# CONVERSION OF 15α-HYDROXY-11-OXO-PROGESTERONE TO 3β,11α,15β-TRIHYDROXY-5-PREGNEN-20-ONE

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ABSTRACT

3β,11α,15β-Trihydroxy-5-pregnen-20-one, an intermediate required for the synthesis of the oogoniols, has been prepared from 15α-hydroxy-11-oxo-progesterone in an overall yield of 16%. The three isomers (at C-11, C-15) of the pregnene were also prepared.

For studies on the synthesis of the oogoniols, female-activating hormones of the aquatic fungus Achlya [1] we required 3β,11α,15β-trihydroxy-5-pregnen-20-one. The hydroxyl groups in this steroid correspond to those on the tetracyclic nucleus of the oogoniols and our plan was to convert the former to the latter by building on the side chain at C-20 [2] and introducing the 7-keto function by photooxygenation and rearrangement. To our knowledge the pregnenolone derivative has never been reported in the literature although microbiological hydroxylation of progesterone with Aspergillus giganteus is known to yield 11α,15β-dihydroxyprogesterone [3], and 11-oxoprogesterone can be converted to the 15α-hydroxy derivative by a number of organisms, e.g., Calonectria decora [4].

This paper describes experiments by which the latter compound, 15α-hydroxy-11-oxoprogesterone, has been converted to our target steroid (10).

We considered that the most direct approach to compound 10 would involve (a) reduction of the ketone at C-3 and rearrangement of the $\Delta^4$-double bond, both of which could be carried out at the same time,

(b) oxidation of the C-15 hydroxyl and selective reduction of the resulting ketone to give the 15β-hydroxy group, (c) reduction of the C-11 ketone to the 11α-hydroxy group. The C-20 ketone would of course have to be protected in all these operations for which there are ample precedents in the literature.

Treatment of the 4-ene-3-ketosteroid 1 with acetic anhydride and acetyl chloride afforded the enol acetate 2 as an unstable viscous oil in almost quantitative yield [5]. An alternative method for making the enol acetate, by allowing a solution of hydroxyketone 1 in ethyl acetate to react with acetic anhydride and a trace of perchloric acid [6] gave inconsistent results. A solution of the enol acetate 2 in benzene was refluxed with ethylene glycol and a trace of p-toluenesulfonic acid, in a Dean-Stark apparatus, to give the ketal at C-20 in high yield. Too long a reaction time led to decomposition of the enol acetate and formation of the 3,20-diketal.

Because of its instability, compound 3 was treated immediately with excess sodium borohydride in 95% ethanol for two hours to give the desired alcohol 4 (68%) together with a small amount (6%) of the corresponding diol 5. Longer reaction times resulted in loss of the acetate group at C-15. The hydroxyl group in compound 4 was protected by forming the tetrahydropyranyl (THP) ether and the acetate group at C-15 was removed by treatment with lithium aluminum hydride in tetrahydrofuran (base hydrolysis required forcing conditions and gave low yields of alcohol).

The diol (6) thus obtained was oxidized with chromium trioxide-pyridine in methylene chloride to give the diketone 7. Reduction of the latter with sodium borohydride in ethanol-tetrahydrofuran afforded

a mixture of the 15β-ol and 15α-ol (5.8:1) which were readily separated. The 15β-ol (8) was next reduced with lithium in liquid ammonia to give the 11α,15β-diol 9, in 88% yield.

The final step in the synthesis involved removal of the protecting groups in the diol 9 by treatment with p-toluenesulfonic acid which afforded the trihydroxyketone 10 in an overall yield of approximately 16% from 15α-hydroxy-11-oxoprogesterone. Three isomers of compound 10 (11, 12, 13) were also prepared by carrying out the appropriate conversions on intermediates used in its preparation. Comparison of the spectral properties of these compounds provided further confirmation of the stereochemical assignments in the trihydroxyketone 10.

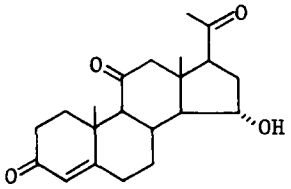
Compound 11 was obtained on removal of the protecting groups in the diol 6 by mild acid treatment. Reduction of diketone 7 with lithium aluminum hydride gave the 11β,15β-diol and a small amount of the 11β,15α-diol (6). Acid treatment of the mixture followed by chromatography yielded the pure triol 12. Reduction of diketone 7 with lithium in liquid ammonia gave two products in approximately equal amounts which were identified as the 11β,15α-diol (6) and the 11α,15α-diol (14). Acid treatment of the diol 14 yielded the triol 13.

The lack of stereoselectivity in the lithium-ammonia reduction of the 11-ketone in 7 was unexpected since there was good literature precedent for the formation of the thermodynamically more stable equatorial alcohol (11α) [7]. The above result may be explained if it is assumed that the 15-ketone is more reactive than the 11-ketone. Formation of the more stable 15α-alcohol (rather than 15β-alcohol) will occur first. The alcohol can then act as an intramolecular proton source which will deliver a proton to the α face of the carbanion intermediate at C-11

formed subsequently. This competes with protonation by ethanol from the β face, leading to loss of stereoselectivity as observed.

The four trihydroxyketones (10, 11, 12, 13) showed significant differences in their NMR spectra. In particular, the C-18 and C-19 proton chemical shifts could be used to distinguish the isomers from one another. The shifts for these compounds as well as for all the other pregnene derivatives in this study were in good agreement with calculated values. Some of them are listed in Table I [8,9].

It was of interest to examine the biological properties of the trihydroxypregnene derivatives which are, presumably, new compounds. Samples of the steroids 10, 11, 12 and 13 were submitted to Dr. C. E. Cook, Research Triangle Institute, Durham, North Carolina, for competitive binding studies with the progesterone receptor. The relative binding affinities (RBA) [10] were found to be very low compared to progesterone (RBA = 100), the values of compounds 12 and 11 (0.004, 0.003) being larger than those for compounds 10 and 13 which possess an 11α-hydroxyl group.

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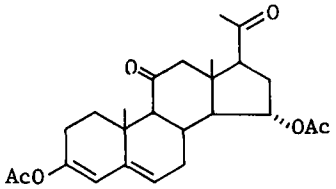


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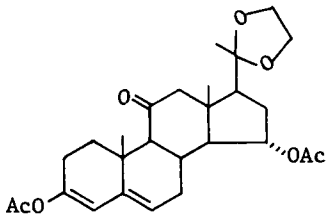


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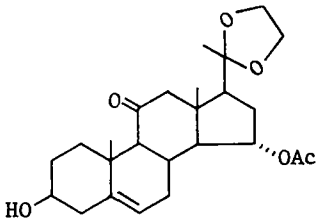


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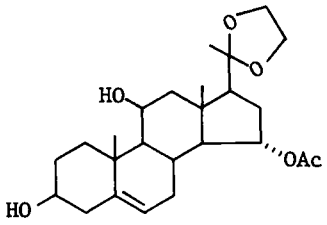


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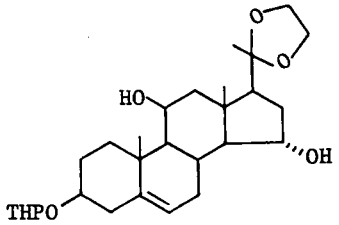


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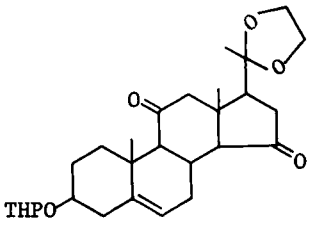


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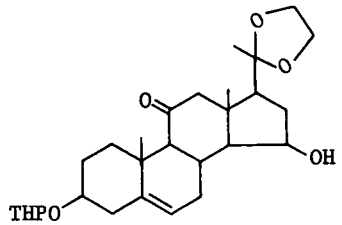


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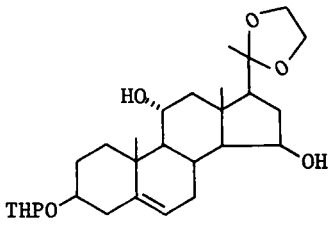


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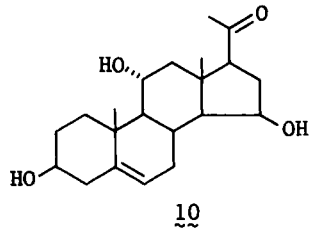


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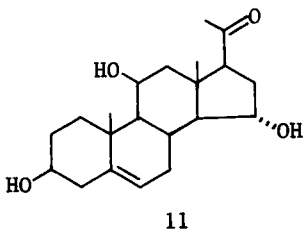


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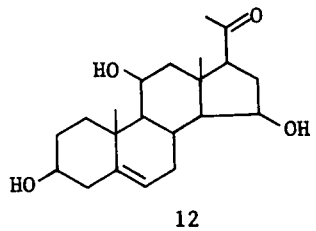


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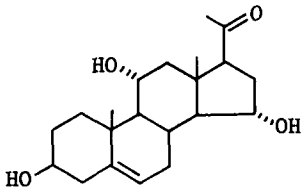


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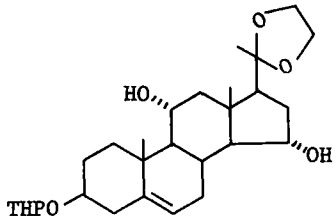


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Table I. Observed and Calculated Values of Chemical Shifts for C-19 and C-18 Protons [8,9].*

| Compound | 19-H | | 18-H | |
|---|---|---|---|---|
| | Observed | Calculated | Observed | Calculated |
| 4 | 1.27 | 1.24 | 0.78 | 0.82 |
| 5 | 1.28 | 1.28 | 1.07 | 1.07 |
| 6 | 1.28 | 1.30 | 1.03 | 1.06 |
| 7 | 1.30 | 1.26 | 0.80 | 0.83 |
| 8 | 1.27 | 1.28 | 0.98 | 1.02 |
| 9 | 1.20 | 1.18 | 1.05 | 1.08 |
| 10 | 1.20 | 1.18 | 0.90 | 0.94 |
| 11 | 1.27 | 1.29 | 0.88 | 0.92 |
| 12 | 1.30 | 1.32 | 1.10 | 1.16 |
| 13 | 1.15 | 1.15 | 0.67 | 0.71 |
| 14 | 1.17 | 1.16 | 0.82 | 0.84 |

*No substituent value was reported in the literature for the tetrahydropyranyloxy group so the value used for the acetoxy group was substituted in its place.

## EXPERIMENTAL

Melting points were taken on a Kofler hot-stage and are uncorrected The following instruments were used to record spectra: Varian Associates EM 390 ($^1$H NMR), Perkin Elmer 550 (UV), Beckman IR 18A-X (IR), LKB 9000 (MS). NMR spectra are reported in parts per million ($\delta$) using TMS as an internal standard. Infrared spectra were taken of KBr pellets. Ionizing voltage for mass spectra was 70 eV. Elemental analyses were performed by Pascher Laboratories, Bonn, West Germany.

Column chromatography was carried out with Merck silica gel 60 (60-230 mesh, or finer than 200 mesh ASTM). Thin-layer chromatography was done on Merck 60F-254 silica gel plates.

3β,15α-Diacetoxy-3,5-pregnadiene-11,20-dione (2)

A solution of 15α-hydroxy-11-oxoprogesterone (1) (2 g) in acetyl chloride (120 mL) and acetic anhydride (60 mL) was refluxed under nitrogen for 2-1/4 h. Sodium bicarbonate (~5 g) was added and the solvent blown down to 50% of the original volume in a nitrogen stream. The remainder of the solvent was removed in vacuo. The resulting yellow gum was taken up in ethyl acetate and washed thoroughly with saturated $NaHCO_3$, water, and dried ($MgSO_4$). The solvent was flash evaporated leaving 2.48 g (98%) of 2 as a yellow oil which was found to decompose slowly on standing. The crude product was used in the next step without purification. Compound 2 had the following spectral properties: NMR ($CDCl_3$) δ 0.67 (s, C-18 Me), 1.15 (s, C-19 Me), 2.03 (s, C-15 OAc), 2.10 (s, C-21 Me and C-3 OAc), 4.88 (m, C-15 H), 5.20 (m, C-6 H), 5.52 (s, C-4 H); IR $\nu_{max}$, 1750, 1740, 1708, 1250, 1225 $cm^{-1}$; UV $\lambda_{max}$ ($CH_3OH$) 233 nm (ε = 17,100); MS m/e 428 ($M^+$), 386, 326, 43 (100%).

3α,15β-Diacetoxy-20-ethylenedioxy-3,5-pregnadien-11-one (3)

The crude enol acetate 2 (2.48 g), benzene (200 mL), ethylene glycol (8 mL), and p-toluenesulfonic acid (120 mg) were stirred vigorously at reflux temperature for 2-1/2 h. Water was removed with a Dean-Stark trap. Sodium bicarbonate (300 mg) was added to the cooled solution (ice bath) and it was then washed with saturated $NaHCO_3$, water (3×) and dried ($MgSO_4$). The solvent was evaporated leaving 2.60 g (96%) of crude 3 as an oil that resisted recrystallization: NMR ($CDCl_3$) δ 0.80 (s, C-18 Me), 1.17 (s, C-19 Me), 1.23 (s, C-21 Me), 2.03 (s, C-15 OAc), 2.10 (s, C-3 OAc), 3.92 (m, ketal H), 4.95 (d of t, J = 3.5, 9 Hz, C-15 H), 5.30 (m, C-6 H), 5.63 (s, C-4 H); IR (film) $\nu_{max}$, 1748, 1740, 1710, 1250, 1225 $cm^{-1}$; UV $\lambda_{max}$ ($CH_3OH$) 228 mm, (ε = 16,800); MS m/e 472 ($M^+$), 430, 472, 87 (100%).

Sodium borohydride reduction of enol acetate ketal 3

To a stirred solution of crude enol acetate ketal 3 (2.50 g) in 95% ethanol (50 mL) was added sodium borohydride (0.36 g). After stirring for 2 h, solid ammonium chloride was slowly added until the bubbling ceased. The solvent was evaporated. Water was added and the mixture was extracted with ether (2×). The ether extracts were combined, washed with water, and dried ($MgSO_4$). The solvent was removed leaving an oil (2.0 g) which was chromatographed on silica gel (60 g) using methylene chloride-ethyl acetate (5:1). Three major components were isolated. The least polar was identified as 15α-acetoxy-3,20-bisethylenedioxy-5-pregnen-11-one (80 mg, 3%): mp 203-205°C. NMR ($CDCl_3$) δ 0.78 (s, C-18 Me), 1.20 (s, C-21 Me), 1.23 (s, C-19 Me), 2.03 (s, C-15 OAc), 3.97 (m, 8, ketal H), 4.97 (m, C-15 H), 5.30 (m, C-6 H); IR $\nu_{max}$ 1735, 1716, 1249, 1105, 1040 $cm^{-1}$; MS m/e 474 ($M^+$), 459, 414, 386, 99 (100%).

The desired compound, 3β-hydroxy-15α-acetoxy-20-ethylenedioxy-5-pregnen-11-one (4) (1.55 g, 68%) was eluted next. Crystallization of a small portion from diethyl ether-methanol afforded white crystals: mp 125-127°C; NMR ($CDCl_3$) δ 0.78 (s, C-18 Me), 1.22 (s, C-21 Me), 1.27 (s, C-19 Me), 2.08 (s, C-15 OAc), 3.53 (m, C-3 H), 3.97 (m, ketal H), 5.00

(m, C-15 H), 5.42 (m, C-6 H); IR $\nu_{max}$ 3450, 2940, 1739, 1705, 1375, 1245, 1045 $cm^{-1}$; MS m/e 432 ($M^+$), 417, 414, 372, 354, 87 (100%).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.14; H, 8.11.

The third component to be isolated was 3β,11β-dihydroxy-15α-acetoxy-20-ethylenedioxy-5-pregnene (5) (150 mg, 6%). All attempts to crystallize this compound failed. The spectral data acquired for this compound are the following: NMR ($CDCl_3$) δ 1.07 (s, C-18 Me), 1.28 (s, C-19, C-21 Me), 2.00 (s, C-15 OAc), 3.50 (m, C-3 H), 3.93 (m, 4, ketal H), 4.33 (m, C-11 H), 4.97 (m, C-15 H), 5.23 (m, C-6 H); IR $\nu_{max}$ 3400, 2940, 1739, 1250, 1050 $cm^{-1}$; MS m/e 434 ($M^+$), 419, 374, 356, 87 (100%).

3β-[(Tetrahydropyran-2'-yl)-oxy]-20-ethylenedioxy-5-pregnene-11β,15α-diol (6).

To a stirred mixture of ketone 4 (1.55 g) and alcohol 5 (0.15 g) in chloroform (10 mL) was added dihydropyran (1.25 mL) and a few crystals of p-toluenesulfonic acid. After stirring for 12 h, methanolic-ammonia (2 mL) was added and the solvent blown down in a stream of nitrogen. The mixture of tetrahydropyranyl ethers was isolated by chromatography on silica gel (60 g) with petroleum ether-ethyl acetate (10:1).. It was dissolved in dry tetrahydrofuran (50 mL) and lithium aluminum hydride (200 mg) was added. After 2 h a saturated solution of magnesium sulfate was added slowly until the bubbling ceased. The mixture was filtered and the residue washed with ethyl acetate. The solvent was removed and the resulting solid taken up in chloroform and the solution was washed with water (2×) and dried ($MgSO_4$). The solvent was removed to give a white solid (1.31 g) identified as 6. An analytical sample was obtained by crystallizing 6 from ethyl acetate: mp 172-174°C; NMR ($CDCl_3$) δ 1.03 (s, C-18 Me), 1.28 (s, C-19, C-21 Me), 3.50 (m, $CH_2$-O- on THP), 3.93 (m, ketal and C-3 H), 4.12 (m, C-15 H), 4.35 (m, C-11 H), 4.73 (m, 1, acetal H), 5.27 (m, C-6 H); IR $\nu_{max}$ 3460, 1156, 1132, 1056, 1027 $cm^{-1}$; MS m/e 476 ($M^+$), 461, 458, 374, 356, 341, 338, 87 (100%).

Anal. Calcd for $C_{28}H_{44}O_6$: C, 70.55; H, 9.31. Found: C, 70.22; H, 9.15.

3β-[(Tetrahydropyran-2'-yl)-oxy]-20-ethylenedioxy-5-pregnene-11,15-dione (7).

Chromium trioxide (6 g) was added to a stirred solution of dry pyridine (9.65 mL) in methylene chloride (150 mL). After stirring for 15 min, 1.30 g of diol 6 in methylene chloride (15 mL) was added in one portion. The solution was stirred for an additional 20 min, then filtered through a short column of silica gel using ethyl acetate to wash the residue. The organic solution was washed with 5% NaOH, 5% HCl, saturated $NaHCO_3$ and dried ($MgSO_4$). The solvent was removed leaving a white solid (1.10 g). Crystallization from methanol-acetone yielded 7 as white needles: mp 262-265°C; NMR ($CDCl_3$) δ 0.80 (s, C-18 Me), 1.18 (s, C-21 Me), 1.30 (s, C-19 Me), 3.48 (m, 2, $CH_2$-O, on THP), 3.95 (m,

ketal and C-3 H), 4.72 (m, 1, acetal H), 5.36 (m, C-6 H); IR $\nu_{max}$ 1739, 1709 $cm^{-1}$; MS m/e 472 ($M^+$), 457, 388, 370, 87 (100%).

Anal. Calcd for $C_{28}H_{40}O_6$: C, 71.16; H, 8.53. Found: C, 71.42; H, 8.35.

Sodium borohydride reduction of diketone 7.

The diketone 7 (1.15 g) was dissolved with heating in 95% ethanol (250 mL) and tetrahydrofuran (80 mL). After cooling, sodium borohydride (570 mg) was added to the stirred solution. After 3 h a saturated solution of ammonium chloride was added slowly until the bubbling had ceased. The solvent was removed. The residue was taken up in chloroform, washed with water and dried ($MgSO_4$). The solvent was removed leaving an oil which was chromatographed on silica gel (20 g) with petroleum ether-ethyl acetate (5:1). Two principal products were isolated. The less polar, 3β[tetrahydropyran-2'-yl)-oxy]15β-hydroxy-20-ethylenedioxy-5-pregnen-11-one (8) (.673 g, 58%) had a mp of 190-193°C; NMR ($CDCl_3$) δ 0.98 (s, C-18 Me), 1.23 (s, C-21 Me), 1.27 (s, C-19 Me), 3.50 (m, $CH_2$-O, on THP), 3.93 (m, ketal and C-3 H), 4.37 (doublet of triplets, J = 2, 6 Hz, C-15 H), 4.72 (m, 1, acetal H), 5.36 (m, C-6 H); IR $\nu_{max}$ 3450, 1695 $cm^{-1}$; MS m/e 459 ($M^+$-15), 390, 372, 354, 87 (100%).

Anal. Calcd for $C_{28}H_{42}O_6$: C, 70.85; H, 8.92. Found: C, 70.90; H, 8.81.

The more polar, 3β[(tetrahydropyran-2'-yl)-oxy]15α-hydroxy-20-ethylenedioxy-5-pregnen-11-one (117 mg, 10%) had a mp of 189-192°C; NMR ($CDCl_3$) δ 0.75 (s, C-18 Me), 1.20 (s, C-21 Me), 1.23 (s, C-19 Me), 3.50 (m, $CH_2$-O, on THP), 3.92 (m, ketal and C-3 H), 4.05 (m, C-15 H), 4.72 (m, acetal H), 5.35 (m, C-6 H); IR $\nu_{max}$ 3430, 1705 $cm^{-1}$.

3β-[(Tetrahydropyran-2'-yl)-oxy]-20-ethylenedioxy-5-pregnene-11α,15β-diol (9)

The keto-alcohol 8 (645 mg) dissolved in absolute ethanol (15 mL) and ethyl ether (10 mL) was added to a refluxing solution of ammonia (250 mL) and absolute ethanol (10 mL). Enough small pieces of lithium wire were added to keep the solution blue for 6 min. Solid ammonium chloride (5 g) was added and the solvent was blown off in a stream of nitrogen. Water was added and the residue was extracted with chloroform (200 mL). The chloroform extract was washed with water, dried ($MgSO_4$), and evaporated, leaving an oil which crystallized on standing. A filtration through silica gel yielded diol 9 (570 mg). Crystallization of a small portion from acetone afforded white crystals, mp 190-192°C; NMR ($CDCl_3$) δ 1.05 (s, C-18 Me), 1.20 (s, C-19 Me), 1.32 (s, C-21 Me), 3.50 (m, $CH_2$-O, on THP), 3.65-4.3 (bm, ketal, C-3, C-11, C-15 H), 4.72 (m, acetal H), 5.43 (m, C-6 H); IR $\nu_{max}$ 3440 $cm^{-1}$; MS m/e 476 ($M^+$) 461, 458, 374, 356, 338.

Anal. Calcd for $C_{28}H_{44}O_6$: C, 70.55; H, 9.31. Found: C, 70.60; H, 9.01.

3β,11α,15β-Trihydroxy-5-pregnen-20-one (10)

To a solution of diol 9 (.416 g) in absolute ethanol (15 mL) was added p-toluenesulfonic acid (39 mg). After standing for 3 h, methanolic-ammonia (3 mL) was added and the solvent was blown down in a stream of nitrogen. Several portions of ethyl acetate were used to dissolve the steroid and filter it through a short silica gel column. The steroid was dissolved in a minimal amount of methanol, diluted with chloroform and chromatographed on silica gel (15 g) using ethyl acetate as an elutant. This gave 10 (246 mg) which could be crystallized from ethyl acetate; mp 218.5-220°C; NMR ($CDCl_3$-$CD_3OD$) δ 0.90 (s, C-18 Me), 1.20 (s, C-19 Me), 2.16 (s, C-21 Me), 3.54 (m, C-3 H), 4.10 (m, C-11 H), 4.30 (m, C-15 H), 5.41 (m, C-6 H); IR $\nu_{max}$ 3450, 1700 $cm^{-1}$; MS m/e 348 ($M^+$), 330, 315, 312, 297, 43 (100%).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26, O, 18.37. Found: C, 72.60; H, 9.33; O, 18.28.

3β,11β,15α-Trihydroxy-5-pregnen-20-one (11).

To a solution of diol 6 (119 mg) in absolute ethanol (4 mL) and dry tetrahydrofuran (4 mL) was added p-toluenesulfonic acid (10 mg). After 10 h, methanolic-ammonia (3 mL) was added and the solution worked up as in the preparation of 10. Chromatography on silica gel (10 g) using chloroform-methanol (5:1) yielded 11 (65 mg, 75%); mp 225.5-227°C; NMR ($CDCl_3$-$CD_3OD$) δ 0.88 (s, C-18 Me), 1.27 (s, C-19 Me), 2.13 (s, C-21 Me), 3.52 (m, C-3 H), 4.13 (m, C-15 H), 4.42 (m, C-11 H), 5.25 (m, C-6 H); IR $\nu_{max}$ 3500, 3300, 1702, 1050 $cm^{-1}$; MS m/e 348 ($M^+$), 330, 315, 312, 297, 294, 43 (100%).

3β,11β,15β-Trihydroxy-5-pregnen-20-one (12).

To a stirred solution of diketone 7 (156 mg) in dry tetrahydrofuran (20 mL) was added lithium aluminum hydride (50 mg). After 3.5 h the solution was worked up (in the same manner as in the preparation of 6) to yield the diol as an oil (150 mg, 97%) which resisted crystallization.

To a solution of crude diol in dry tetrahydrofuran (4 mL) and absolute ethanol (4 mL) was added p-toluenesulfonic acid (15 mg). After 5.5 h methanolic-ammonia (3 mL) was added and the solution worked up as in the preparation of 10. The resulting oil was crystallized from ethyl acetate to yield 12 (70 mg, 64%) as white needles: mp 238.5-240.5°C; NMR ($CDCl_3$-$CD_3OD$) δ 1.10 (s, C-18 Me), 1.30 (s, C-19 Me), 2.17 (s, C-21 Me), 3.47 (m, C-3 H), 4.2-4.5 (m, C-11, C-15 H), 5.25 (m, C-6 H); IR $\nu_{max}$ 3400, 1700 $cm^{-1}$; MS m/e 348 ($M^+$), 330, 315, 312, 297, 43 (100%).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 71.98; H, 9.05.

3β,11α,15α-Trihydroxy-5-pregnen-20-one (13).

The diketone 6 (200 mg) dissolved in dry tetrahydrofuran (15 mL) and absolute ethanol (3 mL), was added to a refluxing solution of ammonia (50 mL) and absolute ethanol (1 mL). Enough small pieces of lithium wire were added in order to keep the solution blue for 5 min. Ammonium chloride (2 g) was added and the solvent was slowly evaporated in a nitrogen stream. The residue was taken up in ethyl acetate and water. The organic phase was separated, washed with water, dried ($MgSO_4$) and evaporated. Chromatography of the oil in silica gel with ethyl acetate-petroleum ether (1:2) yielded two components. The less polar component was identified as 6 (80 mg, 40%) by TLC and NMR comparison. The more polar component was the desired 3β[(tetrahydropyran-2'-yl)-oxy]-20-ethylenedioxy-5-pregnene-11α,15α-diol (14) (98 mg, 49%): mp 181-184°C; NMR ($CDCl_3$) δ 0.82 (s, C-18 Me), 1.17 (s, C-19 Me), 1.27 (s, C-21 Me), 3.50 (m, $CH_2$-O, on THP), 3.93 (m, ketal, C-3, C-11, C-15 H), 4.73 (m, acetal H), 5.43 (m, C-6 H); IR $\nu_{max}$ 3400 $cm^{-1}$; MS m/e 476 ($M^+$), 461, 458, 440, 374, 87 (100%).

To a solution of diol 14 (90 mg) in absolute ethanol (4 mL) was added p-toluenesulfonic acid (15 mg). After 10 h methanolic-ammonia (3 mL) was added and the solution worked up as in the preparation of 10. Chromatography on silica gel using ethyl acetate yielded 13 (60 mg, 91%): mp 213-215°C; NMR ($CDCl_3$-$CD_3OD$) δ 0.67 (s, C-18 Me), 1.15 (s, C-19 Me), 2.15 (s, C-21 Me), 3.50 (m, C-3 H), 3.8-4.2 (m, C-11, C-15 H), 5.43 (m, C-6 H); IR 3400, 1701 $cm^{-1}$; MS m/e 348 ($M^+$), 330, 315, 312, 297, 294, 43 (100%).

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