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An Improved Method for the Synthesis of 2-Acetoxysteroid-4-en-3-ones

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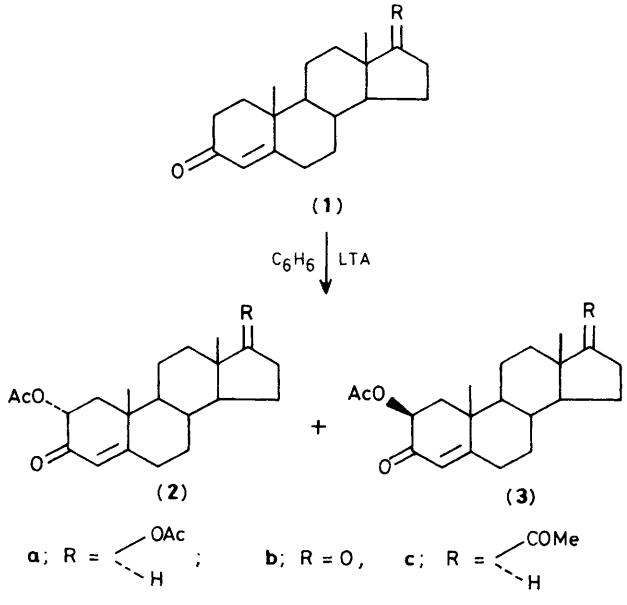
An improved method is described for the one-step preparation of 2-acetoxysteroid-4-en-3-ones using commercially available lead tetra-acetate in dry benzene.

Two methods have previously been reported for the preparation of 2-acetoxysteroid-4-en-3-ones. The first consisted of direct acetoxylation with lead tetra-acetate (LTA) in acetic acid, giving a mixture of 2α- and 2β-acetoxy derivatives in rather low yield.[1—5] The second consisted of acetolysis of a 6-bromosteriod-4-en-3-one with a potassium acetate–acetic acid system.[4—8] Recently, Watt and co-workers reported the direct acetoxylation of steroid-4-en-3-ones with dried manganese(III) triacetate instead of LTA.[9]

We report an efficient and facile synthesis of 2-acetoxysteroid-4-en-3-ones in good yield using LTA in dry benzene. Testosterone acetate (**1a**), androstenedione (**1b**), and progesterone (**1c**) were directly converted into a mixture of 2α- and 2β-acetoxysteriod-4-en-3-ones which were subsequently separated by t.l.c. resulting in 71—74% yield of 2-acetoxy derivatives on isolation.†

A suspension of steroid-4-en-3-one (**1**) (0.175 mmol) and LTA‡ (500 mg, 1.3 mmol) in 20 ml of dry benzene§ was refluxed under a nitrogen atmosphere for 48 h. Additional LTA (100 mg, 0.23 mmol) was then added to the mixture and the suspension was further heated under reflux for 24 h. The cooled mixture was filtered through a pad of Celite and the filtrate was washed sequentially with water, saturated NaCl solution, saturated sodium bicarbonate solution, and saturated NaCl solution. It was then dried over anhydrous sodium sulphate and evaporated under a stream of nitrogen. The residue was purified by t.l.c. on precoated silica gel GF plates (Analtech Inc. Newark, DE). The crude product from (**1a**) was purified by t.l.c. ($CHCl_3$–MeOH 99:1) to yield two fractions. The R_f 0.80 fraction was recrystallized from acetone–hexane to give 19.3 mg (28.4%) of 2α,17β-diacetoxyandrost-4-en-3-one (**2a**): m.p. 208—211 °C (lit.,[1] 210–213 °C); i.r. ($CHCl_3$) 1737, 1685 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 0.83 (3H, s, 18-CH_3), 1.33 (3H, s, 19-CH_3), 2.03 (3H, s, 17-CH_3CO_2), 2.15 (3H, s, 2-CH_3CO_2), 4.60 (1H, t, 17α-H), 5.43 (1H, q, 2β-H), 5.73 (1H, s, 4-H). The R_f 0.72 fraction was recrystallized from acetone–hexane to give 28.9 mg (42.6%) of 2β,17β-diacetoxyandrost-4-en-3-one (**3a**): m.p.199—203 °C



† The following trivial names have been used in this paper: androstenedione = androst-4-ene-3,17-dione, testosterone = 17β-hydroxyandrost-4-ene-3-one, progesterone = pregn-4-ene-3,20-dione.

‡ Lead tetra-acetate (Sigma Chemical Co. St. Louis, MO) was recrystallized from acetic acid and dried in a vacuum desiccator over phosphorous pentoxide for 24 hours before use.

§ Benzene was heated under reflux with sodium metal–benzophenone until the formation of dark blue ketyl and then distilled.

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Table 1. Synthesis of 2-acetoxysteroid-4-en-3-ones.

Parent compd.	Product (%) 2α-AcO deriv.	2β-AcO deriv.	Total	2β : 2α ratio
(**1a**)	(**2a**) 28.4	(**3a**) 42.6	71.0	1.5
(**1b**)	(**2b**) 20.6	(**3b**) 53.0	73.6	2.6
(**1c**)	(**2c**) 10.2	(**3c**) 64.2	74.4	6.3

(lit.,[1] 201—204 °C); i.r. ($CHCl_3$) 1735, 1680 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 0.83 (3H, s, 18-CH_3), 1.20 (3H, s, 19-CH_3), 2.03 (3H, s, 17-CH_3CO_2), 2.13 (3H, s, 2-CH_3CO_2), 4.57 (1H, t, 17α-H), 5.30 (1H, q, 2β-H), 5.77 (1H, s, 4-H).

The crude product from (**1b**) was purified by t.l.c. ($CHCl_3$–MeOH 69 : 1, developed twice) to yield two fractions. The R_f 0.66 fraction was recrystallized from diethyl ether–hexane to give 31.9 mg (53%) of 2β-acetoxyandrostenedione (**3b**): m.p. 156—159 °C (lit.,[7] 156—158 °C); i.r. (KBr) 1755, 1745, 1690 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 0.90 (3H, s, 18-CH_3), 1.23 (3H, s, 19-CH_3), 2.13 (3H, s, 2-CH_3CO_2), 5.30 (1H, q, 2α-H), 5.80 (1H, s, 4-H). The R_f 0.70 fraction was recrystallized from diethyl ether–hexane to give 12.4 mg (20.6%) of 2α-acetoxyandrostenedione (**2b**): m.p. 209—212 °C (lit.,[7] 210—211.5 °C); i.r. (KBr) 1735, 1680 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 0.90 (3H, s, 18-CH_3), 1.35 (3H, s, 19-CH_3), 2.17 (3H, s, 2-CH_3CO_2), 5.43 (1 H, q, 2β-H), 5.77 (1H, s, 4-H).

The crude product resulting from (**1c**) was purified by t.l.c. ($CHCl_3$–MeOH 99 : 1, developed twice) to yield two fractions. The R_f 0.78 fraction was recrystallized from ethyl acetate–cyclohexane to yield 40.0 mg (64.2%) of 2β-acetoxyprogesterone (**3c**): m.p. 122—125 °C (lit.,[7] 126—127 °C); i.r. (KBr) 1740, 1695, 1675 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 0.70 (3H, s, 18-CH_3), 1.20 (3H, s, 19-CH_3), 2.10 (3H, s, 21-CH_3), 2.13 (3H, s, 2-CH_3CO_2), 4.57 (1H, t, 17-H), 5.30 (1H, q, 2α-H), 5.75 (1H, s, 4-H). The R_f 0.67 fraction was recrystallized from ethyl acetate–cyclohexane to yield 6.3 mg (10.2%) of 2α-acetoxyprogesterone (**2c**): m.p. 193—196 °C (lit.,[7] 196.5—197.5 °C); i.r. (KBr) 1737, 1680, 1670 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 0.70 (3H, s, 18-CH_3), 1.30 (3H, s, 19-CH_3), 2.10 (3H, s, 21-CH_3), 2.15 (3H, s, 2-CH_3CO_2), 4.60 (1H, t, 17-H), 5.43 (1H, q, 2β-H), 5.75 (1H, s, 4-H).

The yields of synthesis of 2-acetoxysteroids and their 2β/2α ratios are listed in Table 1. This method combines an improved yield with the advantage of direct acetoxylation. Although the 2α- and 2β-acetoxy derivatives are epimers, each has an equatorial acetoxy group. The 2α-derivative has a normal half-chair conformation of the ring A with an equatorial 2α-acetoxy substituent. In contrast, the 2β-derivative has an inverted half-chair conformation of the ring A resulting in the 2β-acetoxy substituent also at an equatorial conformation.[6,10—13] The 2β/2α product ratios are significantly affected by the 17-side-chain substituents.

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