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HYDROBORATION—V*

A NEW SYNTHESIS OF ANDROSTERONE AND 19-NORANDROSTERONE†

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Abstract—A new approach to androsterone and 19-norandrosterone from androst-5-ene-3β-ol-17-one and 19-nortestosterone is described. The synthesis is accomplished by a stereospecific hydroboration of Δ^3-5α-steroids.

THE recent discovery that intramuscular administration of androsterone causes a considerable reduction in the amount of the serum cholesterol,[1] has drawn attention to this well-known hormone and derivatives. The synthesis of the 19-norandrosterone is of particular interest since other steroids of this series have shown enhanced biological activity.

The syntheses of the 3α-hydroxy-5α-steroids published are in general based on the solvolysis of 3β-tosyl-5α-steroids[3] or on the reduction of the corresponding keto-derivatives with Ni-Raney under controlled conditions.[4]

The application of both these routes is not easy particularly when Δ^4-3-keto-steroids are used as starting materials, since their transformation into the 3β-tosyl-5α- and 3-keto-5α-derivatives respectively is a tedious operation.

We want, therefore, to report a new convenient method which leads to good yields of 3α-hydroxy-5α-steroids, starting from the above mentioned unsaturated ketones.

The most significant feature of this new route is the utilization, in two consecutive stages, of organoboron compounds as intermediate products.

It has recently been demonstrated[5] that diborane readily reacts with $\alpha\beta$-unsaturated $\beta\beta$-disubstituted ketones like cholest-4-ene-3-one yielding organoboron compounds having an oxygen function in the β-position with respect to boron. These compounds, under the action of acetic anhydride or carboxylic acids, eliminate the boron atom and the oxygen atom forming the corresponding Δ^3-5α-derivative in yields of about 70%. (Fig. 1.)

* Part IV: Tetrahedron **19**, 1057 (1963).

† Communicated at the Congress of Chemistry (Italian and Swiss Chemical Society) Napoli, 27 May–2 June (1962).

[1] L. Hellman, H. L. Bradlow, B. Zumoff, D. K. Fukushima and T. F. Gallagher, *J. Clin. Endocrinol. and Metabolism* **19**, 936 (1961).

[3] [a] R. E. Counsell, *Tetrahedron* **15**, 202 (1961);
[b] D. Kupfer, E. Forchielli, R. I. Dorfman, *J. Amer. Chem. Soc.* **82**, 1257 (1960); *J. Org. Chem.* **25**, 1674 (1960);
[c] D. K. Fukushima, S. Dobriner *Ibid.* **26**, 3022 (1961).

[4] cf. F. C. Chang and R. T. Blickenstaff, *J. Amer. Chem. Soc.* **80**, 2906 (1958).

[5] C. Djerassi, A. J. Manson and M. Gorman, *J. Amer. Chem. Soc.* **77**, 4925 (1955).

[5] L. Caglioti, G. Cainelli, G. Maina and A. Selva, *Gazz. Chim. Ital.* **92**, 309 (1962).

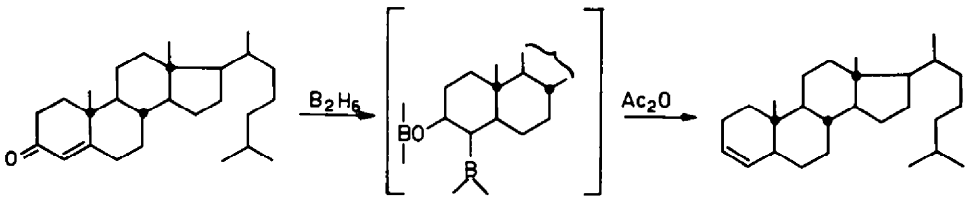

FIG. 1

During research, still in progress in this laboratory,[6] on the hydroboration of 1:2-disubstituted cyclo-olefines, it was observed that hydroboration of the 5α-cholest-3-ene at 0° in tetrahydrofuran with a large excess of diborane, followed by oxidation with alkaline hydrogen peroxide, furnishes in yields higher than 85%, the 3α-hydroxy-5α-cholestane.[7] (Fig. 2.)

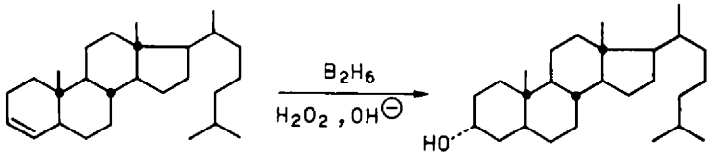

FIG. 2

The high yields and the remarkable simplicity of these two reactions have opened a new route to 3α-hydroxy-5α-steroids and in particular to androsterone and 19-norandrosterone.

For the synthesis of the androsterone, androst-4-ene-3, 17-dione-17-monoethyleneketal (I)[8] was selected as starting material as it is easily accessible and the carbonyl group in position 17 is in a shielded form.

Treatment of I with excess diborane in diethyleneglycoldimethylether (diglyme), followed by ebullition of the reaction mixture with acetic anhydride produces the 5α-androst-3-ene-17-one (II), in a yield of more than 65%.

The protection of the 17-carbonyl through formation of the ketal is, therefore, sufficient to avoid reduction by the diborane. The ketal is quantitatively hydrolysed during treatment with acetic anhydride and it is, therefore, necessary to restore it before effecting the stereospecific hydroboration of the double bond.

The 5α-androst-3-ene-17-one-ethyleneketal (III) is then treated at 0° with a large excess of diborane in tetrahydrofuran. After oxidation of the reaction mixture with hydrogen peroxide and alkali, followed by acid hydrolysis of the ketal, the androsterone (IV) may be isolated in a practically pure form. (Fig. 3.)

The same synthesis was repeated, with slight modifications, in the 19-nor-series. In this case, the starting material, 19-nortestosterone (V) upon hydroboration in diglyme followed by treatment with acetic anhydride, furnishes in a yield of about 60%, the 19-nor-5α-androst-3-ene-17β-ol-acetate (VIa) along with smaller quantities of an isomeric product which at present has not been further examined.

[6] A note on these effects will be published shortly.

[7] Different results were obtained by F. Sondheimer and M. Nussim, *J. Org. Chem.* **26**, 630 (1961).

[8] H. L. Herzog, M. A. Jevnik, M. E. Tully and E. B. Hershberg, *J. Amer. Chem. Soc.* **75**, 4425 (1953).

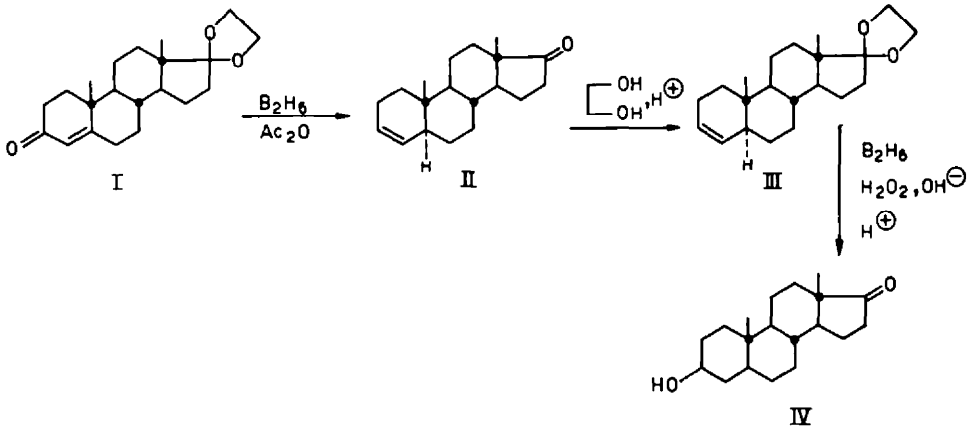

FIG. 3

Hydrolysis of VIa with 5% methanolic potassium hydroxide, furnishes the alcohol (VIb), which may be oxidized to the corresponding ketone (VII) with chromic acid in acetone. The carbonyl group of this compound, is protected through ketalization, and the 19-nor-5α-androst-3-ene-17-one-ethyleneketal (IX) is obtained as previously described for III.

The ketal (IX), undergoing the same treatment as III, furnishes a mixture of products from which it is possible to isolate, in a yield of about 55–65%, a compound m.p. 162°, which proved to be identical to an authentic sample[9] of 19-norandrosterone (VIII) (Fig. 4).

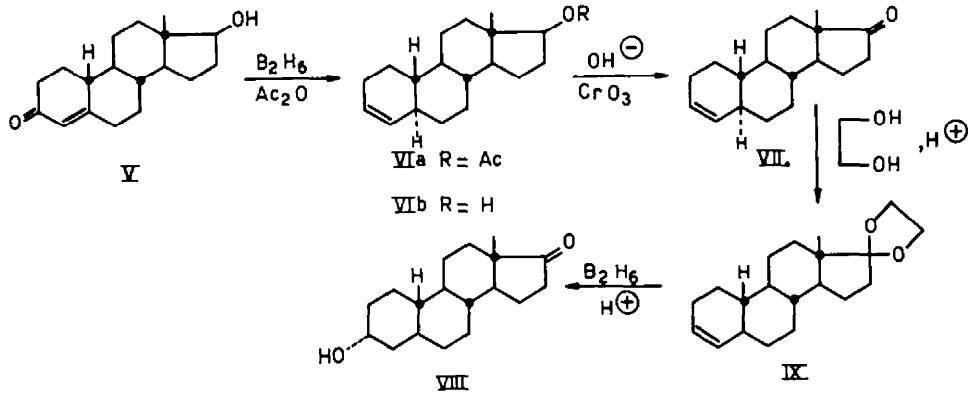

FIG. 4

The absence of the angular methyl group C_{19} in the nor-series reduces the stereospecificity of the hydroboration both at the V → VI stage and in the succesive hydration of the double bond.

This is due to a diminished shielding of the front side of the molecule in the nor-series and results in formation of 5β-derivatives as by-products. The percentage of

[9] We thank Dr. D. K. Fukushima for kindly providing a sample of 19-norandrosterone for identification purposes.

these by-products is however very small, and does not detract from the convenience of the method.

EXPERIMENTAL[10]

5α-Androst-3-ene-17-one (II) *from androst-4-ene-3,17-dione-17-monoethyleneketal* (I). A solution of 500 mg (I) in 20 ml diglyme was treated with a large excess of diborane for 1 hr at room temp and then left to stand 40 min; acetic anhydride (10 ml) were added and the mixture refluxed 1 hr. (All these operations were carried out under an atm. of anhydrous N_2.) The reaction mixture (a dark brown colour) was concentrated *in vacuo* at 80°, poured into water and extracted with ether. The ethereal solution was washed with 10% NaOH, with water to neutrality and dried over Na_2SO_4. Removal of the ethereal solvent yielded 490 mg of a brown, viscous oil which was chromatographed on Alox Woelm II (30 g). Elution with benzene gave 350 mg of 5α-androst-3-ene-17-one (II), m.p. 125–126 . $[\alpha]_D^{20} = +136$. (Found: C, 83·66; H, 10·15. $C_{19}H_{28}O$ requires: C, 83·77; H, 10·36%).

Androsterone (IV) *from 5α-androst-3-ene-17-one-monoethyleneketal* (III). A mixture of 300 g 5α-androst-3-ene-17-one (II), 5 ml of ethylene glycol, 50 mg *p*-toluenesulfonic acid and 50 ml benzene was heated under reflux in a phase separator until no more aqueous phase separated. After neutralization by addition of excess anhydrous Na_2CO_3, the reaction mixture was poured into water and extracted with ether. The ethereal extracts were washed with water to neutrality and dried over Na_2SO_4. Removal of the solvent yielded 285 mg of oil which was dissolved in 10 ml tetrahydrofuran and treated with a large excess of diborane at 0° for 4 hr in an atm. of anhydrous N_2. The reaction mixture was then poured into 30 ml 5% methanolic KOH aq.; when gas development had ceased 3 ml 33% H_2O_2 were added. After about ½ hr the mixture was diluted with water and the whole extracted with ether. The ethereal extracts were washed with a $FeSO_4$ aq. and with water to neutrality, dried over Na_2SO_4 and evaporated to dryness. The residue (290 mg) was a colourless oil, which was dissolved in 5 ml acetic acid and 5 ml water and heated on a water bath for 1 hr. Evaporation of the solvent *in vacuo* left a colourless crystalline residue weighing about 290 mg. Chromatographic separation on Alox Woelm II (5 g) with benzene and benzene-ether 3:1 gave 220 mg of androsterone (IV), m.p. 181–182°. $[\alpha]_D^{22} = +97°$ ($c = 1·20$ in ethanol). (Found: C, 78·54; H, 10·31. $C_{19}H_{30}O_2$ requires: C, 78·57; H, 10·41%).

19-Nor-5α-androst-3-ene-17β-ol (VIb) *from 19-nor-androst-4-ene-17β-ol-3-one* (V). 19-Nor-androst-4-ene-17β-ol-3-one (3 g, V) dissolved in 50 ml diglyme were treated with a great excess of diborane and subsequently with 25 ml acetic anhydride operating under exactly the same conditions and following the same procedure as described for II. About 2·8 g of a crystalline dark-brown coloured product were thus obtained, which after recrystallization from aqueous methanol yielded 19-nor-5α-androst-3-ene-17β-ol-acetate (VIa), m.p. 115–116°. $[\alpha]_D^{22} = -66·7°$ ($c = 1·93$). (Found: C, 79·72; H, 9·77. $C_{20}H_{30}O_2$ requires: C, 79·42; H, 10·00%).

By hydrolysing the 19-nor-5α-androst-3-ene-17β-ol-acetate (VIa) with 5% methanolic KOH aq. at room temp for 14 hr, 19-nor-5α-androst-3-ene-17β-ol (VIb) was obtained, m.p. 107–108°. $[\alpha]_D^{22} = -27·2$ ($c = 1·77$). (Found: C, 83·19; H, 10·69. $C_{18}H_{28}O$ requires: C, 83·02; H, 10·84%).

19-Nor-5α-androst-3-ene-17-one (VII) *from 19-nor-5α-androst-3-ene-17-ol* (VIb). A solution of 1 g 19-nor-5α-androst-3-ene-17β-ol (VIb) in 20 ml acetone was treated with 1 ml 8N Kiliani[11] mixture at 20°. After 15 min, 5 ml methanol was added and the reaction mixture poured into water and extracted with ether. The ethereal extracts were washed with water to neutrality and dried over Na_2SO_4. Removal of the ethereal solvent yielded 985 mg of a crystalline product, which after recrystallization from aqueous methanol yielded 19-nor-5α-androst-3-ene-17-one (VII), m.p. 126–127°. $[\alpha]_D^{22} = +97°$ ($c = 1·02$). (Found: C, 83·64; H, 9·98. $C_{18}H_{26}O$ requires: C, 83·66; H, 10·14%).

19-Norandrosterone (VIII) *from 19-nor-5α-androst-3-ene-17-one* (VII). 19-Nor-5α-androst-3-ene-17-one (400 mg; VII) was ketalized with ethylene glycol and *p*-toluenesulphonic acid following the same procedure as described above for III. 405 mg of a colourless crystalline material were obtained, which after recrystallization from aqueous methanol yielded 380 mg 19-nor-5α-androst-3-ene-17-one-ethylenketal (IX), m.p. 83°. (Found: C, 79·51; H, 9·83. $C_{20}H_{30}O_2$ requires: C, 79·42; H, 10·00%). 443 mg of this product were dissolved in 15 ml tetrahydrofuran and treated for 1 hr at room temp with an excess of diborane and then oxidized with 30 ml 5% methanolic KOH aq. and

[10] M.ps are uncorrected. Optical rotations were determined in chloroform unless otherwise stated.
[11] R. G. Curtis, I. Heilbron, E. R. H. Jones and G. F. Woods, *J. Chem. Soc.* 461 (1953).

3 ml 30% H_2O_2 in the usual manner. Thus about 450 mg oil were obtained, which were dissolved in 5 ml acetic acid and 5 ml water and the mixture heated for 1 hr at 40°. After working up, 230 mg 19-norandrosterone (VIII), m.p. 158–159° were obtained and recrystallized from heptane, m.p. 162–163°. $[\alpha]_D^{23} = +105°$ ($c = 1{\cdot}2$). (Found: C, 78·07; H, 10·28. $C_{18}H_{28}O_2$ requires: C, 78·21; H, 10·21%).

Acknowledgement—We wish to thank Prof. A. Quilico for helpful discussion and for his interest in this work.