The Preparation and Reactions of Some 17α-Hydroxy-15-pregnen-20-ones

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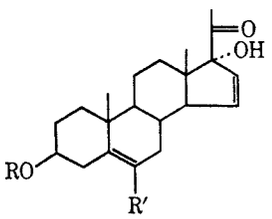
The preparation of the title compounds in one step from 16-pregnen-20-ones by treatment with oxygen and a trialkyl phosphite in the presence of a strong base is described. A novel base-catalyzed acetylation with ketene has been used to prepare a 17α-acetoxy-15-pregnen-20-one because the parent alcohol is unstable in acidic media. A new route to 15-androsten-17-ones is reported.

17α-Hydroxy-16-methyl-15-pregnen-20-ones and 17α-hydroxy-16-methylenepregnan-20-ones are well known as the products of the treatment of 16α,17α-oxido-16β-methylpregnan-20-ones with mineral acids,[2] but only one report has appeared of the preparation of 16-unsubstituted 17α-hydroxy-15-pregnen-20-ones.[3] These were obtained by allylic bromination of 16-pregnen-20-ones with N-bromosuccinimide, and treatment of the resulting 15-bromo-16-pregnen-20-ones with aqueous alkali. Only two examples of the process were given, but it is evident from these that considerable by-product formation can occur, and both examples involved steroids whose only unsaturation was in the 16 position. It seems highly probable that the method would fail if there were more than one allylic position in the molecule.

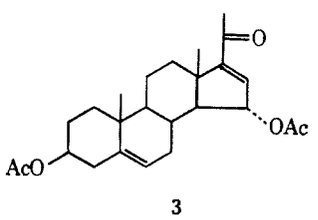
Recently we have described[4] a preparation of steroidal tertiary α-ketols from the corresponding ketones by reaction with oxygen, a trialkyl phosphite, and a strong base at −20 to −25°. The process depends upon the *in situ* reduction by the phosphite of the intermediate α-hydroperoxy ketone, and, by choice of a suitable solvent (usually N,N-dimethylformamide–*t*-butyl alcohol), rapid reaction may be achieved despite the low temperature. The method was particularly successful in the preparation of 17α-hydroxypregnan-20-ones, the average yield being 60–70%. It was evident from mechanistic considerations that, if this process were applied to 16-unsubstituted 16-pregnen-20-ones, reaction of the allyl carbanion with oxygen could occur at either the 15 or the 17 position, with subsequent reduction leading to a hydroxyl group at either of these centers in the final product. It seemed probable that the tertiary 17 position would be favored over the secondary 15 position in the hydroperoxide formation thus opening up a route to 17α-hydroxy-15-pregnen-20-ones.

To test the aforegoing hypothesis, 3β-acetoxy-5,-16-pregnadien-20-one (**1**) was treated with oxygen, triethyl phosphite, and sodium *t*-butoxide in *t*-butyl alcohol–N,N-dimethylformamide at −25°. Thin layer chromatograms of the reaction mixture revealed that, over a period of hours, slow reaction was occurring with formation of many products, one of which was major. In order to improve the reaction rate, we modified a Parr hydrogenator to permit external cooling of the reaction vessel, and, by using this equipment, we were able to run our reactions at −10 to −15° with oxygen pressures of 50–75 lb. Under these conditions, complete conversion of **1** into products occurred in 2–3 hr. Chromatography of the reaction product, after reacetylation (some hydrolysis of the 3-acetate had occurred), resulted in the isolation of **2** and **3** whose structures were established as follows.

Compound **2** had infrared and nmr spectra consistent with the 17α-hydroxy-15-pregnen-20-one structure, the latter spectrum containing bands attributable to the vinyl protons at 15 and 16. The presence of a hydroxyl group which was not acetylated by acetic anhydride in pyridine was strongly in favor of its location at the 17 position, and, on warming with dilute acid, a product having ultraviolet absorption in the range 303–313 mμ was formed. This ultraviolet maximum agrees well with the published data for 14,16-pregnadien-20-ones,[5] which are the expected



2, R = Ac; R′ = H
4, R = H; R′ = H
8, R = Ac; R′ = CH_3
9, R = H; R′ = CH_3



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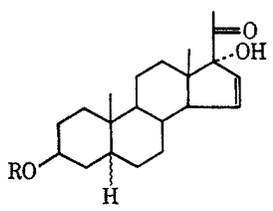
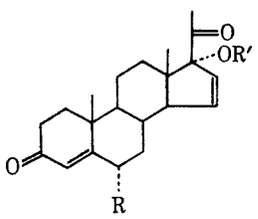


5, 5α; R = Ac
6, 5α; R = H
7, 5β; R = H



10, R = CH_3; R′ = H
11, R = H; R′ = H
15, R = H; R′ = Ac
16, R = H; R′ = Me

products of dehydration of 17α-hydroxy-15-pregnen-20-ones. The final evidence in favor of structure **2** came from selective hydrogenation of the 15 double bond, the product being identical with an authentic sample of 3β-acetoxy-17α-hydroxy-5-pregnen-20-one.

The nmr, ultraviolet, and infrared spectra of **3** were in agreement with the suggested structure. In particular the nmr spectrum revealed the presence of two acetate groups and the ultraviolet absorption [λ_{max}^{MeOH} 233 mμ (ε 8700)] was consistent with the presence of an α,β-

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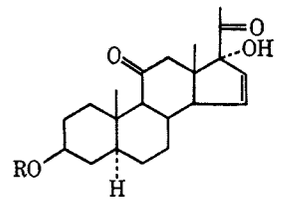
unsaturated ketone in the proposed environment. A compound was sought with which to correlate **3**, and, since both 15α- and 15β-hydroxy-4-pregnene-3,20-dione are known, conversion into one of these was undertaken. Selective hydrogenation over rhodium on alumina reduced the 16 double bond yielding 3β,15α-diacetoxy-5-pregnen-20-one, and microbiological oxidation of this material with *Flavobacterium dehydrogenans*, with concomitant hydrolysis of the 15-acetate, led to the Δ^4-3 ketone, which was identical with an authentic sample of 15α-hydroxy-4-pregnene-3,20-dione.[6]

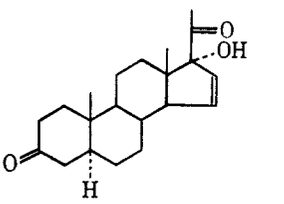
The yields of **2** and **3** by the above procedure were only 11.5 and 3% respectively, but, despite some development work, we have been unable to obtain better results. It is evident that extensive oxidative degradation of the steroids occurs, but, although this is reduced if the hydroxylation is conducted at atmospheric pressure, the rate of formation of the desired products is also slowed. Under the conditions we have elected to use, various by-products can be isolated in small amounts, but, with the exception of **3**, we have not characterized these.

The general utility of the procedure is shown by the following examples. The corresponding 16-pregnen-20-ones yielded, respectively, **5** and **6** (30%), **7** (20%), and **8** (8%). The two Δ^4-3 ketones, **10** and **11**, were prepared by hydroxylation of the derived 3-enol ethers (**11** was also obtained by microbiological oxidation of **2**, *vide infra*) and subsequent hydrolysis of the ethers with aqueous acetic acid, the yields being 1 and 9%. The dione **12**, obtained in 8% yield, is the only compound whose preparation was performed at atmospheric pressure, experiments under our usual conditions having established that they were, if anything, less satisfactory. This greater ease of reaction is perhaps linked to the reported ability of the 11-keto group to promote the formation of 17α-hydroperoxides.[7]

Inspection of the yields in the hydroxylations cited leads to the conclusion that they are lowest for the compounds containing the most unsaturation. This is entirely reasonable since such compounds present more active positions which may enter into oxidative side reactions. However, despite the poor yields with the unsaturated compounds, the method does provide access to the Δ^{15} analogs of steroidal hormones. As 17α-acetoxyprogesterone is a potent orally active progestin, we were interested in the preparation of the corresponding compound having a 15 double bond. One preparation of the 17α-hydroxy compound **11** has been mentioned already, and **11** was also prepared by oxidation of **2** with *F. dehydrogenans*, the yield being 21%. A by-product of this oxidation was **14** (6% yield) which has a saturated ketone in the A ring. This material was identified by comparison with an authentic sample prepared by Sarett oxidation[8] of **6**. The formation of a saturated 3 ketone from such an oxidation with *F. dehydrogenans* has been observed previously.[9] The acetylation of **11** to yield the desired **15** posed certain problems because of the ease of formation of the 14,16-diene on treatment with acid. This precluded the use of the acidic reagents commonly used to acetylate tertiary hydroxyls. The literature describes many acid-catalyzed exhaustive acetylations using ketene, but alkaline catalysis has been used only for unhindered alcohols.[10] We have established that the strength of base required is roughly parallel to the degree of hindrance of the hydroxyl. We were able to prepare **15** from **11** using ketene and potassium *t*-butoxide in tetrahydrofuran. We also prepared the 17-methyl ether (**16**) of **11** using methyl iodide and silver oxide in N,N-dimethylformamide.[11] The analog of Reichstein's substance "S" was obtained by treatment of **2** with calcium oxide and iodine, followed by triethylamine and acetic acid[12] to give **17**, and oxidation of this with *F. dehydrogenans* to yield the desired **18**.



12, R = Ac
13, R = H



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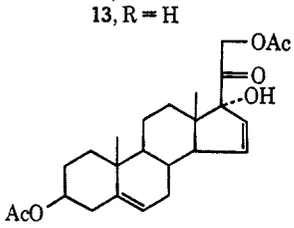

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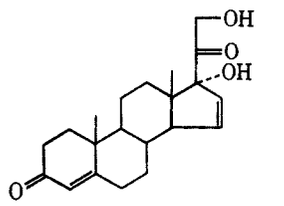
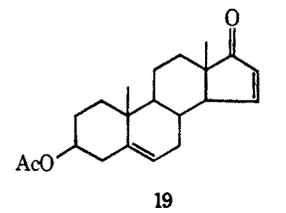
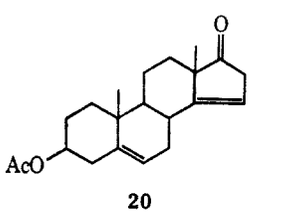


18



19



20

15-Androsten-17-ones are compounds whose preparation has hitherto been rather laborious.[13] We therefore investigated the conversion of **2** into **19** by sodium borohydride reduction of the 20 ketone and cleavage of the 17,20-diol with lead tetraacetate. The reduction went smoothly, but, while the cleavage started rapidly, it could not be made to go to completion. Furthermore, on prolonged standing with lead tetraacetate, the desired ketone **19** was converted into its Δ^{14} isomer **20**.[14] These problems were largely overcome by using a short reaction time, separating **19** by selective extraction, and recycling the unreacted diol. This process gave **19** in 37% yield.

To complete our knowledge of the hydroxylation of 16-pregnen-20-ones, we examined the case of 3β-

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acetoxy-6,16-dimethyl-5,16-pregnadien-20-one. The only material isolated was 3β-acetoxy-17α-hydroxy-6-methyl-16-methylene-5-pregnen-20-one[15] (11% yield), the nmr spectrum of which indicated that, if the isomer with the 15 double bond was present, its concentration cannot have exceeded 5%.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope. Nmr spectra were recorded at 60 MHz for solutions in $CDCl_3$ with $SiMe_4$ as internal standard; ultraviolet spectra refer to solutions in MeOH. Rotations were measured for approximately 1% solutions at 25°. The adsorbent used for tlc was silica gel.

Hydroxylation of 3β-Acetoxy-5,16-pregnadien-20-one (1).—NaH (3 g, 50% in mineral oil) was dissolved in *t*-butyl alcohol (15 ml) and DMF (25 ml). A further 25 ml of DMF was added and the solution was placed in the reaction vessel of a Parr hydrogenator, the vessel having been wrapped with a copper coil through which coolant at −25° was circulated. With the internal temperature −10 to −15°, compound **1** (10 g) was added and the mixture was shaken under 50 to 75 lb of oxygen pressure for 2.5 hr. It was then poured into sufficient AcOH to effect neutralization, water was added, and the product was extracted with EtOAc. The extracts were washed with a saturated solution of $NaHCO_3$ and with water and then were dried, and the solvent was evaporated. The residue was combined with the products from a further nine identical experiments and acetylated at 100° for 0.5 hr in excess Ac_2O and pyridine. This material was chromatographed on Florisil (2.0 kg) in hexane, eluting with increasing proportions of ether. Hexane–ether (7:3) eluted **3** (4.9 g), which on crystallization from hexane–ether gave 3.25 g of almost pure material. Removal of the last traces of a persistent impurity could not be accomplished routinely. The analytical sample was prepared by repeated crystallization from hexane–ether of a particularly pure crude sample: mp 196–204°; λ_{max} 233 mμ (ε 8700); nmr, δ 1.03 (s, 18-CH_3C), 1.07 (s, 19-CH_3C), 2.02 (s, CH_3CO_2), 2.09 (s, CH_3CO_2), 2.27 (s, CH_3CO), and 6.48 (d, J = 1 Hz, 1).

Anal. Calcd for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.13; H, 8.50.

Further elution with the same solvent gave **2** (18.9 g) which was crystallized from acetone–hexane to yield 12 g of material suitable for further transformations. Repeated crystallization from the same solvent gave an analytical sample: mp 206–210°; $[\alpha]_D$ −159° (dioxane); nmr, δ 0.77 (s, 18-CH_3C), 1.05 (s, 19-CH_3C), 2.01 (s, CH_3CO_2), 5.98 (m, $J_{15,16}$ = 6 Hz, $J_{14,15}$ = 3 Hz, 1) and 6.21 (d, $J_{15,16}$ = 6 Hz, 1).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.13; H, 8.42.

3β,17α-Dihydroxy-5,15-pregnadien-20-one (4).—Treatment of **2** (177 mg) in MeOH (50 ml) and THF (2 ml) with aqueous KOH (1.5 ml, 190 mg/ml) at ambient temperature, precipitation of the product by pouring into dilute AcOH, and crystallization from aqueous THF gave **4**: mp 253–270° dec; $[\alpha]_D$ −172° (dioxane).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.30; H, 9.15. Found: C, 76.50; H, 9.15.

Reaction of 2 with Acid.—A solution of **2** (*ca.* 3 mg) in MeOH containing a few milliliters of 1 *N* HCl was warmed at 50° for 18 hr. The resultant solution had λ_{max} 303–313 mμ.

Hydrogenation of 2.—Compound **2** (200 mg) in EtOH (25 ml) was hydrogenated over 10% Pd/C (100 mg) until 1 molecular equiv of hydrogen had been consumed. Crystallization of the product from EtOH gave 3β-acetoxy-17α-hydroxy-5-pregnen-20-one identical (mixture melting point and infrared spectrum) with an authentic specimen.

3β,15α-Diacetoxy-5-pregnen-20-one.—Compound **3** (500 mg) in EtOAc (50 ml) was hydrogenated over 5% Rh–Al_2O_3 (250 mg). The reaction was stopped after 1 molecular equiv of hydrogen had been consumed. The product, after filtration and evaporation, was chromatographed on Florisil (75 g), eluting with 50% ether. Two crystallizations from acetone–hexane afforded 3β,15α-diacetoxy-5-pregnen-20-one (161 mg): mp 146–150°; $[\alpha]_D$ +45.3° ($CHCl_3$).

Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.30; H, 9.00.

15α-Hydroxy-4-pregnene-3,20-dione.—3β,15α-Diacetoxy-5-pregnen-20-one (69 mg) was incubated for 7.25 hr with *F. dehydrogenans*[9] at a concentration of 7.5 mg/100 ml of medium. The product was isolated by tlc developing first in $CHCl_3$–EtOAc (9:1) and then in the same solvents in the ratio of 4:1. Extraction of the appropriate band with $CHCl_3$–acetone and crystallization from acetone gave 15α-hydroxy-4-pregnene-3,20-dione (20 mg) identical (mixture melting point, infrared spectrum, and rotation) with an authentic specimen.[6]

Hydroxylation of 3β-Acetoxy-5α,16-pregnen-20-one (21).—Compound **21** (2.5 g) was hydroxylated as described for compound **1**. The product was precipitated with water from the AcOH–DMF solution, isolated by filtration, washed with water, and dried. This material was chromatographed on Florisil (70 g), eluting with 50% ether to yield **5** (467 mg). Crystallization from acetone–hexane, from aqueous MeOH, and again from acetone–hexane afforded pure material: mp 151–154°; $[\alpha]_D$ −94.9° (dioxane).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.94; H, 9.11.

Further elution with the same solvent and two crystallizations from CH_2Cl_2–acetone gave **6** (224 mg): mp 236–240°; $[\alpha]_D$ −124° ($CHCl_3$) {lit.[3] mp 232–233°; $[\alpha]_D$ −124° ($CHCl_3$)}.

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.51; H, 9.71.

Hydroxylation of 3β-Hydroxy-5β,16-pregnen-20-one (22).—Compound **22** (5 g) was hydroxylated as described for compound **1**. The product was chromatographed on Florisil (315 g), eluting with benzene–ether (3:1) to afford material which on crystallization from EtOAc gave **7** (1.24 g): mp 242–244°; $[\alpha]_D$ −163.1° (pyridine). The analytical sample had mp 243–245.5°.

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.80; H, 9.40.

Hydroxylation of 3β-Acetoxy-6-methyl-5,16-pregnadien-20-one (23).—Compound **23** (5.65 g) was hydroxylated and acetylated as described for **1**. The product was chromatographed on Florisil (250 g), eluting with benzene–ether (9:1) to yield an oil (2.08 g) which was subjected to partition chromatography on Chromosorb W (200 g) in the system ligroin–propylene glycol. Crystallization from CH_2Cl_2–isopropyl ether of the material in the initial fractions yielded **8** (453 mg): mp 167–168.5°; $[\alpha]_D$ −179.5° ($CHCl_3$); nmr, δ 0.77 (s, 18-CH_3C), 1.03 (s, 19-CH_3C), 1.63 (s, 6-CH_3C), 2.04 (s, CH_3CO_2), 2.25 (s, CH_3CO), 5.98 (m, $J_{15,16}$ = 6 Hz, $J_{14,15}$ = 3 Hz, 1), and 6.27 (d, $J_{15,16}$ = 6 Hz, 1) ppm.

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.34; H, 8.91.

3β,17α-Dihydroxy-6-methyl-5,15-pregnadien-20-one (9).—A solution of **8** (151 mg) in MeOH (15 ml) was stirred with 2.5 *N* NaOH (0.5 ml) under nitrogen for 3 hr. The mixture was acidified with AcOH, and the product precipitated by addition of water. Crystallization from MeOH–isopropyl ether gave **9** (98 mg) as a MeOH solvate: mp 224–230°; $[\alpha]_D$ −173.9° (dioxane).

Anal. Calcd for $C_{22}H_{32}O_3 \cdot {}^1/_2CH_4O$: C, 74.96; H, 9.51. Found: C, 74.57; H, 9.24.

Hydroxylation of 3-Methoxy-6-methyl-3,5,16-pregnatrien-20-one (24).—Compound **24**[16] (7 g) was hydroxylated as **1** was. The crude product was precipitated from AcOH–DMF by addition of water, and after isolation was dissolved in AcOH (30 ml) and water (10 ml). This solution was warmed on the steam bath for 1 hr. The product was isolated by precipitation with water and chromatographed on Florisil (200 g), eluting with ether–CH_2Cl_2 (9:1). Crystallization from acetone gave **10** (62 mg) as an acetone solvate: mp 218–221°; λ_{max} 241 mμ (ε 14,900); $[\alpha]_D$ −8.1° (dioxane).

Anal. Calcd for $C_{22}H_{30}O_3 \cdot C_3H_6O$: C, 74.96; H, 9.06. Found: C, 74.67; H, 8.79.

Preparation and Hydroxylation of 3-Ethoxy-3,5,16-pregnatrien-20-one (25).—A solution of H_2SO_4 in dioxane (35 ml; 1 vol. of concentrated acid to 20 vol. of dioxane) was added to a suspen-

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(16) M. J. Weiss, *et al.*, *Tetrahedron*, **20**, 357 (1964).

sion of 4,16-pregnadiene-3,20-dione (50 g) in THF (175 ml), EtOH (5 ml), and ethyl orthoformate (50 ml). In 2 min the solid had dissolved and in 4 min pyridine (20 ml) was added. Crystals began to separate. The mixture was diluted with MeOH (300 ml) containing a few milliliters of pyridine. The solids were isolated by filtration and washed with more MeOH to yield **25** (25 g), sufficiently pure for hydroxylation.

Compound **25** (10 g) was hydroxylated as compound **1** was, and the crude material was treated with warm AcOH as described for the preparation of **10**. This product was chromatographed on Florisil (100 g); elution with ether and crystallization from acetone–hexane yielded **11** (844 mg), mp 210–225°, identical with the material obtained by oxidation of **2**.

Hydroxylation of 3β-Acetoxy-5α,16-pregnene-11,20-dione (26).—NaH (3 g, 50% in mineral oil) was dissolved in *t*-butyl alcohol (20 ml) and DMF (50 ml), and a further 40 ml of the latter solvent was added. After addition of triethyl phosphite (6 ml), the solution was cooled to −25°, and oxygen was passed through it. A solution of **26** (10 g) in THF (60 ml) was added and passage of oxygen was continued for 80 minutes. The reaction mixture was poured into dilute AcOH; the precipitate was isolated by filtration and acetylated in excess acetic anhydride and pyridine. The resultant material was chromatographed on Florisil (250 g), eluting with hexane-ether (1:1) to yield **12** (800 mg), which had mp 164–169° after crystallization from acetone–hexane. Further crystallization from acetone-hexane gave an analytical sample: mp 177–184°; $[\alpha]_D$ −58° (dioxane); nmr δ 0.68 (s, 18-CH_3C), 1.02 (s, 19-CH_3C), 1.97 (s, CH_3CO_2), 2.18 (s, CH_3CO), and 6.12 (m, 2).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.09; H, 8.26.

3β,17α-Dihydroxy-5α,15-pregnene-11,20-dione (13).—Saponification of **12** with KOH in aqueous MeOH at ambient temperature gave the diol **13**: mp 255–265° after crystallization from THF–acetone–hexane; $[\alpha]_D$ +31° (pyridine).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.71; H, 8.70.

Microbiological Oxidation of 2.—Compound **2** (500 mg) was incubated with *F. dehydrogenans*[9] for 15.75 hr at a concentration of 1 g/l. of medium. The product was chromatographed on Florisil (20 g), eluting with 40–45% ether–hexane to yield **14** (78 mg) which on crystallization from CH_2Cl_2–acetone gave 26 mg of almost pure material. The analytical sample, obtained by preparative tlc in $CHCl_3$–EtOAc (3:1), had mp 250–256° and $[\alpha]_D$ −91.9° ($CHCl_3$).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.51; H, 9.50.

Further elution with ether and ether–acetone (9:1) gave **11** (151 mg) which on crystallization from CH_2Cl_2–acetone gave 91 mg of material, mp 210–225°. Repeated crystallization gave an analytical sample: mp 223–233°; $[\alpha]_D$ −51° ($CHCl_3$); λ_{max} 240 mμ (ε 17,100).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.75; H, 8.70.

17α-Hydroxy-5α,15-pregnene-3,20-dione (14).—Compound **6** (136 mg) in pyridine (1.3 ml) was added over 2 min to chromium trioxide (110 mg) in pyridine (1 ml). After 18 hr at ambient temperature, water was added, and the precipitate was isolated and extracted three times with hot acetone. The extract was concentrated to dryness, and the residue partitioned between water and EtOAc. The organic phase was concentrated to dryness and the residue was purified by preparative tlc in $CHCl_3$–EtOAc (3:1). Extraction of the main band with CH_2Cl_2–acetone and crystallization from the same solvent mixture gave **14** identical with material obtained by microbiological oxidation of **2**.

17α-Acetoxy-4,15-pregnadiene-3,20-dione (15).—Compound **11** (541 mg) and potassium *t*-butoxide (150 mg) were stirred together in THF (20 ml), and ketene was passed into the solution until no **11** remained [the reaction was followed by tlc on microscope slides using the solvent system $CHCl_3$–EtOAc (3:1)]. EtOAc was added to the solution which was acidified with AcOH and washed with saturated $NaHCO_3$ solution and brine. The residue obtained by evaporation of the solvent was subjected to partition chromatography on Chromosorb W (100 g) in ligroin–propylene glycol, fractions of 100-ml vol. being collected. The material in fractions 15–31 (459 mg) was crystallized twice from MeOH to yield pure **15** (134 mg): mp 180–185°, with sweating from 172°; λ_{max} 240 mμ (ε 17,600); $[\alpha]_D$ −164.3° (dioxane).

Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.32; H, 8.12.

17α-Methoxy-4,15-pregnadiene-3,20-dione (16).—A solution of **11** (1.0 g) in DMF (20 ml) and MeI (10 ml) was stirred with Ag_2O (2.0 g) at ambient temperature for 20 hr. $CHCl_3$ (100 ml) was added and the mixture was filtered. The filtrate was evaporated to dryness and chromatographed on Florisil (100 g), eluting with hexane–ether (1:2). Crystallization from CH_2Cl_2–isopropyl ether yielded **16** (322 mg): mp 180–183°; $[\alpha]_D$ −0.6° ($CHCl_3$); λ_{max} 239 mμ (ε 17,750); nmr δ 0.78 (s, 18-CH_3C), 1.20 (s, 19-CH_3C), 2.10 (s, 21-CH_3CO), 3.14 (s, 17-CH_3O), 5.76 (s, 1), 6.0 and 6.2 (m, 2).

Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 7.00; H, 8.85.

3β,21-Diacetoxy-17α-hydroxy-5,15-pregnadien-20-one (17).—**2** (5 g) in MeOH (30 ml) and THF (40 ml) was cooled to 15° and CaO (8 g, from the freshly ignited hydroxide) was added. Azobisisobutyronitrile (240 mg) was added, followed by iodine (6.6 g). During the addition of the iodine, which took 10 min, the temperature was maintained at 15° by cooling. After a further 10 min, the mixture was filtered and poured into dilute sodium thiosulfate solution. The precipitate was isolated by filtration, washed with water, and, while still wet, dissolved in acetone (125 ml) and AcOH (25 ml). Triethylamine (30 ml) was added carefully and the resultant suspension was stirred and heated under reflux for 1 hr. Water was added, and the product was isolated by extraction with CH_2Cl_2 and acetylated in excess acetic anhydride and pyridine at ambient temperature for 18 hr. The acetate, obtained by precipitation with water, was dried and crystallized from acetone–hexane to give **17** (3.23 g), mp 185–197°. A further crystallization gave an analytical sample, mp 205–207°.

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.63; H, 8.00.

17α,21-Dihydroxy-4,15-pregnadiene-3,20-dione (18).—**17** (2.42 g) was incubated with *F. dehydrogenans*[9] for 10.25 hr at a concentration of 0.25 g/l. of medium, and the product was extracted into $CHCl_3$. Evaporation of the solvent and crystallization from CH_2Cl_2–acetone gave **18** (968 mg). Two further crystallizations from the same solvent gave an analytical sample: mp 205–214° dec; $[\alpha]_D$ +14.8° (dioxane); λ_{max} 240 mμ (ε 17,000).

Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.25; H, 8.42.

3β-Acetoxy-5,15-androstadien-17-one (19).—Compound **2** (4 g) in MeOH (150 ml) was added to $NaBH_4$ (2 g) in a little water. After 1 hr, acetone was added followed by AcOH; the solution was poured into water; and the precipitate was isolated, dried, and stirred with $CHCl_3$ (300 ml). $Pb(OAc)_4$ (4 g) was added and the reaction mixture was stirred for 2 hr. The solution was washed with aqueous ethylene glycol and water, then dried ($MgSO_4$), and evaporated to dryness. The residue was extracted with hot hexane and the insoluble portion was recycled with fresh $Pb(OAc)_4$ as already described. Following a second such recycling, the total hexane extracts were filtered through Florisil in hexane–ether (4:1) to yield **19** (1.31 g). This material contained a trace of **20** and the analytical sample was obtained by preparative tlc in the system $CHCl_3$–EtOAc (9:1). Pure **19** had mp 192–194° after two crystallizations from aqueous EtOH; $[\alpha]_D$ −144° (dioxane); λ_{max} 230 mμ (ε 7200).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.80; H, 8.40.

3β-Acetoxy-5,14-androstadien-17-one (20).—Compound **20** was isolated by preparative tlc in $CHCl_3$–EtOAc (9:1) of a sample of **19** obtained from an oxidation which was allowed to run for 24 hr. It crystallized from aqueous EtOH: mp 132–134°; $[\alpha]_D$ +50° ($CHCl_3$) {lit.[14] mp 130–132°; $[\alpha]_D$ +54° ($CHCl_3$)}.

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.99; H, 9.00.

Hydroxylation of 3β-Acetoxy-6,16-dimethyl-5,16-pregnadien-20-one (28).—Compound **28** (5 g) was hydroxylated and the product was acetylated as described for **1**. This material was chromatographed on Florisil (125 g) in hexane eluting with 30–40% ether to yield material which after one crystallization from ether and one from acetone–hexane gave 3β-acetoxy-17α-hydroxy-6-methyl-16-methylene-5-pregnen-20-one (660 mg), mp 144–148°. A further crystallization from acetone–hexane afforded a sample with a melting point of 148–150°, identical with an authentic specimen.[15] Examination of the nmr spectrum failed to detect any of the Δ^{15} isomer (lit.[15] mp 147–150°).

Registry No.—**2**, 17392-96-0; **3**, 17392-89-1; **4**, 17414-38-9; **5**, 2233-71-8; **6**, 17392-90-4; **7**, 17414-39-0; **8**, 17393-00-9; **9**, 17392-91-5; **10**, 17393-01-0; **11**, 17392-92-6; **12**, 17397-48-7; **13**, 17392-93-7; **14**, 17392-94-8; **15**, 17392-95-9; **16**, 17448-07-6; **17**, 17392-97-1; **18**, 17392-98-2; **20**, 1239-33-4; 3β-acetoxy-17α-hydroxy-6-methyl-16-methylene-5-pregnen-20-one, 5618-32-6; 3β,15α-diacetoxy-5-pregnen-20-one, 17397-50-1.

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Reaction of Nitrosyl Fluoride and Selected Steroid Enes.[1] A New Synthesis of Δ5-4-Keto Steroids

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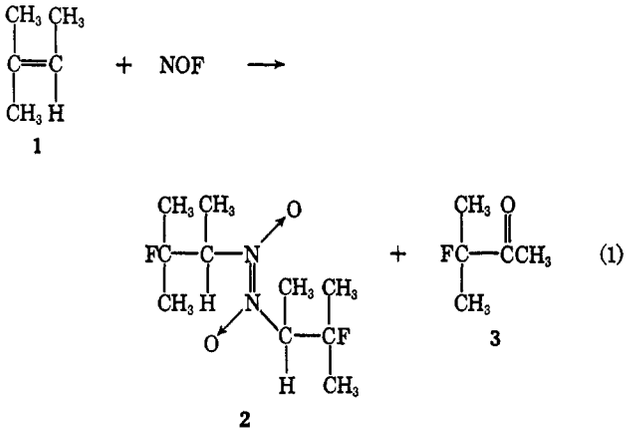
Reaction of steroid 4- and 5-enes with nitrosyl fluoride gave 5α-fluoro-4- and -6-nitrimines which on chromatography on alumina containing 6% water were converted into 5α-fluoro-4 and -6 ketones in high yield. Steroid 5-en-3β-ols were converted into Δ4-3,6-diones in moderate yield. Dehydrofluorination of 5α-fluoro-4 ketones gave Δ5-4 ketones, a relatively inaccessible class of steroids. Transformations of these products are discussed. Reactions of nitrosyl fluoride with various steroid olefins are described.

Since Fried and Sabo discovered that introduction of fluorine[2] at C-9 (α) of cortisone and cortisol significantly enhanced antiinflammatory activity of the parent adrenal hormones, a prodigious effort has been made to prepare fluoro steroid hormones[3] and to develop new methods for introducing fluorine at key positions throughout the steroid nucleus.[4] Although much work has been done in this area, new methods are needed for selectively fluorinating steroids with sensitive functional groups.

There are many examples of nitrosyl chloride addition to carbon–carbon double bonds, particularly in terpenes, to give dimeric chloronitroso compounds or isomeric chloro oximes.[5] However, this reaction with steroid olefins was described only recently; three different groups[6] reported that steroid 5-enes react with excess nitrosyl chloride to give 5α-chloro-6β-nitro steroids in good yield. These reports and the ready availability of nitrosyl fluoride[7,8] suggested its evaluation as a steroid fluorination agent.

Addition of nitrosyl fluoride (NOF) to a simple olefin, 2-methylbut-2-ene (**1**), in carbon tetrachloride, gave as a major product a white crystalline adduct, which, on the basis of its ultraviolet spectrum[9] [λ_{max}^{EtOH} 300 mμ (ε 7100)], was clearly the fluoronitroso dimer **2**. This is analogous to reaction of 2-methylbut-2-ene (**1**) with nitrosyl chloride.[10,11a]



When fluoronitroso dimer **2** was chromatographed on alumina III or refluxed briefly in 2-propanol containing water, it isomerized to the oxime, lost hydrogen fluoride, and finally, hydrated to give 3-methyl-3-hydroxybutan-2-one oxime (**4**)[11] in high yield (eq 2). A second, volatile product was isolated by vpc; structure **3** is suggested from mass and infrared spectra (see Experimental Section).

Reaction of Nitrosyl Fluoride and Steroid 5-Enes.—Cholesteryl acetate (**5a**) underwent reaction with excess NOF at 0° in methylene chloride or carbon tetrachloride to give a crystalline product (72% yield) which was assigned 5α-fluoro-6-nitrimine structure **6a** on the basis of elemental analysis, molecular weight determinations, characteristic imine (6.08 μ) and nitro absorption bands

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