1.55	--	--	--	--	5.68	--		
		13.0	2.00453	1.28	--	--	--	--	5.83			
	V'_{bb}	4.5-9.0	2.00455	1.60	0.28	--	--	--	5.64			

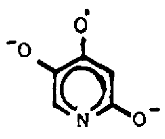
a : acidic media, b : basic media.
(*) Coupling constants are in Gauss.

Figure 1 : **Experimental in-situ radiolysis ESR spectrum of 3-Hydroxy-2-pyridone, III, and the structures of identified radicals ith simulated spectra.**

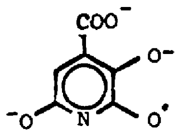




I_{bb}
(III_{bb} and IV_{bb})



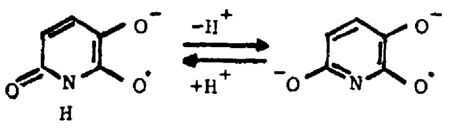
II_{bb}



V_{bb}

The g-value and the nitrogen coupling constant of radical I; which was generated from compounds from I,III, and IV; were found to vary within the pH range of detection (12-13.5). A similar result was seen for the radical V (Table 4). The variation of ESR parameters was seen largely on g-values and nitrogen coupling constants and to a lesser extent on aromatic hydrogens. At moderate pH ranges (5-10) IV and V gave the azasemiquinone tautomer of these secondary radicals.

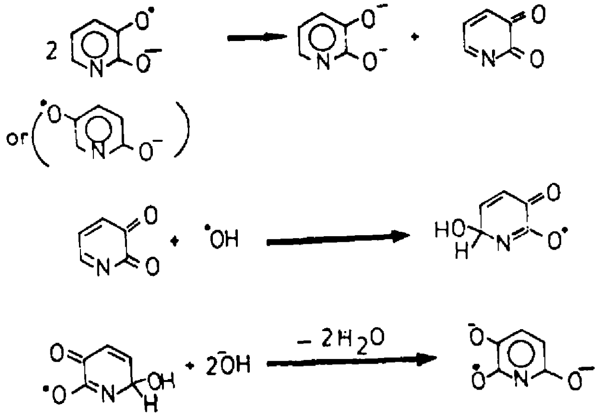
The ESR parameters of azasemiquinone radicals IV, and V, did not vary in the pH ranges of detection. The variation of ESR parameters in strongly alkaline solutions is thought to be due to the rapid deprotonation equilibra, which shifts toward the right at higher pH values.



IV'_{bb} IV_{bb}

..The oxidation of 3- and 5-hydroxy-2-pyridones to azaquinones is suggested in the literature (3-a,b); thus the radical formed on the primary process is assumed to undergo to an auto oxidation-reduction in strongly alkaline solutions forming azaquinone and dioxypyridine. Colour formation was detected in strongly basic solutions of hydroxypyridones after irradiation which may be taken as evidence of the photolytic formation process of some natural pigments. The azaquinone then would react with the hydroxyl radical to form an intermediate azasemiquinone type radical. Deprotonation (12) of this intermediate would lead to the observed secondary radicals.

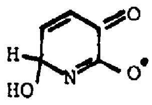
I_b



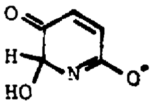
I_{ba}

I_{bb}

The intermediate secondary radicals were assigned speculated to be I and III in moderate pH ranges (Figure 1 and Table 4).

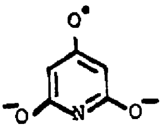


I_{ba}



III_{ba}

An additional radical formed by secondary processes was found in ESR experiments with 4-hydroxy-2-pyridone, II, in strongly basic solutions (Table 4).



II'_{bb}

Few other radical signals were detected in strongly basic solutions .The secondary processes which lead to the formation of these new radicals remain unclear. These ESR parameters were analysed and did not fit any of the radical structures discussed above. It is proposed in the literature that the dihydroxypyridines may form some dimer radicals of bipyridinyl type. The possible structural forms of such dimers are uncertain.

In summary, hydroxypyridones are found to form radicals through azaquinone structures, which may be taken as evidence of formation of some pigments in nature by photolysis.

ACKNOWLEDGEMENTS

The author is indepted to and wishes to thank the Max Planck Institute of Radiation Chemistry at Mülheim-Ruhr for providing the research facilities for this investigation.

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