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INVESTIGATIONS ON STEROLS XXXII 1)

SYNTHESIS OF 6,7-METHYLEN-4-EN-3-ONE STEROIDS

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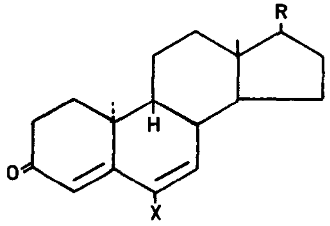
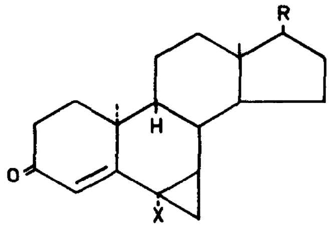
Recently the methylene transfer reaction of dimethyloxosulphonium methylide with steroidal 4,6-dien-3-ones to yield 6,7-methylen-4-en-3-ones has been described 2). This publication has prompted us to report our work in this field.

Treatment of 20β-hydroxy-9β,10α-pregna-4,6-dien-3-one (I) 3) with dimethyloxosulphonium methylide in dimethyl sulphoxide (3 days at room temperature) gave 6β,7β-methylene-20β-hydroxy-9β,10α-pregn-4-en-3-one (II) (m.p. 128.5-130°, $[\alpha]_D^{25}$ = -300°, ε λ259.5 nm = 15 500, N.M.R. 4) 0.83/s(3),CH_3-18; 1.33/s(3), CH_3-19; 5.94/s(1),CH-4), which was oxidized with Jones' reagent to 6β,7β-methylene-9β,10α-pregn-4-ene-3,20-dione (III) (m.p. 210.5-212°, $[\alpha]_D^{25}$ = -189°, ε λ259.5 nm = 15 500, N.M.R. 0.70/s(3),CH_3-18; 1.37/s(3),CH_3-19; 5.96/s(1),CH-4).





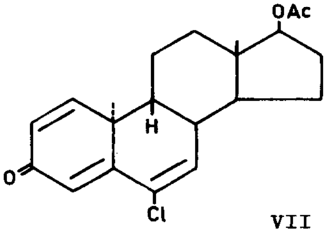
I	X=-H	$R=-\overset{OH(\beta)}{CH}-CH_3$
IV	X=-H	R=-OH
VI	X=-Cl	R=-OAc
VIII	X=-Cl	$R=-CO-CH_3$

II	X=-H	$R=-\overset{OH(\beta)}{CH}-CH_3$
III	X=-H	$R=-CO-CH_3$
V	X=-H	R=-OH
IX	X=-Cl	R=-OH
XI	X=-Cl	$R=-CO-CH_3$

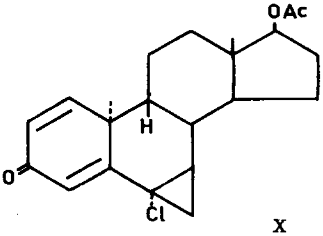
Similar reaction of 17β-hydroxy-9β,10α-androsta-4,6-dien-3-one (IV) [5] with the methylide furnished 6β,7β-methylene-17β-hydroxy-9β,10α-androst-4-en-3-one (V) (m.p. 116.5-118°, after resolidification in the capillary tube 137.5-139°, $[\alpha]_D^{25}$ = -300°, ε λ259.5 nm = 15 300, N.M.R. 0.82/s(3),CH_3-18; 1.31/s(3),CH_3-19; 5.95/s(1),CH-4).

The 6β,7β-configuration was assigned to the compounds (II), (III), and (V) since only one isomer could be detected in the crude reaction products (N.M.R. and G.L.C.). Approach of the 6,7-double bond by the reagent on the α-side of the 9β,10α-steroid molecule is namely strongly hindered by the angular methyl group at C-10 and the C-D ring system. Dyson et al. [2] obtained mixtures of two 6,7-methylene isomers on treatment of 11-unsubstituted 4,6-dien-3-ones of the normal (9α,10β) series. This result can be interpreted as the hindering on the β-side of the normal molecule being less than that on the α-side of the 9β,10α-steroid molecule.

The assigment of the β-configuration only based on the accordance of the found (0.00) with the calculated (-0.04 β; -0.32 α (upfield)) shift of the C-19 protons in the 9β,10α-compounds is not justified, because Dyson et al. [2] found in pairs of two isomers shielding effects of 0.05 and 0.11 for the 6,7-methylene group on the C-19 protons [*].



VII



X

The presence of a 6-chloro substituent in the 4,6-dien-3-one system causes a considerable increase in the reaction rate, which with 6-chloro-1-4-6-trien-3-ones results unexpectedly in attack of the 6,7-double bond in preference to that of the 1,2-double bond [**]. Thus 6-chloro-17β-hydroxy-9β,10α-androsta-4,6

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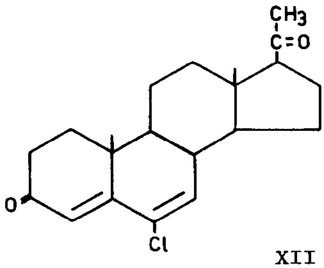
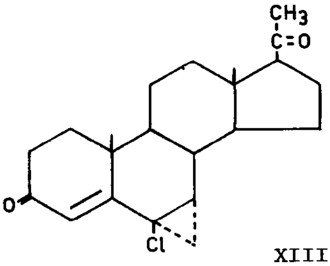
[*] Calculated with the equation of McConnell[6] using the values for $\Delta\chi$ of Bothner-By and Naar-Colin [7], and Tori and Kitahonoki [8].

[**] 6-unsubstituted-1,4,6-trien-3-ones give, on treatment with the methylide, 1,2-methylene-4,6-dien-3-ones, cf.German Pat. 1,183,500 and unpublished results of the authors.

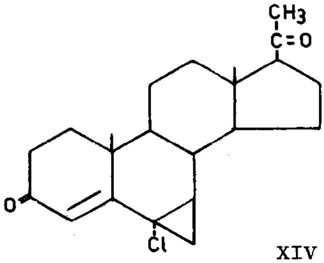
dien -3-one 17-acetate (VI) 9), 6-chloro-17β-hydroxy-9β,10α-androsta-1,4,6-trien-3-one 17-acetate (VII) 9) and 6-chloro-9β,10α-pregna-4,6-diene-3,20-dione (VIII) 9), when treated at room temperature for 30 minutes with the methylide in dimethylsulphoxide, gave 6α-chloro-6,7-methylene-17β-hydroxy-9β,10α-androst-4-en-3-one (IX) (m.p. 163-164°, $[\alpha]_D^{25}$ = -69°, ε λ255.5 nm = 10 000, N.M.R. 0.80/s(3),CH_3-18; 1.41/s(3),CH_3-19; 6.39/s(1),CH-4), 6α-chloro-6,7-methylene-17β-hydroxy-9β,10α-androsta-1,4-dien-3-one 17-acetate (X), after re-acetylation of the reaction product (m.p. 131-133°, ε λ244 nm = 14 000, N.M.R. 0.83/s(3),CH_3-18; 1.53/s(3),CH_3-19; 6.60/s(1),CH-4), and 6α-chloro-6,7-methylene-9β,10α-pregn-4-ene-3,20-dione (XI) (m.p. 188-188.5°, $[\alpha]_D^{25}$ = +4.5°, ε λ257 nm = 10 400, N.M.R. 0.68/s(3),CH_3-18; 1.47/s(3),CH_3-19; 6.39/s(1), CH-4), respectively.



XII



XIII



XIV

In the crude reaction products no 6β-chloro-6,7-methylene isomers could be detected. However, when 6-chloropregna-4,6-diene-3,20-dione (XII) was treated with dimethyloxosulphonium methylide, a mixture of 6β-chloro-6,7-methylene-pregn-4-ene-3,20-dione (XIII)(N.M.R. 0.71/s(3),CH_3-18; 1.22/s(3),CH_3-19; 6.44/s(1),CH-4) and 6α-chloro-6,7-methylene-pregn-4-ene-3,20-dione (XIV) (m.p. 128-130°, $[\alpha]_D^{25}$ = +60°, ε λ263.5 nm = 14 400, N.M.R. 0.64/s(3),CH_3-18; 1.09/s(3),CH_3-19; 6.53/s(1),CH-4) was obtained in a ratio of 2:1.

The 6α-chloro-6β,7β-methylene configuration was assigned to the 9β,10α-compounds (IX), (X) and (XI), since the β-face of the 9β,10α-steroid molecule is less hindered than the α-face (see above). Mutual comparison of the additional chemical shifts of the C-19 methyl protons and the C-4 proton, due to the 6-chloro-6,7-methylene group of the compounds (XIV) (-0.11, 0.80) and (XIII) (0.02, 0.71) with those of compound (XI) (0.09, 0.67), and the ratio found, make the 6β-chloro-6α,7α-methylene configuration of compound (XIII) very probable.

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10. Satisfactory elemental analyses were obtained for the isolated new compounds, which were obtained in yields of 30-60%.