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# NOVEL β-EPOXIDATION OF CHOLESTEROL AND ITS ANALOGS WITH FERRIC ACETYLACETONATE AND HYDROGEN PEROXIDE

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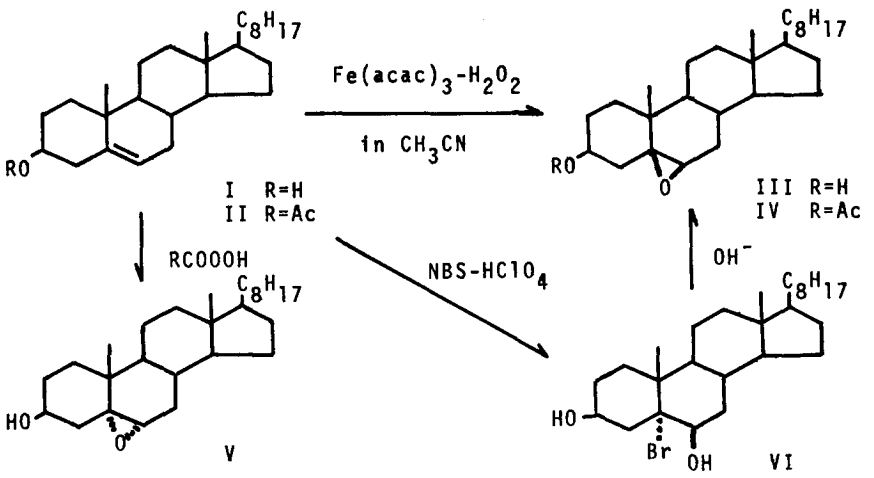
In the course of our investigation of the model reactions on the biological hydroxylation of steroids, we have reported on the stereoselective 15α-hydroxylation of deoxycholic acid with ferrous sulfate and oxygen (Udenfriend's system)[1] and on the oxidation of cholesterol(I) affording 5α-cholestane-3β,5,6β-triol with ferrous sulfate and hydrogen peroxide (Fenton's system) in acetic acid.[2] Formation of the triol was interpreted as a result of hydrolysis of the intermediate epoxide, though the direct hydroxylation with hydroxyl radicals was postulated by Clemo, et al.[3] On the other hand, epoxides have been proposed as the obligatory intermediates in the biological metabolism of olefins to glycols by Boyland,[4] Maynert[5] and Daly[6] groups.

While cholesterol(I) as well as other steroidal olefins formed an α-epoxide (V) with organic peracid, that is stereochemically favorable due to the shielding effect of the angular methyl groups, the β-epoxide(III) was provided by the treatment of the trans-halohydrin(VI) with base as shown in the following chart.[7] In this paper, we wish to report the stereoselective β-epoxidation of cholesterol(I) and its analogs, that was carried out in acetonitrile with ferric acetylacetonate and hydrogen peroxide in one step and in good yield under mild conditions.

In the present reaction, it is necessary to add a large excess of hydrogen peroxide owing to its decomposition with ferric ions, and the temperature represented no considerable effects at 20-80°. The solvent effects of acetonitrile,

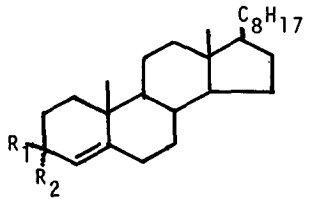



acetone and ethanol afforded a variaty of yields of the epoxide mixture, which were 85, 57 and 10 per cent, respectively, and decreasing in a protic solvent. A typical experiment is described as follows.

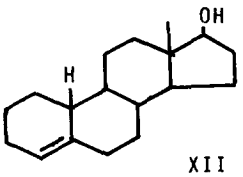
Oxidation of Cholesterol(I)

To a stirred solution of cholesterol(100 mg, $2.6\times10^{-4}$mole) and ferric acetylacetonate(930 mg, $2.7\times10^{-3}$mole) in acetonitrile(100 ml) was added dropwise 30% hydrogen peroxide(5.5 ml, $4.9\times10^{-2}$mole), and the reaction mixture was stirred for 40 mins. at 40°. After excess hydrogen peroxide was decomposed with saturated aqueous solution of sodium sulfite, the organic layer was separated and the aqueous layer was extracted with ether(50 ml x 3). The combined organic layer was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The residue was purified by thin layer and column chromatography on a neutral alumina to give cholesterol β-epoxide(III), mp. 130-133.5° (68%), cholesterol α-epoxide(V), mp. 143.5° (17%), 5α-cholestane-3β,5,6β-triol, mp. 240-242° (5%), and a mixture of 7α- and 7β-hydroxycholesterol (5%) with satisfactiry spectral data, respectively.

It is well known that allylic alcohols such as cholest-4-en-3β-ol(VII) gave β-epoxides with organic peracid by the participation of hydroxyl group, but its acetate(VIII) and cholest-4-en-3α-ol(IX) gave the α-epoxides in the same manner.[7] Other simple allylic alcohols were also epoxidized with organic peroxide or hydrogen peroxide in catalysis of metal ions,[8] though no stereochemical study on the epoxidation has yet appeared in literature.
Our attention was directed further to the epoxidation of cholest-4-ene(XI) and its derivatives by the new method. The results are summarized in Table I, which shows that cholest-4-en-3β-ol(VII), 3α-ol(IX),cholest-4-ene(XI) as well as




| | $R_1$ | $R_2$ |
|---|---|---|
| VII | OH | H |
| VIII | OAc | H |
| IX | H | OH |
| X | H | OAc |
| XI | H | H |




XII

Table I. Epoxidation of Steroidal Olefins with Ferric Acetylacetonate and Hhdrogen Peroxide in acetonitrile.

| Steroidal Olefin | | Yield (%) of α-Epoxide | Yield (%) of β-Epoxide |
|---|---|---|---|
| Cholesterol | (I) | 17 | 68 |
| Cholesterol acetate | (II) | 11 | 46 |
| Cholest-4-en-3β-ol | (VII) | none | 38* |
| Cholest-4-en-3β-ol acetate | (VIII) | no reaction | |
| Cholest-4-en-3α-ol | (IX) | none | 46* |
| Cholest-4-en-3α-ol acetate | (X) | no reaction | |
| Cholest-4-ene | (XI) | 4 | 74 |
| Estr-4-en-17β-ol | (XII) | 4 | 71 |

*) Yield of cholest-4-en-3-one as by-product : (VII) 32%, (IX) 35%.

cholesterol acetate(II) afforded the β-epoxides as major products, while their acetates(VIII and X) were surprisingly inactive under the same conditions and were recovered from the reaction mixtures. It seems that a simple participation of the hydroxyl group is not recognized from these results. The fact that estr-4-en-17β-ol(XII) gave also a β-epoxide is likely to suggest more effective factors than 19-methyl group and thus to require the stereochemical studies of this epoxidation on other steroidal olefins.

The present novel method of the stereoselective β-epoxidation seems to be significant for the biochemical research as well as the synthesis of labile natural products or steroidal hormones. Further studies on the conditions and mechanism of this reaction are in progress.

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