Steric Effects in the Hypervalent Iodine Oxidation of Ketones

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<u>Summary</u> - Oxidation of 3-cholestanone (1) with  $C_{6}H_{5}I(OAc)_{2}$  or  $o-OIC_{6}H_{4}COOH$  or  $C_{6}H_{5}IO_{2}$  in KOH/MeOH yields  $2\alpha$ -carbomethoxy-A-norcholestane (2). This result is interpreted on mechanistic grounds and compared with the course of the reaction with other sterically hindered ketones such as friedelin, 3-keto, 12-keto, 17-keto steroids, and 2,2,6,6-tetramethyl-4-piperidone.

We have shown that various types of ketones, upon treatment with  $C_{6H_5}IO/KOH/MeOH$ , form  $\alpha$ -hydroxydimethyl acetals in high yield.<sup>1</sup> Functional groups such as hydroxyl, amino and olefinic were shown to be compatible under the reaction conditions. The mechanism by which  $\alpha$ -hydroxydimethyl acetal formation occurs is the following:



 $\begin{array}{c} \overbrace{OCH_3} \\ \hline (-C_8H_5I) \end{array} \xrightarrow{OCH_2} \\ OCH_3 \\ \hline OCH_3 \\ OCH_3 \\ \end{array} \xrightarrow{OCH_3} \\ OCH_3 \\ OCH_3 \\ OCH_3 \\ \hline OCH_3 \\ \hline OCH_3 \\ \hline OCH_3 \\ OCH_3 \\ \hline OCH_3 \\$ 

This pathway imposes rather stringent steric demands which are not problematic in simple unencumbered ketones such as acetophenones or cycloalkanones. However, in the case of more highly substituted ketones, alternate modes of decomposition of <u>A</u> intervene and we report now on such typical transformations.

Treatment of cholestanone (1) with  $C_{6}H_{5}I(OAc)_{2}$ -KOH/MeOH/THF or o-iodosobenzoic acid -

KOH/MeOH/ THF or  $C_{6}H_{5}IO_{2}$  - KOH/MeOH/THF yielded  $2\alpha$ -carbomethoxy-A-norcholestane (2) in 60% yield by direct isolation from the reaction. Thin-layer chromatographic examination of the reaction product indicated 90% of 2 and 10% of the isomeric  $3\alpha$ -carbomethoxy-A-norcholestane (3).<sup>2</sup>  $2\alpha$ -Hydroxy-3,3-dimethoxycholestane (4) was not observed.







i. C<sub>6</sub>H<sub>5</sub>I(OAc)<sub>2</sub>-KOH/MeOH/THF

## ii. <u>o</u>-OIC<sub>6</sub>H<sub>4</sub>COOH-KOH/MeOH/THF

## iii. C<sub>6</sub>H<sub>5</sub>IO<sub>2</sub>-KOH/MeOH/THF

This result may be discussed within the mechanistic framework established for the reaction of enolates with hypervalent iodine (Scheme 1). In the first step hyperiodination of the enolate system occurs with  $C_{6H_5I=0}$  (formed in situ). Then  $CH_{30}$  adds to the carbonyl group and the thus formed alkoxide anion displaces intramolecularly iodobenzene with reductive elimination (A + B; Scheme 1).

The formation of 2 (and not 4) may be explained upon conformational and steric

grounds. We propose initial C(2) axial hyperiodination 1 + 5. This intermediate converts torsionally to a twist boat-form (5 + 6). The C-I(III) is now stereoelectronically incorrect for intramolecular epoxide formation but it does have the correct stereoelectronic relationship with the C(3)-C(4) bond in the C(3) tetrahedral intermediate (6) for migration



of the C(3)-C(4) bond. This occurs with inversion of configuration at C(2) to yield the observed  $2\alpha$ -carbomethoxy-A-norcholestane (2). The overall course of the reaction, ring-contraction rather the  $\alpha$ -hydroxydimethylacetal formation, is not unexpected based upon these stereoelectronic considerations.

A second mode of reaction of ketones with  $C_6H_5IO/KOH/MeOH$ , in which steric effects control the course of reaction, is illustrated by 7 + 8, 3 + 10, 4 and  $11 + 12^5$  in which cases an  $\alpha$ -methoxyketone is formed:



11 ≖ 5α-analog

<u>12</u> = 5α-analog

In these cases ring-contraction does not occur; however because of steric crowding, attack of methoxide anion on <u>B</u> (Scheme 1) occurs in the alternate sense with <u>7</u>, <u>9</u>, and <u>11</u>. Importantly, the unmethylated analog of <u>7</u>, namely, 4-ketopiperidone itself, yields the  $\alpha$ -hydroxy dimethylacetal derivative under standard reaction conditions in 42% yield with no  $\alpha$ methoxyketone formation.<sup>6</sup>



Finally, the more highly hindered systems becogenin acetate  $(\underline{13})$ , friedelin  $(\underline{14})$  and 17, 20; 20, 21 - bismethylenedioxypreg-5-ene-3,ll-dione 3-dioxalane  $(\underline{15})$  were essentially unreactive under the standard reaction conditions.

In conclusion, Favorski type rearrangement as well as  $\alpha$ -methoxylation are expected reaction pathways based upon the general mechanism (Scheme 1) operating in the presence of determinative steric interaction.

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## References

- R. M. Moriarty, H. Hu and S. C. Gupta, <u>Tetrahedron Lett.</u>, 22, 1283, (1981); R. M. Moriarty, L. S. John and P. C. Du, <u>J. Chem. Soc.</u>, <u>Chem. Commun.</u>, 641, (1981); R. M. Moriarty, S. C. Gupta, H. Hu, D. R. Berenschot and K. B. White, <u>J. Am. Chem. Soc.</u>, 103, 686, (1981); R. M. Moriarty and H. Hu, <u>Tetrahedron Lett.</u>, 22, 2747, (1981); R. M. Moriarty and K. C., Hou <u>Tetrahedron Lett.</u>, <u>25</u>, 691, (1984). In this latter paper the advantage of using o-iodosylbenzoic acid in this oxidation reaction is described.
- 3-Cholestanone yields 2α-carbomethoxy-A-norcholestane, 60%, m.p. 97-98°C [Lit. 97.2-98°C; H. M. Hellmann and R. Jerussi, <u>Tetrahedron</u>, 20, 741 (1964)], ir(KBr): 1715 cm<sup>-1</sup>; pmr (CDCl<sub>3</sub>) δ: 3.67 (<u>s</u>, 3H, COOC<u>H<sub>3</sub></u>); m/z 416.6 (34)M<sup>+</sup>.
- 2,2,6,6-tetramethyl-4-piperidone yields 3-methoxy-2,2,6,6-tetramethyl-4-piperidone, 20%, m.p. 65-66°, ir (KBr) cm<sup>-1</sup>: 3320 (NH stretching), 1680 (>C=0), pmr (CDCl<sub>3</sub>) δ: 1.33-1.65 (m, 14H), 3.55 (s, 3H, OCH<sub>3</sub>), 5.66 (s, 1H, CH), m/z 185 M<sup>+</sup>.
- 1.65 (m, 14H), 3.55 (s, 3H, OCH<sub>3</sub>), 5.66 (s, 1H, CH), m/z 185 M<sup>+</sup>. 4. <u>10</u>: 10%, ir (KBr) cm<sup>-1</sup>: 1720 (>C=0), 3480 (OH); pmr (CDCl<sub>3</sub>) & 4.1 (br, OH), 3.57 (s, 3H, OCH<sub>3</sub>); m/z 320 (29) M<sup>+</sup>.
- 5. <u>12</u>: 10%, ir (KBr) cm<sup>-1</sup>: 1735 (>C=0), 3440 (OH); pmr (CDCl<sub>3</sub>) δ: 3.4 (s, 3H, OCH<sub>3</sub>); π/z <u>318</u> (93) M<sup>+</sup>.
- 6. To be published Tetrahedron Letters 1984.

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