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Novel Steroids from Cetyltrimethylammonium Permanganate-Initiated Oxidative Rearrangements of 16-Dehydroprogesterone

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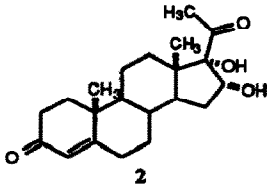
Abstract: Cetyltrimethylammonium permanganate initiates oxidative opening of the D-ring of 16-dehydroprogesterone in CH_2Cl_2. The novel steroids **3** and **4** have been isolated and characterized as the major products obtained from oxidative rearrangement of the steroid backbone. The X-ray crystal structure of the D-homosteroid **3** is provided, and a putative mechanism that invokes a benzilic acid rearrangement for formation of **3** is presented.

In the course of our development of photoaffinity labeling reagents for the progesterone receptor, we required 16α,17α-dihydroxyprogesterone (**2**).[1] This progestin diol has been prepared by *cis*-hydroxylation of 16-dehydroprogesterone (**1**), but the reported yields were low.[2] Our initial attempts at selective oxidation of the sterically encumbered C_{16}-olefin in **1** with potassium permanganate in aqueous acetone or catalytic osmium tetroxide with excess *N*-methylmorpholine-*N*-oxide gave the desired diol **2**, but in low yield (15%-25%). In an attempt to improve the efficiency of this reaction,[3] we used the permanganate phase transfer catalyst, cetyltrimethylammonium permanganate, as an oxidant in dichloromethane.[4] The product isolated after a non-aqueous work up procedure, however, was not the desired 16α,17α-progestin diol **2**, but the novel 5-ring D-homosteroid **3**.



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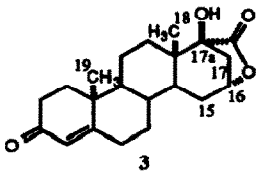

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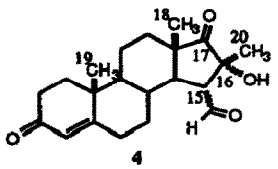


4

Information obtained from ^1H and ^{13}C NMR, IR and mass spectrometry was useful in the initial assignment of the structure of the novel D-homosteroid.[5] The ^1H NMR spectrum revealed only two CH_3 groups; the absence of a singlet downfield of δ 2.0 suggested that the C_{21} methyl group had been lost. There was very little change in the peaks corresponding to the A, B, and C rings of the progestin backbone. The ^{13}C NMR spectrum contained 21 unique carbon signals, which included two carbonyl carbons and two olefinic carbons. One of the carbonyl ^{13}C resonances was shifted upfield to δ 178.2, which suggested that this carbonyl had been transformed from a ketone to an ester. EI mass spectrometry showed a molecular ion at 344, which indicated that the compound had undergone additional oxidation compared to the desired progestin

diol 2. HRMS indicated a molecular formula of $C_{21}H_{28}O_4$. The infrared spectrum contained bands for a hydroxyl (3559 cm^{-1}) and two carbonyl functionalities (1774 and 1664 cm^{-1}). A crystal suitable for X-ray crystallography was grown by slow evaporation of a CH_2Cl_2 solution of 3 at room temperature. The crystal structure[6] (Figure 1) identified 3 as a novel D-homosteroid with an additional lactone ring bridging the ring-expanded D-ring on the α-face between C_{16} and C_{17a}.

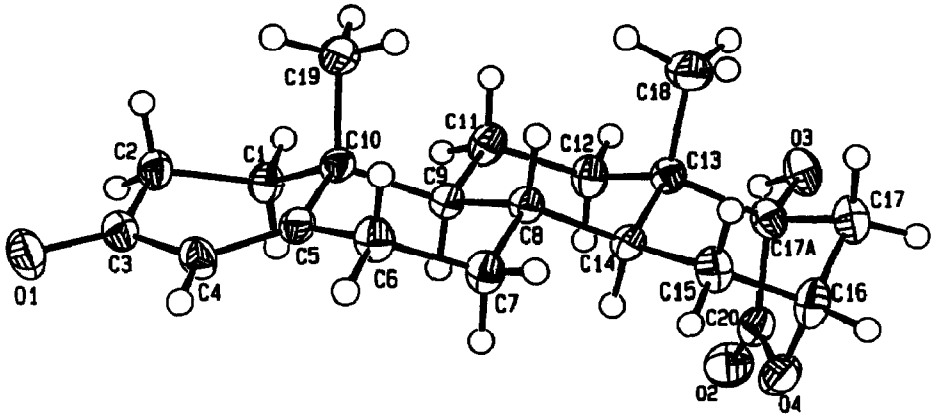


Figure 1. X-ray crystallographic structure of the D-homosteroid 3.

In an attempt to optimize the yield of the D-homo steroid 3, several modifications of the reaction conditions were investigated. We found that forcing reaction conditions (excess CTAP, longer reaction times, or heat) resulted in lower yields of the desired product, presumably due to further oxidative degradation of the progestin backbone. Oxidation using CTAP in a mixture of acetone and 1.0 M potassium hydroxide (1:1 / v:v) resulted in formation of diol 2 in 51% yield.

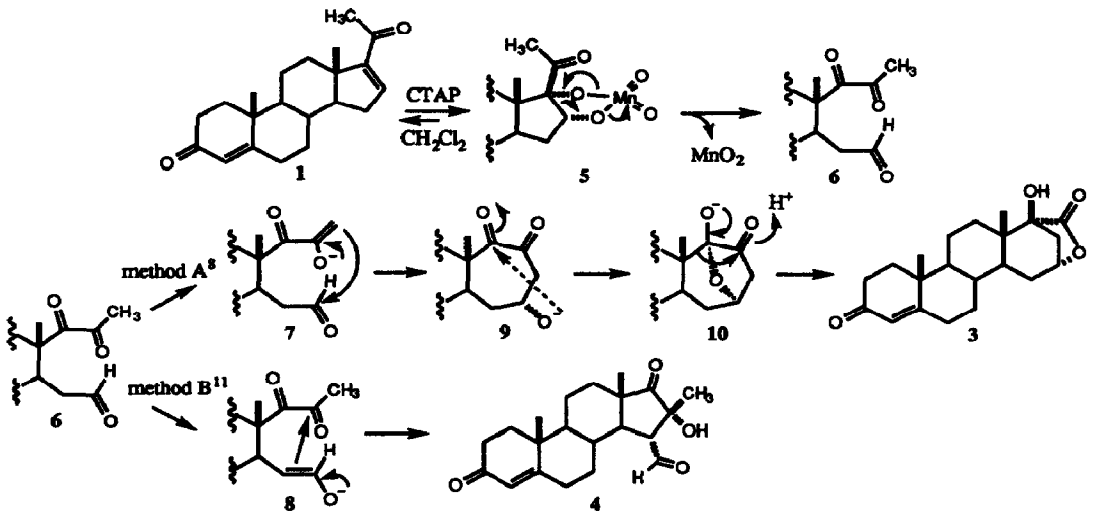
Of particular interest, we found that slow addition of a dichloromethane solution of CTAP via a syringe pump over 8 h to a CH_2Cl_2 solution of 16-dehydroprogesterone resulted in formation of a slightly less polar derivative as the major product (28% based on consumed starting material), together with the D-homo steroid 3 in trace amounts (< 2%). We have identified this less polar derivative as the novel androstane carboxaldehyde 4.[7] The distinguishing features from ^1H NMR spectrum are the aldehydic proton resonance (δ 9.69), and three large singlets (δ 1.03, 1.21, 1.45) that can be attributed to methyl groups. A decoupling experiment established the link between the aldehydic proton and the proton on the C_{15} methine. The ^{13}C NMR shows three resonances (δ 217.47, 203.94, 199.16) assigned to ketone or aldehydic carbons, and the two olefinic carbons in the A-ring (δ 169.20, 124.39). The infrared spectrum revealed bands for the hydroxyl (3572 cm^{-1}) and three carbonyl (1748, 1719, 1665 cm^{-1}) functionalities. EI mass spectrometry identified the molecular ion as 344, placing this compound in the same oxidation state as the D-homosteroid 3. HRMS indicated the molecular formula to be $C_{21}H_{28}O_4$. The structure assigned to compound 4 is consistent with all of these data. This novel compound is especially interesting, as it provides a handle for further manipulation at C_{15} in the androstane backbone, a site that is difficult to access through conventional methods.

The structure assigned to 4 contains two new stereogenic centers at C_{15} and C_{16}. The stereochemistry at these centers was defined via nuclear Overhauser effect (NOE) ^1H NMR studies. Irradiation of the C_{15}

methine proton produced an NOE enhancement of 4.6% at the C_{20} methyl group, 5.0% at the C_{18} methyl group, and 3.3% of the aldehydic resonance. Irradiation of the C_{20} methyl group produced a large NOE enhancement of 5.9% at the C_{15} methine proton and a small enhancement of 1.4% at the C_{18} proton. This establishes that the C_{15} methine proton, the C_{18} methyl group and the C_{20} methyl group are on the same side of the molecule. Since the C_{13} stereogenic center (site of C_{18} methyl attachment) has not changed in the transformation from **1** to **4**, we assign these groups on the β-face of the molecule. This assignment is also consistent with the large coupling constant (12.4 Hz) observed between the anti-disposed C_{15} and C_{14} methine protons.

It is intriguing to speculate on a possible mechanism for the formation of the novel steroids **3** and **4**. In our proposed mechanism (Scheme I), under non-aqueous conditions the breakdown of the cyclic manganese (VI) ester **5** results in scission of the C_{16}-C_{17} bond and opening of the D-ring. The resulting diketone **6** is able to enolize at two different sites. Under reaction conditions in which the permanganate concentration is high (method A[8]), the C_{21} enolate of the diketone (**7**) attacks the aldehyde to form the seven-membered ring intermediate **9**; subsequent attack of the alkoxide at the C_{17} carbonyl forms the 5-membered ketolactol **10**; finally, ring contraction of **10** is accomplished through a mechanism analogous to the benzilic acid rearrangement[9] forming the D-homosteroid **3**. The ring contraction of the D-ring resembles a reported ring contraction of the C-ring in an androstane 11,12-diketone by a benzilic acid rearrangement under basic conditions.[10] If the concentration of permanganate ion is low (method B[11]), the C_{15}-enolate **8** attacks at the C_{20} carbonyl, affording the novel androstane **4**. To investigate whether androstane **4** could be converted to the D-homosteroid **3** under basic conditions we treated it with 1,8-diazabicyclo[5.4.0]undec-7-ene in CH_2Cl_2. This afforded a 4:1 mixture of **4** with its C_{16} epimer, but formation of D-homosteroid **3** was not observed.

Scheme I



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1. Kym, P. R.; Carlson, K. E.; Katzenellenbogen, J. A. *J. Med. Chem.* **1993**, *9*, 1111.
2. Cooley, G.; Ellis, B.; Hartley, F.; Petrow, V. *J. Chem. Soc.* **1955**, 4373.
3. We found that stoichiometric osmium tetroxide in pyridine converts 16-dehydroprogesterone to progestin diol 2 in 82% yield with high regio and stereoselectivity. A detailed experimental section is given in ref. 1.
4. Bhushan, V.; Rathore, R.; Chandrasekaran, S. *Synthesis* **1984**, 431.
5. Spectroscopic data for 3: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 3 H, 19-CH_3), 1.19 (s, 3 H, 18-CH_3), 2.59 (s, 1 H, OH), 4.81 (dd, J = 5.16, 5.24 Hz, 1 H, 16β-CH), 5.72 (s, 1 H, 4-CH); ^{13}C NMR (125 MHz) δ 199.58, 178.25, 170.47, 123.85, 79.87, 75.28, 53.17, 44.26, 39.98, 39.21, 38.75, 35.35, 34.11, 33.91, 32.54, 30.76, 29.44, 27.97, 20.08, 17.46, 12.17; IR ($CHCl_3$) 3559, 1774, 1664 cm^{-1}; MS (EI, 70 eV) *m/z* 344 (M^+), 329, 316, 273. HRMS Calcd for $C_{21}H_{28}O_4$ 344.1988, found 344.1985. Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.02; H, 8.23.
6. Compound 3 crystallizes in an orthorhombic system of space group $P2_12_12_1$with 4 molecules in a unit cell of dimensions a = 6.477 (2), b =12.742 (5), c = 21.121 (8), V = 1743 (1) Å^3. Using a total of 1993 reflections measured on an Enraf-Nonius diffractometer using monochromated MoK_α radiation, the structure was solved by a direct method (SHELXS-86), and a differential Fourier method (for H), and refined by least squares on F2 using SHELXL-93. The final R factor was 4.5%. Final crystallographic coordinates have been deposited in the Cambridge Crystallographic Data Center.
7. Spectroscopic data for 4: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 3 H, 18-CH_3), 1.21 (s, 3 H, 19-CH_3), 1.45 (s, 3 H, 20-CH_3), 2.60 (dd, J = 12.4, 4.2 Hz, 1 H, 15-CH), 5.74 (s, 1 H, 4-CH), 9.69 (d, J = 4.2 Hz, 1 H, aldehyde); ^{13}C NMR (125 MHz) δ 217.47, 203.94, 199.16, 169.20, 124.39, 79.64, 58.24, 53.77, 48.18, 48.10, 38.73, 35.79, 34.99, 33.97, 32.40, 31.95, 31.83, 25.80, 20.04, 17.55, 15.40; IR ($CHCl_3$) 3572, 1748, 1719, 1665 cm^{-1}; MS (EI, 70 eV) *m/z* 344 (M^+), 326, 286, 273, 255, 230, 107. HRMS Calcd for $C_{21}H_{28}O_4$ 344.1988, found 344.1985.
8. Procedure for method A: A CH_2Cl_2 solution of CTAP (0.310 g, 0.77 mmol) was added over 10 min to a stirred solution of 16-dehydroprogesterone (0.200 g, 0.64 mmol) in 10 mL of dry CH_2Cl_2 and the resulting brown solution stirred for 2 h at RT. Evaporation of the CH_2Cl_2 followed by addition of 100 mL ether resulted in a heterogenous mixture of clear liquid and brown solid. The mixture was filtered through a plug of celite and $MgSO_4$ (10 g of each) and the plug was washed twice with 50 mL portions of ether. The ether layer was evaporated to provide 110 mg of white solid. Flash chromatography (1:1 hexanes/ EtOAc) afforded 0.062 g of 3 as a white solid (mp 236-238 °C) and 0.038 g of 16-dehydroprogesterone. The yield based on consumed starting material was 35%.
9. Nace, H. R.; Nelander, D. H. *J. Org. Chem.* **1964**, *29*, 1677.
10. Kurath, P. *J. Org. Chem.* **1967**, *32*, 3626.
11. Procedure for method B: A 30 mL CH_2Cl_2 solution of CTAP (0.149 g, 0.37 mmol) was added over 8 h via syringe pump to a stirred solution of 16-dehydroprogesterone (0.096 g, 0.31 mmol) in 100 mL of dry CH_2Cl_2 and the resulting brown solution stirred for 2 h at RT. The workup was identical to Method A. Flash chromatography (1:1 hexanes/ EtOAc) afforded 0.015 g of 4 , as a white solid (mp 219-221 °C), 0.0013 g of 3, and 0.046 g of 16-dehydroprogesterone. The yield of 4 based on consumed starting material was 28%.

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