Steroids. CLXXXIV.[1] 2-Formyl-Δ^2-androstenes and Related Compounds. A New Class of Potent Anabolic Agents

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Recent work has demonstrated that the absence of the C-3-oxygen atom in certain androstane derivatives is still compatible with high progestational[2-4] or anabolic-androgenic[4-8] activities.

Further studies of compounds with variable electron density patterns around ring A[7,8] led us to investigate the 2-formyl-Δ^2-system. Certain compounds of this type were found to have very high myotrophic activities with low androgenicity.

Sodium borohydride reduction of 2-methoxymethylene-androstane-17β-ol-3-one[5] (Ia) afforded the corresponding 3β-alcohol (Ib) (m.p. 158–160° $[\alpha]_D$ −35°)[9,10] which upon acid treatment afforded 2-formyl-Δ^2-androstene-17β-ol (IIa) (m.p. 196–198°, $[\alpha]_D$ +107°, λ_{max}^{EtOH} 232 mμ, log ϵ 4.14, λ_{max}^{KBr} 1663, 1645 cm.$^{-1}$); characterized as its acetate (IIb) (m.p. 161–163°, $[\alpha]_D$ +84°), and cyclopentylpropionate (IIc) (m.p. 138–141°, $[\alpha]_D$ +75°). A similar reaction sequence from 17α-methyl-2-methoxymethylene-androstane-17β-ol-3-one (m.p. 190–192°, $[\alpha]_D$ +20°), prepared by acid catalyzed methylation of 2-hydroxymethylene-17α-methyl-androstan-17β-ol-3-one[5] in methanol led to 17α-methyl-2-formyl-Δ^2-androstene-17β-ol (IId) (m.p. 138–140°; $[\alpha]_D$ +70°, λ_{max}^{EtOH} 232 mμ, log ϵ 4.11).

Sodium borohydride reduction of IIa and IId led, respectively, to the corresponding 2-hydroxymethyl-Δ^2 analogs (IIe) (m.p. 190–192°,

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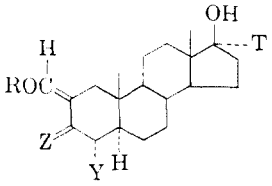
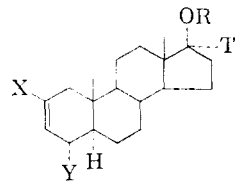
(9) All rotations in chloroform.

(10) All new compounds were analyzed satisfactorily for C, H and O.





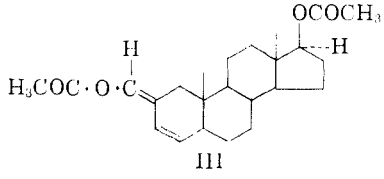
Ia, R = Me, Z = O, Y = T = H

b, R = Me, Z =  , Y = T = H

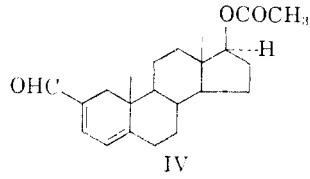
c, R = T = Me, Z = O, Y = H

d, R = Me, Z = O, Y = Me, T = H

IIa, X = CHO, Y = R = T = H
b, X = CHO, Y = T = H, R = $COCH_3$
c, X = CHO, Y = T = H, R = $COCH_2CH(CH_2)_4$
d, X = CHO, Y = H, T = Me, R = H
e, X = CH_2OH, Y = H, R = T = H
f, X = CH_2OH, R = H, T = Me
g, X = COOH, Y = H, R = $COCH_3$, T = H
h, X = $COCH_3$, Y = H, R = T = H
i, X = $COCH_3$, Y = H, R = H, T = Me
j, X = CHO, Y = Me, R = T = H
k, X = CHO, Y = Cl, R = $COCH_3$, T = H



III



IV

$[\alpha]_D$ +58°) and IIf (m.p. 167–169°, $[\alpha]_D$ +26°). Oxidation of IIe and IIf with dichlorodicyanobenzoquinone[11] regenerated IIa and IId in good yield whereas with 8 *N* chromic acid[12] IIb gave the corresponding carboxylic acid IIg (m.p. 267–268°, $[\alpha]_D$+66° λ_{max}^{EtOH} 218 mμ log ϵ 3.96).

Both IIa and IId reacted with methylmagnesium bromide to afford the corresponding 2-(1′-hydroxyethyl)-Δ^2 analogs which underwent oxidation[11] to afford, respectively, 2-acetyl-Δ^2-androstene-17β-ol (IIh) (m.p. 213–215°, $[\alpha]_D$ +110°, λ_{max}^{EtOH} 234 mμ, log ϵ 4.02) and 17α-methyl-2-acetyl-Δ^2-androstene-17β-ol (IIi) (m.p. 191–193°, $[\alpha]_D$ +88°, λ_{max}^{EtOH} 234 mμ log ϵ 4.05).

(11) D. Burn, V. Petrow and G. O. Weston, *Tetrahedron Letters*, **No. 9**, 14 (1960).

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To investigate the effects of methyl and halogen substitution and further unsaturation to the 2-formyl-Δ^2-system the 4α-methyl-, 4α-chloro- and Δ^4- analogs of IIa were prepared. 4α-Methylandrostane-17β-ol-3-one[13] (m.p. 197.5–200°, $[\alpha]_D$ +7°) was converted into 4α-methyl-2-formyl-Δ^2-androstene-17β-ol (IIj) (m.p. 218–222°, $[\alpha]_D$ +24° (dioxane), λ_{max}^{EtOH} 232 mμ, log ϵ 4.15) in the usual way *via* 4α-methyl-2-methoxymethylene-androstane-17β-ol-3-one (Id) (m.p. 218–218.5°). Vigorous acetylation of IIa gave the enol acetate (III) (m.p. 113–116°, $[\alpha]_D$ +41°, λ_{max}^{EtOH} 248 mμ, log ϵ 4.15) which upon treatment with *N*-chlorosuccinimide in acid solution gave 4α-chloro-2-formyl-Δ^2-androstene-17β-ol acetate (IIk) (m.p. 206–207°, $[\alpha]_D$ −24°, λ_{max}^{EtOH} 230–232 mμ, log ϵ 4.08). Similar treatment of III with *N*-bromosuccinimide followed by dehydrobromination with calcium carbonate in dimethylformamide[14] led to 2-formyl-$\Delta^{2,4}$-androstadiene-17β-ol acetate (IV) (m.p. 169–170°, $[\alpha]_D$ +129°, λ_{max}^{EtOH} 320–322 μm, log ϵ 4.17).

Details concerning the extension of this work to the progestational and cortical hormone areas will be described shortly.

Biological Activities.—In preliminary assays IIa (and its esters), IId, IIe and IIf all showed a favorable anabolic-androgenic ratio. Assays[15] were carried out in the immature castrate male rat. The effect on the weight of the seminal vesicle and prostate was a measure of androgenicity and the effect on the levator ani muscle gave the myotrophic (anabolic) activity. By injection IIa and IIe both showed from 0.2 to 0.4 times the androgenicity and 3 to 5 times the anabolic activity of testosterone propionate. The duration of activity of IIa was considerably greater than that of testosterone propionate. Oral administration of IId showed that it had approximately 0.3 to 0.4 times the androgenicity and 3 times the anabolic activity of methyltestosterone.

Introduction of a chlorine atom or a methyl group at C-4α or a Δ^4-double bond did not enhance the activity of the parent compound.

(13) H. J. Ringold and E. Necoechea, unpublished work. We wish to thank Dr. Ringold for the details concerning the preparation of this compound which involved a catalytic hydrogenation of 4-methyltestosterone followed by mild base treatment.

(14) *Cf.* R. Joly, J. Warnant, *et al.*, *Bull. soc. chim. France*, 366, 367 (1958).

(15) We wish to thank Dr. Ralph Dorfman at the Worcester Foundation, Shrewsbury, Mass., and Endocrine Laboratories, Madison, Wisconsin, for the bioassays.