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Syntheses of Equilenin, Equilin, and 17β-Hydroxyœstr-4-en-3-one

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Equilin has been prepared from 19-norsteroids by methods involving a microbiological step,[1] from 10-substituted steroids,[2] and by total synthesis,[3] but no methods have been described for the conversion of equilenin into equilin. Independently of Heller, Lenhard, and Bernstein,[4] we have investigated the preparation of equilenin and related compounds from 9α,11β-dihalogeno- and 9α-halogeno-11β-hydroxy-derivatives of androsta-1,4-diene-3,17-dione. As part of this study, we found that the 1,4,8(9)-trien-11β-ol (I)[5] gave equilenin under acidic conditions at room temperature, for example, in concentrated hydrochloric acid or with hydrogen bromide in dioxan–acetic acid, the 10-methyl group being eliminated as methyl halide. Shaking a suspension of the 1,4,8(9)-trien-11β-ol (I) in ether with dilute hydrochloric acid gave a mixture of the 1,4,7,9(11)-tetraen-3-one (II) together with a smaller quantity of the isomeric 1,4,8(14),9(11)-tetraen-3-one, λ_{max} (in EtOH) 239 nm (ε 19,400), with a known chromophoric system.[4] The purified tetraenone (II), λ_{max} (in EtOH) 235—237 nm (ε 28,000), with concentrated hydrochloric acid or 47% hydrobromic acid also gave equilenin (III; R = H, R^1 = O).

It appears likely that the aromatisation proceeds through the 1,4,6,8(9)-tetraen-3-one, which on protonation would give the resonance-stabilised cation (XII; R=H). Attack by the nucleophile (X^-) at C-19 would then result in the formation of MeX and a β-naphthol system.

Evidence to support this came from experiments in alcoholic solvents, in which the cation (XII; R = alkyl) was expected to be an intermediate.[6] Thus, the 1,4,8(9)-trien-11β-ol (I) or the tetraenone (II) with hydrogen bromide and acetic acid in methanol or ethanol gave the 3-methyl (III; R = Me, R^1 = O) or 3-ethyl (III; R = Et, R^1 = O) ethers of equilenin in up to 88% yield. The tetraenone (II) in isopropyl alcohol furnished a *ca.* 1 : 1 mixture of equilenin and its isopropyl ether and in t-butyl alcohol equilenin (95%) was the sole isolated product. Surprisingly, equilenin methyl ether was also formed when the tetraenone (II) was treated with sulphuric, perchloric, or phosphoric acids in methanol. In these reactions the solvent is perhaps also acting as nucleophile.

Although Birch, Murray, and Smith[7] discussed the possibility of reducing equilenin ethers by metals in ammonia to trienes of type (V) and subsequent re-aromatisation of ring A to give compounds related to equilin (VI; R = H, R^1 = O), attempts to reduce the tetra-substituted ring B of similar β-naphthyl ethers were unsuccessful.[8] Similarly, reduction of 3-methoxyœstra-1,3,5(10),6,8-pentaen-17β-ol (III; R = Me, R^1 = H, β-OH) with sodium in ammonia, in the presence of t-butyl alcohol and tetrahydrofuran, has more recently been reported to give the enol ether (IV).[9]

We have found that the compounds (III; R = Me, R^1 = O), (III; R = Me, R^1 = H, β-OH), and (IV) are reduced by lithium in ammonia, in the presence of t-butyl alcohol and tetrahydrofuran with a reaction period of 4 hr., to give the trienol (V, R^1 = H, β-OH) in *ca.* 40% yield. The trienol is identical with the product from metal–ammonia reduction of dihydro-equilin methyl ether (VI; R = Me; R^1 = H, β-OH)[10] and hence has the 9α-H configuration.

Oppenauer oxidation of the trienol (V; R^1 = H, β-OH) to the 17-one (V; R^1 = O) and aromatisation of ring A with pyridine hydrobromide perbromide

in pyridine gave equilin methyl ether (VI; R = Me, R^1 = O). In aqueous t-butyl alcohol with *N*-bromosuccinimide the 17-one (V; R^1 = O) gave equilin (VI; R = H, R^1 = O) in 43% yield. Alternatively, lithium–ammonia reduction of the 17-ethylene ketal (III; R = Me, R^1 = ·OCH_2-CH_2O·)[11] to (V; R^1 = ·OCH_2·CH_2O·), re-aromatisation with pyridine hydrobromide perbromide, and acid hydrolysis gave equilin methyl ether (VI; R = Me, R^1 = O).

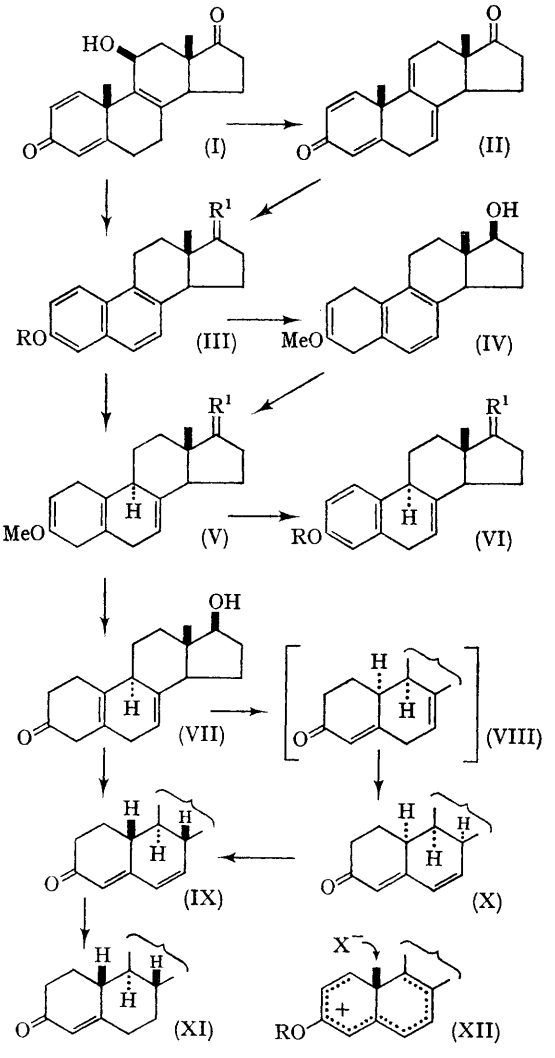
The trienol (V; R^1 = H, β-OH) was readily hydrolysed by acetic acid in methanol to the 5(10),7-dien-3-one (VII).[10] The trienol (V; R^1 = H, β-OH) or the 5(10),7-dien-3-one (VII), on more vigorous treatment with acid, gave the known 4,6-dien-3-one (IX).[1]

The 4,6-dien-3-one (IX) was converted by lithium–ammonia reduction and subsequent treatment with methanolic potassium hydroxide[12] into 19-nortestosterone (XI).

When the 5(10),7-dien-3-one (VII) was boiled with sodium hydrogen carbonate in aqueous methanol a mixture of the 4,6-dien-3-one (IX) and a new isomer, λ_{max} (in EtOH) 286·5 nm (ε 25,800), was formed. The new isomer, isolated in 15% yield by crystallisation, was converted by acid into the normal 4,6-dien-3-one (IX).

The optical rotatory dispersion curve of the new isomer (in ethyl acetate) closely resembled that of 8α,10α-ergosta-4,6,22-trien-3-one (in dioxan),[13] and we therefore assign the same configuration to the isomer (X). Further, the isomer showed a signal at τ 7·25 in its ^{1}H n.m.r. spectrum that can be assigned to the 8α- and 10α-protons, which are axial with respect to the dienone system.[14] The 8α,10α-isomer (X) presumably arises through the intermediate 10α-4,7-dien-3-one (VIII) which, as in the 10α-methyl series,[15] gives the 8α,10α-4,6-dien-3-one (X) on conjugation.

These reactions have also been applied to the preparation of compounds carrying various substituents at the 17-position.



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