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AUTOXIDATION OF HALOGENATED METHYL THYROPROPIONATES CATALYZED BY BIS(3-SALICYLIDENEAMINOPROPYL)AMINECOBALT(II). A MODEL REACTION FOR THE METABOLISM OF THYROXINE

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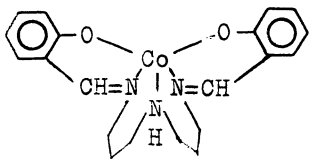
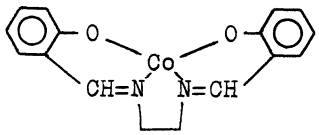
Autoxidation of halogenated methyl thyropropionates catalyzed by bis(3-salicylideneaminopropyl)aminecobalt(II) gave rise to direct cleavage of their diphenyl ether linkage. The reaction provides a model for the enzymic degradation of thyroxine to form diiodotyrosine.

In a previous paper[1] we reported that bis(3-salicylideneaminopropyl)aminecobalt (II) (Co^{II}salpr) (1) as well as salcomine (Co^{II}salen) (2) catalyzed the autoxidation of hindered phenols in organic media.

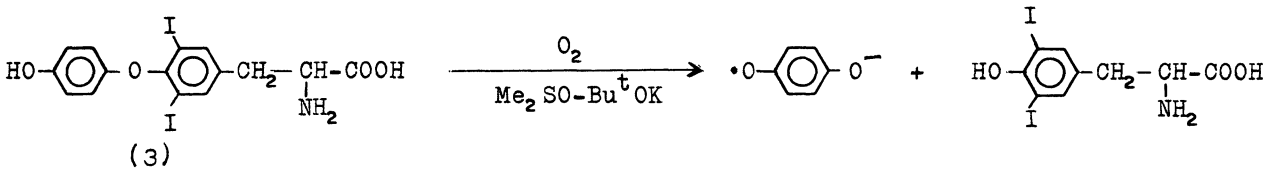


(1)



(2)

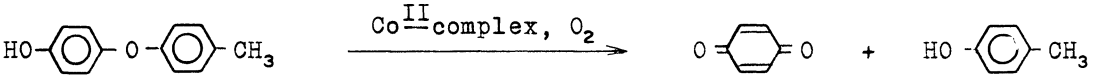
As a part of studies on the model reactions for the metabolism of thyroxine involving cleavage of its diphenyl ether linkage, we investigated the autoxidation of halogenated thyropropionic acid derivatives catalyzed by Co^{II}salpr (1) or Co^{II}salen (2). Although it has been considered that enzymic degradation of thyroxine to form diiodotyrosine would involve hydroxylation at 3'-position followed by autoxidative cleavage of the diphenyl ether linkage of thyroxine[2)-5)], we showed taht 3,5-diiodothyronine (3), when it is dissociated into its phenolate in an aprotic polar solvent such as dimethyl sulfoxide or N,N-dimethylformamide, undergoes autoxidation to give p-benzosemiquinone and 3,5-diiodotyrosine without hydroxylation at 3'-position of (3)[6]. This would provide a model for the enzymic degradation of thyroxine in which direct cleavage of the diphenyl ether linkage of thyroxine could be involved. The present paper reports that autoxidation catalyzed by Co^{II}salpr (1) leads to cleavage of the diphenyl ether bond of tetra-halogenated thyropropionic acid derivatives which are



(3)

unsusceptible to autoxidation in dimethyl sulfoxide/t-BuOK system.

In order to find out suitable conditions for the catalytic autoxidation of desired compounds, autoxidation of p-toluoxyphenol (4) catalyzed by the Co^{II}complexes in methanol or chloroform was investigated. The autoxidation gave rise to splitting of the diphenyl ether linkage of (4) to yield p-benzoquinone (5) and cresol (6). The results are summarized in Table I.



(4) (5) (6)

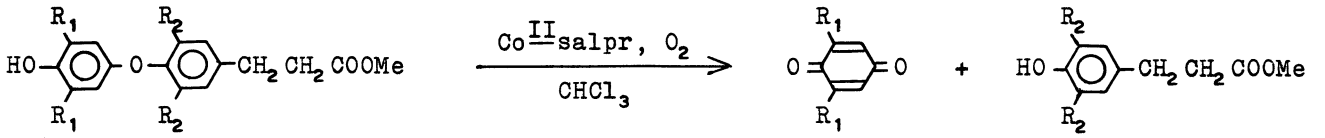
Table I. Autoxidation of (4) catalyzed by Co^{II}complex at 20°

Co^{II}complex	(4)/Co^{II} (mole/mole)	solvent	reaction period(hr)	product[a] (%) recoverd(4)	(5)	(6)
Co^{II}salen	1/1	$CHCl_3$	24	2	32	16
Co^{II}salpr	1/1	$CHCl_3$	24	7	39	41
Co^{II}salpr	1/1	MeOH	24	23	0	30

(a) Products were analyzed by v.p.c. (b) After being reduced to hydroquinone.

As seen in Table I, Co^{II}salen (2) causes lowering the yield of (6), although Co^{II}salpr (1) yields nearly equivalent amounts of (5) and (6). This is attributed to the difference between Co^{II}salen (2) and Co^{II}salpr (1) in their reactivities upon (6) under the conditions. In fact, (6) was quite stable under the conditions of autoxidation using Co^{II}salpr (1) but was subject to intricate oxidative degradation under those using Co^{II}salen (2). In an experiment in methanol no p-benzoquinone was detected probably due to lability of the quinone to the solvent.

In view of the results in the catalytic autoxidation of (4), Co^{II}salpr (1) and chloroform were employed as catalyst and solvent, respectively, for the autoxidation of halogenated derivatives of thyropropionic acid, whose esters (7) were used as substrates because of solubilities in chloroform. Corresponding p-benzoquinones (8) and methyl phloretates (9) were obtained. The results are summarized in Table II.



(7) a; $R_1=R_2=H$ d; $R_1=I$, $R_2=Br$
b; $R_1=H$, $R_2=I$ e; $R_1=I$, $R_2=Cl$
c; $R_1=R_2=I$

(8) a; $R_1=H$
b; $R_1=I$

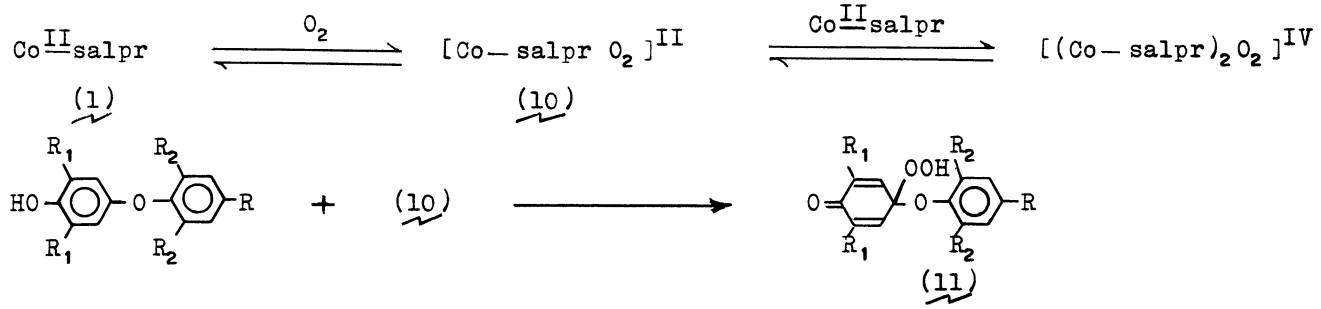
(9) a; $R_2=H$ d; $R_2=Cl$
b; $R_2=I$
c; $R_2=Br$

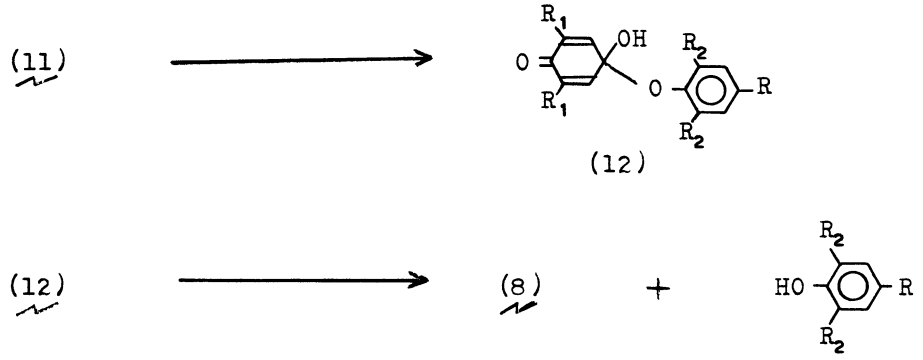
Table II. Autoxidation of (7) catlyzed by Co^{II}salpr (1) in $CHCl_3$

compound	reaction period(hr)	product (%) recovered(7)	(8)	(9)
7a	24	20	9.5(8a)	10(9a)
7b	45	30	8.5(8b)	11(9b)
7c	45	30	1.0(8b)	11(9b)
7d	45	30	1.0(8b)	34(9c)
7e	45	30	1.0(8b)	19(9d)

Methyl thyropropionate (7a) was oxidized much more slowly compared with toluoxyphenol (4) suggesting that the side chain might have some influence, possibly sterochemical or electrostatic interaction with the Co^{II}complex. With halogenated compounds, the reaction proceeded slowly and the yield of diiodobenzoquinone (8b) isolated was very low compared with those of corresponding (9) indicating the quinone might be unstable under the conditions. In fact, diiodobenzoquinone was susceptible to autoxidation catalyzed by Co^{II}salpr (1) in chloroform to give complicated oxidation products.

A mecahnism of the catalytic autoxidation of phenoxyphenols to split at the diphenyl ether bridge is suggested in view of the results obtained in a similar catalytic autoxidation of hindered phenols with Co^{II}salpr (1)[7] as follows:





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