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THE TRANSFORMATION OF JERVINE INTO TESTOSTERONE[1]

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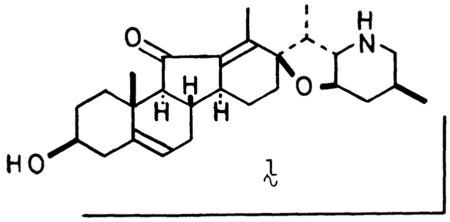
The transformation of jervine into testosterone is described.

We describe herein the transformation of jervine, one of the most readily available veratrum alkaloids, into testosterone, which constitutes the first synthesis of a steroid hormone from naturally occurring C-nor-D-homosteroid alkaloids.

Jervine (1) was degraded, <u>via</u> a known four-step process, into $\Delta^{5,12,17(20)}$-diketone 3-acetal[2] (2), which on reduction (AlH_3 in THF) afforded 11α- and 11β-alcohols (3 and 4)[3] in 59 and 21% yields; δ (19-C$\underline{H}_3$) 1.10 and 1.30 (each s) for 3 and 4.[4] Compound 3 was converted into its 11-acetate and then oxidized by the Lemieux-Johnson procedure to give 11α-acetoxy-Δ^{12}-17-ketone (5) in a 71% yield. Likewise, 4 was oxidized under the same conditions to yield 11β-hydroxy-Δ^{12}-17-ketone (6) (52%). The Birch reduction of 5 and 6 effected removal of the oxygen functions at C_{11} to give Δ^{12}-17-ketone (7) in 86 and 73% yields, respectively. Epoxidation of 7 (H_2O_2 and NaOH in aq CH_3OH) produced 12α,13α-epoxy-17-ketone (8) in an 86% yield (16% from 1). The α-epoxy configuration was based on the following facts. Reduction of 7 (AlH_3 in THF) yielded Δ^{12}-17α-alcohol (9) as a main product (88%) along with its 17β-epimer (10) (6%): $[\alpha]_D$ -25.7° and -77.3° for 9 and 10;[5] δ ($\underline{H}$ at C_{17}) 4.12 and 3.96 (each br W_H = 18 and 8 Hz) for 9 and 10.[6] Epoxidation of 9 and 10 in the presence of transition metals [$\underline{t}$-C_4H_9OOH and $VO(acac)_2$][7] gave 12α,13α-epoxy-17α- and 12β,13β-epoxy-17β-alcohols (11 and 12) as the respective isolable epoxides (57 and 83%), which on oxidation (CrO_3 in Py) formed the corresponding 17-ketones (8 and 13) in 90 and 86% yields, showing negative and positive Cotton effects (a = -119° and +125°) in the respective ORD curves.[4b]



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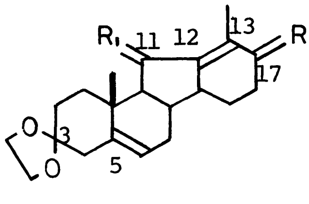
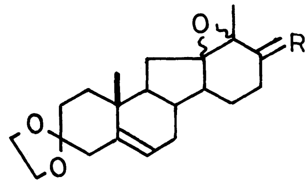


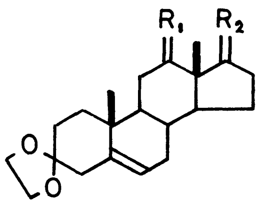


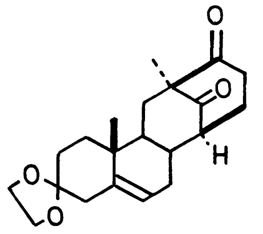
2 R_1=O, R_2=CH(CH_3)
3 R_1=α-OH,β-H, R_2=CH(CH_3)
4 R_1=β-OH,α-H, R_2=CH(CH_3)
5 R_1=α-$OCOCH_3$,β-H, R_2=O

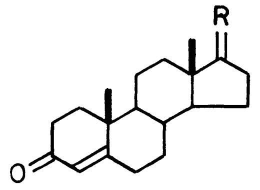
6 R_1=β-OH,α-H, R_2=O
7 R_1=H_2, R_2=O
9 R_1=H_2, R_2=α-OH,β-H
10 R_1=H_2, R_2=β-OH,α-H

8 α-O-, R=O
11 α-O-, R=α-OH,β-H
12 β-O-, R=β-OH,α-H
13 β-O-, R=O

Irradiation of 8 by a 15-watt low pressure lamp in dioxane (room temp, 1 d8))9) produced two isomeric ketones (14 and 15) in 14 and 10% yields, 67% of the starting ketone (8) being recovered unchanged. The structures of 14 and 15 were assigned on the basis of the spectral data and mechanistic grounds:9) 14, m/e 344 (M^+); ν_{max} 1752 and 1707 cm^{-1}; δ 1.13 and 1.23 (each 3H, s, 19- and 18-C$\underline{H}_3$): 15, m/e 344 (M^+); ν_{max} 1745 and 1708 cm^{-1}; δ 0.97 and 1.23 (each 3H, s). The former (14) could be isolated in a 40% yield by repeated photo-isomerizations. Hydride reduction of 14 [$LiAlH(\underline{t}\text{-}C_4H_9O)_3$ in THF, 8 h] resulted in predominant formation of 12β-hydroxy-17-ketone (16) (96%), which was converted into its 17-acetal (17) and then oxidized (CrO_3 in Py) to the corresponding 12-ketone (18). The Wolff-Kishner reduction of 18 produced 3,17-diacetal (19), mp 175-176°C and $[\alpha]_D$ -64.0°, which on deacetalization (H^+ in aq acetone) gave androst-4-ene-3,17-dione (20), mp 175-176°C and $[\alpha]_D$ +198.8°, in a 40% yield from 16; m/e 286 (M^+) and 244; ν_{max} 1740, 1662, and 1613 cm^{-1}; δ 0.93 and 1.23 (each 3H, s, 18- and 19-C$\underline{H}_3$), and 5.71 (1H, s, $\underline{H}$ at C_4). Compound 20 was transformed by a known procedure10) into testosterone (21). The overall yield from jervine amounted to 1.8%.







14 $R_1=R_2=O$
16 R_1=β-OH,α-H, R_2=O
17 R_1=β-OH,α-H, $R_2=-OC_2H_4O-$
18 R_1=O, $R_2=-OC_2H_4O-$
19 $R_1=H_2$, $R_2=-OC_2H_4O-$

15

20 R=O
21 R=β-OH,α-H

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