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A NEW PRACTICAL SYNTHESIS OF 1-DEHYDRO-3-KETO STEROIDS OF THE A/B CIS SERIES[1]

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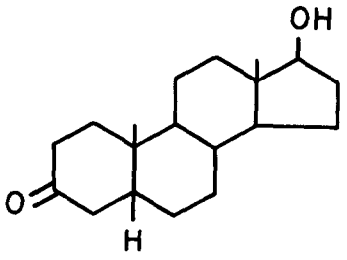
At present there are no convenient procedures for the preparation of 1-dehydro-3-keto-steroids of the A/B cis series. Usually for the introduction of unsaturation in conjugation with a carbonyl advantage is taken of the direction of enolization of the ketone. Consequently, methods employed for the synthesis of 5α-Δ^1-3-ketones are not applicable in the 5β-series[2]. In the A/B cis series circuitous routes requiring selective hydrogenation of 1,4-dien-3-one's[3] or selective dehydrobromination of 2,4-dibromo-3-one's[4] are used. These procedures are cumbersome and unsatisfactory. We wish to present a convenient and practical method for the introduction of unsaturation at C-1 in 5β-3-ketones.

The approach chosen was based on the preferential formylation at C-2 of A/B-cis-3-ketones[5,6]. Thus, 17β-hydroxy-5β-androstan-3-one (1) was converted to the known 2-hydroxymethylene 2 in over 90% yield. The 2-hydroxymethylene's of the A/B trans series undergo facile dehydrogenation at C-1 upon treatment with dichloro dicyano quinone (D.D.Q.) and yield the corresponding Δ^1-2-formyl-3-ketones[7]. We anticipated that a

similar reaction may take place in the 5β-series. Indeed, upon refluxing a benzene solution of 2 with 1.1 mole of D.D Q., 2-formyl-17β-hydroxy-5β-androst-1-en-3-one (3) was obtained in over 60% yield. The analytical sample showed m.p. 159-163°; $[\alpha]_D^{22°}$ + 17° (c = 0.94, $CHCl_3$); λ_{max}^{EtOH} 249 mμ (ε 5700); $\lambda_{max}^{EtOH-NaOH}$ 306 mμ (ε = 10800); ν_{max}^{KBr} cm^{-1} 3550 (OH), 1710 (CHO), 1660 (C=O). Anal. Calcd. for $C_{20}H_{38}O_3$; C, 75.91; H, 8.92. Found: C, 76.04; H, 9.04.

Removal of the formyl group was executed with the use of chlorotris (triphenylphosphine) rhodium[8,9] (m.p. 140°, decomp.). The aldehyde 3 (1 g.) was dissolved in benzene, the rhodium complex (3 g., 1.04 eq.) was added and the mixture was refluxed for 3 hr. under nitrogen. The solid yellow chlorocarbonylbis-(triphenylphosphine)-rhodium (m.p. 198-205°) was collected (2.1 g.; 93%). Chromatography of the reaction products on alumina gave triphenylphosphine oxide, m.p. 158-161° (0.6 g.)[10] and 17β-hydroxy-5β-androst-1-en-3-one (4) (0.63 g.; 68%), m.p. 200-202°, $[\alpha]_D^{22°}$ + 100° (c = 2.4, $CHCl_3$); λ_{max}^{EtOH} 230 mμ (ε = 7000); ν_{max}^{KBr} cm^{-1} 3450 (OH), 1665 (C=O,C=C), 845, 785; n.m.r. 9.23 (3H, $18CH_3$), 8.82 (3H, $19CH_3$), 6.40 (1H, 17H), 4.16, 3.20 (C 1,2 protons; AB pattern, J_{AB} = 10.0 cps). Anal. Calcd. for $C_{19}H_{28}O_2$; C, 79.12; H, 9.76. Found: C, 78.80; H, 9.68. The acetate 5 was prepared in the conventional manner, m.p. 150-152°, $[\alpha]_D^{22°}$ + 85° (c = 2.0, $CHCl_3$)[11], λ_{max}^{EtOH} 231 mμ (ε 7300), ν_{max}^{KBr} cm^{-1} 1735, 1250 (acetate), 1665 (C=O, C=C), 840, 785.

The method is also applicable to the introduction of a double bond on the methylene side of ketones of the type $R_2R_1 \cdot CH \cdot CH_2 \cdot CO \cdot CHR_3 \cdot CH_2R_4$, particularly in cases when enolization towards the methine moiety is preferred.



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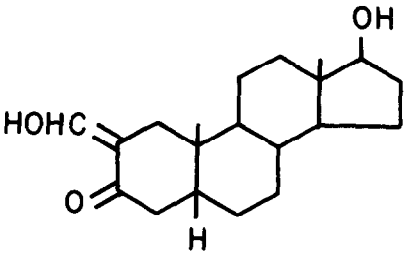

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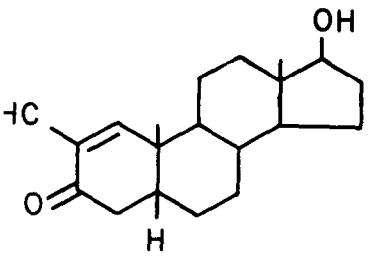

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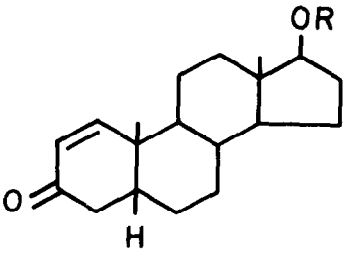

4. R = H
5. R = Ac

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10. Triphenylphosphine is the expected product (cf. ref. 8).
11. This acetate is described in the patent of Joly and Warnant[4b]. They give m.p. 147°, $[\alpha]_D$ + 125°.