Synthesis of Steroidal Extranucleo 1,3,4-Oxadiazoles

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Cholest-5en-3β-ol **1**, 3,3-ethylenedioxy-androst-4-en-17β-ol **2** and 17,17-ethylenedioxy-1,3,5(10)-estratrien-3β-ol **3** were converted into ethyl ester **1a**, **2a** and **3a** by reaction with ethyl chloroacetate in the presence of potassium. The ethyl esters **1a**, **2a** and **3a** on reaction with hydrazine gave hydrazides **1b**, **2b** and **3b**, which on reaction with cyanogen bromide afforded 1,3,4-oxadiazoles **1c**, **2c** and **3c**.

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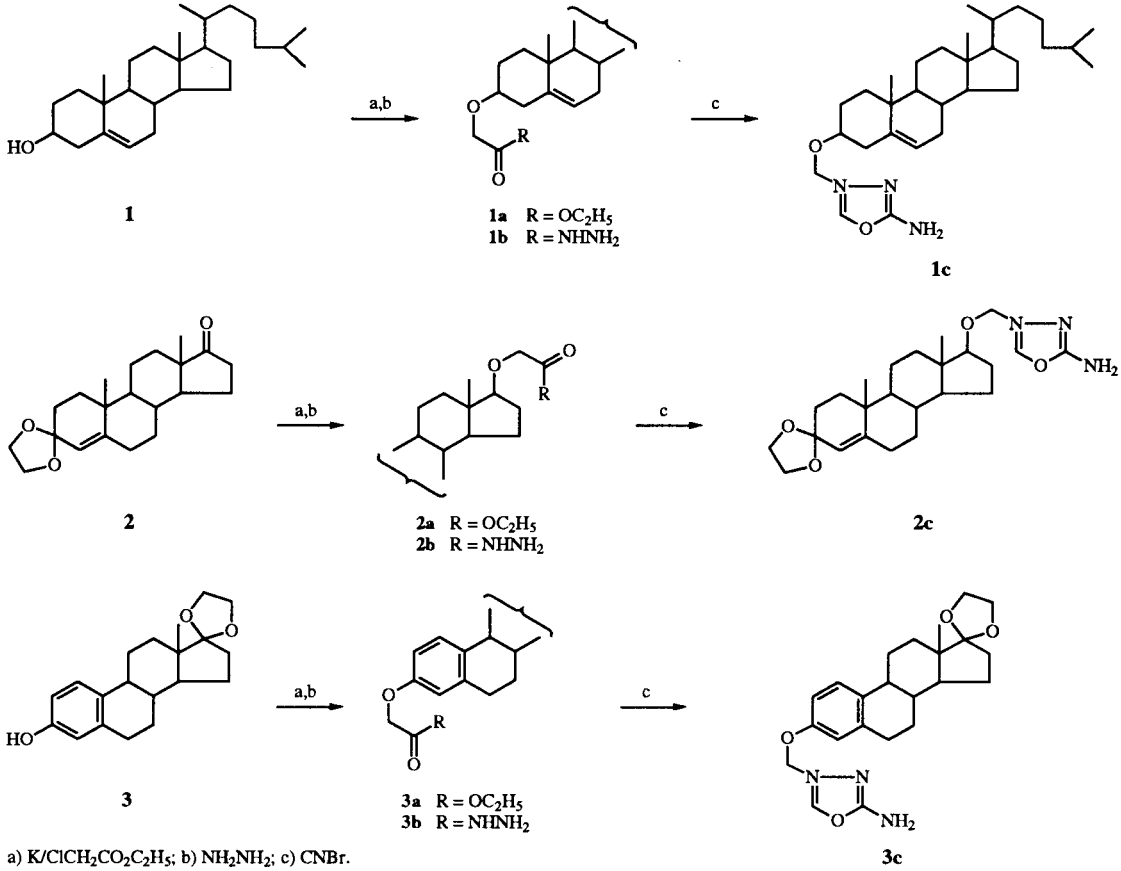
In view of useful biological activities of oxadiazoles derivatives [2-5] and in continuation of our work on extranuclear modification of steroids [6-8], we report here the synthesis of steroidal extranucleo 1,3,4-oxadiazoles.

Scheme 1

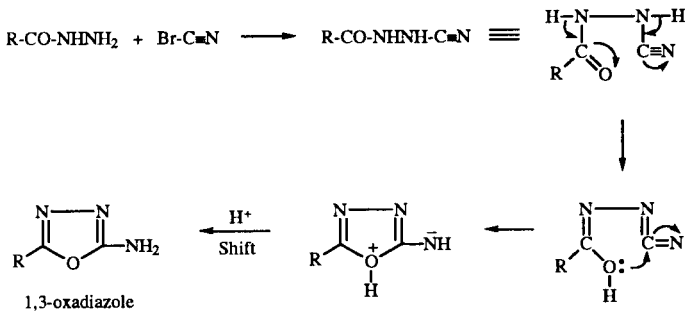


a) K/ClCH$_2$CO$_2$C$_2$H$_5$; b) NH$_2$NH$_2$; c) CNBr.

Cholest-5-en-3β-ol **1**, 3,3-ethylenedioxy-androst-4-en-17β-ol **2** and 17,17-ethylenedioxy-1,3,5(10)-estratrien-3β-ol **3** on reaction with ethyl chloroacetate in the presence of potassium gave ethyl cholest-5-en-3β-*O*-acetate **1a**, ethyl 3,3-ethylenedioxyandrost-4-en-17β-*O*-acetate **2a** and ethyl 17,17-ethylenedioxy-1,3,5(10)-estratrien-3β-*O*-acetate **3a**. The ^{1}H nmr spectra of **1a**, **2a** and **3a** gave a singlet at δ 4.8 (OCH_2CO), quartet at δ 4.1 (CO_2CH_2), and a triplet at δ 1.2 (CH_2CH_3). The ethyl esters **1a**, **2a** and **3a** on reaction with hydrazine gave hydrazide **1b**, **2b** and **3b**, whose ^{1}H nmr spectra showed broad singlets at δ 4.3 (NH_2) and at δ 8.5 (CONH) which disappeared upon treatment with deuterium oxide.

The reaction of hydrazides **1b**, **2b** and **3b** with cyanogen bromide afforded 1,3,4-oxadiazoles **1c**, **2c** and **3c** (Scheme 2). The infrared spectra of **1c**, **2c** and **3c** showed absorption bands at 3200 (NH_2), 1650 cm^{-1} (C=N) and ^{1}H nmr spectra revealed a broad singlet at δ

Scheme 2



6.9 for NH_2 protons and a singlet at δ 4.95 for OCH_2 protons.

EXPERIMENTAL

Melting points are uncorrected. The infrared spectra were recorded as potassium bromide pellets using Perkin-Elmer 137 spectrometer. The ^1H nmr spectra were obtained in deuteriochloroform on a Varian XL-200 spectrometer with TMS as internal standard. Chemical shifts are given in ppm (δ).

3,3-Ethylenedioxy-androst-4-en-17β-ol **2** and 17,17-Ethylenedioxy-1,3,5(10)-estratrien-3β-ol **3** was prepared according to the literature procedures [9,10].

General Procedure for the Preparation of Ethyl Esters **1a**, **2a** and **3a**.

To a solution of **1** or **2** or **3** (6 mmoles) in dry benzene (50 ml) was added potassium metal (0.70 g, 18 mmoles) and the mixture was refluxed for 1 hour. After cooling ethyl chloroacetate (4.5 g, 36 mmoles) was added and the mixture was further refluxed for 3 hours. Excess potassium metal was destroyed by the addition of methanol (1 ml), the mixture was concentrated under reduced pressure and then poured onto ice and extracted with ether. The ether extract was concentrated and the material obtained was crystallized from ethanol.

Ethyl Cholest-5-en-3β-*O*-acetate (**1a**).

This compound was obtained as colorless needles from ethanol (79%), mp 145-147°; ir: ν max 1745 (ester), 1610 (C=C), 1140 (ketal) cm^{-1}; ^1H nmr: δ 5.40 (m, 1H, C_6-H), 4.86 (s, 2H, OCH_2CO_2), 4.60 (m, 1H, C_3-αH), 4.10 (q, 2H, $CO_2CH_2CH_3$), 3.88 (s, 4H, OCH_2CH_2O), 1.20 (t, 3H, $CO_2CH_2CH_3$), 1.02 (s, 3H, C_{19}-H), 0.69 ppm (s, 3H, C_{18}-H).

Anal. Calcd. for $C_{31}H_{52}O_3$: C, 78.76; H, 11.09. Found: C, 78.85; H, 11.03.

Ethyl 3,3-Ethylenedioxy-androst-4-en-17β-*O*-acetate (**2a**).

This compound was obtained as colorless needles from ethanol (80%), mp 191-192°; ir: ν max 1740 (ester), 1600 (C=C), 1140 (ketal) cm^{-1}; ^1H nmr: δ 5.70 (m, 1H, C_4-H), 4.84 (s, 2H, OCH_2CO_2), 4.12 (q, 2H, $CO_2CH_2CH_3$), 3.86 (s, 4H, OCH_2CH_2O), 3.60 (t, 1H, C_{17}-αH), 1.25 (t, 3H, $CO_2CH_2CH_3$), 1.18 (s, 3H, C_{19}-H), 0.80 ppm (s, 3H, C_{18}-H).

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.80; H, 9.24.

Ethyl 17,17-Ethylenedioxy-1,3,5(10)-estratrien-3β-*O*-acetate (**3a**).

This compound was obtained as colorless needles from ethanol (80%), mp 139-140°; ir: ν max 1735 (ester), 1600 (C=C), 1140 (ketal) cm^{-1}; ^1H nmr: δ 7.07 (d, 1H, J = 8.7, C_1-H), 6.69 (dd, 1H, J = 2.4, 8.7, C_2-H), 6.58 (d, 1H, J = 2.4, C_4-H), 4.84 (s, 2H, OCH_2CO_2), 4.12 (q, 2H, $CO_2CH_2CH_3$), 3.88 (s, 4H, OCH_2CH_2O), 1.25 (t, 3H, $CO_2CH_2CH_3$), 0.79 ppm (s, 3H, C_{18}-H).

Anal. Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.12; H, 8.15.

General Procedure for the Preparation of Hydrazides **1b**, **2b** and **3b**.

A solution of ethyl ester **1a** or **2a** or **3a** (5 mmoles) and hydrazine hydrate (6.41 g, 20 mmoles) in methanol (100 ml) was refluxed with a drop of acetic acid for 6 hours. The mixture was concentrated *in vacuo* and then poured onto ice. The resulting precipitate was filtered, washed with water and recrystallized from methanol.

Cholest-5-en-3β-*O*-acethydrazide (**1b**).

This compound was obtained as colorless solid from methanol (72%), mp 152-153; ir: ν max 3280, 3180 (NH_2, NH), 1640 (CONH), 1610 (C=C), 1138 (ketal) cm^{-1}; ^1H nmr: δ 8.60 (br s, 1H, CONH), 5.40 (m, 1H, C_6-H), 4.84 (s, 2H, OCH_2CO), 4.60 (m, 1H, C_3-αH), 4.3 (br s, 2H, NH_2), 3.88 (s, 4H, OCH_2CH_2O), 1.03 (s, 3H, C_{19}-H), 0.70 ppm (s, 3H, C_{18}-H).

Anal. Calcd. for $C_{29}H_{50}N_2O_2$: C, 75.93; H, 10.99; N, 6.11. Found C, 76.01; H, 11.06; N, 6.16.

3,3-Ethylenedioxyandrost-4-en-17β-*O*-acethydrazide (**2b**).

This compound was obtained as colorless solid from methanol (75%), mp 201-202°; ir: ν max 3280, 3170 (NH_2, NH), 1640 (CONH), 1600 (C=C), 1140 (ketal) cm^{-1}; ^1H nmr δ 8.50 (br s, 1H, CONH), 5.72 (m, 1H, C_4-H), 4.85 (s, 2H, OCH_2CO), 4.32 (br s, 2H, NH_2), 3.88 (s, 4H, OCH_2CH_2O), 3.62 (t, 1H, C_{17}-αH), 1.20 (s, 3H, C_{19}-H), 0.79 ppm (s, 3H, C_{18}-H).

Anal. Calcd. for $C_{23}H_{36}N_2O_4$: C, 68.29; H, 8.97; N, 6.92. Found C, 68.35; H, 8.91; N, 6.98.

17,17-Ethylenedioxy-1,3,5(10)-estratrien-3β-*O*-acethydrazide (**3b**).

This compound was obtained as colorless solid from methanol (80%), mp 156-157°; ir: ν max 3280, 3070 (NH_2, NH), 1640 (CONH), 1600 (C=C), 1138 (ketal) cm^{-1}; ^1H nmr δ 8.50 (br s, 1H (CONH), 7.10 (d, 1H, J = 8.7, C_1-H), 6.72 (dd, 1H, J = 2.4, 8.7, C_2-H), 6.59 (d, 1H, J = 2.4, C_4-H), 4.86 (s, 2H, OCH_2CO), 3.90 (s, 4H, OCH_2CH_2O), 0.80 ppm (s, 3H, C_{18}-H).

Anal. Calcd. for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.48; H, 7.86; N, 7.32.

General Procedure for the Preparation of 1,3,4-Oxadiazoles **1c**, **2c** and **3c**.

To a solution of **1b** or **2b** or **3b** (2.5 mmoles) in methanol (50 ml) was added cyanogen bromide (1.06 g, 10 mmoles) and the mixture was refluxed at 55-60° for 1 hour. After cooling the mixture was neutralized with potassium bicarbonate (5%) and then poured onto ice and extracted with ether. The ether extract was washed with water, dried over sodium sulfate and concentrated to a colorless solid.

3β-*O*-Methyl-(2'-amino-1',3',4'-oxadiazoliden-5'yl)cholest-5-ene (**1c**).

This compound was obtained as colorless solid from methanol (68%), mp 118-120°; ir: ν max 3150, 3065 (NH_2), 1650 (C=N),

1140 (ketal) cm^{-1}; ^1H nmr: δ 6.95 (br s, 2H, NH_2), 5.35 (m, 1H, C_6-H), 5.02 (s, 2H, OCH_2), 4.60 (m, 1H, C_3-αH), 3.90 (s, 4H, OCH_2CH_2O), 1.05 (s, 3H, C_{19}-H), 0.72 ppm (s, 3H, C_{18}-H).

Anal. Calcd. for $C_{30}H_{49}N_3O_2$: C, 74.49; H, 10.21; N, 8.69. Found: C, 74.60; H, 10.28; N, 8.74.

3,3-Ethylenedioxy-3β-*O*-methyl-(2'-amino-1',3',4'-oxadiazoliden-5'yl)-androst-4- ene (**3b**).

This compound was obtained as colorless needles from methanol (70%), mp 185-187°; ir ν max 3160, 3070 (NH_2), 1655 (C=N), 1140 (ketal) cm^{-1}; ^1H nmr: δ 6.98 (br s, 2H, NH_2), 5.70 (m, 1H, C_4-H), 4.95 (s, 2H, OCH_2), 3.86 (s, 4H, OCH_2CH_2O), 3.65 (t, 1H, C_{17}-αH), 1.18 (s, 3H, C_{19}-H), 0.80 ppm (s, 3H, C_{18}-H).

Anal. Calcd. for $C_{24}H_{35}N_3O_4$: C, 67.11; H, 8.21; N, 9.78. Found: C, 67.20; H, 8.28; N, 9.88.

17,17-Ethylenedioxy-3β-*O*-methyl-(2'-amino-1',3',4'-oxadiazoliden-5'yl)-1,3,5(10)-estratriene (**3c**).

This compound was obtained as colorless solid from methanol (65%), mp 212-214°; ir: ν max 3160, 3065 (NH_2), 1655 (C=N), 1600 (C=C), 1140 (ketal) cm^{-1}; ^1H nmr: δ 7.10 (d, 1H, J = 8.7, C_1-H), 6.96 (br s, 2H, NH_2), 6.69 (dd, 1H, J = 2.4, 8.7, C_2-H), 6.58 (d, 1H, J = 2.4, C_4-H), 4.98 (s, 2H, OCH_2), 3.88 (s, 4H, OCH_2CH_2O), 0.81 ppm (s, 3H, C_{18}-H).

Anal. Calcd. for $C_{23}H_{29}N_3O_4$: C, 67.13; H, 7.10; N, 10.21. Found: C, 67.18; H, 7.16; N, 10.30.

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