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10β-AMINO-STEROIDS: A NEW CLASS OF STEROID DERIVATIVES

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The considerable difference in biological properties between steroids possessing a 10β-methyl angular group and their corresponding 19-nor-analogs clearly indicates that the nature of the 10β-angular substituent plays an important role in structure-activity relationship. In view of this fact, we wished to investigate a heretofore unreported class of steroids, namely the 10β-amino steroids.

The reaction of 19-carboxylic acids (Ia,b,c) with thionyl chloride in benzene under reflux (4) allows to isolate, quantitatively, the corresponding carboxylic acid chlorides (IIa,b,c), from which, by reaction with activated sodium azide (5) in anhydrous acetone, the corresponding 19-carboxy-azido derivatives (IIIa,b,c,) are obtained.

These compounds easily undergo Curtius transposition in aqueous acetic acid (6) to give the corresponding 10β-amino derivatives (IVa,b,c) in satisfactory yields.

IIIa - 3β-hydroxy-pregn-5-ene-20-one-19β-carboxy-acid-azido-3-acetate, m.p. 100-101°C.

IVa - 3β-hydroxy-10β-amino-19-nor-pregn-5-ene-20-one-3-acetate, m.p. 141-142.5°C; $[\alpha]_D$= -13° ($CHCl_3$).

IVb - 3β-hydroxy-10β-amino-19-nor-androst-5-ene-17-one-3-acetate, m.p. 181-182°C: $[\alpha]_D$= -35° ($CHCl_3$).

IVc - 3β,17β-dihydroxy-10β-amino-19-nor-androst-5-ene-3,17-diacetate, m.p. 162-164°C; $[\alpha]_D$= -100° ($CHCl_3$).

NMR ($CDCl_3$): 9.17 τ (s. 3H, 18-CH_3), 8.95 τ (s. 2H, -NH_2-[7]), 7.95 τ (s. 6H, 3 and 17β CH_3-COO), 5.53-5.10 τ (m. 2H in 3β and 17β), 4.60-4.35 τ (m. 1H, H in 6).

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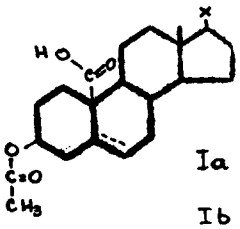
Similarly, starting from 3β,17β-dihydroxy-5α-androstane-19-oic-acid-3,17-diacetate (Id), m.p. 205-207°C, $[\alpha]_D$= -51° ($CHCl_3$), we obtained 3β,17β-dihydroxy-10β-amino-19-nor-5α-androstane-3,17-diacetate (IVd), m.p. 154-157°C, $[\alpha]_D$= -76° ($CHCl_3$).

Starting from IIIc and performing the Curtius transposition in anhydrous ethanol we prepared 3β,17β-dihydroxy-10β-ethyl-urethane-19-nor-androst-5-ene-3, 17-diacetate (IVe), m.p. 180-182°C.

The saponification of IVa,b,c with potassium carbonate in aqueous methanol allowed us to obtain 3β-alcohols [Va: m.p. 169-170°; Vb: m.p. 181-182°; $[\alpha]_D$= -45° ($CHCl_3$); Vc: m.p. 205-208°C; $[\alpha]_D$= -92° (dioxane)]. The oxidation, according to Oppenauer, of these 3β-alcohols gave, respectively, 10β-amino-19-nor-pregn-4-ene-3, 20-dione (10β-amino-19-nor-progesterone) (VIa), m.p. 151-153°C; $[\alpha]_D$= +206°($CHCl_3$); λ_{max}^{EtOH} 235 mμ (ε = 13,750) and 10β-amino-19-nor-androst-4-ene-3,17-dione (VIb), m.p. 203-205°C, $[\alpha]_D$= +195° ($CHCl_3$); λ_{max}^{EtOH} 233 mμ (ε = 15,400); NMR ($CDCl_3$): 9.04 τ (s. 3H, 18-CH_3), 8.55 τ (s. 2H, -NH_2[7]), 4.19 τ (d. 1H, H in 4); N-benzylidene-derivatives (VIc), m.p. 222-224°C; λ_{max}^{EtOH} 247 mμ (ε = 19,300).



Ia Δ^5 x = 3-OCOCH$_3$

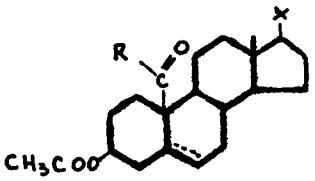
Ib Δ^5 x = =O

Ic Δ^5 x = 3-OCOCH$_3$

Id 5α x = 3-OCOCH$_3$

II R = Cl

III R = N_3

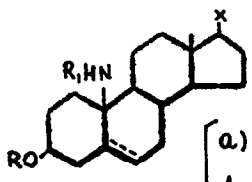


a) Δ^5 x = 3-OCOCH$_3$

b) Δ^5 x = =O

c) Δ^5 x = 3-OCOCH$_3$

d) 5α x = 3-OCOCH$_3$



IV R = CH_3CO

V R = H

a) Δ^5 x = 3-OCOCH$_3$ R_1 = H

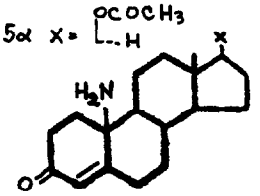
b) Δ^5 x = =O R_1 = H

c) Δ^5 x = 3-OCOCH$_3$ R_1 = H

d) 5α x = 3-OCOCH$_3$ R_1 = H

e) Δ^5 x = 3-OCOCH$_3$ R_1 = -$OCOC_2H_5$

f) Δ^5 x = 3-OCOCH$_3$ R_1 = H

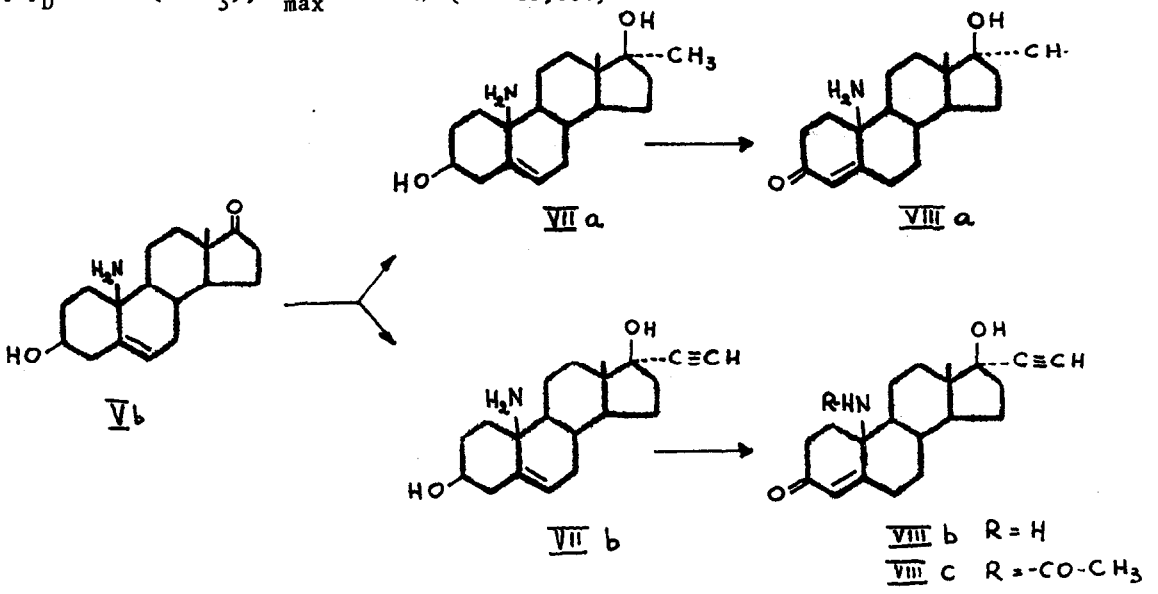


VI a) x = 3-OCOCH$_3$

VI b) x = =O

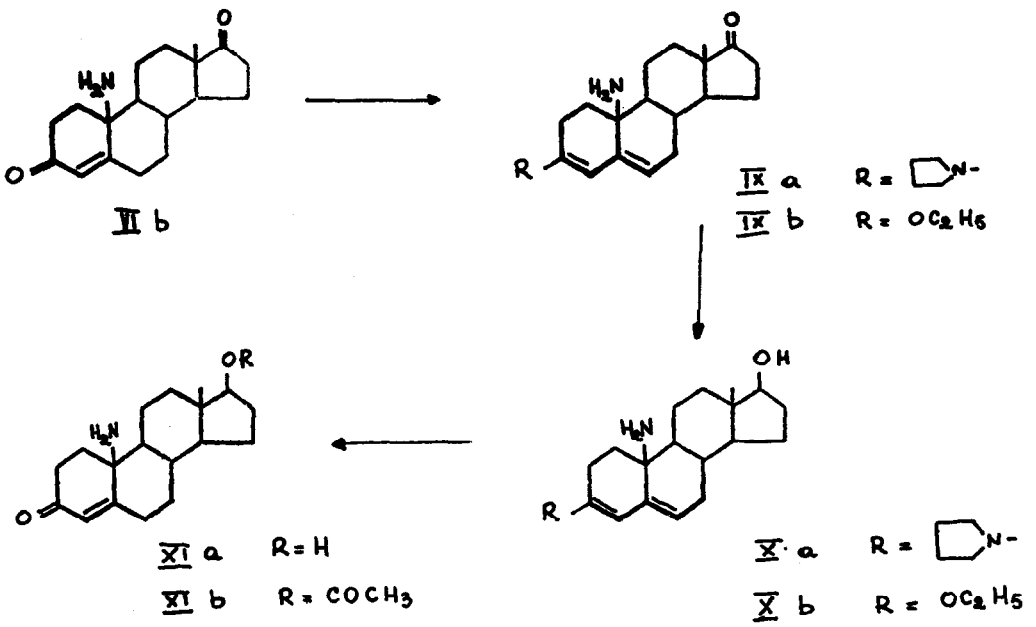
By reaction of Vb with methyl magnesium bromide in tetrahydrofurane or with acetylene potassium-tert-butoxide in tetrahydrofurane we obtained, respectively, 10β-amino-17α-methyl-19-nor-androst-5-ene-3β,17β-diol (VIIa), m.p. 221-223°C; $[\alpha]_D$= -119° (dioxane) and 10β-amino-17α-ethynyl-19-nor-androst-5-ene-3β,17β-diol, m.p. 185-188°C and 212-213.5°C; $[\alpha]_D$= -160° (dioxane).

By the Oppenauer reaction performed on these androstenediols we were able to obtain 17α-methyl-10β-amino-19-nor-testosterone (VIIIa), m.p. 177-179°C; $[\alpha]_D$= +79° ($CHCl_3$), λ_{max}^{EtOH} 235 mμ (ε = 13,000)



and 17α-ethynyl-10β-amino-19-nor-testosterone (VIIIb), m.p. 275-277°C; $[\alpha]_D$= +32° (dioxane); λ_{max}^{EtOH} 234 mμ (ε = 13,200); this latter, by acetylation with acetic anhydride in pyridine gives the corresponding 10β-acetamido derivative (VIIIc), m.p. 173-175°C; λ_{max}^{EtOH} 246 mμ (ε = 10,000).

In addition, starting from VIb, we prepared 3-N-pyrrolidyl-10β-amino-19-nor-androstane-3,5-diene-17-one (IXa); λ_{max}^{EtOH} 275 mμ (ε = 11,000), I.R.: 1740 cm^{-1} (17-ketone), 1642, 1610 cm^{-1}; 3-ethoxy-10β-amino-19-nor-androsta-3,5-diene-17-one (IXb); m.p. 172-175°C; λ_{max}^{EtOH} 243 mμ (ε = 21,500); I.R.: 1740 cm^{-1} (17-ketone), 1655, 1628 cm^{-1} (3-ethoxy-3,5-diene); NMR ($CDCl_3$): 9.03 τ (s. 3H, 18-CH_3), 8.70 τ (s. 2H, -NH_2[7]), 8.67 τ (s. 2H, -NH_2[7]), 8.67 τ (t. 3H, CH_3-C(H_2)-), 6.15 τ (q. 2H, CH_3-CH_2-O-), 4.80 τ(d. 1H, H in 4), 4.80-4.50 τ (m. 1H, H in 6).

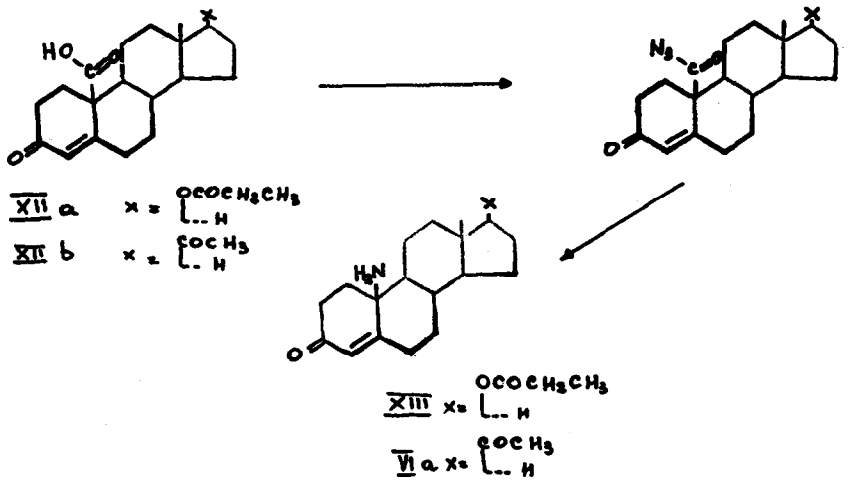


The reduction with $NaBH_4$ of IXb affords 3-ethoxy-10ß-amino-19-nor-androsta-3,5-diene-17ß-ol (Xb), m.p. 134-136°C; λ_{max}^{EtOH} 243 mμ (ε = 21,900); similarly the reduction with $LiAlH_4$ of IXa and the subsequent hydrolysis of enamine Xa gave 10ß-amino-19-nor-testosterone (XIa), m.p. 169-172°C.

The selective saponification of IVc to 3ß-acetoxy and the oxidation, according to Oppenauer of the resulting 3ß,17ß-diol-17-acetoxy-derivative (Vf) enabled us to obtain 10ß-amino-19-nor-testosterone-acetate (XIb), m.p. 155-157°C; λ_{max}^{EtOH} 234 mμ (ε = 14,500), NMR ($CDCl_3$), 9.12 τ (s. 3H, 18-CH_3), 8.52 τ (s. 2H, -NH_2[7]); 7.94 τ (s. 3H, 17ß CH_3COO), 5.54-5.10 τ (m. 1H, H in 17α), 4.20 τ (d. 1H, H in 4).

A further approach to 10ß-amino-derivatives is the application of Curtius reaction directly to 19-carboxy-azido-Δ^4-3-keto-steroids, which are prepared from the corresponding carboxylic acids (sodium salt and oxalyl chloride) or more profitably with the method of mixed anhydrides (8).

In this way, starting from androst-4-ene-17ß-ol-3-one-19-oic-acid-17-propionate (XIIIa), m.p. 122-124°C; $[\alpha]_D$= +129°, after Curtius transposition conducted on 19-carboxy-azido prepared according to (8), we obtained 10ß-amino-19-nor-testosterone-17-propionate, m.p. 119-121°C (XIII) and similarly from 19-nor-pregn-4-ene-3,20-dione-19-carboxylic acid (XIIb) we obtained 10ß-amino-19-nor-progesterone(VIa).



Experimental: Unless otherwise stated, specific rotations were measured in chloroform solution, U.V. spectra were taken in methanol solution and infrared spectra in nujol.
NMR spectra were recorded on a Varian A-60 (60 MC/S)-spectrometer in $CDCl_3$, with TMS as internal reference (ε = 10,000 ppm).

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