Synthesis of A- and D-Homoazasteroidalisoxazoles

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Dedicated to the memory of Professor Panayotis Catsoulacos

The synthesis of the isomeric D-homoazasteroido[3,2-*c*]- (**3**) and -[2,3-*d*]isoxazoles (**4**) and A-homoazasteroido[17,16-*c*]isoxazole (**6**) are reported by the reaction of 2-hydroxymethylene-17α-aza-D-homo-5α-androstan-3,17-dione (**2**) and 16-hydroxymethylene-3-aza-A-homo-4α-androsten-4,17-dione (**5**) correspondingly with hydroxylammonium chloride.

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Steroidal lactams have been reported to possess unusual anticancer activity [1,2]. On the other hand, steroidalisoxazole derivatives possess biological action [3-5].

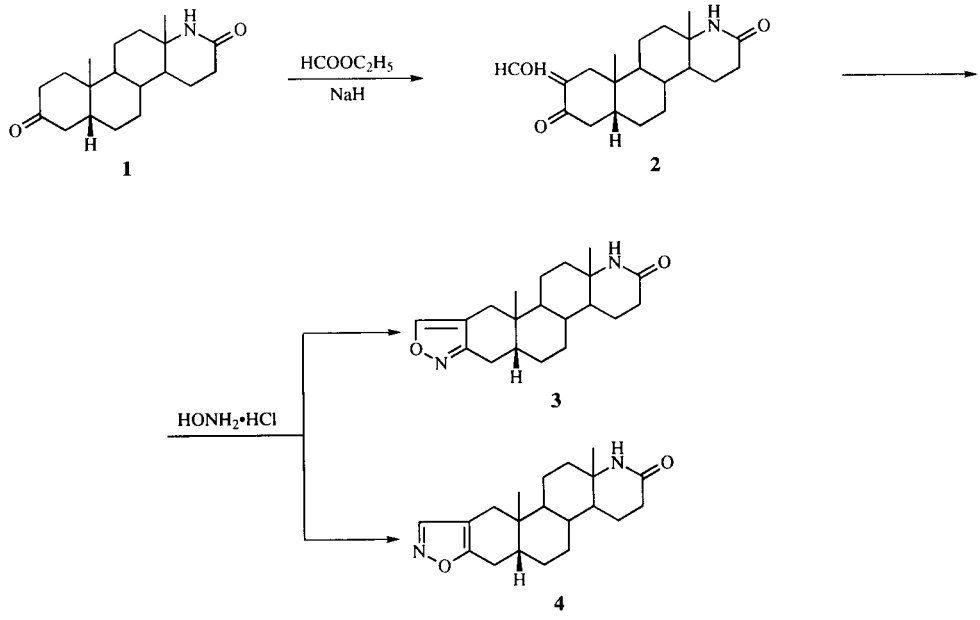
It appeared to us to be of interest to combine the isoxazole ring to the steroid lactam and to study their biological activity.

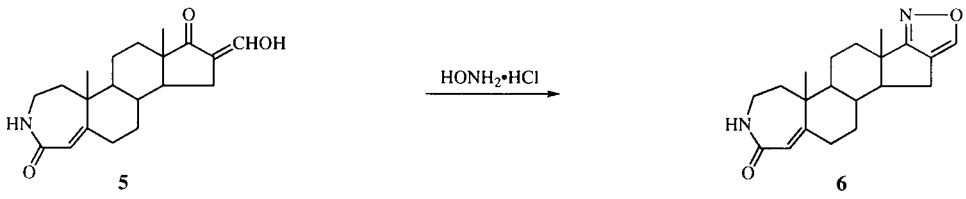
Starting from the 17α-aza-D-homo-5α-androstan-3,17-dione [6] and ethyl formate in the presence of sodium hydride in dry benzene we obtained the 2-hydroxymethylene-17α-aza-D-homo-5α-androstan-3,17-dione (**2**) in 61% yield.

The condensation of compound **2** with hydroxylammonium chloride gave a mixture of isomeric 17-oxo-17α-aza-D-homo-5α-androstan[3,2-*c*]- (**3**) and -[2,3-*d*]isoxazoles (**4**), which were separated by column chromatography.

Under the same reaction conditions the 16-hydroxymethylene-3-aza-A-homo-4α-androsten-4,17-dione (**5**) [7] gave the 4-oxo-3-aza-A-homo-4α-androsten[17,16-*c*]isoxazole (6).

It should be noted that product **6** is the only compound formed as already reported in the literature [7,8]. The formation of only one compound has been attributed to stereochemical inhibition of the methyl group at position 18.





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EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 298 in the solid phase in potassium bromide with polystyrene as a reference peak. The uv spectra are measured in methanol on Perkin-Elmer 515 S instrument. Column chromatography was performed utilizing Aldrich silica gel 70-230 mesh, and neutral alumina, 150 mesh. Elemental analyses were performed by the Analytical Laboratory of Nuclear Research Center "Demokritos" Greece.

2-Hydroxymethylene-17α-aza-D-homo-5α-androstan-3,17-dione (**2**).

A mixture of 17α-aza-D-homo-5α-androstan-3,17-dione (**1**, 3.03 g, 10 mmoles), dry benzene (70 ml), ethyl formate (5 ml) and 80% sodium hydride (1.2 g, 40 mmoles) was stirred in an ice bath for 30 minutes and then at room temperature for 120 hours. The solvent was evaporated under reduced pressure and to the residue was added cold water (100 ml). The mixture was acidified with dilute hydrochloric acid and extracted with chloroform (3 x 100 ml). Drying with sodium sulfate and evaporation of the solvent affords the crude 2-hydroxymethylene derivative **2** in 65% yield. The product was chromatographed on a silica gel column using chloroform as the eluent to give after recrystallization from ethyl acetate 2 g (61%) of **2**, mp 242-245°; ir: 3260 (NH), 1700 (CO), 1640 (NHCO) cm^{-1}; uv: λ max = 203, ε = 15320.

Anal. Calcd. for $C_{20}H_{29}NO_3$: C, 72.50; H, 8.76; N, 4.22. Found: C, 72.89; H, 8.95; N, 4.02.

17-Oxo-17α-aza-D-homo-5α-androstan[3,2-*c*]- (**3**) and -[2,3-*d*]-isoxazoles (**4**).

To a solution of 2-hydroxymethylene-17α-aza-D-homo-5α-androstan-3,17-dione (**2**, 1.655 g, 5 mmoles) in a mixture of ethanol (30 ml) and pyridine (30 ml), hydrochloric hydroxylamine (382 mg, 5.5 mmoles) was added. The solution was heated under reflux for 2 hours. The reaction mixture was poured into ice water and extracted with chloroform (3 x 100 ml). The organic layer was washed with water and dried over sodium sulfate. After evaporation of the solvent, the residue was chromatographed on a column of neutral alumina. Elution with benzene-ethyl acetate (1:1) gave: i: 315 mg (19%) of 17-oxo-17α-aza-D-homo-5α-androstan[3,2-*c*]isoxazole (**3**) after recrystallization from ethyl acetate, mp 294-296°; ir: 3160 (NH), 1650 (NHCO), 1380 (=NO-) cm^{-1}; uv λ max = 203, ε = 10.000.

Anal. Calcd. for $C_{20}H_{28}N_2O_2$: C, 73.17; H, 8.53; N, 8.53. Found: C, 73.00; H, 8.35; N, 8.60. ii: A mixture of **3** and **4**, 215 mg (13%). iii: 17-Oxo-17α-aza-D-homo-5α-androstan[2,3-*d*]isoxazole (**4**), (265 mg, 16%) after recrystallization from ethyl acetate, mp 280-282°; ir 3160 (NH), 1640 (NHCO), 1385 (=NO-) cm^{-1}; uv: λ max = 200, ε = 8486.

Anal. Calcd. for $C_{20}H_{28}N_2O_2$: C, 73.17; H, 8.53; N, 8.53. Found: C, 72.95; H, 8.72; N, 8.65.

4-Oxo-3-aza-A-homo-4α-androsten[17,16-*c*]isoxazole (**6**).

To a solution of 16-hydroxymethylene-3-aza-A-homo-4α-androsten-4,17-dione (**5**, 329 mg, 1 mmole) in a mixture of ethanol (6 ml) and pyridine (6 ml) hydrochloric hydroxylamine (76.4 mg, 1.1 mmoles) was added. The solution was refluxed for 2 hours. The reaction mixture was poured into ice water and extracted with chloroform (3 x 20 ml). The organic layer was washed with water and dried over sodium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on neutral alumina using chloroform-methanol (99:1) as the eluent to give after recrystallization from ethyl acetate 200 mg (61%), mp 214-215°; ir: 3300 (NH), 1650 (NHCO), 1435 (=NO-) cm^{-1}; uv: λ max = 216.6, ε = 39960.

Anal. Calcd. for $C_{20}H_{26}N_2O_2$: C, 73.61; H, 7.97; N, 8.58. Found: C, 73.80; H, 8.05; N, 8.35.

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