A chemoselective method for nitration of steroids containing aromatic ring *A*

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A convenient chemoselective procedure was developed for *O*-nitration of steroids containing aromatic ring *A* under the action of $Cu(NO_3)_2$ in Ac_2O. The procedure allows one to obtain either mono- or dinitrates of diols depending on the reaction conditions.

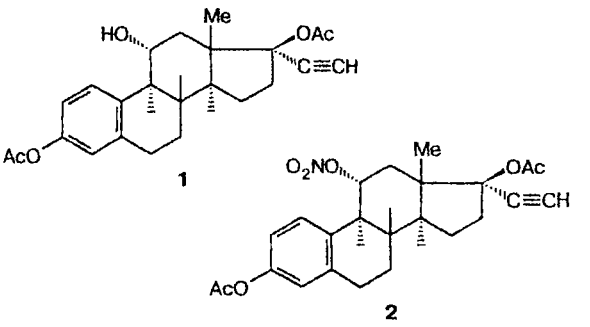
Key words: *O*-nitration, steroid nitrates, copper nitrate.

Examples of the synthesis of steroid nitrates are scarce. These compounds, unlike a number of other esters of inorganic acids, for example, sulfates, do not occur in nature, and nitration was used only for protecting hydroxy groups in steroids.[1] The detection of high biological activity of 11-nitrates of 9α,11β-dihydroxy derivatives of natural estrogens has aroused interest in this class of compounds.[2] New prospects of their use as physiologically active compounds may be associated with the ability of steroid nitrates to generate nitric oxide, which is a polyfunctional natural bioregulator.[3] Evidence that some 11β-nitroxyestra-1,3,5(10)-trienes inhibit platelet aggregation[4] suggests that steroid nitrates can serve as NO donors.[3] A combination of bioregulatory properties of steroids and nitric oxide in one compound can substantially extend the spectrum of steroid structures for searching for new drugs. Hence, the synthesis of these compounds is a topical problem.

A general procedure for the synthesis of steroid nitrates involves nitration of the corresponding alcohols with acetyl nitrate.[1] We used a mixture of concentrated HNO_3 and Ac_2O as a source of acetyl nitrate[5] and found that nitration under acidic conditions was not chemoselective. Thus, the reaction of compound **1** afforded 2- and 4-*C*-nitro derivatives of 11α-*O*-nitrate **2** rather than **2** as such (Scheme 1). It is needless to say that nitration under acidic conditions is unsuitable for acid-labile steroids. This gave impetus to a search for a procedure for chemoselective and mild nitration proceeding in the absence of a strong acid. Nitration with acetyl nitrate generated from copper nitrate and acetic anhydride, which does not require an acid, can be used for this purpose (see Ref. 6 and references therein).

We examined this procedure with the use of estradiol 3-acetate (**3**) as well as of 11α-hydroxyestradiol 3-acetate (**4**) and 11α-hydroxy-17α-ethynylestradiol

Scheme 1



3,17-diacetate (**1**), which we have synthesized previously.[7] The regioselectivity of the procedure was evaluated with the use of diol **4**.

The OH groups at the C(11) and C(17) atoms in steroids **1** and **3** were readily nitrated with an excess of acetyl nitrate at −10 °C. The nitration products, *viz.*, nitrates **2** and **5**, were obtained in 84 and 85% yields, respectively (Scheme 2). Mild methanolysis of acetate **5** (Et_3N in MeOH) afforded alcohol **6**.

The chemoselectivity of the proposed procedure was also confirmed by the results of nitration of steroid **1**. Unlike the procedure reported previously,[5] we did not observe C-nitration even in the case of a 20-fold excess of acetyl nitrate.

Nitration of diol **4** with 6 equivalents of acetyl nitrate afforded a representative of very rare steroid dinitrates, *viz.*, compound **7**. The proposed procedure allows one to perform selective nitration of the hydroxy group at the C(17) atom in diol **4** with the use of 3 equivalents of acetyl nitrate and decreasing the reaction time from 1.5 to 0.5 h. The structure of mononitrate **8** as 17-*O*-nitrate

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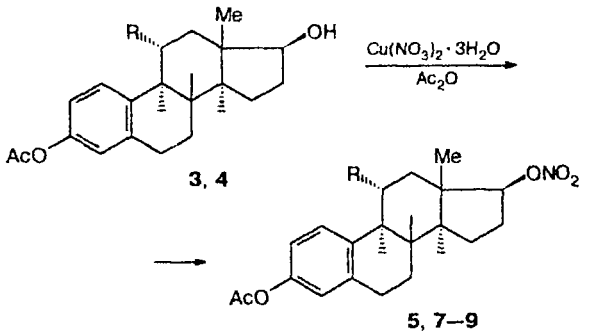
Scheme 2



R = H (**3**, **5**), OH (**4**, **8**), ONO_2 (**7**), OAc (**9**)

is evident from the comparison of the ^{1}H NMR spectra of steroids **4** and **8**, which have identical signals for the proton at the C(11) atom. Nitrate **8** was additionally characterized as diacetate **9**.

Experimental

The melting points were determined on a Boetius heating microtable. The optical rotation was measured on a Polamat A polarimeter in $CHCl_3$. The UV spectra were recorded on a Specord UV-VIS instrument in EtOH. The IR spectra were obtained on a Perkin—Elmer spectrometer in KBr pellets. The ^{1}H NMR spectra (in $CDCl_3$) were measured on a Bruker AM-300 spectrometer operating at 300 MHz with HMDS as the internal standard.

General procedure for nitration. A 20% solution of steroid **1**, **3**, or **4** (1 mmol) in Ac_2O (dinitrate **7** was prepared with the use of diol **4** (0.5 mmol)) was added to a solution of acetyl nitrate (3.0 mmol), which was prepared by stirring $Cu(NO_3)_2 \cdot 3H_2O$ (1.5 mmol) in Ac_2O (3 mL) at 10—15 °C under an Ar atmosphere for 1 h and cooled to a temperature from −15 to −20 °C. The suspension was stirred for 30 min to obtain nitrates **5** and **8** or for 1.5 h to obtain nitrates **2** and **7**. Then the mixture was diluted with a large amount of water and stirred at 20 °C for 1 h. The precipitate that formed was filtered off and washed with water to pH 7. The solution of the crude product in benzene was filtered through Al_2O_3 (neutral, activity II) and the solvent was evaporated.

3-Acetoxy-17β-nitroxyestra-1,3,5(10)-triene (5), the yield was 85%, m.p. 107—109 °C (ether—hexane). Found (%): N, 3.61. $C_{20}H_{25}NO_5$. Calculated (%): N, 3.89. $[\alpha]_D^{25}$ +63°±6° (*c* 1.02). UV, λ_{max}/nm (lg ε): 270 (2.96), 276 (2.97). IR, ν/cm^{-1}: 1760 (C=O); 1210 (C—OAc); 1620, 1280 (ONO_2); 1490 (Ar). ^{1}H NMR, δ: 0.90 (s, 3 H, Me); 2.30 (s, 3 H, OAc); 4.93 (t, 1 H, H(17), J = 7.5 Hz); 6.80 (m, 1 H, H(4)); 6.86 (dd, 1 H, H(2), J = 2.0 and 8.5 Hz); 7.30 (d, 1 H, H(1), J = 8.5 Hz).

17β-Nitroxyestra-1,3,5(10)-trien-3-ol (6) was prepared by methanolysis of acetate **5** (Et_3N, MeOH, 25 °C, 20 h), in 85% yield, m.p. 187—189 °C (ether—hexane) (*cf.* Ref. 8: m.p. 188 °C), $[\alpha]_D^{25}$ +62°±6° (*c* 1.09). UV, λ_{max}/nm (lg ε): 282 (3.20), 289 (3.16). IR, ν/cm^{-1}: 3550 (OH); 1610, 1275 (ONO_2); 1500 (Ar). ^{1}H NMR, δ: 0.90 (s, 3 H, Me); 4.92 (t, 1 H, H(17), J = 7.5 Hz); 4.61 (br.s, 1 H, OH); 6.59 (m, 1 H, H(4)); 6.66 (dd, 1 H, H(2), J = 2.0 and 8.5 Hz); 7.17 (d, 1 H, H(1), J = 8.5 Hz).

3-Acetoxy-17β-nitroxyestra-1,3,5(10)-trien-11α-ol (8), the yield was 65%, m.p. 78—80 °C (ethyl acetate—hexane), $[\alpha]_D^{25}$ −63°±6° (*c* 1.03). UV, λ_{max}/nm (lg ε): 267 (2.80), 275 (2.71). IR, ν/cm^{-1}: 3420 (OH); 1760, 1745 sh (C=O); 1210 (C—OAc); 1630, 1280 (ONO_2); 1490 (Ar). ^{1}H NMR, δ: 0.85 (s, 3 H, CH_3); 2.28 (s, 3 H, OAc); 4.20 (td, 1 H, H(11), J = 10 and 5 Hz); 4.92 (t, 1 H, H(17), J = 7.5 Hz); 6.83—6.92 (m, 2 H, H(2), H(4)); 7.98 (d, 1 H, H(1), J = 8.5 Hz).

3,11α-Diacetoxy-17β-nitroxyestra-1,3,5(10)-triene (9) was prepared by acetylation of alcohol **8** (Ac_2O—Py, 1 : 1, 20 °C, 12 h), m.p. 105—107 °C (ethyl acetate—hexane). Found (%): C, 62.97; H, 6.36; N, 3.01. $C_{22}H_{27}NO_7$. Calculated (%): C, 63.29; H, 6.52; N, 3.36. $[\alpha]_D^{25}$ −77°±6° (*c* 1.01). UV, λ_{max}/nm (lg ε): 267 (2.86), 276 (2.78). IR, ν/cm^{-1}: 1756 (C=O in 3-OAc); 1725 (C=O in 11-OAc); 1195 (C—OAc); 1620, 1280 (ONO_2); 1490 (Ar). ^{1}H NMR, δ: 0.91 (s, 3 H, Me); 2.07 (s, 3 H, 11-OAc); 2.28 (s, 3 H, 3-OAc); 4.91 (t, 1 H, H(17), J = 7.5 Hz); 5.4 (td, 1 H, H(11), J = 10.5 and 5 Hz); 6.81—6.84 (m, 2 H, H(2), H(4)); 7.04 (d, 1 H, H(1), J = 8.5 Hz).

3-Acetoxy-11α,17β-dinitroxyestra-1,3,5(10)-triene (7), the yield was 77%, m.p. 156—158 °C (ethyl acetate—hexane). Found (%): C, 56.99; H, 6.09; N, 6.79. $C_{20}H_{24}N_2O_8$. Calculated (%): C, 57.13; H, 5.75; N, 6.66. $[\alpha]_D^{25}$ −93°±6° (*c* 0.99). UV, λ_{max}/nm (lg ε): 267 (2.93), 271 (2.91). IR, ν/cm^{-1}: 1765 (C=O); 1190 (C—OAc); 1290, 1625 (ONO_2); 1490 (Ar). ^{1}H NMR, δ: 0.97 (s, 3 H, Me); 2.30 (s, 3 H, OAc); 4.97 (t, 1 H, H(17), J = 7.5 Hz); 5.58 (td, 1 H, H(11), J = 10 and 5 Hz); 6.82—6.95 (m, 2 H, H(2), H(4)); 7.18 (d, 1 H, H(1), J = 8.5 Hz).

3,17β-Diacetoxy-11α-nitroxy-17α-ethynylestra-1,3,5(10)-triene (2), the yield was 84%, m.p. 202—203 °C (ethyl acetate—hexane), $[\alpha]_D^{25}$ −162±10° (*c* 1.13); (*cf.* Ref. 5: m.p. 197—199 °C, $[\alpha]_D^{25}$ −162±10°). A mixture with a known sample[5] did not give a melting point depression.

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References

1. *Protective Groups in Organic Chemistry*, Ed. J. F. W. McOmie, Plenum Press, London—New York, 1973, 119.
2. V. M. Rzheznikov, T. I. Ivanenko, E. V. Pokrovskaya, and V. L. Fedotov, *Khim.-Farm. Zh.*, 1986, **20**, 9, 1057 [*Pharm. Chem. J.*, 1986, **20** (Engl. Transl.)]; R. H. Peters, D. F. Crowe, M. A. Avery, W. K. M. Chong, and M. Tonabe, *J. Med. Chem.*, 1989, **32**, 10, 2306.
3. J. F. Kerwin, J. R. Lancaster, and P. L. Feldman, *J. Med. Chem.*, 1996, **38**, 22, 4343.
4. P. V. Sergeev, A. N. Karachentsev, A. S. Dukhamin, L. E. Golubovskaya, and V. M. Rzheznikov, *Abstrs. 2-nd Intern. Symp. Chem. Natur. Comp. Eskisehir*, Turkey, 1996, 167.
5. L. E. Golubovskaya and V. M. Rzheznikov, *Zh. Org. Khim.*, 1997, **33**, 619 [*Russ. J. Org. Chem.*, 1997, **33** (Engl. Transl.)].
6. I. L. Dalinger, V. A. Litosh, and S. A. Shevelev, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 1198 [*Russ. Chem. Bull.*, 1997, **46**, 1149 (Engl. Transl.)].
7. V. M. Rzheznikov, *Bioorg. Khim.* 1991, **17**, 7, 1002 [*Sov. J. Bioorg. Chem.*, 1991, **17** (Engl. Transl.)].
8. Fr. Pat. 5421 (1966); *Chem. Abstrs.*, 1970, **72**, 44008z.

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