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18-DEOXYALDOSTERONE, ITS CHEMICAL AND MICROBIAL REDUCTION PRODUCTS

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Abstract—Reduction of the diketal **1** with sodium aluminum bis-(methoxyethoxy) hydride afforded the crystalline 18-hydroxycorticosterone diketal (**2**), an intermediate in the formation of 18-deoxyaldosterone acetate (**4b**). The hitherto unreported but anticipated metabolites of **4** were prepared as follows: hydrogenations of **4b** furnished the 5α- and 5β isomers **6** and **5b**, and thence the tetra- and hexahydro derivatives **10**, **11**, **8**, **9** and **7**, and the 3-deoxy compounds **12** and **13**. Anaerobic fermentations of **4b** with *Clostridium paraputrificum* gave the tetrahydro derivative **8b** in high yield.

18-Deoxyaldosterone (18-DAL) (**4a**) is easily prepared by dehydration of 18-hydroxycorticosterone, a naturally occurring corticoid; it has been suggested that **4a** is identical with the "less polar" form of the latter, and may be formed in the organism by non-enzymatic dehydration.[1] 18-DAL has been shown to possess a high affinity for mineralocorticoid receptors and is a partial agonist/predominant antagonist to aldosterone in rat and toad mineralocorticoid test systems. Because of this low affinity for androgen receptors it may offer advantages over spironolactone, a therapeutic agent used in the treatment of hypertension, whose main drawback is associated with estrogenic effects.[2,3]

Since di- and tetrahydro metabolites of aldosterone exhibit mineralocorticoid activity,[4] we decided to synthesize several reduced derivatives of 18-DAL for biological testing, in order to find out if, by analogy, the antimineralocorticoid properties of 18-DAL are retained in them; this objective could now be reached by the employment of chemical and microbiological methods.

18-DAL had previously been synthesized in several ways. In the first method (Scheme 1), LAH reduction of the racemic lactone **1** furnished the 18-hydroxycortiscosterone derivative **2**, which on boiling in 90% acetic acid afforded racemic **4**.[5-7] 18-Hydroxycorticosterone itself was converted into **4a** by *p*-toluenesulfonic acid in boiling ethylene dichloride.[2] In the second method, microbial hydroxylation of corticosterone with *Corynespora cassiicola* yielded the dimer of 18-hydroxycorticosterone (**3**), which, following treatment with boiling acetic acid, gave mostly the acetate **4b**.[8] In the third method, 1-dehydrocorticosterone acetate was converted into its iodo derivative via the 11-nitrite and then directly transformed into 1-dehydro-18-DAL acetate, which on reduction with Wilkinson's catalyst gave **4b**.[9]

While the last route is the shortest, the first is the method of choice when the lactone or its diketal **1** is readily available. We have now found that this approach can be simplified if sodium aluminum bis-(methoxyethoxy) hydride (SAMH) is used instead of LAH in the reduction of **1** to afford the crystalline 3,20-diketal of 18-hydroxycorticosterone (**2**) in high yield. Undoubtedly other complex hydrides soluble in organic solvents can also be used. Heating the ketal **2** in methylene dichloride (MDC) containing *p*-toluenesulfonic acid furnished predominantly the dimer **3**, with some free 18-DAL (**4a**). The dimer was converted into **4a** with hot acetic acid, essentially as previously described,[8] and then acetylated. With **4b** readily available, we set out to prepare several hitherto unreported reduced derivatives.

For conversion into the di- and tetrahydro derivatives, **4b** was hydrogenated with Pd to the 5α-dihydro compound **6**. The 5β-epimer **5b** could be isolated from the filtrate in the crystalline form only after seeding with material obtained by the microbial route described below. Catalytic reduction of **6** with raney Ni in dioxane gave the hexahydro compound **7**, and not the expected[10,11] tetrahydro derivative **10b**. Verification of structure was obtained by treatment of **7** with the Jones reagent which caused reversal of the reaction with formation of the dione **6**. Alternatively, hydrogenation of **6** with Pd in ethanol in the presence of acetic acid for 2 days at 30 psi yielded the 3β-ol **10b**, in analogy with related conversions of other 3-ketosteroids under these conditions.[12,13] Hydrolysis of the acetate group in position 21 was performed with hydrochloric acid in a MDC–methanol mixture to give the free diol **10a**, having a broad m.p. However, acetylation of this product furnished the sharp-melting diacetate **10c**. No appreciable epimerization at position 17 occurred during the acid hydrolysis of **10b**, as was shown by acetylation of the monoacetate **10b**, whereupon the diacetate **10c** was obtained, identical with the sample obtained by acetylation of **10a**. This proof for retention of configuration was desirable since extensive inversion of 18-DAL acetate (**4b**) at position 17 can easily occur.[9]

Inversion of configuration at position 3 was effected by treatment of **10b** with *p*-toluenesulfonyl chloride in pyridine to afford the tosylate **10d**, followed by solvolysis in dimethylformamide. Two new compounds were isolated: the elimination product **12**, which could be hydrogenated with Pd in ethyl acetate to the saturated ester **13**, and the 3α-formate **11b**. Acidic hydrolysis of the latter, under conditions identical with those used for **10b**, yielded the diol **11a**; this on acetylation afforded the diacetate **11c**.

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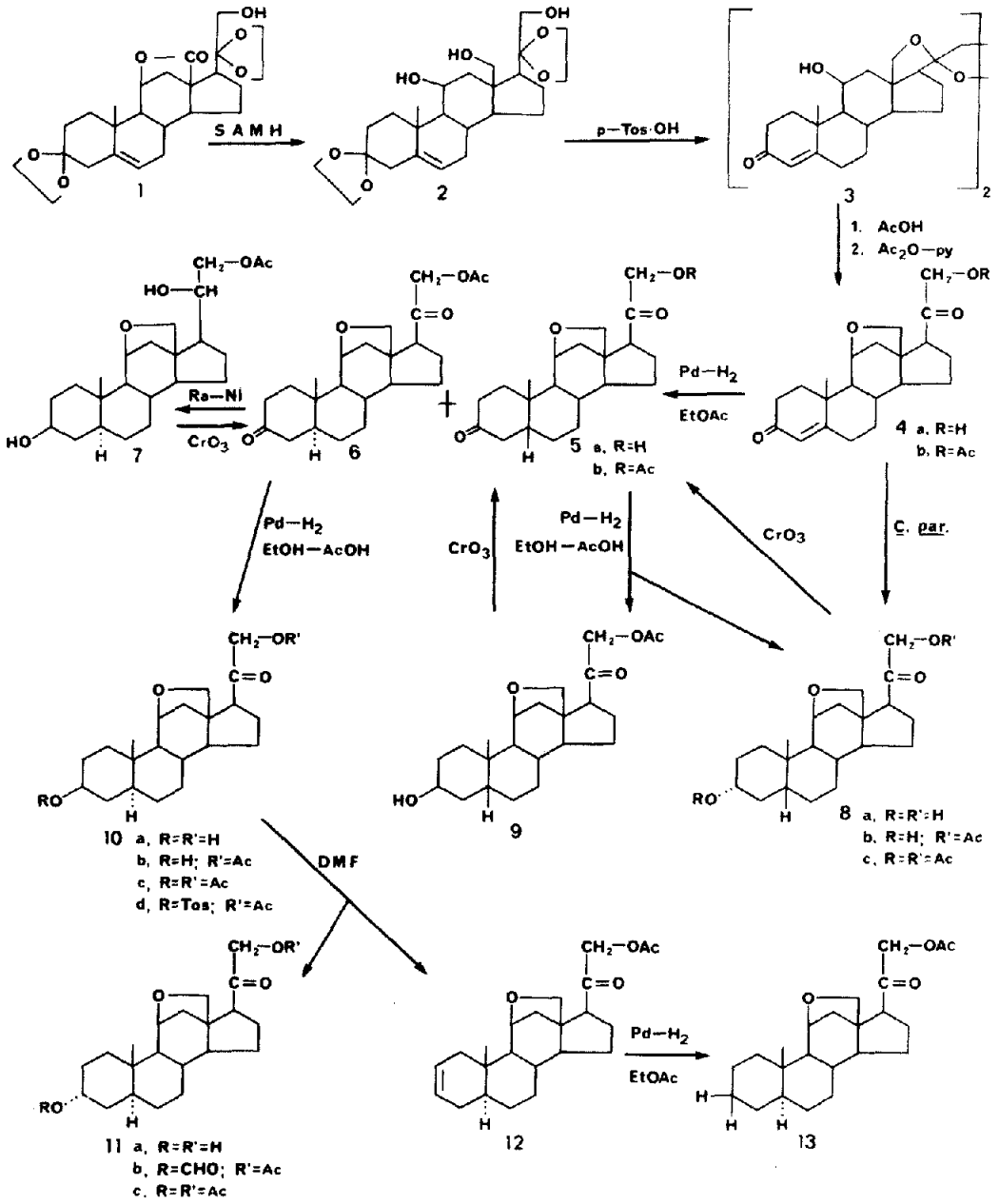
Since the 5β-dihydro siomer **5b** could not be obtained in crystalline form by the Pd in ethyl acetate hydrogenation of **4b**, the application of a microbial bioconversion step was also investigated and found to be extremely useful in solving this synthetic problem. Anaerobic sterospecific reductions with *Clostridium paraputrificum* to afford the 5β di- and 3α,5β-tetrahydro derivatives had been successfully applied to a variety of Δ^4-3-ketosteroids,[14b] although aldosterone could not be satisfactorily reduced by this method.[15] We have now found that incubation of 18-DAL acetate **4b** for 24 h with this organism furnished the desired 3α,5β-tetrahydroester **8b** in high yield. In contrast to a corresponding reduction of 18-hydroxy-11-deoxycorticosterone 21-acetate by this organism, which gave the free 21-hydroxy-3α,5β-tetrahydro derivative,[14a] there was no hydrolytic cleavage of the acetate during the fermentation of **4b**. Acetylation of **8b** furnished the diacetate **8c**, and acidic hydrolysis of the latter gave the diol **8a**; as in the case of **10b**, no detectable inversion took place at position 17, since acetylation of this diol gave a product identical with **8c**. Jones oxidation of **8b** furnished the 3-one **5b**, identical with the material accompanying the 5α-isomer **6** in the mild Pd hydrogenation of **4b**. Acidic hydrolysis of **5b** yielded the 21-ol **5a**, and reacetylation of **5a** regenerated the starting acetate **5b**, showing again that the 17β-configuration was preserved.

As in the case of the 5α-isomer **6**, prolonged hydrogenation of **5b** in ethanol containing some acetic acid at 20 psi in the presence of Pd caused reduction of the



Scheme 1.

ketone function at position 3, and the two epimeric 3α- and 3β-ols **8b** and **9**, obtained in the ratio 1:10, were separated by chromatography. As with **8b**, **9** could be reoxidized to **5b** with the Jones reagent, confirming the relationship between these 3 compounds.

EXPERIMENTAL

Merk A.G. silica gel 60 was employed in all column chromatograms. NMR spectra were obtained in $CDCl_3$ (TMS) on a Jeol 60 MHz spectrophotometer. IR spectra were taken on a Perkin–Elmer 297 spectrometer in KBr pellets. Mass spectra were recorded with a Dupont 21-491B spectrometer. TLC spots were visualized by spraying with 10% H_2SO_4 in EtOH prior to heating.

11β,18,21 - *Trihydroxy* - 5 - *pregnene* - 3,20 - *dione* 3,20 - *di* - (*ethylene glycol*) *ketal* (3,20 - *diketal of* 18 - *hydroxycorticosterone*) (**2**). A suspension of 9.00 g of 11β,21 - dihydroxy - 5 - pregnene - 3,20 - dione - 18 - oic acid 3,20-di-(ethylene glycol) ketal (18→11) lactone (**1**)[5] in 150 ml dry benzene was cautiously treated with 20 ml of 70% soln of SAMH in benzene. After the initial vigorous reaction subsided, the clear soln was refluxed for 1 h, cooled, and then cautiously treated with swirling with a total of 200 ml 10% NaOHaq. The mixture was diluted with 300 ml MDC and magnetic stirring applied. After 15 min the ppt was collected and washed with water to afford 6.20 g of **2**, m.p. 191–197° (sinter at 173°). The aqueous phase was extracted twice with MDC, the extracts washed with 10% NaClaq., dried with Na_2SO_4, treated with 0.5 ml Et_3N and concentrated *in vacuo* to furnish 2.67 g of the same material, m.p. 185–190°. Further concentration gave 0.30 g, m.p. 155–185°.

18-*Deoxyaldosterone acetate* (**4b**). A suspension of 9.8 g of **2** in 500 ml MDC was treated with 1.05 g *p*-toluenesulfonic acid monohydrate and the mixture was refluxed for 40 min. A few min after the solid dissolved the crystalline dimer **3** began to precipitate. The mixture was cooled in ice, treated with 200 ml sat. $NaHCO_3$aq., and mechanically stirred for 15 min. The dimer **3** was collected and washed with water to afford 3.53 g, m.p. 295–303° (reported[8] 293–296°). The organic layer, containing mostly a mixture of **3** and **4a**, was taken to dryness, combined with the solid **3** isolated above and refluxed in 250 ml AcOH for 80 min, during which time the solid gradually dissolved. The solvent was removed *in vacuo*, the crude product acetylated overnight at room temp. with 60 ml each of Ac_2O and pyridine, and worked up by adding ice and water up to a volume of 1 l., extracting with MDC, washing with dil. HCl and finally with $NaHCO_3$aq. Evaporation of solvent afforded the crude 18-DAL acetate (**4b**), m.p. 150–162°, which was then chromatographed. Elution with 20% acetone in petroleum ether followed by crystallization from MDC–ether furnished 5.26 g of material, m.p. 165–168° (reported 160–161°;[8] 161–163°[9]).

Hydrogenation of **4b**. A soln of 2.057 g of **4b** in 150 ml EtOAc was hydrogenated for 2 h in the presence of 0.23 g of 5% Pd–C. The filtered soln was evaporated *in vacuo* and the solid was washed with cold ether to afford 1.451 g of 21 - *hydroxy* - 11β,18 - *oxido* - 5α - *pregnane* - 3,20 - *dione acetate* (**6**). The pure sample (MDC–ether) had the m.p. 191–193°; λ_{max}^{KBr} 5.72, 5.78 and 5.85 μ; δ 1.09 (s, 19-CH_3), 2.16 (s, 21-OAc), 2.97 (t, J = 7.9, 17α-H), 3.37 and 3.64 (ABq, J = 8.8, 18-CH_2), 4.43 (d, J = 6.4, 11α-H), 4.62 (s, 21-CH_2) ppm; *m/e* 388. The ether filtrate was seeded with 21 - *hydroxy* - 11β,18 - *oxido* - 5β - *pregnane* - 3,20 - *dione acetate* (**5b**) to deposit 0.115 g of this material of m.p. 95–100°. Chromatography of the filtrate (elution with 25% acetone in petroleum ether) gave additional 0.32 g of **5b**, m.p. 101–104° (ether–petroleum ether), identical with the material described below.

3β,20β,21 - *Trihydroxy* - 11β,18 - *oxido* - 5α - *pregnane* 21 - *acetate* (**7**). A soln of 202 mg of **6** in 15 ml dry dioxane was hydrogenated in the presence of 500 mg raney Ni for 2 h at atmospheric pressure. The filtered soln was evaporated to dryness and the residue triturated with ether to yield 76 mg of **7**, m.p. 177–191°. The pure sample melted at 195–198° (EtOAc) and displayed in TLC a blue coloration with ethanolic H_2SO_4; λ_{max}^{KBr} 5.86 μ; δ 0.87 (s, 19-CH_3), 2.06 (s, 21-OAc), *ca* 3.80 (broad m, 3α-H, 17α-H), 3.95 and 4.07 (ABq, 21-CH_2), 4.32 (d, J = 6.5, 11α-H) ppm; *m/e* 392.

Oxidation of **7** *to* **6**. A cooled soln of 20 mg of **7** in 12 ml acetone was treated with 0.1 ml Jones reagent. After 5 min at 5° 0.5 ml MeOH was added, and after a further 5 min, 10 ml water. The clear soln was concentrated *in vacuo* at room temp. to remove the acetone. The colorless crystals were collected and washed with water to furnish 15 mg of material, m.p. 186–191°, whose IR spectrum and TLC were identical with those of **6** obtained above.

3β,21 - *Dihydroxy* - 11β,18 - *oxido* - 5α - *pregnane* - 20 - *one* 21 - *acetate* (**10b**). A hot soln of 1.45 g of **6** in 250 ml EtOH was quickly cooled to room temp., 2 ml AcOH and 1.6 g 5% PdC was added, and the mixture was hydrogenated at room temp. at 30 psi for 44 h in a Parr apparatus. The filtered soln was evaporated *in vacuo* and the oily residue crystallized by dissolving in 30 ml ether and chilling, to give 0.95 g of **10b**, m.p. 154–158°. A second crop of 0.25 g of slightly less pure material was obtained by concentration, and some more by chromatography, eluting with 20% acetone in petroleum ether. The pure sample melted at 158–159.5° (ether); λ_{max}^{KBr} 2.83, 5.70 and 5.80 μ; δ 0.89 (s, 19-CH_3), 2.14 (s, 21-OAc), 3.60 (m, 3α-H), 3.01 (t, J = 8, 17α-H), 3.34 and 3.54 (ABq, J = 8.2, 18-CH_2), 4.33 (d, J = 6.5, 11α-H), 4.55 (s, 21-CH_2) ppm; *m/e* 390.

3β,21 - *Dihydroxy* - 11β,18 - *oxido* - 5α - *pregnane* - 20 - *one* 3 - *tosylate* 21 - *acetate* (**10d**). A soln of 0.91 g of the 3β-ol **10b** in 15 ml pyridine was treated with 4 g *p*-toluenesulfonyl chloride and the mixture was magnetically stirred for 19 h at room temp. Additional 4 g *p*-toluenesulfonyl chloride was then added and stirring was continued for additional 24 h. Ice and water were added up to a volume of 110 ml and the mixture was stirred for 1 h at 0°. The crystals were collected and washed with water to furnish 1.23 g of **10d**, about 85% pure, which after recrystallization from ether melted at 162–163° (dec); λ_{max}^{KBr} 5.71, 5.80 and 6.26 μ.

21 - *Hydroxy* - 11β,18 - *oxido* - 5α - *pregn* - 1 - *ene* - 20 - *one acetate* (**12**) *and* 3α,21 - *dihydroxy* - 11β,18 - *oxido* - 5α - *pregnane* - 20 - *one* 3-*formate* 21 - *acetate* (**11b**). A soln of 1.23 g of crude **10d** in 15 ml DMF was kept at 80° for 68 h, whereupon the solvent was distilled *in vacuo*, and ice and water were added up to a volume of 20 ml. The soft solid was collected, washed with water and chromatographed. Elution with 20% acetone in petroleum ether gave first the Δ^2 compound **12**, which after recrystallization from MeOH weighed 0.22 g and melted at 129–131°; a further recrystallization gave the m.p. 131–132°; λ_{max}^{KBr} 5.70 and 5.83 μ; δ 0.84 (s, 19-CH_3), 2.15 (s, 21-OAc), 3.01 (t, J = 8, 17α-H), 3.28 and 3.58 (ABq, J = 8.2, 18-CH_2), 4.30 (d, J = 6.5, 11α-H), 4.52 (s, 21-CH_2), 5.58 (2H s, 2-H,3-H) ppm; *m/e* 372.

Further elution afforded **11b**, which after recrystallization from MeOH weighed 0.44 g, m.p. 180–191° (single TLC spot), narrowed by another recrystallization to 185–186°; λ_{max}^{KBr} 5.72–5.82 μ; m/e 418.

Continued elution with 20% acetone in petroleum ether afforded 0.04 g of the starting tosylate **10d**, m.p. 158–159° (dec).

A repeat chromatography of the combined filtrates effected separation of further amounts of **12**, **11b** and **10d**.

3α,21 - *Dihydroxy* - 11β,18 - *oxido* - 5α - *pregnane* - 20 - *one* (**11a**). A soln of 50 mg of **11b** in 1.3 ml MDC and 4.3 ml MeOH was treated with a mixture of 0.6 ml conc HCl and 0.33 ml water, and allowed to stand at room temp. for 3 days. The soln was diluted with MDC and extracted with sat. $NaHCO_3$aq. The aqueous phase was backwashed with MDC, the combined MDC extracts were evaporated and the residue was treated with ether to afford 17 mg, m.p. 183–187°. Recrystallization from MDC yielded the diol **11a** of m.p. 192–196° (dec); λ_{max}^{KBr} 5.84 μ; *m/e* 348.

3α,21 - *Dihydroxy* - 11β,18 - *oxido* - 5α - *pregnane* - 20 - *one diacetate* (**11c**). A 79 mg sample of **11a** of m.p. 174–181° (about 80% pure) was treated overnight with 1 ml each of pyridine and Ac_2O. Addition of 15 ml ice and water afforded a solid which was collected, washed with water and recrystallized from MeOH to furnish 48 mg of 11c, m.p. 172–175°. The pure sample melted at 175–177°; λ_{max}^{KBr} 5.72–5.80 μ; δ 0.87 (s, 19-CH_3), 2.01 (s, 3-OAc), 2.13 (s, 21-OAc), 3.02 (t, J = 8, 17α-H), 3.35 and 3.57 (ABq, J = 8, 18-CH_2), 4.39 (d, J = 6.5, 11α-H), 4.59 (s, 21-CH_2), 5.00 (t, 3β-H) ppm; *m/e* 372 (M-60).

3β,21 - *Dihydroxy* - 11β,18 - *oxido* - 5α - *pregnane* - 20 - *one* (**10a**). A soln of 85 mg of **10b** in 2.2 ml MDC and 7 ml MeOH was

treated with a mixture of 1 ml conc. HCl and 0.55 ml water. After letting stand for 3 days at room temp. the mixture was worked up as described above for the preparation of **11a**. The ether-washed product (45 mg) was homogeneous in TLC but displayed a wide m.p. (140–158°), not much changed on recrystallization from MDC–petroleum ether.

3β,21 - *Dihydroxy* - 11β,18 - *oxido* - 5α - *pregnane* - 20 - *one diacetate* **10c**

(a) *From the diol* **10a**. A soln of 35 mg of diol in 0.4 ml of each pyridine and Ac_2O was stored overnight at room temp. Quenching with ice–water furnished the diacetate, over 90% pure (TLC), which after recrystallization from MeOH melted at 164–167°, and whose IR spectrum was identical with that of a sample of **10c** described below.

(b) *From the monoacetate* **7a**. Treatment of 151 mg of **10b** with 1.5 ml each of pyridine and Ac_2O furnished **10c** which was recrystallized from MeOH to yield 125 mg, m.p. 168–170°. The pure sample melted at 170–172°; λ_{max}^{KBr} 5.68, 7.72 and 5.78–5.81 μ; δ 0.93 (s, 19-CH_3), 2.03 (s, 3-OAc), 2.18 (s, 21-OAc), 3.04 (t, $J = 8$, 17α-H), 3.34 and 3.63 (ABq, $J = 8$, 18-CH_2), 4.38 (d, $J = 6.5$, 11α-H), 4.60 (m, 3α-H), 4.62 (s, 21-CH_2) ppm; *m/e* 372 (M-60).

Microbiological conversion of 18-*DAL acetate* (**4b**) *into* 3α,21 - *dihydroxy* - 11β,18 - *oxido* - 5β - *pregnane* - 20 - *one* 21 - *acetate* (**8b**). A 200 ml narrow-mouth bottle was charged with 120 ml of a sterile nutrient soln prepared as described.[14a] Finely powdered 18-DAL acetate (**4b**) (200 mg) was then added under sterile conditions under N_2, and the mixture was anaerobically inoculated with a pregrown (without added steroids) culture of *Clostridium paraputrificum* ATCC 25780 and shaken in a gyratory shaker (250 rpm) at 37° for 24 h. At the end of that period the culture (pH 5.3–5.8) containing a voluminous white ppt was stirred with 50 ml of MDC for 15 min, the mixture was filtered with suction through a celite pad, and the aqueous phase was twice reextracted with 30 ml MDC. The combined extracts were washed with $NaHCO_3$aq., dried and evaporated to a gum which crystallized on contact with ether to afford 155 mg of **8b**, having a double m.p. 100–105° and 125–130°. A further 20 mg was obtained by chromatography of the filtrate. The pure material melted at 134–135° (EtOAc–petroleum ether); λ_{max}^{KBr} 5.71 and 5.75 μ; δ 0.97 (s, 19-CH_3), 2.13 (s, 21-OAc), 3.01 (t, $J = 8$, 17α-H), 3.25 and 3.55 (ABq, $J = 8.2$, 18-CH_2), 4.24 (d, $J = 6.5$, 11α-H), 4.53 (m, 3β-H), 4.53 (s, 21-CH_2) ppm; *m/e* 330 (M-60).

The diacetate **8c** was prepared by dissolving **8b** in 5 weights each of pyridine and Ac_2O. Next day the product was ppt with ice–water and recrystallized from MeOH, m.p. 126–128°; λ_{max}^{KBr} 5.72 and 5.78 μ; *m/e* 432.

3α,21 - *Dihydroxy* - 11β,18 - *oxido* - 5β - *pregnane* 20 - *one* (**8a**). A soln of 203 mg of **8c** in 2.6 ml MDC and 8.3 ml MeOH was treated with a mixture of 1.2 ml conc HCl and 0.65 ml water. After storing for 3 days at room temp. the mixture was worked up as for preparation of **11a** and the oily product chromatographed. Elution with petroleum ether–acetone 1:1 furnished 85 mg of **8a**, m.p. 145–151°, which after recrystallization from EtOAc–ether melted at 148–152°: λ_{max}^{KBr} 2.94 and 5.79 μ.

Acetylation of **8a** with Ac_2O–pyridine afforded a compound identical with the starting **8c**.

21 - *Hydroxy* - 11β,18 - *oxido* - 5β - *pregnane* - 3,20 - *dione acetate* (**5b**). A soln of 100 mg of **8b** in 4 ml acetone was treated at 0° with 0.5 ml of Jones reagent. After 5 min 1.5 ml MeOH was added, followed by 15 ml water. The soln was concentrated *in vacuo* at room temp. to a volume of 5 ml, and the crystalline dione **5b** was collected and washed with water to afford 72 mg, m.p. 103–106°. Two recrystallizations from MDC–ether–petroleum ether raised the m.p. to 109–111°; λ_{max}^{KBr} 5.70, 5.79 and 5.88 μ; δ 1.05 (s, 19-CH_3), 2.13 (s, 21-OAc), 3.01 (t, $J = 8$, 17α-H), 3.30 and 3.60 (ABq, $J = 8$, 18-CH_2), 4.28 (d, $J = 6.5$, 11α-H), 4.54 (s, 21-CH_2) ppm; *m/e* 328 (M-60).

Acidic hydrolysis of **5b**, as described for the preparation of **11a**, afforded the 21-ol **5a**. After chromatography (elution with 20% acetone in petroleum ether) the product was recrystallized from MDC–ether and melted at 153–155°; λ_{max}^{KBr} 2.88 and 5.85 μ; *m/e* 346.

Acetylation of **5a** with Ac_2O–pyridine as described gave **5b**, identical with the sample described.

Hydrogenation of the ketoester **5b**. A suspension of 325 mg of **5b**, m.p. 100–104°, in 30 ml EtOH containing 0.3 ml AcOH, was hydrogenated for 96 h in a Parr apparatus at 20 psi at room temp. in the presence of 500 mg 5%Pd–C. The filtered soln was evaporated *in vacuo* to dryness, the residue taken up in MDC and washed with $NaHCO_3$aq. The organic soln was evaporated and the residue chromatographed: elution with 20% acetone in petroleum ether yielded at first unreacted **5b** (77 mg), then 3β,21 - *dihydroxy* - 11β,18 - *oxido* - 5β - *pregnane* - 20 - *one* 21 - *acetate* **9** (146 mg), m.p. 146–148° (ether or MDC–petroleum ether); λ_{max}^{KBr} 2.83, 5.75 and 5.82 μ; δ 0.99 (s, 19-CH_3), 2.13 (s, 21-OAc), 3.21 and 3.50 (ABq, $J = 8.2$, 18-CH_2), 3.92 (m, 3α-H), 4.00 (m, 17α-H), 4.22 (d, $J = 6.5$, 11α-H), 4.47 (s, 21-CH_2) ppm; *m/e* 330 (M-60).

Further elution yielded 15 mg of the 3α-epimer **8b**, m.p. 100–105° (ether).

Oxidation of **9** *into* **5b** was carried out as described for the conversion of the 3α-isomer **8b** into **5b**: starting with 20 mg of **9**, 12 mg of air-dried **5b** was isolated, m.p. 104–107°, identical with authentic material.

21 - *Hydroxy* - 11β,18 - *oxido* - 5α - *pregnane* - 20 - *one acetate* (**13**). A soln of 120 mg of **12** in 25 ml EtOAc was hydrogenated at atmospheric pressure for 2.5 h in the presence of 200 mg 5% Pd–C. The product was best purified by passage through a column of silica gel (elution with 5% acetone in petroleum ether) to furnish 87 mg of m.p. 132–135° (petroleum ether); λ_{max}^{KBr} 5.70 and 5.80 μ; δ 0.87 (s, 19-CH_3), 2.16 (s, 21-OAc), 3.07 (t, $J = 8.5$, 17α-H), 3.34 and 3.70 (ABq, $J = 8.2$, 18-CH_2), 4.41 (d, $J = 6.5$, 11α-H), 4.63 (s, 21-CH_2) ppm; *m/e* 314 (M-60).

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