

Methoxylation of Enolizable Steroidal 4-Ene-3-ones using Hypervalent Iodine

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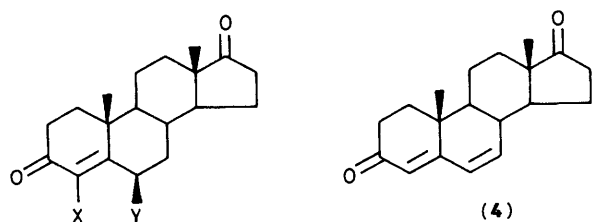
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Reaction of androst-4-ene-3,17-dione (1) with *o*-iodosylbenzoic acid in methanolic potassium hydroxide gave the methoxylated products, the 4- and 6 β -methoxides (2) and (3), along with the dehydrogenated compound, the 4,6-dienone (4).

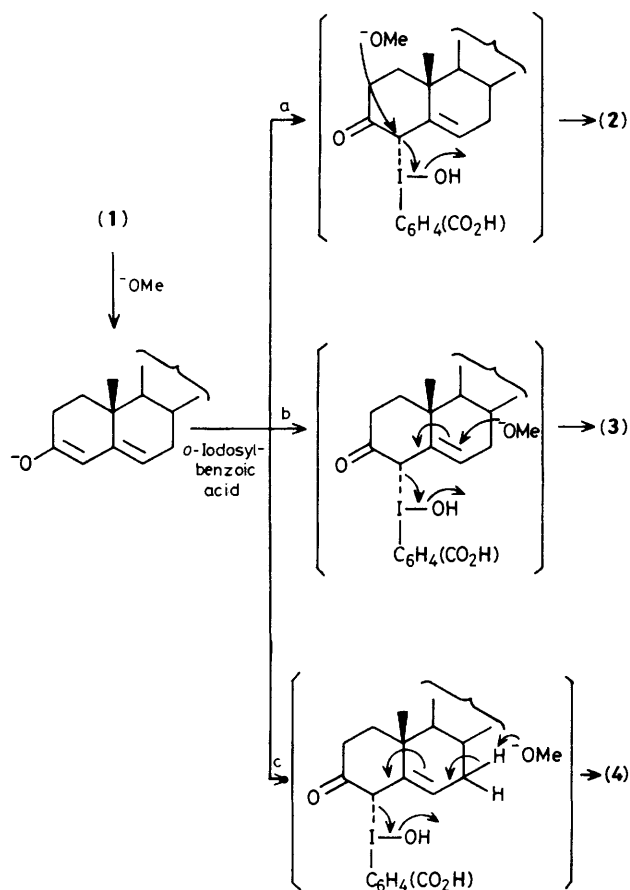
In recent years, it has been reported that hypervalent iodines, iodosylbenzene and *o*-iodosylbenzoic acid, are useful reagents for the conversion of enolizable ketones into α -hydroxydimethylacetals.¹ More recently, α,β -unsaturated ketones, which cannot form anions by α -hydrogen abstraction, have been shown to react with hypervalent iodine, giving the α -hydroxy- β -methoxydimethylacetal derivatives.²

We now report on the *o*-iodosylbenzoic acid–MeOH–KOH reaction applied to an enolizable steroidal α,β -unsaturated ketone, androst-4-ene-3,17-dione (1).

Treatment of the steroid (1) with 1.2 equiv. of *o*-iodosylbenzoic acid and 3.3 equiv. of KOH in dry MeOH (70 °C, 1 h, N₂ atmosphere) afforded a mixture of the 4-methoxide (2), the 6 β -methoxide (3), and the dehydrogenated product, 4,6-dienone (4). Silica gel column chromatography of the crude product gave a 25% yield of (2) [m.p. 135–136 °C (lit.,³ m.p. 136–138 °C); ¹H n.m.r. (CDCl₃) δ 0.93 (s, 18-Me), 1.22 (s, 19-Me), 3.60 (s, 4-OMe); ν_{\max} (KBr) 1740, 1675 cm⁻¹], a 33% yield of (3) [m.p. 161–162 °C (lit.,⁴ m.p. 164–166 °C); ¹H n.m.r. (CDCl₃) δ 0.93 (s, 18-Me), 1.32 (s, 19-Me), 3.21 (s, 6 β -OMe), 3.72 (m, 6 α -H), 5.80 (br s, 4-H); ν_{\max} (KBr) 1740, 1680 cm⁻¹], and a 20% yield of (4) [m.p. 171–172 °C (lit.,⁵



- (1) X = Y = H
 (2) X = OMe, Y = H
 (3) X = H, Y = OMe



Scheme 1

m.p. 170—172 °C); ^1H n.m.r. (CDCl_3) δ 0.98 (s, 18-Me), 1.16 (s, 19-Me), 5.73 (br s, 4-H), and 6.22 (br s, 6- and 7-H); ν_{max} (KBr) 1740, 1660 cm^{-1}]. When the reaction was carried out at room temperature (36 h), similar results were obtained. These products were not isolated in the reaction without KOH and/or the iodosyl compound, but the starting material was quantitatively recovered.

Previous results from the PhIO-dependent alkene epoxidation⁶ and the conversion of the 4,5-epoxide of (1) into (2) on treatment with methanolic sodium hydroxide³ suggested that (2) might be produced *via* the epoxide in this study. However, when the epoxide was subjected to the above reaction with or without the iodosyl compound, (2) was not produced. Moreover, similar treatment of the dienone (4) gave neither (2) nor (3). The reaction thus probably proceeds *via* the kinetically-preferred 2,4-dienolate which is allowed to equilibrate in favour of the stable 3,5-isomer⁷ owing to the low reactivity of the iodosyl compound (Scheme 1); subsequent electrophilic addition to the C-4 position of the 3,5-isomers through the less hindered α -face gives an adduct. Finally, addition of MeO^- at the C-4 and C-6 positions yields (2) with elimination of *o*-iodobenzoic acid followed by isomerization (path a) and (3) (path b), respectively. The β -face addition of MeO^- in path b is predicted in view of the steric hindrance of the *o*-iodosylbenzoic acid substituent at C-4 α which is bulkier than the C-19 angular methyl. Deprotonation at C-7 with the elimination of the iodo compound affords (4) (path c).

The above reaction represents a striking way of functionalizing the C-4 and C-6 positions without affecting the C-17 carbonyl function. The methoxide (2) is an obvious precursor for the synthesis of 4-hydroxyandrost-4-ene-3,17-dione, a potent inhibitor of the estrogen synthetase.^{3,8}

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References

- 1 R. M. Moriarty, H. Hu, and S. C. Gupta, *Tetrahedron Lett.*, 1981, **22**, 1283; R. M. Moriarty, L. S. John, and P. C. Du, *J. Chem. Soc., Chem. Commun.*, 1981, 641; R. M. Moriarty, S. C. Gupta, H. Hu, D. R. Berenschot, and K. B. White, *J. Am. Chem. Soc.*, 1981, **103**, 686; R. M. Moriarty and K.-C. Hou, *Tetrahedron Lett.*, 1984, **25**, 691.
- 2 R. M. Moriarty, O. Prakash, and W. A. Freeman, *J. Chem. Soc., Chem. Commun.*, 1984, 927.
- 3 J. Mann and B. Pietrzak, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2681.
- 4 P. B. Sollman and R. M. Dodson, *J. Org. Chem.*, 1961, **26**, 4180.
- 5 A. M. M. Hossain, D. N. Kirk, and G. Mitra, *Steroids*, 1976, **27**, 603.
- 6 M. Fontecave and D. Mansuy, *J. Chem. Soc., Chem. Commun.*, 1984, 879.
- 7 D. N. Kirk and M. P. Hartshorn in 'Steroid Reaction Mechanism,' Elsevier, Amsterdam, 1968, p. 168.
- 8 A. M. H. Brodie and C. Longcope, *Endocrinology*, 1980, **106**, 19.