An Improved Method for the Synthesis of 2β-Hydroxytestosterone

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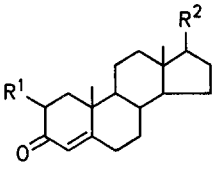
A few years ago we have described a general method for the synthesis of 2β-hydroxysteroids which included the synthesis of 2β-hydroxytestosterone (**1**)[1,2]. Steroid intermediary-metabolism studies in our laboratories and elsewhere required a constant supply of 2β-hydroxytestosterone as a carrier material for reverse isotope-dilution procedure. We now found it advantageous to use 2β-acetoxy-4-androstene-3,17-dione (**2**) as the starting material instead of the 2β,17β-diacetoxy-4-androsten-3-one (**3**) employed earlier[1,2], whereby the yield of 2β-hydroxytestosterone could be considerably improved. Accordingly, 2β-acetoxy-4-androstene-3,17-dione (**2**) was reduced with sodium borohydride at −10° to give 2β-acetoxy-4-androstene-3ξ,17β-diol. Without further purification, the 3ξ,17β-diol was oxidized with manganese dioxide at room temperature to give 2β-acetoxytestosterone (**4**) in 64% yield[3]. The 2β-acetate (**4**) was hydrolyzed under controlled conditions with one equivalent of methanolic potassium hydroxide as described in our earlier procedure[1,2] to give 2β-hydroxytestosterone (**1**) in excellent yield.

2β-Hydroxytestosterone prepared by this procedure melted at 131–132°. We have noted previously that this compound exists in two different polymorphic forms, one with m.p. 87–89° and the other with m.p. 163–164°. The present sample with m.p. 131–132° when dissolved in acetone/petroleum ether and seeded with a small crystal of the higher melting form, resulted in the higher melting product only. The I.R. and N.M.R spectra of the product with m.p. 131–132° are found to be identical in all respects with those of the higher melting sample. It is, therefore, important to recognize that 2β-hydroxytestosterone exists in several different polymorphic forms.



1 R^1 = β-OH, R^2 = β-OH
2 R^1 = β-OAc, R^2 = =O
3 R^1 = R^2 = β-OAc
4 R^1 = β-OAc, R^2 = β-OH

2β-Acetoxy-17β-hydroxy-4-androsten-3-one (4):
2β-Acetoxy-4-androstene-3,17-dione[2] (**2**; 0.1 g) was dissolved in absolute ethanol (20 ml) and cooled to about −20°. Sodium borohydride (20 mg) was then added and the mixture left overnight at this temperature. The reaction mixture was decomposed by addition of acetic acid (0.4 ml) and then the ethanol was evaporated. The residue was extracted with chloroform, washed with brine, dried (Na_2SO_4), and evaporated. The total crude material was dissolved in chloroform (15 ml) and manganese dioxide (0.5 g) added and the mixture stirred overnight at room temperature. The catalyst was filtered, an additional quantity of manganese dioxide (0.5 g) added, and the mixture stirred for 5 hr. The catalyst was then filtered, solvent evaporated, and the residue (0.1 g) chromatographed on silica gel (6 g). Elution of the column with benzene/ether (8:2) gave 2β-acetoxytestosterone (**4**, 64 mg, 64%). The analytical sample was crystallized from ether/petroleum ether: m.p. 137–138°.

$C_{21}H_{30}O_4$	calc.	C 72.80	H 8.73
	found	73.23	8.79

I.R. (KBr): ν_{max} = 1742, 1685, 1615, 1235 cm^{-1}.

N.M.R. ($CDCl_3$): δ = 0.80 (s, 18-CH_3), 1.23 (s, 19-CH_3), 2.17 (s, —OAc), 5.37 (q, J = 6 Hz, 2α-H), 5.83 (s, C-4 olefinic H).

2β,17β-Dihydroxy-4-androsten-3-one (1):
2β-Acetoxytestosterone (**4**; 0.315 g) was dissolved in methanol (12 ml) and a stream of nitrogen was bubbled through the solution. A 1 *N* solution of potassium hydroxide in methanol (0.91 ml) was added and the mixture stirred at room temperature for 4 minutes. Methanol containing several drops of water (20 ml) was added and stirring continued for 4 minutes. 1 *N* Acetic acid (0.91 ml) was added and the methanol evaporated. The crude material was extracted with chloroform, dried (Na_2SO_4), and evaporated. The residue was crystallized from acetone/hexane to give 2β-hydroxytestosterone (**1**); yield: 200 mg; m.p. 131–132°. The I.R. and N.M.R. spectra were found to be identical in all respects with those of an authentic 2β-hydroxytestosterone, m.p. 163–164°. When the low-melting form was dissolved in acetone/hexane and seeded with the high-melting form only high-melting product was obtained.

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[2] P. N. Rao, H. R. Gollberg, L. R. Axelrod, J. Org. Chem. **28**, 270 (1963).
[3] The yield was based on the amount of pure material actually isolated.