# The Retro-aldol Cleavage of 3β-Hydroxypregna-5,17(20)-dien-16-ones: a Convenient Preparation of 3β-Hydroxyandrost-5-en-16-one

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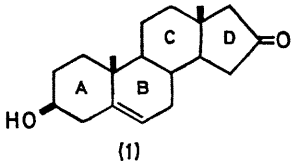
*Summary* Prolonged heating of solutions of 3β-hydroxypregna-5,17(20)-dien-16-ones in aqueous methanol containing sodium hydroxide yields 3β-hydroxyandrost-5-en-16-one.

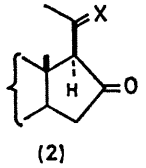
INTEREST in the derivatives of 3β-hydroxyandrost-5-en-16-one (**1**) stems from a number of reasons: some have been patented[1] as hypotensive agents, tranquillizers, and sex-hormone inhibitors, some are urinary metabolites,[2] and yet others appear, in more elaborate modifications, among the Salamander alkaloids.[3]

Reflecting these interests, a number of syntheses of (**1**) (and other androstan-16-ones) have been reported, based on the transposition of a ketone function from C-17 to C-16,[4] *i.e.* obtained by the manipulation of an androst-5-en-17-one derivative.

In contrast, we were interested in the possibility of obtaining (**1**) from pregnene derivatives, such as (**2**; X = O, or X = H,OH), by way of retro-Claisen, or -aldol reactions, particularly as these seemed to represent plausible routes for the biogenesis of the androstan-16-one system. We




(1)

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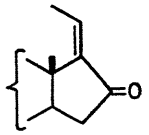
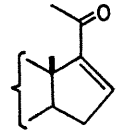



*cis*-(3)




(4)

were encouraged by the report that (**2**; X = Me,OH) underwent retro-aldol cleavage to yield (**1**).[5]

However, in our hands, treatment of (**2**; X = O)[6] with bases yielded predominantly the products arising from ring-D cleavage (a result in accord with the known behaviour of simpler 2-acetylcyclopentanones),[7] while brief treatment of (**2**; X = β-H, α-OH)[8] with bases gave *cis*-(**3**).

We attempted to reverse this dehydration, and drive the reaction towards the retro-aldol products and, indeed, when (**3**)[9] was subjected to prolonged and vigorous treatment with aqueous strong bases [boiling of a solution of *cis*- and *trans*-(**3**) in 2·5N-aqueous methanolic sodium hydroxide for 50 hr.] (**1**) was obtained, m.p. 163—164° (after isolation by p.t.l.c., recrystallization, and sublimation; > 99% pure by g.l.c.) in 38% yield. Under milder conditions, as treatment with Leonard and Paukstelis's reagent,[10] (**3**) was recovered in near quantitative yield, with only some *cis–trans*-isomerisation having taken place.

Since compounds such as (**3**) can readily be prepared from the corresponiing pregn-16-en-20-ones (**4**), which are often commercially available in bulk, the sequence (**4**) → (**3**) → (**1**) appears to constitute a useful route to androsten-16-ones, and complements the classical route from (**4**) to androsten-17-ones.

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[9] W. R. Benn and R. M. Dodson, *J. Org. Chem.*, 1964, **29**, 1142; S. V. Kessar and A. L. Rampal, *Tetrahedron*, 1968, **24**, 887. We have found that acetonitrile is the preferred solvent for the manganese dioxide oxidation of the 17(20)-en-16α-ol system: using manganese dioxide activated according to I. M. Goodman, *J. Org. Chem.*, 1969, **34**, 1979, even the *trans*-enol is oxidized in good yield to the enone.
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