A Ready Synthesis of (±)-D-Homo-oestrone

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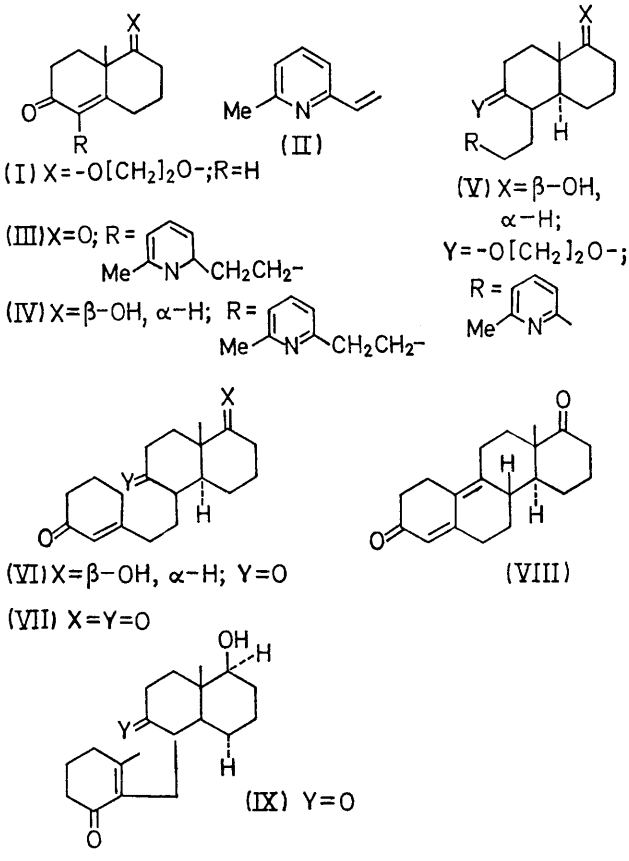
Summary Bis-annelation of the Wieland–Miescher ketone *via* 6-vinyl-α-picoline provides a convenient synthesis of (±)-D-homo-oestrone.

THE bis-annelation of cyclohexanone has been achieved *via* base-induced hydrolytic cyclization of a dihydropyridine.[1] Herein we show an important application of bis-annelation in a ready synthesis of (±)-D-homo-oestrone.

Alkylation of the acetal-enone (I)[2] with 6-vinyl-α-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)† (70%). Reduction ($NaBH_4$) of the latter gave (IV), m.p. 102—105°. Catalytic hydrogenation (H_2–Pd–C–Et_3N–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_3 (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 (±)-D-homo-oestrone.[3]

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)[4] (hydration ⇄ reverse aldol ⇄ aldol ⇄ 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) → (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[4,5] 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.[6] Application 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.

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