On the basis of these observations we suggested\(^a\) that the Fe(II)-induced isomerization 1→2 might serve as a model for the transformation of the prostaglandin endoperoxides to the PGE's in vivo under the influence of Fe(II)-based enzyme systems as shown in the first row of Scheme II. The lower part of the Scheme adumbrates our suggestion for the biosynthesis of PGX and the thromboxanes, using as a model the 2 other reactions of endoperoxides induced by the Fe(II)-Fe(III) redox system which have been discussed in the preceding paragraphs.

Thus in the anion radical C, produced by one-electron reduction of PGH\(_2\), an alternative to oxidation to PGE is attack by the C-9 oxyradical on the double bond of the side chain attached to C-9 in a manner analogous to the reaction A→B of Scheme I. This is consistent with the alteration of double bond geometry (cis→trans). Subsequent oxidation by the enzyme-based redox system would explain the formation of PGX.

Thromboxane biosynthesis requires cleavage of the 11, 12-bond of a precursor derived from PGH\(_2\). This can be rationalized by invoking one-electron reduction of PGH\(_2\) to the isomeric anion radical D whose fragmentation (arrows) and subsequent oxidation by the enzyme-based redox system is analogous to the loss of an isopropyl group (and oxidation of the latter) exhibited by dihydro-ascaridole on treatment with FeSO\(_4\). The circumstance that ring cleavage leads to an allylic radical may conceivably assist the mode of fragmentation of D. The subsequent steps leading to thromboxane A\(_2\) and A\(_3\) are self-explanatory.

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Reductive dechlorination of chlorobiphenylols by rats

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Summary. Dechlorinated products were isolated from the urine of rats that were administered chlorobiphenylols, the primary hydroxylated metabolites of PCB in mammals. The mechanism of chlorine loss from chlorobiphenylols is different from the mechanism of dechlorination via arene oxides whereby concomitant hydroxylation is always observed.

Although extensive metabolic dechlorination is known to occur with compounds in which chlorine is not bound to an aromatic carbon\(^a\), this reaction is much less important in aromatic chlorine compounds\(^a\). The possibility of reductive dechlorination of an aromatic chlorine compound was firstly reported in 1973\(^4\) for hexachlorobenzene (HCB), and recently unambiguously demonstrated: pentachlorobenzene, tetrachlorobenzene and a number of polychlorophenols were found as metabolites from HCB in rats.\(^5\)\(^6\)\(^7\). This reductive dechlorination was shown to be catalysed by an enzyme located in the microsomal fraction of liver, lung, kidney and intestine.\(^6\)\(^7\)

Reductive dechlorination of polychlorinated biphenyls (PCB) is known only as a photochemical pathway.\(^7\) All documented cases of metabolic chlorine loss from PCB involve concomitant hydroxylation via an arene oxide
intermediate\textsuperscript{b,8}. During a study on the metabolism of 4,4'-dichlorobiphenyl in rats\textsuperscript{8}, we recently detected 4'-chloro-3-biphenylol as minor metabolite. This compound was also found in the urine of rats after feeding 4,4'- dichlorobiphenyl, the major metabolite of 4,4'- dichlorobiphenyl in this animal. Such a metabolic reaction cannot be explained by an arene oxide mechanism but suggests direct metabolic dechlorination.

\begin{center}
\begin{tabular}{|c|c|c|}
\hline
\textbf{Compound} & \textbf{Unchanged compound*} & \textbf{Hydroxylated metabolites} \\
 & (\%) & (\%) \\
\hline
1 & 16 & 72 & 12 \\
2 & 37 & 56 & 7 \\
3 & 70 & 25 & 5 \\
4 & 64 & 21 & 13 \\
\hline
\end{tabular}
\end{center}

*Percentages were calculated from peak areas in the total ion chromatogram.

In this study with 4 structurally related compounds (all have a chlorine atom in the ortho position to a hydroxy group), we show that such dechlorination reactions are apparently more common.

\textbf{Materials and methods.} 4,4'-Dichloro-3-biphenylol, 4,4'- dichloro-3,3'-biphenyldiol, 3-chloro-4-biphenylol and 2,6- dichlorophenol of high purity (99.9\% by GC-MS), were dissolved in peanut oil (oleum arachidis) and administered orally to male Wistar rats as a single dose of 100 mg/kg. The animals were housed in individual metabolic cages and supplied with water and food ad libitum during the experimental period of 7 days. Faeces and urine were collected separately in 4 N sulphuric acid to prevent microbial metabolism after excretion. Isolation, purification and methylation of the metabolites were performed as described\textsuperscript{b,9}. We used a Hewlett-Packard 5982 A GC-MS system operating in the El mode at 70 eV, equipped with an 0.4 x 180 cm all glass column, packed with 0.2\% Carbowax 20 M on Chromosorb W 100-120 mesh. Starting material and the methyl ethers of the metabolites were synthesized by reacting an aniline with amyl nitrite in the presence of an excess of aromatic reactant\textsuperscript{10-13}.

\textbf{Results and discussion.} GC-MS investigation of the methylated urine extracts showed that 4,4'-dichloro-3-biphenylol (compound 1, see scheme), 4,4'-dichloro-3,3'- biphenyldiol (compound 2), 3-chloro-4-biphenylol (compound 3) and 2,6-dichlorophenol (compound 4) were dechlorinated to form 4'-chloro-3-biphenylol (1a), 4-chloro-3,3'-biphenyldiol (2a), 4-biphenylol (3a) and 2-chlorophenol (4a) respectively.

Loss of chlorine in compounds 1a to 4a was evident from the change in the specific isotope clusters of the molecular ions. The position of the hydroxy groups in these compounds was clear from the specific fragmentation patterns of their methyl ethers\textsuperscript{9,10,13}, and was further ascertained by synthesis. In all cases the dechlorinated products were minor metabolites (see table) and, except for 2a, could only be detected in the urine.

Since direct dechlorination products were never observed in studies with chlorobiphenyls\textsuperscript{4}, it seems that a hydroxy group in the aromatic nucleus is necessary for the loss of a chlorine atom via reductive dechlorination.

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