reaction as demonstrated in this paper might play an important role in the action of NADH in biological systems.

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Selective Oxidations of Steroids: The Oxidation of 6β-Acetoxy- and 6β-Benzoyloxy-3α,5α-cyclocholestane Using the Gif System

Eun Lee*, Tae Sun Kim, Sang Ku Yoo, Chang Woo Han, Junghun Suh, and Sae-Hee Chang

Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-742

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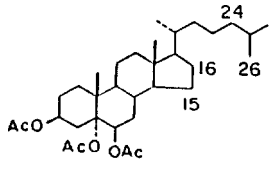
Recently Barton and coworkers described a new system for the oxidation of saturated hydrocarbons. In its most developed form, it consists of an iron catalyst in pyridine-aqueous acetic acid, containing metallic zinc, stirred under oxygen or air at room temperature.[1] Use of iron powder in place of the iron complex and zinc is also known to be effective.[2] For convenience this is called the Gif system and it oxidizes saturated hydrocarbons selectively in secondary positions; primary and tertiary positions are much less prone to be attacked by the oxidizing agents.[3-5]

Several steroid derivatives were oxidized by Barton using the Gif system in an effort to find ways to synthesize useful steroidal compounds from readily available sterols. For example, in the oxidation of 3β,5α,6β-triacetoxycholestane (**1**)[6,7] the three major products were the 20-ketone (**2**) (12%), the 15-ketone (7%) and the 16-ketone (6%). Most of possible ring ketones were also found as minor products as well as the 24-ketone and the 26-aldehyde. Oxidation of 5α-cholestan-3-one (**3**)[8] again produced the 20-ketone (**4**) as the major product, followed by the ring oxidized products at the 6-, 7-, 15-, and 16-positions and the 24-ketone. A dramatic effect in the selectivity of oxidation was discovered with cholest-4-en-3-one (**5**), which gave rise to 15- and 16-ketones as the major ring oxidation products and none of 6- or 7-oxo products. The 20-ketone (**6**) (7.6%) was again found to be the major product together with a smaller quantity of the 24-ketone. Deactivation of ring A and ring B was apparent in this system. Similarly, oxidation of cholesta-1,4-dien-3-one (**7**) led to the formation of the 20-ketone (**8**) (9.4%) and 15- and 24-ketones as the major products. In all these cases 20-ketones



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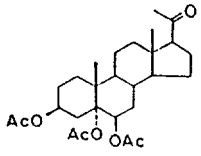

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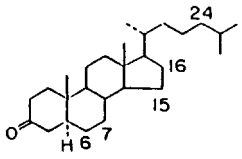

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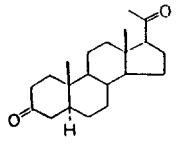

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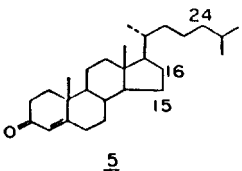

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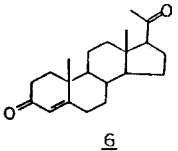
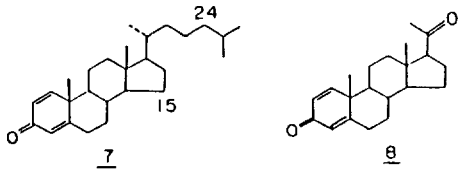


6

were the most abundant major products and the mechanism for the side chain degradation via 25-hydroxyl radical is well documented.[9]

Derivatives of 6β-hydroxy-3α,5α-cyclocholestane[10] are ideal candidates for selective oxidations due to their easy preparation and facile conversion back to cholesterol. Thus



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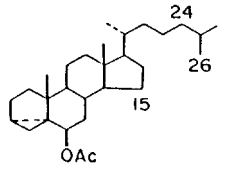

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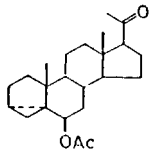

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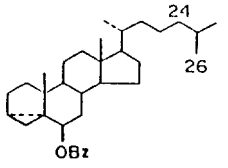

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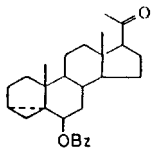

12

6β-acetoxy-3α,5α-cyclocholestane (**9**) was synthesized from 6β-hydroxy-3α,5α-cyclocholestane in acetic anhydride-pyridine and oxidized under standard conditions.[11] Relatively non-polar products (ketones) were separated into three major fractions by column chromatography. The least polar fraction[12] was a mixture of the 24-ketone (3.2%) and the 26-aldehyde (1.4%). The next fraction[13] consisted of the parent alcohol and the 15-ketone (4.7%). The third ketone fraction[14] contained the 20-ketone (**10**) (6.8%). Large amount of quite polar oxidation products was also present, but identification of individual components was impossible. The result of the oxidation of **9** thus closely parallels outcome of the oxidation of **1**.

Under the same oxidation conditions,[15] 6β-benzoyloxy-3α, 5α-cyclocholestane (**11**) was transformed into generally fewer number of products in lower yield. The major product was again the 20-ketone (**12**) (4.7%) accompanied by the 24-ketone (1.5%) and the 26-aldehyde (1.2%). It is remarkable that none of the ring ketones was isolated from the oxidation of **11**. Isolated products were all oxygenated on the side chain, which implies that there was considerable steric effect in the oxidation of the benzoate **11**.

To increase the yield of the oxidation products, various modifications were attempted without any success. For example, ultrasonication did not improve the yield or the selectivity. Present study shows that there is a room for improving selectivity by judicious choice of the cholesterol derivatives, but the goal of attaining more efficient Gif oxidation system is still elusive.

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11. The substrate (8.4 mmol), iron powder (84 mmol), tartaric acid (84 mmol), and hydrogen sulfide (0.042 mmol) in pyridine were dissolved in 160 m*l* of pyridine containing 6.6% water. The suspension was stirred for 8 hours at 30° under a slow stream of oxygen gas. The reaction mixture was worked up after addition of 100 m*l* of aqueous 2N HCl solution. Unreacted substrate was recovered in 57% yield from the least polar fraction upon silica gel column chromatography using hexane-ethyl acetate (20:1).
12. The yield reported is based on the consumed substrate. The 24-ketone and the 26-aldehyde were difficult to separate from each other. The mixture was reduced with sodium borohydride in ethanol and the corresponding 24-and 26-alcohol were separated on a silica gel column. The nmr spectrum of the 26-alcohol was characteristic that it showed the methylene signal at δ3.47 (ABX system). Both alcohols can be reoxidized to the 24-ketone and the 26-aldehyde via pcc oxidation in methylene chloride containing molecular sieve (3 Å) powder. The nmr spectrum of the 24-ketone showed a characteristic doublet at δ1.10 due to the methyl groups in the isopropyl ketone moiety.
13. The mixture was reacted in acetic anhydride-pyridine to convert the parent alcohol back to the acetate, which is separable from the 15-ketone. The 15-ketone is best identified by acid cleavage to the known 15-ketocholesterol. See E. Lee, H. H. Lee, H. K. Chang, D. Y. Lim, Tet. Lett., **29**, 339 (1988).
14. The 20-ketone can be separated from an unknown product by treating the mixture with thionyl chloride-pyridine at 0° for 2 hours. It can be unambiguously identified by converting it to pregnenolone under acidic conditions.
15. Unreacted substrate was recoverd in 49% yield.