Synthesis of 18-Norandrosta-8,11,13-trienes from Testosterone Derivatives in Methanoic Acid †

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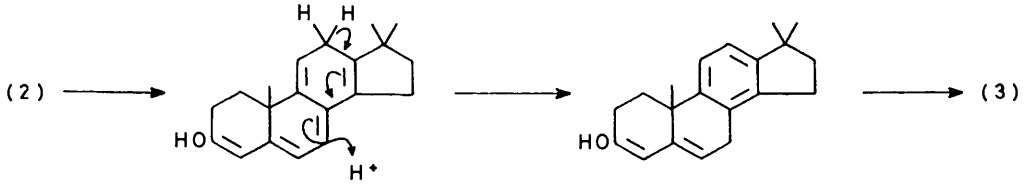
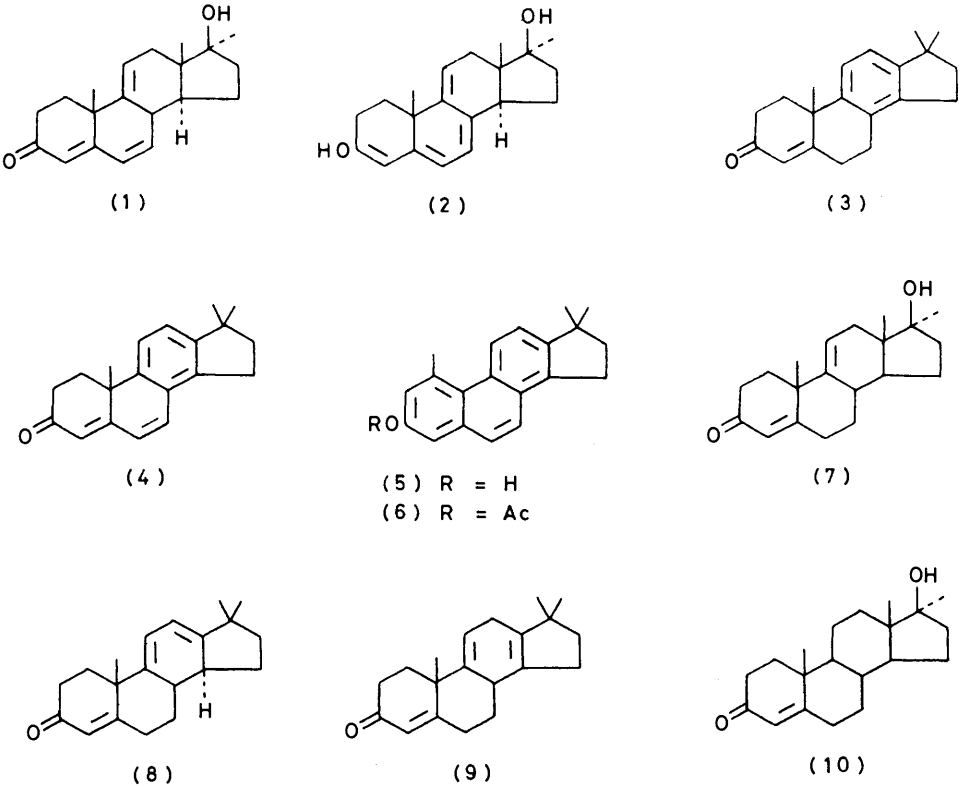
Rearrangement of $\Delta^{9(11)}$-17α-methyltestosterone derivatives to 18-norandrosta-8,11,13-trienes occurs readily in boiling methanoic acid. Activation of the 14α-hydrogen in the thermodynamic enol may facilitate the aromatisation of ring C in the case of $\Delta^{6,9(11)}$-17α-methyltestosterone. 17α-Ethynyloestradiol similarly gives a perhydrochrysene derivative, but cyanohydrins derived from 17-ketones are resistant to rearrangement under these conditions.

AROMATISATION of ring C of steroids without disruption of the steroid nucleus involves elimination or migration of the 13β-methyl group. Examples of the migration of this angular methyl group to the C-12 position have been described by Stevenson *et al.*[1] and migration to C-17 (well known in the formation of steroidal phenanthrenes) has been employed extensively by the Organon group.[2] Our previous work on 17α-methyl-$\Delta^{9(11)}$-testosterone derivatives [3] suggested that dehydration is most readily accompanied by rearrangement when the tertiary 14α-hydrogen atom is allylic or benzylic, and prompted an investigation of the behaviour of 17β-hydroxy-17α-methylandrosta-4,6,9(11)-trien-3-one (1) under acid conditions, since the 14α-hydrogen is subject to allylic activation in its thermodynamically preferred enol (2).



Treatment of the steroid (1) with 90% methanoic acid [4] under reflux gave, as the main product, a colourless material which was separated by t.l.c. from a more-polar yellow product.‡ These two compounds were also formed in methanoic acid at room temperature. The



† Part of this work has appeared in preliminary form: A. B. Turner, *Chem. and Ind.*, 1972, 932.

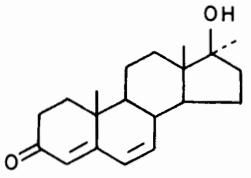
‡ This material appeared to consist mainly of the fully-conjugated ketone (4) by g.l.c., but it could not be purified.

colourless compound showed an AB-quartet in the aromatic region of its ^{1}H n.m.r. spectrum, indicative of a 1,2,3,4-tetrasubstituted benzene ring, together with signals for a single olefinic proton and a *gem*-dimethyl group. This and other data were in accord with the ring C-aromatic structure (3) for the major product, which probably arises by the mechanism outlined in the Scheme. Other possible intermediates having conjugated diene systems in ring C are considered less likely to lead to the C-aromatic product (3), although they could give rise to the fully-conjugated product (4) by further oxidation.

Further evidence for the proposed structure (3) was obtained by treating the compound with chloranil (tetrachloro-*p*-benzoquinone), a reagent known to convert 4-en-3-ones into 4,6-dien-3-ones.[5] Dehydrogenation occurred rapidly in boiling t-butyl alcohol, to give a yellow compound having intense u.v. absorption at 360 nm, indicative of a chromophore (4) extended well beyond that of a 4,6-dien-3-one. This compound could also be obtained by chloranil dehydrogenation of the crude product of rearrangement of the trienone (1). The new product was strongly fluorescent on thin-layer plates and showed carbonyl absorption at 1 660 cm^{-1} in the i.r. region, 20 cm^{-1} below that of the 4-en-3-one (3). Its ^{1}H n.m.r. spectrum exhibited a new AB-quartet in the olefinic region, assigned to the *cis*-CH=CH system in ring B, while the 17-methyl signals appeared as singlets at δ 1.23 and 1.28. This contrasts with the compound (3), in which the methyl groups of the *gem*-dimethyl group are coincident at δ 1.25, and it appears that introduction of the double bond into ring B distorts ring D sufficiently to force the 17-methyl groups to become unsymmetrically disposed towards the aromatic ring C. The protons of the *gem*-dimethyl groups of the phenanthrenes (5) and (6) appear as a singlet at δ 1.35.[3] The phenol (5) was also formed in the choranil dehydrogenation of the ketone (3). Although chloranil does not introduce the Δ^1-bond into Δ^4-3-ketones, it is capable of forming $\Delta^{1,4,6}$-trien-3-ones from $\Delta^{4,6}$-dienones.[5] The phenol (5) arises by Δ^1-dehydrogenation and rearrangement of the ketone (4).

A complex mixture of products was formed when 17α-methyl-$\Delta^{9(11)}$-testosterone (7) was heated with methanoic acid, and g.l.c. analysis indicated that the ring C-aromatic ketone (3) was present. This was confirmed by dehydrogenation of the crude material with chloranil, and isolation of the pentaenone (4). Migration of the Δ^4-bond into ring B or C was also evident in the original mixture, since mobile fractions from t.l.c. plates showed carbonyl absorption at 1 715 cm^{-1}, but attempts to isolate the unconjugated 3-ketone were not successful. It is likely that the tetraenone (3) arises by aerial oxidation or disproportionation of intermediates (8) and (9) following rearrangement in methanoic acid. No reaction of the 17α-methyl-$\Delta^{9(11)}$-testosterone took place in refluxing ethanoic acid under nitrogen.

Britten and Njau [6] have recently reported the formation of the pentaenone (4) directly from 17α-methyltestosterone (10) or its 6,7-didehydro-derivative (11) in the presence of trichloroacetic acid. The pentaenone (4) was isolated in 7% yield after the testosterone (10) had been heated under reflux with trichloroacetic acid in aqueous ethanol, but was not formed when the reaction was run



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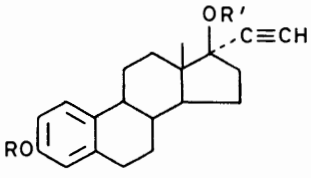
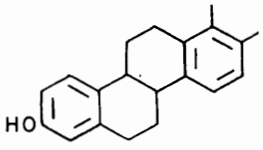


(12) R = R' = H
(14) R = Me; R' = H
(15) R = Me; R' = CHO



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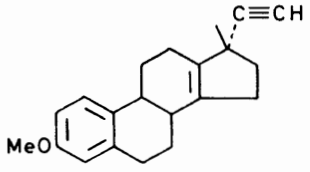

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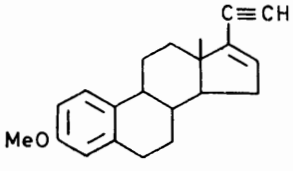

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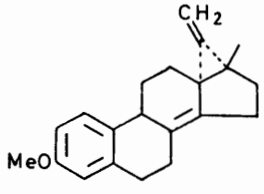

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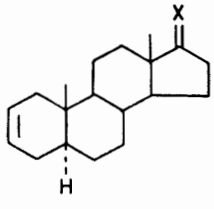

(19) X = O
(20) X = β-OH, α-CN

under nitrogen. In this case it appears that three double bonds are introduced by aerial oxidation, or a combination of aerial oxidation and hydrogen transfer to other steroids in the mixture.

When ethynyloestradiol (12) was subjected to similar conditions (90% methanoic acid), the chrysene derivative (13) was the predominant product. The yield of this material was slightly improved when 98—100% methanoic acid was used, and the number of by-products appeared smaller by t.l.c. Rearrangement of 17α-ethynyltestosterone and related compounds in boiling methanoic

acid has been shown by Jacques *et al.*[7,8] to yield D-homo-aromatic structures. Attempts to isolate intermediates in this transformation were unsuccessful, although in the case of ethynyloestradiol methyl ether (14), two intermediates of short retention time were detected by g.l.c. It appeared likely that these were the formate ester (15) and the rearranged Δ^{13}-yne (16) [9] [or possibly the Δ^{16}-yne (17), although this is less likely to survive], since only dehydration products having a five-membered ring D would be expected to have shorter retention times than the starting material (14). D-Homo-rearranged products show much longer retention times. Evidence for the presence of the formate ester (15) in the crude product mixture was available in the form of a singlet at δ 8.14 in the n.m.r. spectrum. It is possible that the vinylmethylenecyclopropane (18) is an intermediate in the further rearrangement of the Δ^{13}-derivative (16); Dreiding models suggest that the π-orbital on the α-face of the Δ^{13}-bond is favourably disposed for overlap with π-orbital of the triple bond, leading to bond formation between C-13 and C-20.* However, no n.m.r. evidence could be obtained for the presence of a methylenecyclopropane in the crude product mixture. Similarly, C-17 allenes [10] appear not to be involved as intermediates. Dehydration, with or without concomitant rearrangement, must be the initial step in the formation of the D-homo-aromatic structures, since ring expansion of the ethynyl alcohols without loss of the hydroxy-group would lead to D-homo-ketones.

The behaviour of the cyanohydrin mixture (20) derived from 5α-androst-2-ene-17-one (19) was also investigated. No appreciable rearrangement was observed upon treatment of the 17-cyanohydrins with boiling methanoic acid, presumably because the electron-withdrawing effect of the cyano-group inhibits carbonium ion formation at C-17. Instead, hydrolysis of the cyano-group appears to be the main reaction. Following acid treatment, a complex mixture was obtained which lacked cyanide absorption in the i.r. region. Approximately 25% of the cyanohydrin reverted to the original 17-ketone under these conditions.

EXPERIMENTAL

90% Methanoic acid was employed unless otherwise stated. Gas chromatography was carried out on a Perkin-Elmer F-11 instrument, using 2 m × 3 mm (i.d.) glass columns, packed with 2.5% silicone gum rubber E-301 on AW-DMCS chromosorb G (80—100 mesh) at 250 °C with a nitrogen flow rate of 30 ml min^{-1}.

For other general directions see ref. 11.

17,17-*Dimethyl*-18-*norandrosta*-4,8,11,13-*tetraen*-3-*one* (3).—A solution of 17β-hydroxy-17α-methylandrosta-4,6,9(11)-trien-3-one (1.0 g) in methanoic acid (15 ml) was heated for 18 h under reflux. The solution was evaporated under reduced pressure and the residual brown gum was dissolved in ethyl acetate and filtered through a pad of neutral alumina and evaporated to give a yellow-orange gum (0.98 g). This was separated by p.l.c. (5 developments in benzene–hexane, 9 : 1), when elution of the main colourless, u.v. absorbing zone (R_F 0.48) gave the *tetraenone* (0.42 g, 45%) as colourless needles, m.p. 100—102 °C (from hexane), raised upon recrystallisation from ethanol to 104—105 °C (Found: M^+, 280.1808. $C_{20}H_{24}O$ requires 280.1814), t_R 8.0, $\lambda_{max.}$ 238 and 278 nm (log ε 4.29 and 3.13), Δε +7.22 (234 nm), −2.56 (278 nm), and +0.52 (337 nm) at 0.2 g/MeOH,[12] $\nu_{max.}$ 1 680, 1 630, and 835 cm^{-1}; δ 1.25 (s, 17-*gem*-diMe), 1.59 (s, 19-Me), 5.91 (s, 4-olefinic H), 7.09 (q, *J* 8 Hz, 11- and 12-aromatic H); *m/e* 280 (M^+, 31%), 226 (21), 265 (100), 250 (10), 209 (12), and 117 (15).

17,17-*Dimethyl*-18-*norandrosta*-4,6,8,11,13-*pentaen*-3-*one* (4).—(i) A solution of the tetraenone (3) (100 mg) in t-butyl alcohol (3 ml) containing chloranil (78 mg) was heated under reflux for 30 min. The cooled solution was evaporated *in vacuo* to give a brown glass which was taken up in ether. The ethereal solution was extracted with 2% aqueous sodium hydroxide (3×) and water (2×) and dried ($MgSO_4$). Evaporation of the ether gave a yellow-brown gum (64 mg) which was purified by t.l.c. (silica gel; benzene–hexane, 2 : 1) to give as the main band (R_F 0.28) the *pentaenone* (29 mg, 29%) as yellow needles, m.p. 152—154 °C (from hexane) (Found: M^+, 278.1663. $C_{20}H_{22}O$ requires 278.1668), t_R 9.1, $\lambda_{max.}$(MeOH) 245 and 360 nm (log ε 4.17 and 4.16); $\nu_{max.}$ 1 660, 1 620, 1 600, 1 350, 1 255, 1 230, 880, and 830 cm^{-1}; δ 1.23 and 1.28 (ss, 17-*gem*-diMe), 1.44 (s, 19-Me), 5.86 (s, 4-olefinic H), 6.62 (q, *J* 8 Hz, 60 and 7-olefinic H), and 7.14 (q, *J* 8 Hz, 11- and 12-aromatic H); *m/e* 278 (50%), 264 (24), 263 (100), 250 (12), 248 (12), 235 (25), 194 (12), 179 (20), 107 (10), 85 (24), and 83 (30).

(ii) A solution of 17α-methyl-$\Delta^{9(11)}$-testosterone (270 mg) in methanoic acid (3 ml) was heated under reflux for 48 h. The mixture was evaporated to dryness, and the resulting brown gum was dissolved in ethyl acetate and filtered through a short column of neutral alumina. The crude oil was dissolved in t-butyl alcohol (10 ml) and heated under reflux with choranil (500 mg) for 15 min. Solid material (330 mg) was collected, and the solvent was removed under reduced pressure. The residue was dissolved in diethyl ether and filtered through a short column of neutral alumina, to give a brown foam (220 mg). Isolation of the major yellow zone on t.l.c. gave the *pentaenone* (76 mg; 31%) as needles, identical with the material described above.

Rearrangement of 17α-*Ethynyloestradiol*.—A solution of 17α-ethynyloestradiol (178 mg) in 98—100% methanoic acid (2.5 ml) was heated under reflux for 5 h. Water (1.5 ml) was added to the cooled solution, and the mixture was refrigerated for 3 h. The precipitated solid (160 mg) was collected, washed with water, and purified by preparative t.l.c. [benzene–ethyl acetate (2 : 1)]. The pale blue fluorescent band at R_F 0.60—0.65 (1.6 relative to ethynyloestradiol) was eluted to give 3-*hydroxy*-9,10-*dimethyl*-5,6,11,12,13,14-*hexahydrochrysene* (102 mg, 61%) as needles, m.p. 160—166 °C (from hexane), raised upon recrystallisation to 173—176 °C (Found: M^+, 278,1670. $C_{20}H_{22}O$ requires 278.1668), t_R 18.9 (1.26 relative to ethynyloestradiol, 1.0); $\lambda_{max.}$ 281 nm (log ε 3.52); $\nu_{max.}$ 3 320, 1 610, 1 595, 1 260, 1 225, 1 210, 1 155, 920, 870, 815, and 805 cm^{-1}; δ 2.19 and 2.30 (ss, 9- and 10-Me), 6.70 (m, 2- and 4-ArH), and 7.16 (m, 1-, 7-, and 8-ArH); *m/e* 278 (M^+, 100%), 263 (17), 171 (21), 159 (15), 157 (14), 145 (19), 133 (12), 119 (40), and 118 (11).

* The resulting methylenecyclopropyl C-14 cation could rearrange directly to a cross-conjugated methylenecyclohexadiene, leading to the observed D-aromatic product (13), or could lose the 8β-proton to give compound (18).

Acetylation of the phenol by overnight treatment with acetic anhydride and pyridine gave **3**-*acetoxy*-9,10-*dimethyl*-5,6,11,12,13,14-*hexahydrochrysene* as colourless plates, m.p. 141—143 °C (from hexane) (Found: M^+, 320.1775; $C_{22}H_{24}O_2$ requires 320.1776), t_R 23.7, $\nu_{max.}$ 1 750, 1 200, 1 010, and 800 cm^{-1}; δ 2.19 (s, aromatic Me), 2.29 (s, OCOMe and aromatic Me), and 6.85—7.30 (m, 5 aromatic H's); *m/e* 320 (14%), 279 (11), 278 (100), 263 (10), 149 (12), and 119 (12).

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[12] *cf.* P. Crabbé in ' Modern Methods of Steroid Analysis,' ed. E. Heftmann, Academic Press, 1973, pp. 337—338, for concentration effects upon the c.d. properties of compound (3). A localised orbital interaction between the π-electrons of one molecule and the aromatic ring of another is proposed.