

An Improved Preparation of 11,19-Oxidopregn-4-ene-3,20-dione and 6,19-Oxidopregn-4-ene-3,11,20-trione

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11,19-Oxidopregn-4-ene-3,20-dione, 11,19-Oxidoprogesterone.

6,19-Oxidopregn-4-ene-3,11,20-trione, 6,19-Oxido-11-ketoprogesterone, Synthesis

A synthesis of 11,19-oxidopregn-4-ene-3,20-dione and 6,19-oxidopregn-4-ene-3,11,20-trione is described starting from pregn-4-ene-3,11,20-trione and *via* the common intermediate 3 β ,20 β -diacetyloxy-5 α -bromo-6,19-oxidopregnan-11-one, in 30 and 32% yield, respectively.

Introduction

Steroid molecules derived from progesterone with highly flat overall conformation, have gained interest as aldosterone analogues which could give rise to compounds with antimineralocorticoid activity [1]. Also mimicking mineralocorticoid activity with functionally "simple" molecules may throw light into the mechanism of action of the natural compounds and on the conformational requirements for binding to the mineralocorticoid receptor without interference from the action of particular functional groups. Previous approaches to the problem have focused on 19-nor [2] and 11,12-dehydrosteroids [1]. These structures tend to adopt a more planar conformation than the normal steroid nucleus because of diminished steric effects on the β -face of the molecule. However it should be expected that these molecules would be fairly flexible and may be deformed upon interaction with the receptor molecule.

Our interest has been on the study of highly planar steroids with rigid conformations. Molecular mechanics calculations using the MM2 and MMP2 force fields [3], indicated that this could be achieved by the introduction of an 11,19-oxido bridge. Hence 11,19-oxidoprogesterone (**1**) would be the simplest such structure containing the key groups that have been established as necessary for mineralocorticoid activity [4]. On the other hand, a 6,19-oxido bridge as that in 6,19-oxido-pregn-4-ene-3,11,20-trione (**2**), distorts the A ring of the

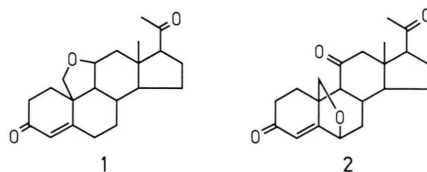
progesterone molecule which may then adopt either a 2 β -sofa or the more stable (3.3 kcal/mol by molecular mechanics calculation) 1 β -sofa conformation. This renders a fairly planar structure for rings B–D, with the C-3 carbonyl pointing towards the α -face.

Previous preparations of 11,19-oxidoprogesterone (**1**) had very poor yields [5, 6] or gave mixtures with the 5,6-ene isomer [7]. We now describe an improved preparation of this compound and a derivation that leads to 6,19-oxidopregn-4-ene-3,11,20-trione (**2**).

Results and Discussion

Commercially available pregn-4-ene-3,11,20-trione (**3**) was selected as the starting material for both target compounds. Its conversion to the 11,19-oxido-steroid (**1**) is depicted in Fig. 1. The 3-enol acetate of **3** was reduced with sodium borohydride and acetylated to give the diacetate **4** [8]. As variable amounts of reduction at the C-11 position were observed, the crude acetylation product was oxidized with Jones reagent in order to regenerate the 11-ketone, obtaining **4** in almost quantitative yield.

Functionalization of the 19 angular methyl was carried out by conversion of **4** to the 5 α -bromo-



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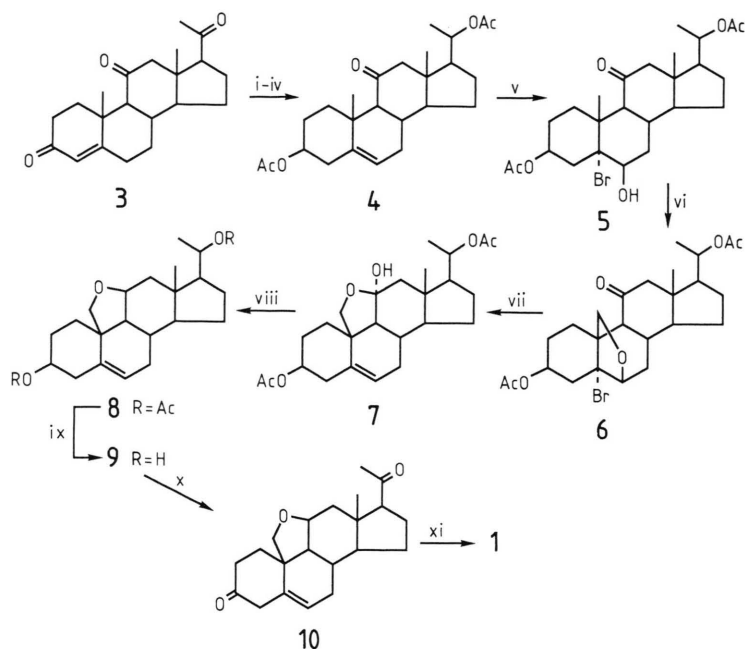


Fig. 1. Reagents: i, Ac_2O , AcCl ; ii, NaBH_4 , EtOH ; iii, Ac_2O , pyridine; iv, H_2CrO_4 , acetone; v, NBA , HClO_4 ; vi, HgO , I_2 , CCl_4 , $h\nu$; vii, Zn , aq. AcOH , I_2 ; viii, NaCNBH_3 , MeOH , $\text{pH} = 2-3$; ix, LiAlH_4 , THF ; x, PDC , DCM , molecular sieves ($3\text{\AA}$); xi, aq. HCl , MeOH , DCM . Ac = acetyl; NBA = N-bromoacetamide; THF = tetrahydrofuran; PDC = pyridinium dichromate; DCM = dichloromethane.

6 β -hydroxy derivative (5) with N-bromoacetamide/perchloric acid and treatment of the bromohydrin with mercuric oxide/iodine (CCl_4 , $h\nu$) [9] to yield the 6,19-oxide (6). Opening of the 6,19-oxido bridge of 6 was attempted with several of the published procedures [10]; finally we found that the use of activated zinc in aqueous acetic acid in the presence of a catalytic amount of iodine gave the best yield of the hemiketal 7. ^{13}C NMR of the latter compound indicated that it was mainly in hemiketalic form (C-11 at 107.5 ppm) containing *ca.* 30% of the 19-hydroxy-11-ketosteroid (C-11 at 208.3 ppm) in contrast with a previous report that proposed the existence of the latter form exclusively [5, 6]. In a previous synthesis of a related compound the author proposed that this type of hydroxy ketones may exist in open or cyclized form [11].

The key step in the synthesis of the 11,19-oxido bridge was the direct reduction of the 11,19-hemiketal (7) to the cyclic ether. This was accomplished by treatment of 7 with sodium cyanoborohydride in methanol at $\text{pH} 2-3$ [12], which afforded smoothly and in high yield the 11,19-oxido steroid

(8). The structure of 8 was confirmed by ^{13}C and ^1H NMR.

Saponification of the acetate group at position 3 could be effected by treatment with methanolic sodium hydroxide at room temperature, however the C-20 acetate required long reaction times and the overall yield was poor. After several attempts, the acetate groups could be eliminated efficiently with lithium aluminum hydride (THF, reflux) rendering diol 9. Oxidation with Jones reagent produced large amounts of overoxidized products (mainly the 6-keto derivative) and so other oxidizing agents were considered. Pyridinium dichromate in dichloromethane, in the presence of activated molecular sieves powder ($3\text{\AA}$) produced the diketone 10. Finally, isomerization of the 5, 6 double bond to the 4, 5 position could be carried out in acidic medium in a two phase system (HCl , methanol-dichloromethane-water, 25°) rendering 1 in a 30% overall yield from 3.

The reaction sequence followed for obtention of compound 2 is presented in Fig. 2 starting from the common intermediate 6. Although at first sight this appeared as a straightforward transformation

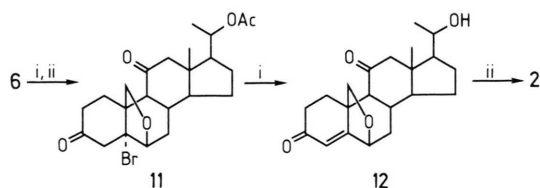


Fig. 2. Reagents: i, NaOH, MeOH; ii, H_2CrO_4 , acetone.

involving saponification of the acetate groups and oxidation, the 5-bromo-3,20-diketone formed, required a basic treatment to afford the desired 4-ene-3-ketosteroid (**2**). Under these conditions, partial epimerization at C-17 was observed due to the presence of the 20-ketone, lowering the yield of the transformation. Hence diacetate **6** was subjected to a mild alkaline hydrolysis (NaOH, methanol, 15 min at 25°) to afford the 3-hydroxy compound which was oxidized with Jones reagent to the 3-ketone **11**. Treatment of the latter with sodium hydroxide as above but for 22 h, afforded **12**, where both saponification of the C-20 acetate and dehydrohalogenation at positions 4, 5 had proceeded simultaneously. Finally oxidation with Jones reagent afforded **2** in 32% overall yield from **3**.

A detailed study of the mineralocorticoid activity of the oxidosteroids **1** and **2** and other related compounds will be published shortly.

Experimental

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were determined at 100.1 and 25.2 MHz respectively in deuterochloroform in a Varian XL-100-15 NMR spectrometer operating in the FT mode. Chemical shifts are expressed in ppm downfield from internal TMS. Mass spectra were measured by direct inlet in a Varian MAT CH 7 A mass spectrometer. Preparative high performance liquid chromatography was performed on a Micromeritics liquid chromatograph, equipped with a refractive index detector, using a Whatman partisol ODS-2 10μ column (500×10 mm) and methanol:water mixtures as eluent. All solvents used were of reagent grade quality. Extractive workup included exhaustive extraction with the solvent indicated, washing with water, drying with anhydrous sodium sulfate and evaporation of the solvent at reduced pressure and *ca.* 40 – 60°C . Homogeneity of all compounds was confirmed by TLC.

3 β ,20 β -Diacetyloxy-5 α -bromo-6,19-oxido-pregnan-11-one (**4**)

A solution of 11-ketoprogesterone (**3**) (2.04 g) in acetic anhydride (40 ml) and acetyl chloride (60 ml) was heated for 4 h at 70 – 75°C under a nitrogen atmosphere. Evaporation to dryness afforded the 3-enol acetate (2.3 g) which was dissolved in 95% ethanol (1.3 l) and cooled to 5°C . A solution of sodium borohydride (4.7 g) in ethanol (83 ml) and water (35 ml) was added, the reaction mixture was stirred for 2 h at 5°C , treated with 5% aqueous sodium hydroxide (23 ml) and heated to the boiling point. The resulting solution was concentrated, diluted with water and extracted with dichloromethane. The product obtained after evaporation of the solvent was acetylated with acetic anhydride (15 ml) and pyridine (15 ml) for 24 h at room temperature. The crude acetate was dissolved in acetone and treated with an excess of Jones reagent at 0°C . Extractive workup afforded **4** (2.56 g), m.p. 135 – 137°C (lit. 134 – 139°C [13]); ^1H NMR: 0.55 (s, 3H, H-18), 1.11 (d, $J = 6$ Hz, 3H, H-21), 1.20 (s, 3H, H-19), 2.04 (s, 6H, acetates), 4.38–4.96 (m, 2H, H-3 and H-20), 5.30 (m, 1H, H-6).

3 β ,20 β -Diacetyloxy-5 α -bromo-6,19-oxido-pregnan-11-one (**6**)

To a stirred solution of **4** (2.56 g) in ether (26 ml) and tetrahydrofuran (10 ml) cooled to 10°C was added 7.5% aqueous perchloric acid (3 ml) followed by N-bromoacetamide (1.32 g) in 8 portions during a 25 min period at 10 – 15°C protected from light. After 30 min at room temperature, 1% aqueous sodium thiosulfate was added and the mixture was poured over dichloromethane:methanol (10:1). Extractive workup afforded the 5 α -bromo-6 β -hydroxy derivative (**5**) (3.1 g); ^1H NMR: 0.61 (s, 3H, H-18), 1.16 (d, $J = 6$ Hz, 3H, H-21), 1.53 (s, 3H, H-19), 2.03 (s, 6H, acetates), 4.18 (m, 1H, H-6), 5.50 (m, 1H, H-3).

The crude bromohydrin was dissolved in recently distilled carbon tetrachloride (254 ml) and red mercuric oxide (8.7 g) and iodine (12.8 g) added. The reaction mixture was vigorously stirred while irradiating with a 300 watt tungsten lamp (5000 lumen) for 30 min at 25°C . After filtration, the solution was diluted with dichloromethane, washed with aqueous sodium thiosulfate and evaporated to dryness yielding **6** (2.9 g); ^1H NMR: 0.65 (s, 3H, H-18), 1.17 (d, $J = 6$ Hz, 3H, H-21), 2.04 (s, 6H, acetates), 3.90 (d, $J = 9$ Hz, 1H, H-19a), 4.08 (m, 1H, H-6), 4.09 (d, $J = 9$ Hz, 1H, H-19b), 4.78 (m, 1H, H-20), 5.18 (m, 1H, H-3); MS, m/z (rel. ab.) 392 and 390 (1%, $\text{M} - 2\text{AcOH}$).

3 β ,20 β -Diacetyloxy-11,19-oxidopregn-5-ene (8)

To a solution of **6** (1.4 g) in acetic acid (45 ml) and water (2.0 ml), was added activated zinc powder (8.0 g) in small portions and a crystal of iodine. The reaction mixture was stirred for 5 h at 75 °C, filtered and poured over 5% aqueous sodium bicarbonate. Extractive workup with ether:dichloromethane (4:1), rendered crude **7** (1.14 g) containing *ca.* 30% of 19-hydroxy-11-ketone; ¹H NMR: 0.72 (s, 3H, H-18), 1.17 (d, *J* = 6 Hz, 3H, H-21), 2.04 (s, 6H, acetates), 3.84 (d, *J* = 8 Hz, 1H, H-19a), 4.18 (d, *J* = 8 Hz, 1H, H-19b), 4.40–5.10 (m, 2H, H-3 and H-20), 5.64 (m, 1H, H-6).

The previous compound without further purification, was dissolved in methanol (61 ml) containing a trace of methyl orange and sodium cyanoborohydride (670 mg) added. The solution was kept at 25 °C maintaining the pH between 2 and 3 (red to orange color) by periodic additions of 1 N HCl: methanol (1:1). The reaction mixture was acidified with aqueous HCl, concentrated at reduced pressure and diluted with water. Extractive workup with dichloromethane followed by preparative reverse phase HPLC afforded the 11,19-oxide (**8**) (687 mg), m.p. 118–120 °C (from MeOH); ¹H NMR: 0.78 (s, 3H, H-18), 1.15 (d, *J* = 6 Hz, 3H, H-21), 2.04 (s, 6H, acetates), 3.70 (d, *J* = 8 Hz, 1H, H-19a), 3.94 (d, *J* = 8 Hz, 1H, H-19b), 4.25 (m, 1H, H-11), 4.50–5.00 (m, 2H, H-3 and H-20), 5.60 (bd, *J* = 6 Hz, 1H, H-6); MS, *m/z* (rel. ab.) 416 (1%, M⁺), 356 (56%, M–AcOH), 296 (59%, M–2AcOH), 266 (59%, 296–CH₂O).

11,19-Oxidopregn-5-ene-3,20-dione (10)

Compound **8** (211 mg) was dissolved in anhydrous tetrahydrofuran (14 ml) and lithium aluminum hydride (507 mg) added. The mixture was heated under reflux in a nitrogen atmosphere for 5 h rendering after workup diol **9** (164 mg); ¹H NMR: 0.88 (s, 3H, H-18), 1.13 (d, *J* = 6 Hz, 3H, H-21), 3.70–3.90 (m, 2H, H-3 and H-20), 3.70 (d, *J* = 8 Hz, 1H, H-19a), 3.96 (d, *J* = 8 Hz, 1H, H-19b), 4.28 (m, 1H, H-11), 5.57 (bd, *J* = 6 Hz, 1H, H-6). The crude diol was dissolved in dry dichloromethane (4 ml) and treated with pyridinium dichromate (410 mg) and activated molecular sieves (3 Å) powder (410 mg). The reaction mixture was vigorously stirred under nitrogen for 24 h at 25 °C, diluted with ether and filtered through Hyflo Supercell. The residue obtained after evaporation of the solvent (141 mg) was further purified by preparative reversed phase HPLC rendering diketone **10** (92 mg), m.p. 165–167 °C

(from MeOH); ¹H NMR: 0.80 (s, 3H, H-18), 2.16 (s, 3H, H-21), 3.92 (dd, *J*_{gem} = 8 Hz, *J*_{19a-9} = 1 Hz, 1H, H-19a), 4.15 (d, *J* = 9 Hz, 1H, H-19b), 4.38 (m, 1H, H-11), 5.58 (m, 1H, H-6).

Analysis for C₂₁H₂₈O₃

Calcd C 76.79 H 8.59,

Found C 76.68 H 8.70.

11,19-Oxidopregn-4-ene-3,20-dione (1)

To a solution of diketone **10** (92 mg) in dichloromethane (3.4 ml) and methanol (11.5 ml), was added water (0.8 ml) and conc HCl (1.7 ml). The mixture was vigorously stirred 16 h at 25 °C, diluted with water and extracted with dichloromethane. Evaporation of the solvent yielded the 4-ene-3,20-dione (**1**) (92 mg), m.p. 166–168 °C (from MeOH) (lit. 167–170 °C [6]); UV λ_{max} (ethanol), 242 nm (ϵ = 9237); ¹H NMR: 0.83 (s, 3H, H-18), 2.16 (s, 3H, H-21), 3.82 (dd, *J*_{gem} = 9 Hz, *J*_{19a-9} = 1.5 Hz, 1H, H-19a), 4.01 (d, *J* = 9 Hz, 1H, H-19b), 4.42 (m, 1H, H-11), 5.91 (s, 1H, H-4); ¹³C NMR: 15.5 (C-18), 22.7 (C-16), 23.3 (C-15), 28.0 (C-7), 31.0 (C-21), 32.7 (C-6), 33.4 (C-2), 34.5 (C-8), 34.6 (C-1), 41.1 (C-12), 44.1 (C-13), 47.3 (C-10), 52.7 (C-14), 57.2 (C-9), 64.0 (C-17), 69.5 (C-19), 77.9 (C-11), 128.0 (C-4), 163.1 (C-5), 198.2 (C-3), 208.2 (C-20); MS, *m/z* (rel. ab.) 328 (6%, M⁺), 298 (77%, M–CH₂O), 255 (13%), 213 (9%), 161 (100%).

Analysis for C₂₁H₂₈O₃

Calcd C 76.79 H 8.59,

Found C 76.56 H 8.87.

6,19-Oxidopregn-4-ene-3,11,20-trione (2)

To a solution of compound **6** (1.022 g) in methanol (100 ml) was added dropwise 10% aqueous sodium hydroxide (11.8 ml) under a nitrogen atmosphere and the reaction mixture stirred for 15 min at 25 °C. Acidification with dilute HCl and extractive workup afforded the 3-hydroxy derivative (784 mg) which was dissolved in acetone and treated at 0 °C with an excess of Jones reagent until persistent orange color yielding the bromoketone **11** (688 mg). The latter product in methanol (200 ml) was treated with 10% aqueous sodium hydroxide (21 ml) as above for 22 h. After acidification with dilute HCl and extractive workup with dichloromethane the crude product (**12**, 436 mg) was oxidized with Jones reagent as above rendering after purification by flash chromatography triketone-oxide (**2**) (240 mg), m.p. 188–189 °C (from MeOH) (lit. 190–191 °C [6]); UV λ_{max} (ethanol),

238 nm ($\epsilon = 3482$); ^1H NMR: 0.72 (s, 3H, H-18), 2.13 (s, 3H, H-21), 3.64 (dd, $J_{\text{gem}} = 8$ Hz, $J_{19a-9} = 1$ Hz, 1H, H-19a), 4.36 (d, $J = 8$ Hz, 1H, H-19b), 4.72 (d, $J = 5$ Hz, 1H, H-6), 5.91 (s, 1H, H-4); ^{13}C NMR: 14.3 (C-18), 22.8 (C-16), 23.6 (C-7), 26.2 (C-15), 30.9 (C-8), 33.5 (C-1), 34.5 (C-21), 40.6 (C-2), 43.8 (C-12), 48.0 (C-10), 54.2 (C-9), 55.3 (C-13), 58.3 (C-14), 61.4 (C-17), 76.0 (C-19), 76.5 (C-6), 116.4 (C-4), 169.0 (C-5), 198.5 (C-3), 207.3

(C-20), 207.6 (C-11); MS, m/z (rel. ab.) 342 (91%, M^+), 314 (66%), 286 (100%), 269 (77%).

Analysis for $\text{C}_{21}\text{H}_{26}\text{O}_4$

Calcd	C 73.66	H 7.66,
Found	C 73.48	H 7.81.

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