COMMUNICATIONS TO THE EDITOR

Steroids. CLXXX.[1] 2-Methyl-Δ^2-androstenes and 2-Methylene-androstanes. A New Class of Potent Anabolic Agents

A. D. Cross, J. A. Edwards, and A. Bowers

Research Laboratories, Syntex, S.A., Mexico, D.F.

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The recent finding[1] that a series of Δ^2-androstene analogs had relatively high androgenic and anabolic activities led us to investigate the effects of substitution on this double bond. This communication reports the preparation of some 2-methyl-Δ^2-androstenes as well as their double bond isomers, the corresponding C-2 exocyclic methylene analogs. High anabolic activity with low androgenicity was observed for this series of compounds.

2α-Methylandrostane-17β-ol-3-one propionate[2] (Ia) was reduced with sodium borohydride to the corresponding 3β-alcohol (Ib) (m.p. 162–164°, $[\alpha]_D$ −12°).[3,4] The corresponding tosylate (Ic) (m.p. 148–149°, $[\alpha]_D$ −33°, λ_{max}^{EtOH} 226 mμ, log ϵ 4.10) was heated under reflux for 2 hr. in collidine solution to afford 2-methyl-Δ^2-androstene-17β-ol propionate (IIa) (m.p. 116–117°, $[\alpha]_D$ + 46°, λ_{max}^{KBr} 795 cm^{-1}, trisubstituted double bond).

Mild alkaline hydrolysis of IIa led to the 17β-alcohol (IIb) (m.p. 108–109° and 119–120°, (two polymorphic forms), $[\alpha]_D$ +78°) which upon treatment with an excess of 8 *N* chromic acid in acetone solution[5] gave C-17-ketone (IIc) (m.p. 83–85°, $[\alpha]_D$ +148°, λ_{max}^{KBr} 1743 cm.$^{-1}$). Reaction of IIc with an excess of methylmagnesium bromide in benzene solution under reflux for 3 hr. furnished 2,17α-dimethyl-Δ^2-androstene-17β-ol (IId) (m.p. 112–114°, $[\alpha]_D$ +36°).

The analogous 2-methylene compounds were prepared *via* the corresponding 2-ketones. 17α-Methyl-Δ^2-androstene-17β-ol (IIe)[1]

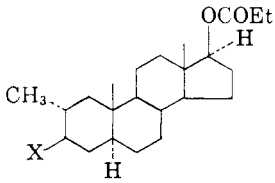
(1) Part CLXXIX. J. A. Edwards and A. Bowers, *Chem. and Ind.*, **48**, 1962 (1961).

(2) H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, *J. Am. Chem. Soc.*, **81**, 427 (1959).

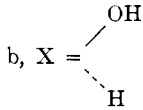
(3) All rotations in chloroform.

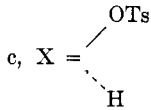
(4) All new compounds were analyzed satisfactorily for C, H, and O.

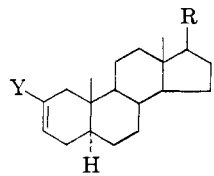
(5) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).



Ia, X = O

b, X = 

c, X = 



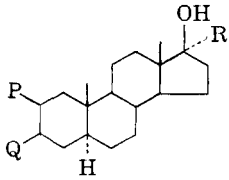
IIa, Y = Me; R = 

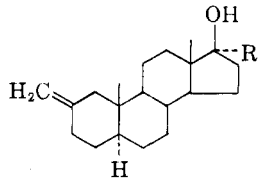
b, Y = Me; R =

c, Y = Me; R = =O

d, Y = Me; R =

e, Y = H; R = 





IIIa, P = 

Q = 

R = Me

IVa, R = Me

b, P = 

Q = 

R = Me

b, R = H

c, P = 

Q = O, R = Me

d, P = =O; Q = 

; R = Me

e, P = =O; Q = 

; R = H

was treated with an excess of diborane[6] and the resulting organoboron compound was oxidized with alkaline hydrogen peroxide to afford a mixture[7] of the 3α-alcohol (IIIa)[8] (m.p. 187–189°, $[\alpha]_D$ −14°) and the 2α-alcohol (IIIb) (m.p. 231–232°, $[\alpha]_D$ −4°). Oxidation of IIIa and IIIb with 8 *N* chromic acid[5] gave respectively 17α-methylandrostane-17β-ol-3-one (IIIc), identical with an authentic sample and 17α-methylandrostane-17β-ol-2-one (IIId) (m.p. 180–181°, $[\alpha]_D$ +19°). In the 17-desmethyl series the 2-ketone (IIIe) (m.p. 123–126°, $[\alpha]_D$ +40°) was prepared by an alternate procedure to be described shortly.[9] Wittig[10] reactions on IIId and IIIe gave in good yields the corresponding 2-methylene compounds (IVa) (m.p. 150–153°, $[\alpha]_D$ −44°, λ_{max}^{KBr} 892 and 1655 m.$^{-1}$) and (IVb) (m.p. 116–120° λ_{max}^{KBr} 890 and 1650 cm.$^{-1}$), respectively.

Biological Activities.—The full details of the biological testing will be published elsewhere. However in preliminary assays compounds IIb, IId, IVa and IVb all showed a favorable separation of androgenic and anabolic activities. Assays were carried out in the immature castrate male rat.[11] 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. Oral administration of IId and IVb showed that both compounds had from 0.3 to 0.5 times the androgenicity and 4 to 6 times the anabolic activity of methyltestosterone.

(6) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **81**, 6428 (1959).

(7) *Cf.* F. Sondheimer and M. Nussim, *J. Org. Chem.*, **26**, 630 (1961), for an analogous reaction with Δ^2-cholestene.

(8) L. Ruzicka, M. W. Goldberg and J. Meyer, *Helv. Chim. Acta*, **18**, 994 (1935), report m.p. 184–185° for IIIa.

(9) Addition of HOBr to the Δ^2-olefin and oxidation to the 3-bromo-2-ketone and reductive removal of the bromine with zinc; P. G. Holton and A. Bowers, manuscript in preparation.

(10) For an excellent review of U. Schöllkopf, *Angew. Chem.*, **71**, 260 (1959).