Photo-oxidation of 4-Hydroxy-3,5-di-iodophenylpyruvic Acid: a New Synthetic Route to Thyroxine[1]

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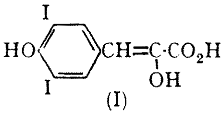
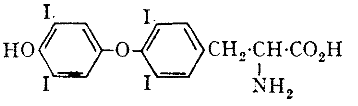
A NONENZYMATIC model reaction for the biosynthesis of thyroxine was reported by Meltzer and Stanaback,[2] who demonstrated that autoxidation of 4-hydroxy-3,5-di-iodophenylpyruvic acid (I) at pH 7·5 in the presence of 3,5-di-iodotyrosine (II) gives thyroxine (III) in moderate yield. Nishinaga and his co-workers[3] found that the reaction takes place in two distinct steps: the enolic form of (I) is autoxidised to a hydroperoxide (IV), which then reacts anaerobically with (II) to form (III) ($\leqslant 40\%$). We now report that the hydroperoxide (IV) can be obtained by photo-oxidation of (I) in organic solvents in which (I) exists in its enolic form. This provides a new synthetic route to thyroxine (III) and a further example of resemblance between biological and photochemical oxidations.[1,4]

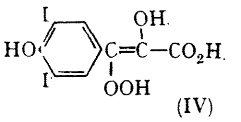
A solution of (I) in methanol was irradiated while oxygen was bubbled through with a high-pressure mercury arc lamp through a Pyrex filter at *ca.* 5°. After the absorption of oxygen ceased, the mixture was treated with (II) in borate buffer (pH 7·8) under nitrogen to yield thyroxine (III) (18·6%). Sodium borohydride reduction of the photo-oxidation mixture, which contained the hydroperoxide (IV), gave a diol-acid (V) (57%).[3] Similar photo-oxidations were carried out in several organic solvents. The results are shown in the Table.

The mechanisms for the photo-oxidation and the coupling reaction between (IV) and (II) to yield (III) have not yet been elucidated. Acetone may act as sensitizer, since the reaction rate was higher than in the case of direct irradiation in methanol. Induced oxidation of tetrahydrofuran might occur, since an excess of oxygen was absorbed in the solvent. Photo-induced chain autoxidation is less probable, since no oxygen absorption was observed when the irradiation was interrupted during photo-oxidation. Dissociation of the phenolic and carboxylic protons of (I) is required for the autoxidation in aqueous media (pH 7·5)[3] but not for the photo-oxidation in organic solvents.


(I)


(II)


(III)


(IV)

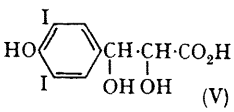

(V)

Photo-oxidation of (I) *and formation of thyroxine* (III)

Solvent	Irrad. time (min.)	O_2 absorbed (%)	Yield of (III) (%)
MeOH	40	90	18·6
MeCN–MeOH(8 : 1)..	47	57	10·8
Acetone	25	81	11·0
Tetrahydrofuran ..	40	152	2·8
Pyridine	153	95	None

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[1] Part of the series, "Photo-induced Reactions"; for Part XXXI, see T. Matsuura, A. Nishinaga, N. Yoshimura, T. Arai, K. Omura, H. Matsushima, S. Kato, and I. Saito, *Tetrahedron Letters*, 1969, in the press.

[2] R. I. Meltzer and R. J. Stanaback, *J. Org. Chem.*, 1961, **26**, 1977.

[3] A. Nishinaga, H. J. Cahnmann, H. Kon, and T. Matsuura, *Biochemistry*, 1968, **7**, 388.

[4] T. Matsuura, H. Matsushima, and H. Sakamoto, *J. Amer. Chem. Soc.*, 1967, **89**, 6370; T. Matsuura and H. Matsushima, *Tetrahedron*, 1968, **24**, 6615; A. C. Waiss, jun., R. E. Lundin, A. Lee, and J. Corse, *J. Amer. Chem. Soc.*, 1967, **89**, 6213; J. E. Baldwin, H. H. Basson and H. Krauss, jun., *Chem. Comm.*, 1968, 984 and references cited therein.