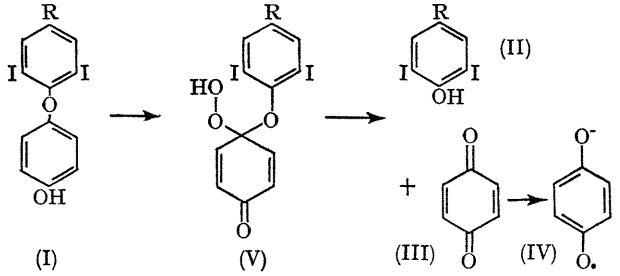
Autoxidation of *p*-Hydroxyphenyl Phenyl Ethers in Dimethyl Sulphoxide: a Model Reaction for the Metabolism of Thyroxine

By AKIRA NISHINAGA, TOMOAKI NAGAMACHI, and TERUO MATSUURA*
(*Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto, Japan*)

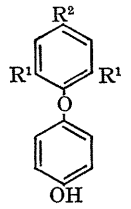
Summary Autoxidation of 3,5-di-iodothyronine and analogous *p*-hydroxyphenyl phenyl ethers in dimethyl sulphoxide containing t-butoxide ion results in rupture of the diphenyl ether linkage.

IT has been considered that rupture of the diphenyl ether linkage of thyroxine is one of the pathways in the metabolism of thyroxine. The first step would be an oxidative deiodination at the 3′-position to form 3′-hydroxy-3,5,5′-tri-iodothyronine which in turn cleaves at the diphenyl ether bridge to form 3,5-di-iodotyrosine.[1–4] We have now found that 3,5-di-iodothyronine (I) is not susceptible to autoxidation in aqueous alkaline solutions but is easily autoxidized in Me_2SO in the presence of Bu^tOK to give 3,5-di-iodotyrosine (II) and the *p*-benzosemiquinone anion radical (IV).

When (I) was dissolved in Me_2SO containing Bu^tOK under air, a yellow solution was obtained. The solution, after replacing air with nitrogen, gave an e.s.r. spectrum (quintet, 4H, a_H 2·34 Oe.) which was not observed when either oxygen or (I) was absent. A solution of (I) in Me_2SO containing Bu^tOK under completely degassed conditions did not give an e.s.r. spectrum, but gave the same quintet when the solution was exposed to air. The spectrum was identical with that of (IV) generated from hydroquinone and *p*-benzoquinone in Me_2SO containing Bu^tOK.



R=$CH_2{\cdot}CH(NH_2)CO_2H$



(VI) R^1 R^2

a; H $CH_2{\cdot}CH_2{\cdot}CO_2H$
b; H H
c; H Me
d; Pr^i $CH_2{\cdot}CH(NH_2)CO_2H$
e; Br $CH_2{\cdot}CH_2{\cdot}CO_2H$
f; Cl $CH_2{\cdot}CH_2{\cdot}CO_2H$

Autoxidation of (I) for 27 hr. on a preparative scale gave (II) in 14% yield with recovered (I) (30%). The results suggest that (I) is split at the diphenyl ether bridge during

the autoxidation to give (II) and *p*-benzoquinone (III) which could give (IV). In fact, (III) in Me_2SO containing Bu^tOK under nitrogen gave the e.s.r. spectrum of (IV). The splitting reaction of (I) is rationalized by assuming a quinol ether intermediate (V). The autoxidation of (I) in the presence of Bu^tOK also takes place in dimethylformamide but not easily in MeOH, EtOH, Bu^tOH, or aqueous Me_2SO.

Analogous *p*-hydroxyphenyl phenyl ethers (VIa–d) also gave the e.s.r. spectrum of (IV) under the same conditions indicating that they are also split at the diphenyl ether linkage. For (VIe) or (VIf), only a weak signal was observed. Among (I) and its analogues, (VId) gave the highest concentration of (IV). Thyroxine and 3,5,3′,5′-tetrahalogenothyropropionic acids were not susceptible to autoxidation under the same conditions. It seems that the autoxidation is influenced by substituents.

The present results suggest that there may be an alternative pathway for cleavage of the diphenyl ether linkage in the metabolism of thyroxine. That is, the first step would be simple deiodination to form (I)[2] which in turn cleaves directly at the diphenyl ether linkage to form (II) without hydroxylation at the 3′-position.

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[1] T. Matsuura, T. Nagamachi, A. Nishinaga, H. Kon, and H. J. Cahnmann, *J. Org. Chem.*, 1969, **34**, in the press.
[2] J. E. Rall, J. Robins, and C. G. Lewallen, in "The Hormones," eds. G. Pincus, K. V. Thimann, and E. B. Astwood, Vol. V, Academic Press, New York, 1964, p. 249.
[3] S. Lissitzky and S. Bouchilloux, *Bull. Soc. Chim. biol.*, 1957, **39**, 133, 1215.
[4] S. Lissitzky, M. T. Bénévent, J. Nunez, C. Jacquemin, and J. Roche, *Compt. rend Soc. Biol.*, 1960, **154**, 267.