

## A Ready Synthesis of ( $\pm$ )-D-Homo-oestrone

By S. DANISHEFSKY\* and A. NAGEL

(Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15213)

**Summary** Bis-annulation of the Wieland-Miescher ketone via 6-vinyl- $\alpha$ -picoline provides a convenient synthesis of ( $\pm$ )-D-homo-oestrone.

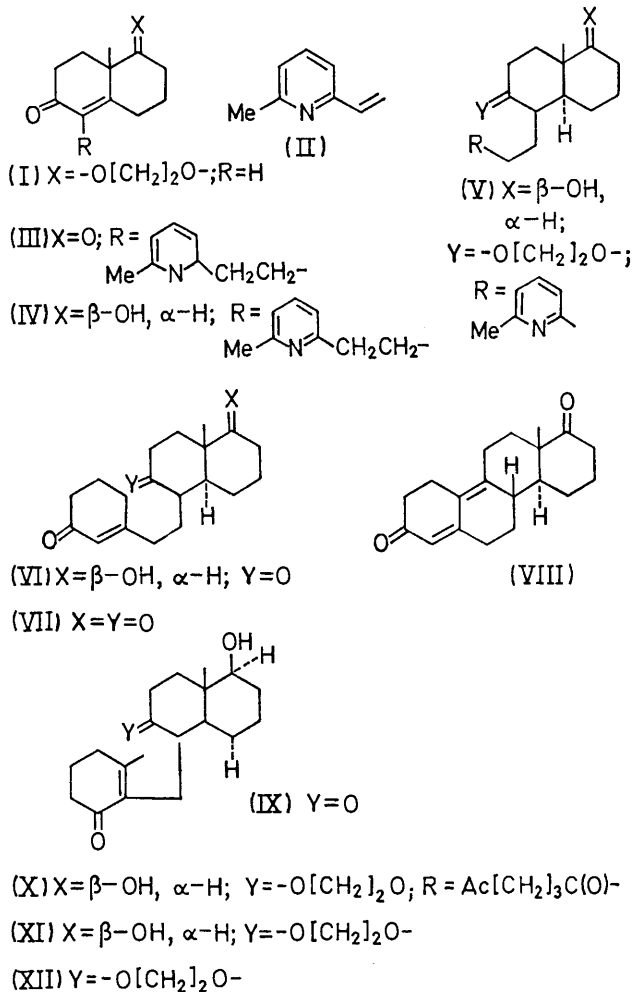
THE bis-annulation of cyclohexanone has been achieved via base-induced hydrolytic cyclization of a dihydropyridine.<sup>1</sup> Herein we show an important application of bis-annulation in a ready synthesis of ( $\pm$ )-D-homo-oestrone.

Alkylation of the acetal-enone (I)<sup>2</sup> with 6-vinyl- $\alpha$ -picoline (II) [1 equiv. each of (I), (II), and potassium t-pentoxide in t-pentyl alcohol under reflux for 24 h] followed by acidic deacetalization gave (III)<sup>+</sup> (70%). Reduction (NaBH<sub>4</sub>) of the latter gave (IV), m.p. 102–105°. Catalytic hydrogenation (H<sub>2</sub>-Pd-C-Et<sub>3</sub>N-AcOEt) and acetalization afforded (V), † m.p. 128–130° [28% from (III)], which was smoothly transformed into (90%) the seco-hydroxyenedione (VI)† by reduction [Na-NH<sub>3</sub> (1.2 equiv.)-EtOH (1.0 equiv.)], hydrolytic cyclization [NaOH-aqueous EtOH (3 equiv.); room temp.; 3 h], and deacetalization (aqueous HCl, 45°). Jones oxidation of (VI) gave enetrione (VIII), † m.p. 100–102°, which upon cyclodehydration (NaOEt-EtOH; reflux) gave (VIII), m.p. 162–164° (45%). The latter has previously been isomerized to ( $\pm$ )-D-homo-oestrone.<sup>3</sup>

Within the limits of detectability, (IX) was not a product of the hydrolytic cyclization of the dihydro-derivative of (V). It was of interest to determine the course of base-catalysed aldolization of the *bona fide* diketone (X), and so (V) was reduced as before but then treated with aqueous NaOH for 1 min. Compound (X)† was obtained (ca. 40%). Treatment of (X) with aqueous-ethanolic NaOH (3 equiv.) cleanly gave (XI) with no detectable (XII). Furthermore, attempted isomerization of (XI) to (XII)<sup>4</sup> (hydration  $\rightleftharpoons$  reverse aldol  $\rightleftharpoons$  aldol  $\rightleftharpoons$  dehydration) by heating the former in aqueous ethanolic alkali gave only recovered starting material. Finally, aldolization of (X) under reflux conditions again gave only (XI).

The overall conversion (V)  $\rightarrow$  (VI) is thus consistent with the intermediacy of (X). The usual propensity for 7-substituted heptane-2,6-diones to provide 2,3-disubstituted cyclohexenones<sup>4,5</sup> is dramatically reversed in the case of (X), possibly as a consequence of a hitherto unknown branching effect which raises the energy of the pathway leading to (XII). The generality of these findings is discussed further in the following communication.<sup>6</sup> Appli-

cation of this new route to 19-norsteroids is under investigation.



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† The structures of all new compounds are based on their i.r., n.m.r. and mass spectra. All enones were also characterized by their u.v. spectra. Combustion analyses within 0.3% of theory were obtained for all crystalline products.

<sup>1</sup> S. Danishefsky and R. Cavanaugh, *J. Amer. Chem. Soc.*, 1968, **90**, 520.

<sup>2</sup> For the best preparation see: J. E. McMurry, *J. Amer. Chem. Soc.*, 1968, **90**, 6821.

<sup>3</sup> S. H. Douglas, J. M. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 1963, 5072.

<sup>4</sup> Cf. R. N. Lacey, *J. Chem. Soc.*, 1960, 1639.

<sup>5</sup> G. Stork and R. Borch, *J. Amer. Chem. Soc.*, 1964, **86**, 935.

<sup>6</sup> S. Danishefsky, A. Nagel, and D. Peterson, following communication.