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Reaction of Steroid-17α-hydroxy-17-carboxylic Acids with Carbodiimides. Synthesis of Steroid-17-spiro-5′-[2′-imino-4′-oxazolidinones] and 17-Spiro-5′-[2′,4′-oxazolidinediones][1)]

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Steroid-17α-hydroxy-17-carboxylic acids (2) were allowed to react with carbodiimides (DCCI, DPCI, DTCI, EDCI) to afford 17-spiro-5′-[2′-imino-4′-oxazolidinones] (3—5, 11), 17-spiro-5′-[2′,4′-oxazolidinediones] (7—9) and *N*-acylureas (10), depending on the reaction conditions. The reaction in acetonitrile in the presence of $CuCl_2$ gave 3—5, while that in *N,N*-dimethylformamide gave 7—9. The reaction with DTCI under basic conditions afforded 10 along with 9.

Keywords steroid-17-spiro compound; steroid-17α-hydroxy-17-carboxylic acid; carbodiimide; 2-imino-4-oxazolidinone; 2,4-oxazolidinedione; anti-angiogenic activity

A variety of steroid-17-spiro-heterocycles[2)] have been synthesized in the search for new bioactive steroids. Recently, Ginanneschi *et al.*[3)] reported the synthesis of steroid-17-spiro-5′-[2′,4′-oxazolidinediones] from the parent 17-ketones, and Weindel *et al.*[4)] investigated the inhibitory effects of various steroid-17-spiro compounds, including 17-spiro-5′-[2′-oxazolidinones], on aldosterone biosynthesis. It is known that α-hydroxyesters condense with carbodiimides to afford 2-imino-4-oxazolidinones; for example, Schmidt and Carl[5)] reported the synthesis of 3-alkyl-2-alkylimino-4-oxazolidinones by the reaction of ethyl glycolate or ethyl lactate with 1,3-dialkylcarbodiimides in acetone in the presence of $CuCl_2$. On the other hand, Schulte *et al.*[6)] claimed to have obtained 1,3-diphenyl-5-methoxycarbonylmethyl-2,4-imidazolidinedione from dimethyl malate and 1,3-diphenylcarbodiimide by heating in the presence of CuCl and 1,4-diazabicyclo-[2.2.2]octane (DABCO). These reports prompted us to treat steroid-17α-hydroxy-17-carboxylic acids or their esters with carbodiimides, anticipating the formation of steroid-17-spiro compounds. This paper describes the reaction of steroid-17α-hydroxy-17-carboxylic acids with carbodiimides, resulting in the formation of 17-spiro-5′-[2′-imino-4′-oxazolidinones] or 17-spiro-5′-[2′,4′-oxazolidinediones], depending on the reaction conditions (Chart 1). Some compounds prepared in the present study exhibited anti-angiogenic activity.

The methyl ester of 17α-hydroxy-3-oxoandrost-4-ene-17-carboxylic acid (**2a**),[7)] which is easily obtained from cortexolone (**1a**) by periodate oxidation,[8)] was treated with 1,3-dicyclohexylcarbodiimide (DCCI) in acetone in the presence of $CuCl_2$, according to Schmidt and Carl,[5)] but no reaction was observed even when the mixture was heated. When free carboxylic acid (**2a**) was used instead of the ester, the reaction proceeded unsatisfactorily, giving a mixture of products. After attempts to find an appropriate reaction solvent, it was found that acetonitrile afforded essentially a single product.

Thus, the reaction of 1 eq of **2a** with 2 eq of DCCI in acetonitrile[9)] in the presence of $CuCl_2$ was carried out at room temperature. The structure of the product, as expected, was determined to be (17*R*)-3′-cyclohexyl-2′-

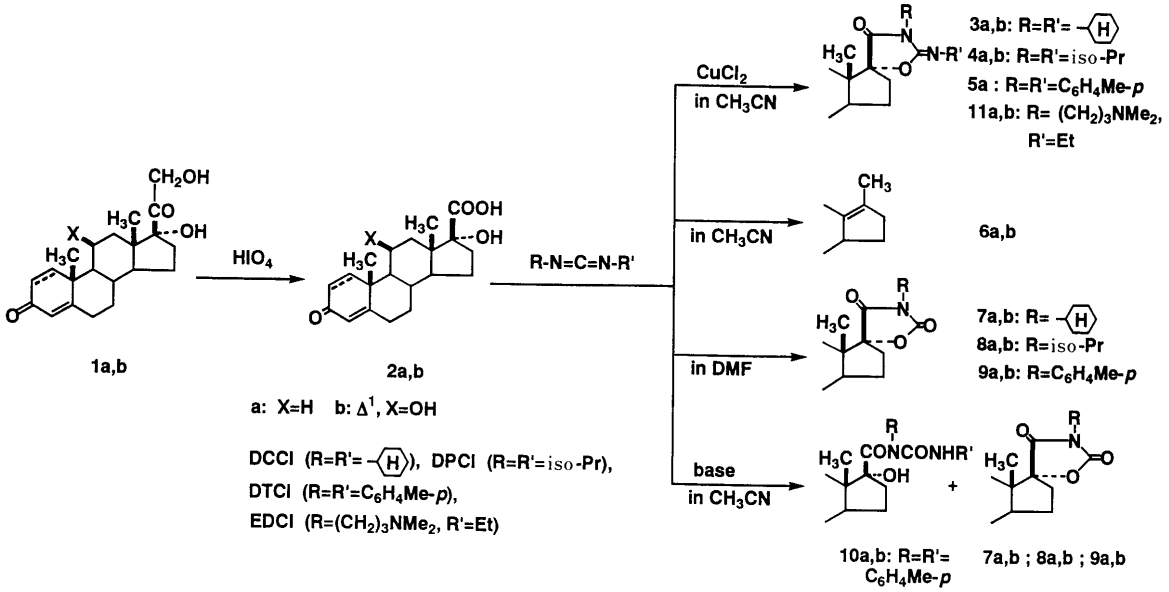

Chart 1

cyclohexyliminospiro[androst-4-ene-17,5′-oxazolidine]-3,4′-dione (**3a**) on the basis of the mass, IR and NMR spectra. When this reaction was carried out in the absence of $CuCl_2$, a less polar substance was obtained as the main product. The NMR data revealed the presence of a tetra-substituted olefinic bond, showing olefinic carbon resonances at δ 128.40 and 135.26 in the ^{13}C-NMR and no appearance of olefinic protons in ^{1}H-NMR. The structure of the product was finally confirmed to be 17-methyl-18-norandrosta-4,13(17)-dien-3-one (**6a**), formed through migration of the 18-methyl group from C-13 to C-17,[10] on the basis of the appearance of the molecular ion peak at *m/z* 270 in the electron impact-mass spectra (EI-MS) and also the good accordance of the melting point and optical rotation with those reported in the literature.[11]

Interestingly, when this reaction was carried out in *N*,*N*-dimethylformamide (DMF), a different compound was obtained. Its structure was assigned as (17*R*)-3′-cyclohexylspiro[androst-4-ene-17,5′-oxazolidine]-2′,3,4′-trione (**7a**) on the basis of the spectral data, which were in good accordance with those of (17*R*)-3′-pentylspiro-[androst-4-ene-17,5′-oxazolidine]-2′,3,4′-trione reported by Ginanneschi *et al.*[3] Compound **7a** could also be obtained in good yield by hydrolysis of **3a** in 85% aqueous acetic acid.

The reactions of **2a** with aliphatic 1,3-diisopropylcarbodiimide (DPCI) and aromatic 1,3-di-*p*-tolylcarbodiimide (DTCI) in acetonitrile in the presence of $CuCl_2$ or in DMF gave similar results, yielding the corresponding iminooxazolidinones (**4a**, **5a**) or oxazolidinediones (**8a**, **9a**) although the reaction with DTCI proceeded very slowly compared with that with DCCI or DPCI, and in the case of the reaction in acetonitrile in the presence of $CuCl_2$ the desired iminooxazolidinone compound (**5a**) was obtained in only poor yield along with a small amount of **9a**.

The reaction of **2a** with unsymmetrical 1-ethyl-3-dimethylaminopropylcarbodiimide (EDCI) in acetonitrile in the presence of $CuCl_2$ gave a single product, although the formation of two positional isomers, a 2′-ethylimino-3′-dimethylaminopropyl compound (**11a**) and a 3′-ethyl-2′-dimethylaminopropylimino compound, was expected, depending on the positions of attachment of substituents. The same product was also obtained by the reaction in DMF. The product, which showed a molecular ion peak at *m/z* 469 in the EI-MS, was hydrolyzed to an oxazolidinedione compound by heating in aqueous acetic acid in order to confirm locations of substituents. The EI-MS of the oxazolidinedione compound obtained by the hydrolysis showed a molecular ion peak at *m/z* 442, which supported the conclusion that the product was **11a** bearing the dimethylaminopropyl group at N-3′.

Furthermore, the reaction under basic conditions was investigated. The reaction of **2a** with alicyclic DCCI and aliphatic DPCI in the presence of DABCO or triethylamine gave the corresponding oxazolidinediones, **7a** and **8a**, respectively. On the other hand, the reaction of **2a** with aromatic DTCI proceeded very slowly compared with that with DCCI or DPCI, and gave the *N*-carbamoylcarboxamide (*N*-acylurea) derivative (**10a**) along with the oxazolidinedione compound (**9a**).

These reactions were also carried out using 11β,17α-dihydroxy-3-oxoandrosta-1,4-diene-17-carboxylic acid (**2b**),[12] which was prepared by the periodate oxidation of prednisolone (**1b**). The reactions of **2b** with DCCI, DPCI and EDCI gave results similar to those of **2a**, affording the corresponding products, **3b**, **4b**, **6b**, **7b**, **8b** and **11b**, respectively. The reaction of **2b** with DTCI, however, gave slightly different results. While the reactions with DTCI in DMF and in acetonitrile in the presence of base gave **9b** and **10b**, respectively, that in acetonitrile in the presence of $CuCl_2$ gave a mixture of oxazolidinedione (**9b**) and *N*-acylurea (**10b**), not the desired iminooxazolidinone compound (Chart 1).

In the present study, the reaction of steroid-17α-hydroxy-17-carboxylic acids (**2a, b**) with carbodiimides was investigated extensively, and 17-spiro compounds (**3**—**5**, **7**—**9**, **11**) and *N*-acylureas (**10**) were obtained as shown in Chart 1,[13] though 17-spiro-5′-[2′,4′-imidazolidinedione] (17-spiro-5′-hydantoin) compounds were not obtained. The compounds prepared in this study were tested for the anti-angiogenic activity in rat blood vessel organ culture assay.[14] 11β-Hydroxylated 17-spiro-5′-[3′-isopropyl-2′-isopropylimino-4′-oxazolidinone] (**4b**) exhibited a potent, specific inhibition of capillary-like tube formation *in vitro* at concentrations from 1 ng/ml to 10 μg/ml. Details of these biological results will be reported elsewhere.

Experimental

All melting points were taken on a Yanaco MP micro-melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. UV spectra were recorded on a Shimadzu UV-260 spectrophotometer. IR spectra were obtained with a Shimadzu FTIR-8500 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were determined with a JEOL FX-100 (100 MHz for ^{1}H, 25 MHz for ^{13}C) and chemical shifts are given in ppm with tetramethylsilane as the internal standard. EI-MS were recorded on a JEOL JMS-AX505W. TLC was performed on Kieselgel 60 F-254 precoated plates (Merck Art. 5715) and detection was carried out by UV irradiation (254 nm). Column chromatography was done with Kieselgel 60 (Merck Art. 7734).

(17*R*)-3′-Cyclohexyl-2′-cyclohexyliminospiro[androst-4-ene-17,5′-oxazolidine]-3,4′-dione (3a) $CuCl_2$ (160 mg) and DCCI (3.11 g, 15.07 mmol) were added to a suspension of **2a** (2.00 g, 6.02 mmol) in CH_3CN–dioxane (2:1) (90 ml) and the mixture was stirred for 1 h at room temperature. It was diluted with acetone and the precipitate (dicyclohexylurea) was filtered off. The filtrate was concentrated to afford a residue under reduced pressure. The resulting residue was chromatographed on silica gel with $CHCl_3$–AcOEt (20:1) to give **3a** (2.03 g, 65%), which was recrystallized from MeOH, mp 176—179 °C, $[\alpha]_D^{20}$ +6.7 (c=0.2, EtOH). UV λ_{max}^{EtOH} nm (ε): 233 (23000). IR (KBr): 1697 (C=O), 1670, 1620 (Δ^4-3-one) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, s, 18-Me), 1.21 (3H, s, 19-Me), 3.53, 3.91 (each 1H, m, 2 × NCH), 5.76 (1H, br s, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 92.43 (C-17), 124.06 (C-4), 145.29 (C-2′), 170.59 (C-5), 172.47 (C-4′), 199.33 (C-3). EI-MS *m/z*: 520 (M^+).

The following compounds (**3b**, **4a**, **4b**, **5a**) were prepared by the reaction of **2a** or **2b** with carbodiimides in the same manner as described for **3a**.

(17*R*)-3′-Cyclohexyl-2′-cyclohexylimino-11β-hydroxyspiro[androsta-1,4-diene-17,5′-oxazolidine]-3,4′-dione (**3b**): Eluted with $CHCl_3$–AcOEt (4:1), yield 47%, mp 229—242 °C, $[\alpha]_D^{20}$ +14.9° (c=0.2, EtOH). UV λ_{max}^{EtOH} nm (ε): 228 (21000). IR (KBr): 3481 (OH), 1697 (C=O), 1659, 1622, 1603 ($\Delta^{1,4}$-3-one) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, s, 18-Me), 1.49 (3H, s, 19-Me), 3.43, 3.91 (each 1H, m, NCH), 4.45 (1H, m, 11α-H), 6.04 (1H, br s, 4-H), 6.27 (1H, dd, J=9.9, 2.3 Hz, 2-H), 7.27 (1H, d, J=9.9 Hz, 1-H). ^{13}C-NMR ($CDCl_3$) δ: 92.05 (C-17), 122.50 (C-4), 127.92 (C-1), 144.86 (C-2′), 156.22 (C-2), 169.95 (C-5), 172.25 (C-4′), 186.68 (C-3). EI-MS *m/z*: 534 (M^+).

(17*R*)-3′-Isopropyl-2′-isopropyliminospiro[androst-4-ene-17,5′-oxazolidine]-3,4′-dione (**4a**): Eluted with $CHCl_3$–AcOEt (12:1), yield 59%, mp 111—115 °C, $[\alpha]_D^{20}$ +15.2° (*c*=0.2, EtOH). UV λ_{max}^{EtOH} nm (ε): 234 (20000). IR (KBr): 1697 (C=O), 1670 sh, 1616 (Δ⁴-3-one) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, s, 18-Me), 1.11, 1.15 (each 3H, d, *J*=7.1 Hz, $CHMe_2$), 1.21 (3H, s, 19-Me), 1.41 (6H, d, *J*=7.1 Hz, $CHMe_2$), 3.86, 4.33 (each 1H, m, 2×$NCHMe_2$), 5.74 (1H, brs, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 92.53 (C-17), 124.00 (C-4), 145.66 (C-2′), 170.59 (C-5), 172.41 (C-4′), 199.33 (C-3). EI-MS *m/z*: 440 (M^+).

(17*R*)-3′-Isopropyl-2′-isopropylimino-11β-hydroxyspiro[androsta-1,4-diene-17,5′-oxazolidine]-3,4′-dione (**4b**): Eluted with $CHCl_3$–AcOEt (2:1), yield 86%, mp 173—176 °C, $[\alpha]_D^{20}$ +36.0° (*c*=0.2, EtOH). UV λ_{max}^{EtOH} nm (ε): 234 (18000). IR (KBr): 3350 (OH), 1699 (C=O), 1655, 1616, 1597 (Δ¹·⁴-3-one) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07, 1.40 (each 6H, d, *J*=7.1 Hz, 2×$CHMe_2$), 1.25 (3H, s, 18-Me), 1.48 (3H, s, 19-Me), 3.80, 4.32 (each 1H, m, 2×$CHMe_2$), 4.46 (1H, brs, 11α-H), 6.04 (1H, brs, 4-H), 6.28 (1H, dd, *J*=9.9, 2.3 Hz, 2-H), 7.27 (1H, d, *J*=9.9 Hz, 1-H). ^{13}C-NMR ($CDCl_3$) δ: 92.21 (C-17), 122.45 (C-4), 127.81 (C-1), 145.23 (C-2′), 156.44 (C-2), 170.22 (C-5), 172.25 (C-4′), 186.68 (C-3). EI-MS *m/z*: 454 (M^+).

(17*R*)-3′-*p*-Tolyl-2′-*p*-tolyliminospiro[androst-4-ene-17,5′-oxazolidine]-3,4′-dione (**5a**): Reaction period 6 d. Eluted with $CHCl_3$–acetone (10:0.8), yield 17%, mp 125—128 °C, $[\alpha]_D^{20}$ −42.0° (*c*=0.2, EtOH). UV λ_{max}^{EtOH} nm (ε): 239 (31000). IR (KBr): 1697 (C=O), 1670 sh, 1608 (Δ⁴-3-one) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.09 (3H, s, 18-Me), 1.22 (3H, s, 19-Me), 2.32, 2.40 (each 3H, s, 2×C_6H_4Me), 5.76 (1H, brs, 4-H), 7.07, 7.32 (each 4H, brs, 2×C_6H_4Me). ^{13}C-NMR ($CDCl_3$) δ: 95.00 (C-17), 123.25, 126.74, 129.31, 129.69, 133.06, 138.48, 141.86 (each C-Ar), 124.11 (C-4), 146.68 (C-2′), 170.32 (C-5), 171.66 (C-4′), 199.22 (C-3). EI-MS *m/z*: 536 (M^+). Continued elution gave **9a** (11%).

17-Methyl-18-norandrosta-4,13(17)-dien-3-one (6a) DCCI (3.11 g, 15.07 mmol) was added to a suspension of **2a** (2.00 g, 6.02 mmol) in CH_3CN–dioxane (2:1) (90 ml) and the mixture was stirred for 1 h at room temperature. The reaction solution was diluted with acetone and the precipitate was filtered off. The filtrate was concentrated to give a residue under reduced pressure. The resulting oily residue was chromatographed on silica gel with $CHCl_3$ to give **6a** (430 mg, 26%), which was recrystallized from MeOH, mp 114—116 °C (lit. mp 110—111.5 °C[11a] and mp 113—114 °C[11b]), $[\alpha]_D^{20}$ +82.5 (*c*=0.2, EtOH) (lit. +84°[11a] and +87°[11b] ($CHCl_3$)). UV λ_{max}^{EtOH} nm (ε): 240 (17000). IR (KBr): 1670, 1616 (Δ⁴-3-one) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, s, 19-Me), 1.62 (3H, s, 17-Me), 5.75 (1H, brs, 4-H), (lit.[11b]) 1.13, 1.60, 5.75, respectively). ^{13}C-NMR ($CDCl_3$) δ: 123.68 (C-4), 128.40, 135.26 (C-13 and C-17), 171.50 (C-5), 199.54 (C-3). EI-MS *m/z*: 270 (M^+).

11β-Hydroxy-17-methyl-18-norandrosta-1,4,13(17)-trien-3-one (**6b**) was obtained from **2b** and DCCI according to the procedure described for **6a**. Eluted with $CHCl_3$–AcOEt (2:1), yield 88%, mp 183—184 °C, $[\alpha]_D^{20}$ +31.7° (*c*=0.2, EtOH). UV λ_{max}^{EtOH} nm (ε): 240 (16000). IR (KBr): 3362 (OH), 1649, 1609, 1599 (Δ¹·⁴-3-one) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, s, 19-Me), 1.67 (3H, s, 17-Me), 4.39 (1H, brs, 11α-H), 6.06 (1H, brs, 4-H), 6.26 (1H, dd, *J*=9.9, 2.3 Hz, 2-H), 7.27 (1H, d, *J*=9.9 Hz, 1-H). ^{13}C-NMR ($CDCl_3$) δ: 123.09 (C-4), 127.54 (C-1), 130.22, 135.26 (C-13 and C-17), 156.06 (C-2), 169.68 (C-5), 186.30 (C-3). EI-MS *m/z*: 284 (M^+).

(17*R*)-3′-Cyclohexylspiro[androst-4-ene-17,5′-oxazolidine]-2′,3,4′-trione (7a) DCCI (1.55 g, 7.52 mmol) was added to a solution of **2a** (1.00 g, 3.01 mmol) in DMF (30 ml) and the mixture was stirred for 7 h at room temperature. The reaction solution was diluted with acetone and the precipitate (dicyclohexylurea) was filtered off. The filtrate was concentrated to a residue under reduced pressure. After addition of water, an insoluble material was collected, washed with water and dried to give crude **7a**. The crude product was chromatographed on silica gel with $CHCl_3$–AcOEt (20:1) to give **7a** (490 mg, 37%), which was recrystallized from MeOH, mp 226—228 °C, $[\alpha]_D^{20}$ +130.7° (*c*=0.2, EtOH). UV λ_{max}^{EtOH} nm (ε): 239 (18000). IR (KBr): 1803 (C(2′)=O), 1732 (C(4′)=O), 1680, 1616 (Δ⁴-3-one) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, s, 18-Me), 1.20 (3H, s, 19-Me), 3.88 (1H, m, NCH), 5.76 (1H, brs, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 93.87 (C-17), 124.13 (C-4), 154.30 (C-2′), 170.09 (C-5), 173.36 (C-4′), 199.10 (C-3). EI-MS *m/z*: 439 (M^+).

The following compounds (**7b**, **8a**, **8b**, **9a**, **9b**) were prepared by the reaction of **2a** or **2b** with carbodiimides in the same manner as described for **7a**.

(17*R*)-3′-Cyclohexyl-11β-hydroxyspiro[androsta-1,4-diene-17,5′-oxazolidine]-2′,3,4′-trione (**7b**): Eluted with benzene–AcOEt (2:1), yield 48%. mp 248—250 °C. $[\alpha]_D^{20}$ +150.9° (*c*=0.2, EtOH). UV λ_{max}^{EtOH} nm (ε): 242 (17000). IR (KBr): 3335 (OH), 1809 (C(2′)=O), 1736 (C(4′)=O), 1655, 1614, 1599 (Δ¹·⁴-3-one) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, s, 18-Me), 1.46 (3H, m, 19-Me), 3.86 (1H, m, NCH), 4.48 (1H, m, 11α-H), 6.02 (1H, brs, 4-H), 6.25 (1H, dd, *J*=9.9, 2.3 Hz, 2-H), 7.24 (1H, d, *J*=9.9 Hz, 1-H). ^{13}C-NMR ($CDCl_3$) δ: 93.48 (C-17), 122.53 (C-4), 127.89 (C-1), 154.11 (C-2′), 155.81 (C-2), 169.61 (C-5), 173.12 (C-4′), 186.42 (C-3). EI-MS *m/z*: 453 (M^+).

(17*R*)-3′-Isopropylspiro[androst-4-ene-17,5′-oxazolidine]-2′,3,4′-trione (**8a**): Eluted with $CHCl_3$–AcOEt (12:1), yield 46%, mp 210—215 °C, $[\alpha]_D^{20}$ +130.2° (*c*=0.2, EtOH). UV λ_{max}^{EtOH} nm (ε): 240 (17000). IR (KBr): 1800 (C(2′)=O), 1732 (C(4′)=O), 1682, 1616 (Δ⁴-3-one) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, s, 18-Me), 1.20 (3H, s, 19-Me), 1.42 (6H, d, *J*=7.1 Hz, $CHMe_2$), 4.30 (1H, m, $CHMe_2$), 5.74 (1H, brs, 4-H). ^{13}C-NMR ($CDCl_3$) δ: 93.98 (C-17), 124.11 (C-4), 154.13 (C-2′), 170.16 (C-5), 173.33 (C-4′), 199.17 (C-3). EI-MS *m/z*: 399 (M^+).

(17*R*)-3′-Isopropyl-11β-hydroxyspiro[androsta-1,4-dien-17,5′-oxazolidine]-2′,3,4′-trione (**8b**): Eluted with $CHCl_3$–AcOEt (2:1), yield 66%, mp 235—236 °C, $[\alpha]_D^{20}$ +128.0° (*c*=0.2, EtOH). UV λ_{max}^{EtOH} nm (ε): 242 (16000). IR (KBr): 3472 (OH), 1801 (C(2′)=O), 1728 (C(4′)=O), 1654, 1616, 1599 (Δ¹·⁴-3-one) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.28 (3H, s, 18-Me), 1.38 (6H, d, *J*=7.1 Hz, $CHMe_2$), 1.48 (3H, s, 19-Me), 4.27 (1H, m, $CHMe_2$), 4.48 (1H, m, 11α-H), 6.02 (1H, brs, 4-H), 6.25 (1H, dd, *J*=9.9, 2.3 Hz, 2-H), 7.26 (1H, d, *J*=9.9 Hz, 1-H). ^{13}C-NMR ($CDCl_3$) δ: 93.61 (C-17), 122.45 (C-4), 127.81 (C-1), 153.92 (C-2′), 156.06 (C-2), 169.84 (C-5), 173.06 (C-4′), 186.46 (C-3). EI-MS *m/z*: 413 (M^+).

(17*R*)-3′-*p*-Tolylspiro[androst-4-ene-17,5′-oxazolidine]-2′,3,4′-trione (**9a**): Reaction period 7 d. Purified by recrystallization (CH_2Cl_2–MeOH), yield 64%, mp 290—291 °C, $[\alpha]_D^{20}$ +176.0° (*c*=0.2, EtOH). UV λ_{max}^{EtOH} nm (ε): 237 (22000). IR (KBr) cm^{-1}: 1809 (C(2′)=O), 1746 (C(4′)=O), 1670, 1616 (Δ⁴-3-one) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, s, 18-Me), 1.21 (3H, s, 19-Me), 2.40 (3H, s, C_6H_4Me), 5.75 (1H, brs, 4-H), 7.28 (4H, s, C_6H_4Me). ^{13}C-NMR ($CDCl_3$) δ: 94.95 (C-17), 124.16 (C-4), 125.50, 128.35, 129.85, 138.91 (each C-Ar), 153.49 (C-2′), 170.06 (C-5), 172.36 (C-4′), 199.11 (C-3). EI-MS *m/z*: 447 (M^+).

(17*R*)-3′-*p*-Tolyl-11β-hydroxyspiro[androsta-1,4-diene-17,5′-oxazolidine]-2′,3,4′-trione (**9b**): Reaction period 7 d. Eluted with $CHCl_3$–AcOEt (5:1), yield 50%, mp 278—282 °C, $[\alpha]_D^{20}$ +4.9° (*c*=0.2, EtOH). UV λ_{max}^{EtOH} nm (ε): 236 (22000). IR (KBr): 3350 (OH), 1807 (C(2′)=O), 1746 (C(4′)=O), 1655, 1614, 1597 (Δ¹·⁴-3-one) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, s, 18-Me), 1.47 (3H, s, 19-Me), 2.39 (3H, s, C_6H_4Me), 4.44 (1H, m, 11α-H), 6.03 (1H, brs, 4-H), 6.26 (1H, dd, *J*=9.9, 2.3 Hz, 2-H), 7.20 (1H, d, *J*=9.9 Hz, 1-H), 7.27 (4H, s, C_6H_4Me). ^{13}C-NMR ($CDCl_3$) δ: 94.57 (C-17), 122.50 (C-4), 125.50, 128.24, 129.90, 139.07 (each C-Ar), 127.86 (C-1), 153.28 (C-2′), 155.96 (C-2), 169.68 (C-5), 172.25 (C-4′), 186.46 (C-3). EI-MS *m/z*: 461 (M^+).

17α-Hydroxy-3-oxo-*N*-*p*-tolyl-*N*-(*p*-tolylaminocarbonyl)androst-4-ene-17-carboxamide (10a) a) DABCO (2.03 g, 18.10 mmol) and DTCI (3.35 g, 15.07 mmol) were added to a suspension of **2a** (2.00 g, 6.02 mmol) in CH_3CN (100 ml) and the mixture was heated for 1 h at 80 °C on a water bath. After cooling, the reaction solution was concentrated to a residue under reduced pressure. The resulting residue was chromatographed on silica gel with $CHCl_3$–AcOEt–acetone (13:2:1) to give **9a** (700 mg). Continued elution with the same solvent gave **10a** (1.07 g, 32%), which was recrystallized from CH_2Cl_2–MeOH, mp 265—268 °C, $[\alpha]_D^{20}$ +47.0° (*c*=0.2, EtOH). UV λ_{max}^{EtOH} nm (ε): 240 (47000). IR (KBr): 3500—3250 (NH, OH), 1738 (C(20)=O), 1678 (urea C=O, C(3)=O), 1603 (Δ⁴) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, s, 18-Me), 1.21 (3H, s, 19-Me), 2.29 (6H, s, 2×C_6H_4Me), 5.77 (1H, brs, 4-H), 7.00—7.42 (8H, m, 2×C_6H_4Me). ^{13}C-NMR ($CDCl_3$) δ: 92.91 (C-17), 118.59, 120.46, 129.36, 129.90, 132.90, 133.92, 135.05, 135.26 (each C-Ar), 123.84 (C-4), 151.93 (C-urea), 168.07 (C-5), 172.04 (C-20), 199.70 (C-3). EI-MS *m/z*: 554 (M^+).

b) The reaction in the presence of Et_3N (6.10 g, 60.2 mmol) instead of DABCO was carried out in the same manner as method a, and gave **10a** (2.46 g, 74%) and **9a** (420 mg).

11β,17α-Dihydroxy-3-oxo-*N*-*p*-tolyl-*N*-(*p*-tolylaminocarbonyl)-androsta-1,4-diene-17-carboxamide (**10b**) was obtained from **2b** and DTCI according to the procedure described for **10a** (method a). Eluted with $CHCl_3$–AcOEt–acetone (5:2:1), yield 63%, mp 258—261 °C, $[\alpha]_D^{20}$ +85.7° (*c*=0.2, EtOH). UV λ_{max}^{EtOH} nm (ε): 240 (44000). IR (KBr): 3500—3250 (NH, OH), 1734 (C(20)=O), 1674 (urea C=O), 1661, 1614, 1605 (Δ¹·⁴-3-one) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, s, 18-Me), 1.44 (3H, s, 19-Me), 1.61 (6H, s, 2×C_6H_4Me), 4.47 (1H, m, 11α-H), 6.04

(1H, br s, 4-H), 6.26 (1H, dd, J=9.9, 2.3 Hz, 2-H), 7.28 (1H, d, J=9.9 Hz, 1-H), 7.04—7.37 (8H, m, 2×$C_6\underline{H}_4$Me). ^{13}C-NMR (DMSO-d_6) δ: 91.19 (C-17), 117.68, 121.11, 128.51, 128.99, 131.03, 132.26, 136.23, 136.33 (each C-Ar), 121.43 (C-4), 126.95 (C-1), 151.88 (C-urea), 156.81 (C-2), 170.70 (C-5), 185.01 (C-3). EI-MS m/z: 568 (M^+).

(17*R*)-2′-Ethylimino-3′-dimethylaminopropylspiro[androst-4-ene-17,5′-oxazolidine]-3,4′-dione (11a) EDCI hydrochloride (1.44 g, 7.51 mmol) was added to a solution of **2a** (1.00 g, 3.01 mmol) in DMF (30 ml) and the mixture was stirred for 3 h at room temperature. The reaction solution was concentrated to a residue under reduced pressure. After addition of water, the aqueous solution was adjusted to pH 8 with 5% aqueous $NaHCO_3$. An oily material that separated was extracted with AcOEt. The organic layer was washed with water, dried over Na_2SO_4 and evaporated to dryness under reduced pressure to give crude oily **11a**. The crude product was chromatographed on silica gel with the lower layer of $CHCl_3$–MeOH–H_2O (15:5:2) to give oily **11a** (440 mg, 31%), which crystallized upon standing for several days, mp 102—104 °C, $[\alpha]_D^{20}$ +25.9° (c=0.2, EtOH). UV λ_{max}^{EtOH} nm (ε): 234 (20000), 240 (19000). IR (KBr): 1701 (C=O), 1668, 1624 (Δ^4-3-one) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, s, 18-Me), 1.20 (3H, s, 19-Me), 2.20 (6H, s, NMe), 3.33 (2H, q, J=7.1 Hz, NC$\underline{H}_2$CH$_3$), 3.64 (2H, t, J=7.1 Hz, NC$\underline{H}_2$CH$_2$), 5.75 (1H, br s, 4-H). ^{13}C-NMR($CDCl_3$) δ: 93.77 (C-17), 123.99 (C-4), 147.43 (C-2′), 170.34 (C-5), 172.39 (C-4′), 199.23 (C-3). EI-MS m/z: 469 (M^+).

(17*R*)-2′-Ethylimino-11β-hydroxy-3′-dimethylaminopropylspiro-[androsta-1,4-dien-17,5′-oxazolidine]-2′,3,4′-trione (**11b**) was obtained from **2b** and EDCI hydrochloride according to the procedure described for **11a**. Eluted with the lower layer of $CHCl_3$–MeOH–H_2O (10:5:2), yield 47%, mp 89—92 °C, $[\alpha]_D^{20}$ +40.0° (c=0.2, EtOH). UV λ_{max}^{EtOH} nm (ε): 224 (18000), 242 (16000). IR (KBr): 3350 (OH), 1697 (C=O), 1655, 1618, 1600 ($\Delta^{1,4}$-3-one) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, s, 18-Me), 1.46 (3H, s, 19-Me), 2.17 (6H, s, NMe_2), 3.26 (2H, q, J=10 Hz, NC$\underline{H}_2$CH$_3$), 3.53 (2H, t, J=10 Hz, NC$\underline{H}_2$CH$_2$), 4.47 (1H, br s, 11α-H), 6.00 (1H, br s, 4-H), 6.23 (1H, dd, J=9.9, 2.3 Hz, 2-H), 7.23 (1H, d, J=9.9 Hz, 1-H). ^{13}C-NMR ($CDCl_3$) δ: 93.61 (C-17), 122.45 (C-4), 127.81 (C-1), 147.38 (C-2′), 156.44 (C-2), 170.16 (C-5), 172.41 (C-4′), 186.62 (C-3). EI-MS m/z: 483 (M^+).

Hydrolysis of 3a to 7a A solution of **3a** (100 mg) in 85% aqueous AcOH (1.5 ml) was heated for 9 h at 80 °C on a water bath. After standing overnight, crystals that had deposited were collected, washed with water and dried to give the product (70 mg). The product obtained was identical, on the basis of infrared spectral and melting point comparisons, with the sample of **7a** prepared by the reaction of **2a** with DCCI in DMF as described above.

Acid Hydrolysis of 11a A solution of **11a** (380 mg, 0.81 mmol) in 85% aqueous AcOH (25 ml) was heated for 3 h at 80 °C on a water bath. The reaction solution was concentrated to a residue under reduced pressure. After addition of water, the resulting clear solution was neutralized with $NaHCO_3$ and an oily product that separated was extracted with AcOEt. The organic layer was washed with water, dried over Na_2SO_4 and evaporated to dryness under reduced pressure to give oily (17*R*)-3′-dimethylaminopropylspiro[androst-4-ene-17,5′-oxazolidine]-2′,3,4′-trione (310 mg), which was subjected to IR spectral and EI-MS measurements. IR (KBr): 1809 (C(2′)=O), 1734 (C(4′)=O), 1670, 1616 (Δ^4-3-one) cm^{-1}. EI-MS m/z: 442 (M^+).

References and Notes

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12) Glaxo Laboratories Ltd., Fr. Patent 2122539 (1972) [*Chem. Abstr.*, **79**, 126710 (1973)].
13) Various reaction mechanisms have been put forward to account for the formation of 2-imino-4-oxazolinone [F. Kurzer, K. Douraghi-Zadeh, *Chem. Rev.*, **67**, 118 (1967)], 2,4-oxazolidinedione [G. Rapi, M. Ginanneschi, M. Chelli, S. Chimichi, *Steroids*, **46**, 665 (1985); M. Robba, D. Maume, *C. R. Acad. Sci., Ser. C*, **272**, 475 (1971)] and *N*-acylurea [H. G. Khorana, *J. Chem. Soc.*, **1952**, 2081; I. Muramatsu, A. Hagitani, *Nippon Kagaku Zasshi*, **80**, 1497 (1959)]. In the present case, the reactions presumably proceed *via* the *N*-acylurea intermediate derived from carboxylic acid and carbodiimide. Compounds **3**—**5** will be formed by cyclization of the intermediate in the enolic form and **7**—**9** from the keto form. The possibility of the formation of **7**—**9** from **3**—**5** by hydrolysis was excluded by TLC observation of the reaction solution. The mechanisms of the formation of **11** in the reaction with EDCI in DMF and its selective formation, however, are not clear.
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