

Bridged Steroids with a Bicyclo[2.2.1]heptane Ring A System

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Summary Thermal rearrangement of 3-oxo-5-vinylsteroids at 350 °C gives bridged steroids with a bicyclo[2.2.1]-heptane ring A system; a second, minor product from 5-vinyl-5 β -oestrane-3,17-dione (**6**) has been identified as 5-*trans*-propenyl-A-nor-5 β -oestrane-3,17-dione (**9**).

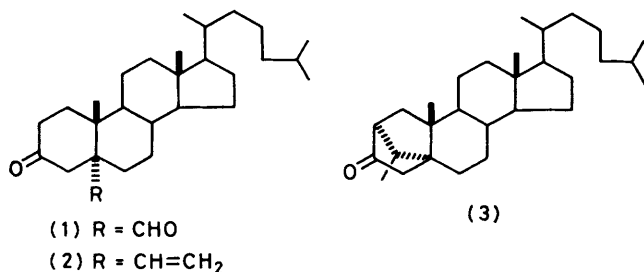
SEVERAL syntheses of carbon-bridged steroids having bicyclo[2.2.2]octane¹ and bicyclo[3.2.1]octane² ring A systems have been reported; we now report the first synthesis of steroids having a bicyclo[2.2.1]heptane ring A system.

Treatment of the 3-ethylene acetal of 5-formyl-5 α -cholestan-3-one (**1**)³ with methylenetriphenylphosphorane followed by hydrolysis of the acetal gave 5-vinyl-5 α -cholestan-3-one (**2**).[†] When a solution of this in decalin was heated in a sealed tube at 350 °C, an isomeric compound was obtained in 41% yield, which is assigned the bridged ring structure (**3**).⁴ Its ¹H n.m.r. spectrum showed the

analysis of its ¹H n.m.r. spectrum in the presence of Eu(fod)₃ and is in accord with the mechanistic interpretation of the reaction as an ene reaction of the Δ^2 -enol of (**2**).⁴

Treatment of 19-nortestosterone (**4**) in tetrahydrofuran with the complex formed from vinyl-lithium and tetrakis[iodo-tri-n-butylphosphinecopper(I)]⁵ gave the conjugate addition product (**5**) (85%), whose stereochemistry was assigned by analogy with the known stereochemistry of conjugate addition of other organocuprate reagents to steroidal 4-en-3-ones.^{6,7} Oxidation of (**5**) with chromium trioxide and pyridine in dichloromethane gave 5-vinyl-5 β -oestrane-3,17-dione (**6**) (81%). Thermal rearrangement of (**6**) as in the case of (**2**) gave (**7**) (41%) [λ_{\max} 5.74 μm ; δ 0.88 (d, *J* 8 Hz, 3H) and 0.90 (s, 3H), with no signals with $\delta > 2.90$; δ (¹³C) 216.9 and 220.5 p.p.m.]. The configuration at the one-carbon bridge in (**7**) was assigned by analogy with (**3**). Similar treatment of (**5**) gave a complex mixture of products from which (**8**), the analogue of (**7**), was isolated in 11% yield only, owing to the lability of the C-17 hydroxy-group under the reaction conditions; attempts to improve the yield of bridged ring product by protection of the hydroxy-group as the acetate or *t*-butyldimethylsilyl ether were unsuccessful. The structure of (**8**) was established by its spectra [λ_{\max} 2.80 and 5.75 μm ; δ 0.76 (s, 3H), 0.87 (d, *J* 8 Hz, 3H), 1.86 (br s, exchangeable, 1H), and 3.5–3.8 (m, 1H)], its formation upon selective reduction of (**7**) with sodium borohydride absorbed on neutral alumina (NaBH₄/Al₂O₃),⁸ and its oxidation to the latter on treatment with chromium trioxide and pyridine.

An interesting minor product (7%) was isolated in addition to (**7**) from the thermal rearrangement of (**6**). It is isomeric with (**6**) and (**7**) and is assigned structure (**9**) on the following basis. Its i.r. and n.m.r. spectra together show the presence of a *trans*-propenyl and two five-membered

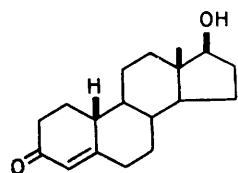


absence of vinyl protons (no signals with $\delta > 2.70$) and its i.r. (λ_{\max} 5.74 μm) and ¹³C n.m.r. (δ 218.5 p.p.m.) spectra indicated a five-membered cyclic ketone. The configuration at the one-carbon bridge is assigned on the basis of an

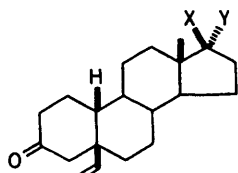
[†] Satisfactory elemental analyses or accurate mass measurements were obtained for all new compounds.

[‡] Although both lithium dimethylcopper and diethylcopper reagents have been used for the introduction of 5 β -alkyl groups by conjugate addition to cholest-4-en-3-one,⁶ we were not able to carry out the analogous addition with lithium divinylcuprate under a variety of conditions.

cyclic ketone groups [λ_{\max} 5.74 and 10.35 μm ; δ 0.90 (s, 3H), 1.61 (br d, J 5 Hz, 3H), and 5.2—5.4 (m, 2H); δ (^{13}C ; single-frequency off-resonance decoupled) 13.9 (q), 18.2 (q), 121.6 (d), 134.1 (d), 218 (s), and 220.8 p.p.m. (s)].

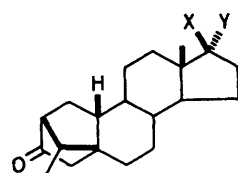


(4)



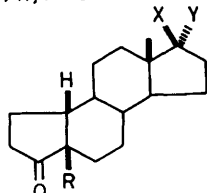
(5) X = OH, Y = H

(6) X, Y = O

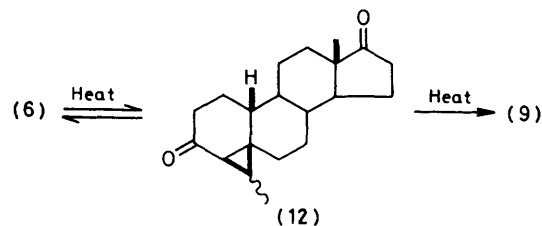


(7) X, Y = O

(8) X = OH, Y = H

(9) R = *trans* CH=CHMe,
X, Y = O(10) R = Prⁿ, X, Y = O(11) R = *trans* CH=CHMe,
X = OH, Y = H

Hydrogenation over platinum gave a dihydro-product (10) whose mass spectrum showed a base peak at m/e 260 ($M - 42$) resulting from the loss of C_3H_6 , as shown by accurate mass measurement. This is considered to arise by a McLafferty rearrangement involving the n -propyl substituent, which must then have an α relationship to a ketone group. The presence of a $\beta\gamma$ -unsaturated ketone group in (9) was confirmed by its u.v. spectrum [λ_{\max} (MeOH) 296 nm (ϵ 200)]. The configuration assigned at C-5 in (9) is indicated by the positive Cotton effect observed in the c.d. spectrum of (11),^{6b} formed by selective reduction of (9) with $\text{NaBH}_4/\text{Al}_2\text{O}_3$.⁸ We propose that (9) arises *via* an ene reaction of the Δ^5 -enol of (6) to give (12)⁴ and the thermal rearrangement of this to (9).⁹



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