SYNTHESIS OF SOME STEROIDAL OXAZOLINES

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This paper is dedicated to the memory of Professor Václav Černý, DrSc.

Steroidal oxazolines **4a**–**4d** and **5a**–**5f** were synthesized. The acid-catalyzed reactions of 21-azido-20-hydroxy- and 21-hydroxy-20-azidosteroids with substituted aromatic aldehydes led to the formation of androst-5-en-3β-ols substituted in position 17β with oxazoline residues.

Keywords: Steroids; *Vicinal*-azidoalcohols; Oxazolines; Schmidt reaction.

Prostatic cancer is the second leading cause of cancer-related mortality worldwide. Considerable attention has been devoted to the development of drugs active against prostate cancer that intervene in the processes of tumour growth, and especially in the steroid metabolism pathways leading to testosterone[1]. Androgen deprivation by the inhibition of human cytochrome $P450_{17\alpha}$ (17α-hydroxylase/$C_{17,20}$-lyase), the enzyme responsible for the conversion of the C_{21} steroids to the C_{19} androgens, has been devised as a potential therapeutic approach to the treatment of this disease, which is frequently androgen dependent[2]. The syntheses of Abiraterone [(17-(3-pyridyl)androsta-5,16-dien-3β-ol] and its 4-en-3-one analogue were reported recently; these displayed a high inhibitory activity toward $P450_{17\alpha}$. It has been suggested that this activity is related to the presence of the heterocyclic moiety in the ring D, with the nitrogen atom lone pair coordinating to the heme iron atom at the active site of the enzyme[3]. A broad class of steroid derivatives substituted at C-17 with heterocyclic rings such as imidazole or triazole are also good inhibitors of this enzyme[4].

We set out to synthesize a novel series of steroidal oxazolines, containing the heterocycle with two heteroatoms at position 17β of androst-5-en-3β-ol.

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EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured in chloroform (*c* 1.0) on a Polamat-A (Zeiss, Jena) polarimeter at 23 °C and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. NMR spectra were recorded on Bruker AM 400 and Bruker DRX 500 instruments. Chemical shifts are reported in ppm (δ-scale), coupling constants (*J*) in Hz. For determination of multiplicities, the J-MOD pulse sequence was used. Elemental analysis data were determined with a Perkin–Elmer CHN analyser model 2400. The reactions were monitored by TLC (Merck Silica gel 60 F_{225}). Products were isolated by flash chromatography (Merck Kieselgel 60, 40–63 μm). In deacetylation reactions, alkaline alumina (pH 8–9) of activity I–II, standardized according to Brockmann (Aldrich Chemical Co. Ltd.), was used. All solvents were distilled prior to use.

3β,21-Diacetoxypregn-5-en-20-one (**1**)

To a stirred solution of 3β-acetoxypregn-5-en-20-one (1.8 g, 5 mmol) in benzene (50 ml), a solution of methanol (5 ml) in benzene (50 ml), a solution of $BF_3{\cdot}OEt_2$ (12 ml) in benzene (50 ml) and powdered $Pb(OAc)_4$ (3.5 g, 8 mmol) were added simultaneously in the course of 4 h. The mixture was diluted with diethyl ether (100 ml), and successively washed with 5% hydrochloric acid and water. The organic phase was evaporated and the resulting crude product was chromatographed on silica gel with *tert*-butyl methyl ether–light petroleum (20 : 80), yielding pure **1** (2 g, 90%), m.p. 164–165 °C, $[\alpha]_D$ +35 (ref.[5] gives 166–167.5 °C, $[\alpha]_D$ +29.3). ^{1}H NMR ($CDCl_3$): 0.67 s, 3 H (18-H_3); 1.00 s, 3 H (19-H_3); 2.02 s, 3 H (3-OAc-CH_3); 2.16 s, 3 H (21-OAc-CH_3); 2.50 m, 1 H; 4.53 d, 1 H, *J* = 16.8 and 4.71 d, 1 H, *J* = 16.8 (21-H_2); 4.60 m, 1 H (3-H). ^{13}C NMR ($CDCl_3$): 13.0 (C-18); 19.2 (C-19); 20.3 and 21.3 (2 × Ac-CH_3); 21.0, 22.8, 24.6, 27.7, 31.7, 31.8, 36.6, 37.1, 38.0, 38.5, 44.6, 49.8, 56.9, 59.2, 69.1 (C-21); 73.7 (C-3); 122.1 (C-6); 139.7 (C-5); 170.1 and 170.3 (2 × Ac-CO); 203.6 (C-20). For $C_{25}H_{36}O_5$ (416.6) calculated: 72.08% C, 8.71% H; found: 72.16% C, 8.83% H.

3β,21-Diacetoxypregn-5-en-20β-ol (**2b**)

Compound **1** (2.1 g, 5 mmol) was suspended in ethanol (100 ml), and KBH_4 (1.5 g, 30 mmol) was added in small portions while cooling the mixture in ice. pH of the reaction mixture was maintained between 6.5 and 7.5 by addition of acetic acid in the presence of Bromothymol Blue as indicator. At the end of the reduction, the reaction mixture was acidified with dilute hydrochloric acid. The resulting solution was diluted with water, and the precipitate was filtered off, washed until neutral, dissolved in chloroform and subjected to chromatographic separation on silica gel with a mixture of ethyl acetate–chloroform (2.5 : 97.5). The product was **2b** (1.7 g, 80%), m.p. 134–136 °C, $[\alpha]_D$ –50 (ref.[6] gives m.p. 136–137 °C, $[\alpha]_D$ –46). ^{1}H NMR ($CDCl_3$): 0.77 s, 3 H (18-H_3); 1.02 s, 3 H (19-H_3); 2.02 s, 3 H (3-OAc-CH_3); 2.09 s, 3 H (21-OAc-CH_3); 2.31 m, 2 H; 3.77 m, 1 H (20-H); 3.90 dd, 1 H, *J* = 11.5, 7.1 and 4.15 dd, 1 H, *J* = 11.5, 2.1 (21-H_2); 4.58 m, 1 H (3-H); 5.36 m, 1 H (6-H). ^{13}C NMR ($CDCl_3$): 12.2, 19.3, 20.8, 20.9 and 21.4 (2 × Ac-CH_3); 24.6, 24.8, 27.7, 31.6, 31.9, 36.6, 37.0, 38.1, 39.5, 42.5, 50.0, 52.3, 55.8, 68.8 (C-21); 72.6, 73.9, 122.3 (C-6); 139.7 (C-5); 170.5 (3-OAc-CH_3); 171.2 (21-OAc-CH_3). For $C_{25}H_{38}O_5$ (418.6) calculated: 71.74% C, 9.15% H; found: 71.85% C, 9.02% H.

3β,21-Diacetoxy-20β-tosyloxypregn-5-ene (**2c**)

Compound **2b** (2.09 g, 5 mmol) was dissolved in pyridine (20 ml) and a solution of tosyl chloride (1.05 g, 5.5 mmol) dissolved in pyridine (5 ml) was added while cooling the mixture in ice. The reaction mixture was allowed to stand at room temperature for 24 h and then saturated with water. The resulting precipitate was filtered off, washed and dried. The product was crystallized from methanol giving **2c** (2.5 g, 83%), m.p. 147–149 °C, $[\alpha]_D$ –41 (ref.[6] gives m.p. 149–150 °C, $[\alpha]_D$ –36). ^{1}H NMR ($CDCl_3$): 0.76 s, 3 H (18-H_3); 1.00 s, 3 H (19-H_3); 1.95 s, 3 H (21-OAc-CH_3); 2.02 s, 3 H (3-OAc-CH_3); 2.30 m, 2 H; 2.43 s, 3 H (tosyl-CH_3); 3.95 dd, 1 H, *J* = 12.8, 4.5 and 4.22 dd, 1 H, *J* = 12.8, 2.3 (21-H_2); 4.59 m, 1 H (3-H); 4.86 m, 1 H (20-H); 5.35 m, 1 H (6-H); 7.31 d, 2 H, *J* = 8.0 (3′-H and 5′-H); 7.79 d, 2 H, *J* = 8.0 (2′-H and 6′-H). ^{13}C NMR ($CDCl_3$): 11.7 (C-18); 19.3 (C-19); 20.6, 21.4 and 21.6 (tosyl-CH_3 and 2 × Ac-CH_3); 20.7, 24.1, 24.9, 27.7, 31.7, 31.8, 36.6, 37.0, 37.7, 37.9, 42.1, 49.9, 50.1, 56.0, 64.6 (C-21); 73.9 (C-3); 82.2 (C-20); 122.2 (C-6); 127.5 (2 C, C-2′ and C-5′); 129.6 (2 C, C-3′ and C-5′); 135.2 (C-1′); 139.8 (C-5); 144.4 (C-4′); 170.5 (2 C, 2 × Ac-CO). For $C_{32}H_{44}O_7S$ (572.8) calculated: 67.11% C, 7.74% H; found: 67.28% C, 7.55% H.

3β-Acetoxypregn-5-ene-20β,21-diol (**2a**)

Compound **2b** (4.18 g, 10 mmol) was dissolved in dichloromethane (25 ml) and the solution was added to alkaline alumina (200 g). The solvent was evaporated *in vacuo* at ambient temperature. The dry residue was placed in a Pyrex tube and irradiated at 90 W for 12 min inside a MAXIDIGEST-350 microwave oven. The product was eluted with ethyl acetate (500 ml) and the eluate was evaporated to dryness. The residual yellow oil was subjected to chromatographic separation on silica gel with a mixture of ethyl acetate–chloroform (2.5 : 87.5). The product was crystallized from methanol yielding **2a** (3.2 g, 76%), m.p. 174–175 °C, $[\alpha]_D$ –63 (ref.[6] gives m.p. 163–164 °C, $[\alpha]_D$ –49). ^{1}H NMR ($CDCl_3$): 0.79 s, 3 H (18-H_3); 1.03 s, 3 H (19-H_3); 2.03 s, 3 H (Ac-CH_3); 3.40 m, 1 H (20-H); 3.67 m, 2 H (21-H_2); 4.63 m, 1 H (3-H); 5.35 m, 1 H (6-H). ^{13}C NMR ($CDCl_3$): 12.3, 19.3, 20.9, 21.4, 24.6, 24.7, 27.7, 31.7, 31.9, 36.6, 37.0, 38.1, 39.6, 42.4, 50.1, 52.4, 55.9, 66.4 (C-21); 74.0, 74.6, 122.4 (C-6); 139.7 (C-5); 170.6 (Ac-CH_3). For $C_{23}H_{36}O_4$ (376.5) calculated: 73.37% C, 9.64% H; found: 73.10% C, 9.82% H.

3β-Acetoxy-21-iodopregn-5-en-20β-ol (**2d**)

To dry dichloromethane (20 ml) were successively added triphenylphosphine (1.57 g, 6 mmol), imidazole (408 mg, 6 mmol), iodine (760 mg, 6 mmol) and a solution of compound **2a** in dichloromethane (20 ml), and the mixture was stirred at room temperature. The disappearance of the starting material was followed by TLC. When the reaction was complete, most of the solvent was removed *in vacuo* and the residual oil was dissolved in chloroform for chromatographic separation with chloroform on silica gel. The product was **2d** (2.1 g, 72%), m.p. 169–170 °C, $[\alpha]_D$ –72. ^{1}H NMR ($CDCl_3$): 0.79 s, 3 H (18-H_3); 1.03 s, 3 H (19-H_3); 2.03 s, 3 H (Ac-CH_3); 3.20 dd, 1 H, *J* = 10.1, 6.5 and 3.47 dd, 1 H, *J* = 10.1, 2.3 (21-H_2); 3.29 m, 1 H (20-H); 4.60 m, 1 H (3-H); 5.37 m, 1 H (6-H). ^{13}C NMR ($CDCl_3$): 12.6 (C-18); 19.2, 19.3 (C-19); 20.7, 21.3, 24.5, 25.0, 27.5, 31.8, 36.5, 37.3, 38.1, 39.2, 42.6, 49.9, 55.7 (2 C); 72.8, 73.8 (C-39); 122.3 (C-6); 139.7 (C-5); 170.4 (Ac-CO). For $C_{23}H_{35}IO_3$ (486.4) calculated: 56.79% C, 7.25% H; found: 56.88% C, 7.36% H.

3β-Acetoxy-21-azidopregn-5-en-20β-ol (**2e**)

Compound **2d** (973 mg, 2 mmol) was dissolved in dimethylformamide (25 ml), NaN_3 (520 mg, 8 mmol) was added, the mixture was stirred at 80 °C for 3 h and then poured into water (250 ml). The resulting precipitate was filtered off, dissolved in chloroform and chromatographed on silica gel with *tert*-butyl methyl ether–light petroleum (20 : 70), which afforded **2e** (650 mg, 81%), m.p. 170–171 °C, $[\alpha]_D$ –57. ^{1}H NMR ($CDCl_3$): 0.78 s, 3 H (18-H_3); 1.03 s, 3 H (19-H_3); 2.04 s, 3 H (Ac-CH_3); 3.21 dd, 1 H, *J* = 12.4, 7.1 and 3.88 dd, 1 H, *J* = 12.4, 2.4 (21-H_2); 3.70 m, 1 H (20-H); 4.60 m, 1 H (3-H); 5.37 m, 1 H (6-H). ^{13}C NMR ($CDCl_3$): 12.1 (C-18); 19.2 (C-19); 20.7 (Ac-CH_3); 21.3, 24.5, 24.8, 27.6, 31.6, 31.8, 36.5, 42.4, 49.9, 53.1, 55.8, 57.1 (C-21); 73.3, 73.8 (C-3); 122.2 (C-6); 139.6 (C-5); 170.5 (Ac-CO). For $C_{23}H_{35}O_3N_3$ (401.5) calculated: 68.80% C, 8.79% H; found: 68.92% C, 8.65% H.

3β,21-Diacetoxy-20α-azidopregn-5-ene (**3a**)

Method A. Compound **2c** (2.86 g, 5 mmol) was dissolved in dimethylformamide (50 ml), NaN_3 (1.3 g, 20 mmol) was added, the mixture was stirred at 80 °C for 4 h and then poured into water (500 ml). The precipitate was filtered off, dissolved in chloroform and chromatographed on silica gel with ethyl acetate–chloroform (2.5 : 97.5) to afford **3a** (1.9 g, 86%).

Method B. Compound **2b** (420 mg, 1 mmol) was dissolved in toluene (15 ml), then triphenylphosphine (510 mg, 2 mmol) and $Zn(N_3)_2 \cdot (pyridine)_2$ (230 mg, 0.75 mol) were added as a suspension. To this stirred mixture, diethyl diazenedicarboxylate (0.4 ml, 2 mmol) was added dropwise at room temperature, which resulted in a slightly exothermic reaction. Stirring was continued until the disappearance of the starting compound (TLC monitoring). The heterogeneous mixture was filtered through a Celite pad, concentrated *in vacuo* and chromatographed on silica gel as described in method *A* yielding **3a** (280 mg, 63%), m.p. 141–143 °C, $[\alpha]_D$ –38. ^{1}H NMR ($CDCl_3$): 0.75 s, 3 H (18-H_3); 1.02 s, 3 H (19-H_3); 2.05 s, 3 H (3-OAc-CH_3); 2.11 s, 3 H (21-OAc-CH_3); 2.32 m, 2 H; 3.47 m, 1 H (20-H); 3.99 dd, 1 H, *J* = 11.6, 8.2 and 4.41 dd, 1 H, *J* = 11.6, 2.9 (21-H_2); 4.61 m, 1 H (3-H); 5.37 m, 1 H (6-H). ^{13}C NMR ($CDCl_3$): 12.3 (C-18); 19.2 (C-19); 20.6 and 21.3 (2 × Ac-CH_3); 20.7, 24.1, 26.1, 27.7, 31.6, 31.7, 36.6, 36.9, 38.1, 38.4, 41.8, 49.9, 50.9, 56.2, 63.4 (C-20); 66.3 (C-21); 73.8 (C-3); 122.3 (C-6); 139.7 (C-5); 170.4 and 170.6 (2 × Ac-CO). For $C_{25}H_{37}N_3O_4$ (443.6) calculated: 67.69% C, 8.41% H; found: 67.52% C, 8.50% H.

3β,21-Dihydroxy-20α-azidopregn-5-ene (**3b**)

Compound **3a** (443 mg, 1 mmol) was dissolved in methanol (20 ml) containing MeONa (11 mg, 0.2 mmol) and the solution was left standing at ambient temperature for 24 h. It was then diluted with water, the formed precipitate was filtered off and crystallized from acetone–water yielding pure **3b**, m.p. 140–143 °C, $[\alpha]_D$ –38. ^{1}H NMR ($CDCl_3$): 0.74 s, 3 H (18-H_3); 1.01 s, 3 H (19-H_3); 3.38 m, 1 H (20-H); 3.52 m, 1 H (3-H); 3.55 dd, 1 H, *J* = 11.5, 7.9 and 3.85 dd, 1 H, *J* = 11.5, 3.0 (21-H_2); 5.35 m, 1 H (6-H). ^{13}C NMR ($CDCl_3$): 12.4 (C-18); 19.4 (C-19); 20.8, 24.2, 26.1, 31.6, 31.7, 31.8, 36.5, 37.3, 38.6, 41.9, 42.1, 50.1, 51.3, 56.3, 64.9 (C-21); 67.6 (C-20); 71.7 (C-3); 121.4 (C-6); 140.8 (C-5). For $C_{21}H_{33}N_3O_2$ (359.5) calculated: 70.16% C, 9.25% H; found: 70.02% C, 9.34% H.

General Procedure for Preparation of Compounds **4a**, **4c**, **4e** and **5b**, **5d**

A solution of compound **2e** or **3b** (l mmol) and a 4-substituted benzaldehyde (1.1 equivalent) in dichloromethane (20 ml) was cooled to 0 °C, followed by dropwise addition of $BF_3{\cdot}OEt_2$ (2.0 equivalents); the addition of acid was accompanied by gas evolution. The reaction mixture was allowed to warm to room temperature and the solution was stirred for 2 h. Saturated $NaHCO_3$ solution was added slowly and the mixture was stirred until bubbling ceased. The reaction mixture was extracted with dichloromethane, the organic layer was washed with brine, dried and concentrated *in vacuo* to afford the crude product, which was purified by chromatography on silica gel; **4a**, **4c** and **4e** were eluted with ethyl acetate–chloroform (30 : 70), and **5b** and **5d** with ethyl acetate–chloroform (2.5 : 97.5).

*17*β-*[2-(4-Bromophenyl)-4,5-dihydrooxazol-4-yl]androst-5-en-3*β-*ol* (**4a**). Yield 358 mg (72%), m.p. 178–180 °C, $[\alpha]_D$ –27. ^{1}H NMR ($CDCl_3$): 0.77 s, 3 H (18-H_3); 1.02 s, 3 H (19-H_3); 3.52 m, 1 H (3-H); 4.02 t, 1 H, *J* = 8.4 and 4.50 t, 1 H, *J* = 8.4 (21-H_2); 4.15 q, 1 H, *J* = 9.4 (20-H); 5.35 m, 1 H (6-H); 7.52 d, 2 H, *J* = 8.4 (3′-H and 5′-H); 7.79 d, 2 H, *J* = 8.4 (2′-H and 6′-H). ^{13}C NMR ($CDCl_3$): 13.3 (C-18); 19.4 (C-19); 20.8, 24.4, 26.5, 31.6, 31.7 (C-8); 31.8, 36.8, 37.3, 38.9, 42.1, 42.3, 50.2, 56.0, 56.5, 69.2 (C-20); 71.7 (C-3); 72.3 (C-21); 121.5 (C-6); 125.7 (C-4′); 127.0 (C-1′); 129.7 (2 C, C-2′ and C-6′); 131.5 (2 C, C-3′ and C-5′); 140.7 (C-5); 162.2 (C(N,O)). For $C_{28}H_{36}BrNO_2$ (498.5) calculated: 67.46% C, 7.28% H; found: 67.50% C, 7.12% H.

*17*β-*[2-(4-Nitrophenyl)-4,5-dihydrooxazol-4-yl]androst-5-en-3*β-*ol* (**4c**). Yield 292 mg (63%), m.p. 196–198 °C, $[\alpha]_D$ –29. ^{1}H NMR ($CDCl_3$): 0.79 s, 3 H (18-H_3); 1.03 s, 3 H (19-H_3); 3.52 m, 1 H (3-H); 4.08 dd, 1 H, *J* = 9.7, 8.1 and 4.57 dd, 1 H, *J* = 9.2, 8.1 (21-H_2); 4.22 q, 1 H, *J* = 9.5 (20-H); 5.36 m, 1 H (6-H); 8.09 d, 2 H, *J* = 8.5 (2′-H and 6′-H); 8.24 d, 2 H, *J* = 8.5 (3′-H and 5′-H). ^{13}C NMR ($CDCl_3$): 13.4 (C-18); 19.4 (C-19); 20.8, 24.4, 26.5, 31.6, 31.7 (C-8); 31.8, 36.6, 37.3, 38.9, 42.2, 42.3, 50.2, 56.0, 56.4, 69.5 (C-20); 71.7 (C-3); 72.7 (C-21); 121.5 (C-6); 123.4 (2 C, C-3′ and C-5′); 129.2 (2 C, C-2′ and C-6′); 133.9 (C-1′); 140.7 (C-5); 149.4 (C-4′); 161.2 (C(N,O)). For $C_{28}H_{36}N_2O_4$ (464.6) calculated: 72.39% C, 7.81% H; found: 72.45% C, 7.92% H.

*17*β-*[2-(4-Methoxyphenyl)-4,5-dihydrooxazol-4-yl]androst-5-en-3*β-*ol* (**4e**). Yield 247 mg (55%), m.p. 160–163 °C, $[\alpha]_D$ –26. ^{1}H NMR ($CDCl_3$): 0.77 s, 3 H (18-H_3); 1.02 s, 3 H (19-H_3); 3.52 m, 1 H (3-H); 3.83 s, 3 H (OCH_3); 4.00 t, 1 H, *J* = 8.1 and 4.48 t, 1 H, *J* = 8.1 (21-H_2); 4.14 q, 1 H, *J* = 9.4 (20-H); 5.36 m, 1 H (6-H); 6.89 d, 2 H, *J* = 8.6 (3′-H and 5′-H); 7.87 d, 2 H, *J* = 8.6, (2′-H and 6′-H). ^{13}C NMR ($CDCl_3$): 13.3 (C-18); 19.4 (C-19); 20.8, 24.5, 26.5, 31.6, 31.7, 31.8 (C-8); 36.6, 37.3, 38.9, 42.1, 42.3, 50.2, 55.3, 56.0, 56.6, 69.0 (C-20); 71.7 (C-3); 72.0 (C-21); 113.6 (2 C, C-3′ and C-5′); 120.6 (C-1′); 121.6 (C-6); 129.9 (2 C, C-2′ and C-6′); 140.7 (C-5); 161.9 and 162.7 (C(N,O) and C-4′). For $C_{29}H_{39}NO_3$ (449.6) calculated: 77.47% C, 8.74% H; found: 77.56% C, 8.82% H.

*3*β-*Acetoxy-17*β-*[2-(4-bromophenyl)]-4,5-dihydrooxazol-5-yl]androst-5-ene* (**5b**). Yield 464 mg (86%), m.p. 103–105 °C, $[\alpha]_D$ –40. ^{1}H NMR ($CDCl_3$): 0.86 s, 3 H (18-H_3); 1.05 s, 3 H (19-H_3); 2.02 s, 3 H (Ac-CH_3); 3.62 dd, 1 H, *J* = 14.5, 8.1 and 4.03 dd, 1 H, *J* = 14.5, 9.4 (21-H_2); 4.61 m, 2 H (3 H and 20-H); 5.37 m, 6 H; 7.53 d, 2 H, *J* = 8.4 (3′-H and 5′-H); 7.78 d, 2 H, *J* = 8.4 (2′-H and 6′-H). ^{13}C NMR ($CDCl_3$): 12.7 (C-18); 19.3 (C-19); 20.8, 21.4 (Ac-CH_3); 23.7, 27.8, 31.7, 31.9, 36.7, 37.0, 38.1, 39.0, 42.7, 50.1, 54.9, 55.9, 59.8 (C-21); 73.9 (C-3); 82.0 (C-20); 122.4 (C-6); 125.8 (C-4′); 127.1 (C-1′); 129.6 (2 C, 2-C′ and C-6′); 131.6 (2 C, C-3′ and C-5′); 139.8 (C-5); 163.4 (C(N,O)); 170.5 (Ac-CO). For $C_{30}H_{38}BrNO_3$ (540.5) calculated: 66.66% C, 7.09% H; found: 66.53% C, 7.22% H.

3β-Acetoxy-*17*β-*[2-(4-nitrophenyl)-4,5-dihydrooxazol-5-yl]androst-5-ene* (**5d**). Yield 445 mg (88%), m.p. 111–113 °C, $[\alpha]_D$ –34. ^{1}H NMR ($CDCl_3$): 0.88 s, 3 H (18-H_3); 1.06 s, 3 H (19-H_3); 2.03 s, 3 H (Ac-CH_3); 3.69 dd, 1 H, *J* = 14.9, 8.2 and 4.11 dd, 1 H, *J* = 14.9, 9.4 (21-H_2); 4.58 m, 1 H (3-H); 4.72 dd, 1 H, *J* =17.9, 8.8 (20-H); 5.38 m, 1 H (6-H); 8.08 d, 2 H, *J* = 8.8 (2′-H and 6′-H); 8.25 d, 2 H, *J* = 8.8 (3′-H and 5′-H). ^{13}C NMR ($CDCl_3$): 12.6 (C-18); 19.3 (C-19); 20.7, 21.3, 23.6, 24.6, 27.7, 31.6, 31.8, 36.6, 36.9, 38.4, 38.9, 42.6, 50.0, 54.9, 55.8, 60.0 (C-21); 73.8 (C-3); 82.4 (C-20); 122.2 (C-6); 123.4 (2 C, C-3′ and C-5′); 129.0 (2 C, C-2′ and C-6′); 133.9 (C-1′); 139.7 (C-4′); 149.3 (C-5); 162.2 (C(N,O)); 170.4 (Ac-CO). For $C_{30}H_{38}N_2O_5$ (506.6) calculated: 71.12% C, 7.56% H; found: 71.25% C, 7.65% H.

General Procedure for Acetylation of Compounds **4a**, **4c** and **4e**

Compound **4a**, **4c** or **4e** (1 mmol) was dissolved in a mixture of pyridine (5 ml) and acetic anhydride (3 ml, 0.03 mol), the solution was left standing for 24 h and then poured onto ice (50 g). The resulting precipitate was filtered off, washed and dried. The crude products **4b**, **4d** or **4f** were crystallized from methanol.

4-β-*Acetoxy-17*β-*[2-(4-bromophenyl)-4,5-dihydrooxazol-4-yl]androst-5-ene* (**4b**). After acetylation of **4a** by the general method, yield 486 mg (90%), m.p. 185–189 °C, $[\alpha]_D$ –30. ^{1}H NMR ($CDCl_3$): 0.77 s, 3 H (18-H_3); 1.04 s, 3 H (19-H_3); 2.03 s, 3 H (Ac-CH_3); 2.33 m, 2 H; 4.02 dd, 1 H, *J* = 9.5, 8.1 and 4.50 dd, 1 H, *J* = 9.0, 8.1 (21-H_2); 4.15 q, 1 H, *J* = 9.4 (20-H); 4.62 m, 1 H (3-H); 5.38 m, 1 H (6-H); 7.52 d, 2 H, *J* = 8.4 (3′-H and 5′-H); 7.79 d, 2 H, *J* = 8.4 (2′-H and 6′-H). ^{13}C NMR ($CDCl_3$): 13.3 (C-18); 19.3 (C-19); 20.7, 21.4 (Ac-CH_3); 24.4, 26.4, 27.7, 31.7 (C-8); 31.8, 36.6, 37.0, 38.1, 38.8, 42.1, 50.1, 55.9, 56.5, 69.1 (C-20); 72.3 (C-21); 73.9 (C-3); 122.5 (C-6); 125.7 (C-4′); 127.0 (C-1′); 129.7 (2 C, C-2′ and C-6′); 131.5 (2 C, C-3′ and C-5′); 139.6 (C-5); 162.2 (C(N,O)); 170.5 (Ac-CO). For $C_{30}H_{38}BrNO_3$ (540.5) calculated: 66.66% C, 7.09% H; found: 66.52% C, 6.98% H.

*3*β-*Acetoxy-17*β-*[2-(4-nitrophenyl)-4,5-dihydrooxazol-4-yl]androst-5-ene* (**4d**). After acetylation of **4c** by the general method, yield 466 mg (92%), m.p. 78–80 °C, $[\alpha]_D$ –32. ^{1}H NMR ($CDCl_3$): 0.79 s, 3 H (18-H_3); 1.00 s, 3 H (19-H_3); 2.03 s, 3 H (Ac-CH_3); 2.34 m, 2 H; 4.10 t, 1 H, *J* = 8.6 and 4.57 t, 1 H, *J* = 8.6 (21-H_2); 4.22 q, 1 H, *J* = 9.5 (20-H); 4.60 m, 1 H (3-H); 5.39 m, 1 H (6-H); 8.10 d, 2 H, *J* = 8.5 (2′-H and 6′-H); 8.24 d, 2 H, *J* = 8.5 (3′-H and 5′-H). ^{13}C NMR ($CDCl_3$): 13.4 (C-18); 19.3 (C-19); 20.7, 21.4 (Ac-CH_3); 24.4, 26.4, 27.8, 31.7 (C-8); 31.8, 36.6, 37.0, 38.1, 38.8, 42.1, 50.1, 55.9, 56.4, 69.5 (C-20); 72.7 (C-21); 73.9 (C-3); 122.5 (C-6); 123.4 (2 C, C-3′ and C-5′); 129.2 (2 C, C-2′ and C-6′); 133.9 (C-1′); 139.6 (C-5); 149.4 (C-4′); 161.2 (C(N,O)); 170.5 (Ac-CO). For $C_{30}H_{38}N_2O_5$ (506.6) calculated: 71.12% C, 7.56% H; found: 71.28% C, 7.62% H.

*3*β-*Acetoxy-17*β-*[2-(4-methoxyphenyl)-4,5-dihydrooxazol-4-yl]androst-5-ene* (**4f**). After acetylation of **4e** by the general method, yield 432 mg (96%), m.p. 188–190 °C, $[\alpha]_D$ –28. ^{1}H NMR ($CDCl_3$): 0.77 s, 3 H (18-H_3); 1.02 s, 3 H (19-H_3); 2.03 s, 3 H (Ac-CH_3); 2.33 m, 2 H; 3.83 s, 3 H (OCH_3); 4.00 t, 1 H, *J* = 8.5 and 4.47 t, 1 H, *J* = 8.5 (21-H_2); 4.14 q, 1 H, *J* = 9.3 (20-H); 4.47 m, 1 H (3-H); 5.38 m, 1 H (6-H); 6.88 d, 2 H, *J* = 8.6 (3′-H and 5′-H); 7.87 d, 2 H, *J* = 8.6 (2′-H and 6′-H). ^{13}C NMR ($CDCl_3$): 13.3 (C-18); 19.3 (C-19); 20.7, 21.4, 24.4 (Ac-CH_3); 26.5, 27.7, 31.7 (C-8); 31.8, 36.6, 37.0, 38.1, 38.8, 42.0, 50.1, 55.3, 55.9, 56.6, 68.9 (C-20); 72.0 (C-21); 73.9 (C-3); 113.5 (2 C, C-3′ and C-5′); 120.6 (C-1′); 122.5 (C-6); 129.9 (2 C, C-2′ and C-6′); 139.6 (C-5); 161.9 and 162.7 (C(N,O) and C-4′); 170.5 (Ac-CO). For $C_{31}H_{41}NO_4$ (491.7) calculated: 75.73% C, 8.41% H; found: 75.92% C, 8.26% H.

General Procedure for Deacetylation of Compounds **5b**, **5d**

Compound **5b** or **5d** (1 mmol) was dissolved in methanol (20 ml) containing MeONa (11 mg, 0.2 mmol), the solution was left standing for 24 h and then poured into water (50 ml). The formed precipitate of **5a** or **5c** was filtered off and crystallized from acetone–light petroleum.

*17*β-*[2-(4-Bromophenyl)-4,5-dihydrooxazol-5-yl]androst-5-en-3*β-*ol* (**5a**). After deacetylation of **5b** by the general method, yield 463 mg (93%), m.p. 202–203 °C, $[\alpha]_D$ –38. ^{1}H NMR ($CDCl_3$): 0.87 s, 3 H (18-H_3); 1.04 s, 3 H (19-H_3); 3.52 m, 1 H (3-H); 3.62 dd, 1 H, *J* = 14.1, 8.0 and 4.04 dd, 1 H, *J* = 14.1, 9.6 (21-H_2); 4.65 m, 1 H (20-H); 5.35 m, 1 H (6-H); 7.54 d, 2 H, *J* = 7.6 (3′-H and 5′-H); 7.78 d, 1 H, *J* = 7.6 (2′-H and 6′-H). ^{13}C NMR ($CDCl_3$): 12.7 (C-18); 19.4 (C-19); 20.9, 23.7 (Ac-CH_3); 24.7, 31.7, 31.8, 31.9, 36.6, 37.3, 39.1, 42.3, 42.7, 50.3, 55.0, 56.0, 59.9 (C-21); 71.7 (C-3); 82.0 (C-20); 121.4 (C-6); 125.8 (C-4′); 127.1 (C-1′); 129.6 (2 C, C-2′ and C-6′); 131.6 (2 C, C-3′ and C-5′); 140.9 (C-5); 163.4 (C(N,O)). For $C_{28}H_{36}BrNO_2$ (498.5) calculated: 67.46% C, 7.28% H; found: 67.35% C, 7.36% H.

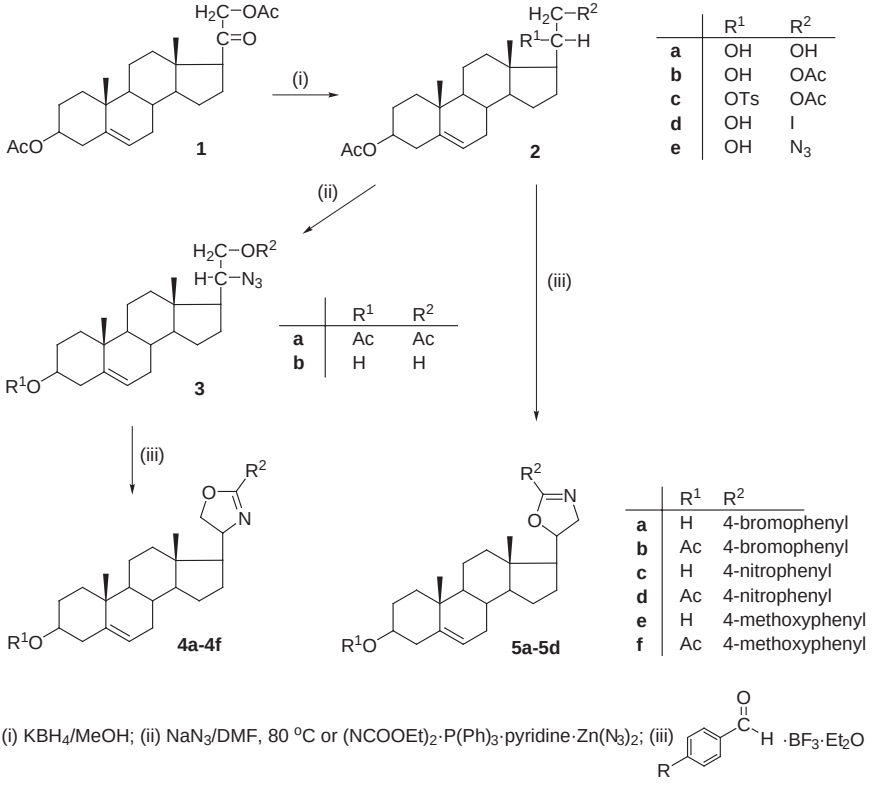
*17*β-*[2-(4-Nitrophenyl)-4,5-dihydrooxazol-5-yl]androst-5-en-3*β-*ol* (**5c**). After deacetylation of **5d** by the general method, yield 427 mg (92%), m.p. 236–238 °C, $[\alpha]_D$ –48. ^{1}H NMR ($CDCl_3$): 0.88 s, 3 H (18-H_3); 1.05 s, 3 H (19-H_3); 3.52 m, 1 H (3-H); 3.69 dd, 1 H, *J* = 14.6, 8.1 and 4.11 dd, 1 H, *J* =14.6, 7.7 (21-H_2); 4.73 dd, 1 H, *J* =17.9, 8.9 (20-H); 5.35 m, 1 H (6-H); 8.09 d, 2 H, *J* = 8.2 (2′-H and 6′-H); 8.26 d, 2 H, *J* = 8.2 (3′-H and 5′-H). ^{13}C NMR ($CDCl_3$): 12.7 (C-18); 19.4 (C-19); 20.9, 23.7, 24.7, 31.6, 31.7, 31.9, 36.6, 37.3, 39.1, 42.3, 42.7, 50.2, 54.9, 56.0, 60.0 (C-21); 71.6 (C-3); 82.5 (C-20); 121.3 (C-6); 123.5 (2 C, C-3′ and C-5′); 129.1 (2 C, C-2′ and C-6′); 133.9 (C-1′); 140.9 (C-4′); 149.2 (C-5); 162.4 (C(N,O)). For $C_{28}H_{36}N_2O_4$ (464.6) calculated: 72.39% C, 7.81% H; found: 72.55% C, 765% H.

RESULTS AND DISCUSSION

The reaction between a carbonyl compound (ketone or aldehyde) and hydrazoic acid is a method for the insertion of an NH group between the carbonyl group and an alkyl group, converting the starting compound into an amide[7]. In an extension of this classic Schmidt reaction, Boyer and Hammer found that the reactions of alkyl azides with aromatic aldehydes could be carried out with H_2SO_4 in benzene to afford amides in moderate yields. In contrast, the use of β- or γ-azidoalcohols under similar conditions afforded oxazolines or dihydrooxazines, respectively, with much greater efficiency[8]. Later on, a variety of Lewis acids were examined, of which $BF_3{\cdot}OEt_2$ was found to be the most convenient[9].

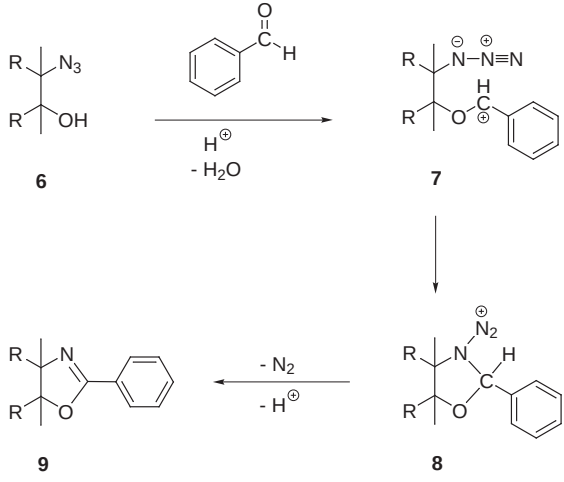
This observation provides a possibility for the preparation of compounds containing various substituted oxazolines condensed to ring D of the androstane skeleton, which are potentially biologically active compounds. In our synthesis, 3β,21-diacetoxypregn-5-en-20-one (**1**) was used as starting material. Reduction with KBH_4 gave two compounds, 3β,21-diacetoxypregn--5-en-20β-ol (**2b**) and its 20α epimer, in a ratio of 9 : 1. The required pure epimer **2b** was obtained by flash chromatography. The 20β-tosyloxy compound **2c**, prepared with tosyl chloride in pyridine, was reacted with NaN_3

in dimethylformamide to furnish **3a**. For the preparation of **3a**, we also used a simple one-step reaction[10]. Treatment of **2b** with the zinc azide/bis-pyridine complex, triphenylphosphine and diethyl diazenedicarboxylate afforded the corresponding azide **3a** in moderate yield. Compound **3b** for cyclization was obtained after deacetylation of **3a** by the Zemplen method. The other starting compound for cyclization to obtain steroids with the 20β configuration was **2b**. Their selective deacetylation was carried out at the secondary acetoxy group by an earlier developed method[11]. Compound **2b** was subjected to microwave irradiation at 90 W on alkaline alumina in a household microwave apparatus. After irradiation of **2b**, **2a** was obtained in 86% yield. Iodination by the Appel reaction[12] produced the iodohydrin **2d**. Nucleophilic exchange with NaN_3 in dimethylformamide led to the required 21-azido-20β-ol **2e**. Compound **2e** was suitable for the cyclization of heterocycles with the 20β configuration, while **3b** resulted in the 20α configuration (Scheme 1).



SCHEME 1

Mechanistically, it can be presumed[13] that the first step in the Schmidt reaction involves hemiacetal formation between the aromatic aldehyde and the steroid azidoalcohol **6**, which undergoes elimination to afford a benzyl carbocation **7**. Intramolecular attack of the azide group on the carbocation furnishes intermediate **8**, and subsequent proton elimination and N_2 detachment give the product **9** (Scheme 2).



SCHEME 2

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