18267-65-7; **21**, 18267-66-8; **22**, 18267-67-9; **23**, 18267-68-0; **24**, 18267-69-1; **26**, 18267-70-4; **27**, 18267-71-5; **28**, 18267-72-6; **29**, 18267-73-7.

Acknowledgments.—The authors are indebted to Dr. V. Toome, Dr. F. Vane, Dr. T. Williams, and Mr. S. Traiman for the measurement and interpretation of spectra. They also wish to thank Mr. H. Jenney and Dr. A. Steyermark for determination of gas chromatographic and microanalytical data.

Oxidation of Steroidal Ketones. VII. Cleavage of Steroidal Conjugated Ketones with Ruthenium Tetroxide[1,2]

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Received June 4, 1968

Ruthenium tetroxide has been utilized for the cleavage of conjugated and cross-conjugated steroidal ketones. In some instances the yields have been superior to those found for ozone. The unexpected formation of enediones has been observed in the oxidation of 1,4-diene-3,11-diones.

An important step in the partial synthesis of steroid analogs having one or several atoms replaced with heteroatoms is the synthesis of appropriate intermediates. The intermediates are usually prepared by the cleavage and removal of a portion of the steroid nucleus. Subsequently, the removed carbons are replaced with other atoms, and the ring system is reconstructed. A convenient route for the synthesis of the intermediates is the oxidative cleavage of conjugated olefins and particularly of the readily available conjugated ketones. Unfortunately, reagents[5,6] such as chromium trioxide, permanganate, ozone, hypohalites, etc., used for the cleavage of such entities are not easy to control and frequently overoxidation and/or low yields occur. Our work[7] with ruthenium tetroxide as an oxidant for ring A aromatic steroids prompted us to explore the possibilities of this rarely used and versatile reagent with the steroidal ketone system. The reagent appeared to provide the advantage of attacking double bonds and hydroxyl groups without further oxidation[8] of the products. Although no attempts were made to optimize the conditions, the yields were in most instances considerably better than those obtained by other methods. Of particular interest was its applicability to the 5β-9(11)-en-12-one system which has been reported as being unusually resistant to oxidative cleavage by other methods.[9]

As with the aromatic steroids the oxidation conditions involved the use of acetone–water mixtures. The ruthenium tetroxide was initially generated *in situ* from ruthenium dioxide and sodium periodate and was then regenerated throughout the reaction by the addition of a sodium periodate solution. The progress of the reaction was followed visually since the dioxide was black and the tetroxide yellow.

The oxidation of ring A or ring C α,β-unsaturated ketones gave the expected products in very good yield. Testosterone acetate easily provided the known[10,11] keto acid **1** in an 80% yield. Cleavage of another ring A enone, 17β-acetoxy-3-oxo-5α-androst-1-ene, gave diacid **2** in an 85% yield. Application of the ruthenium tetroxide procedure to the hindered ring C conjugated ketone **3** resulted in an 80% yield of the keto acid **4**. In the latter two cases the structure of the products followed from their elemental analyses and spectroscopic data.

Ruthenium tetroxide was also found to be a good oxidant for conjugated systems where the double bond was exocyclic to the ring containing the ketone, as exemplified by the diacetate[12] **7**. In this instance the 5α-16,17-diacid **8** results. Again, elemental analyses and spectroscopic data were used to establish the structure of the products.

Rather unexpectedly oxidation of 3β-acetoxy-5β-pregnan-16-en-20-one (**5**) did not proceed to completion, and instead of the anticipated 16,17-diacid the seco-17,20-diketo-16-carboxylic acid **6** was formed. Elemental analysis indicated the $C_{21}H_{32}O_5$ composition. The mass spectrum was devoid of the molecular ion peak (M^+ 364), but had fragments at *m/e* 321 (M − CH_3CO), 293 (M − CH_3COCO), 275 [M − (CH_3CO-CO + H_2O)], 257 (275 − H_2O), and 215 (257 − C_2H_2O). The results are in full agreement with the proposed structure **6**.

We next turned our attention to more complex cross-conjugated systems. It was expected that by utilizing systems with extended conjugation, we should be able to eliminate from two to three carbons from the nucleus.[13] This phase of the study began with the known[10] compound **9**. Oxidation of this cross-conjugated system

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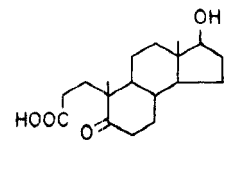

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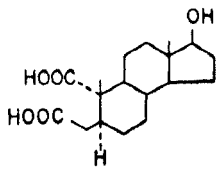

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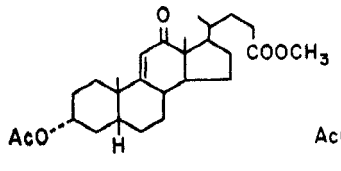

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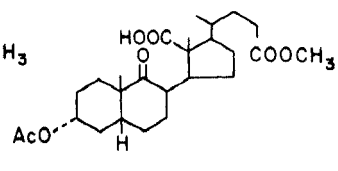

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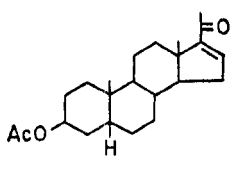

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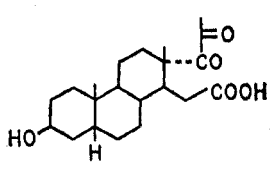

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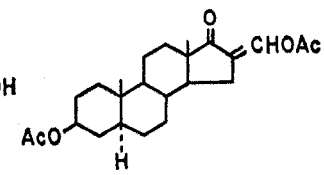

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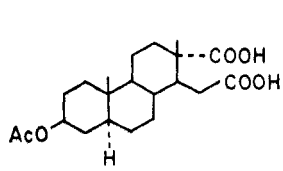

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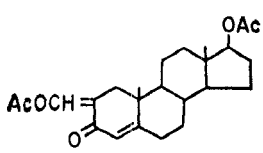

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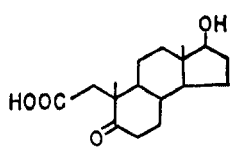

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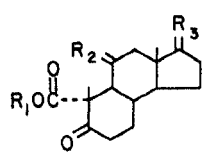
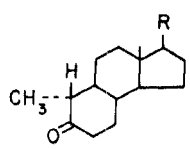


11

a) R_1=H; R_2=H_2; R_3=OH, ---H
b) R_1=CH_3; R_2=H_2; R_3=OH, ---H
c) R_1=H; R_2=H_2; R_3=OAc, ---H
d) R_1=CH_3; R_2=H_2; R_3=OAc, ---H
e) R_1=H; R_2=H_2; R_3=$COCH_3$, ---H
f) R_1=CH_3; R_2=H_2; R_3=$COCH_3$, ---H
g) R_1=H; R_2=O R_3=O
h) R_1=H; R_2=O; R_3=(17αOH)$COCH_2OAc$
i) R_1=CH_3; R_2=O; R_3=(17α OH)$COCH_2OAc$



12

a) R = OH
b) R = $OCOC_6H_5$
c) R = $COCH_3$

eliminated carbons 3 and 4 as expected and the previously described[10] keto acid **10** was obtained.

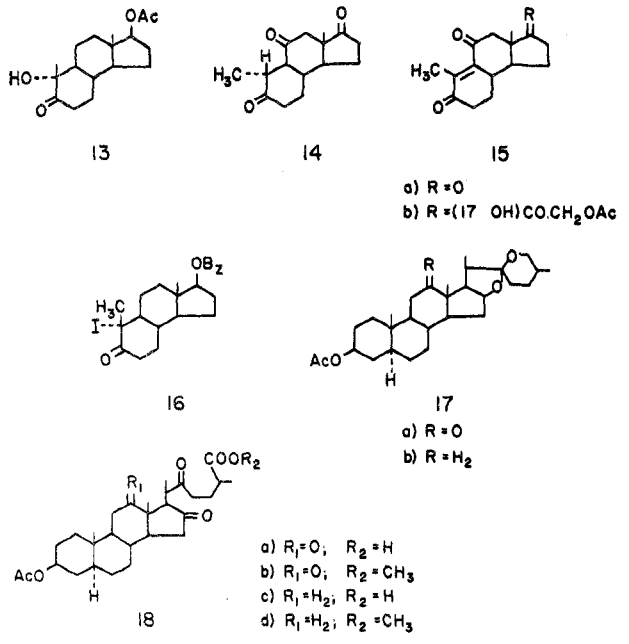
The 1,4-dien-3-one systems were the next type of cross-conjugated compounds to be studied. Here elimination of carbons 2, 3, and 4 and formation of γ-keto acids was anticipated. Previously, these systems had been cleaved by ozone to β-keto aldehydes and β-keto acids in poor yields.[6] The various 1,5-seco products were accompanied by polymeric substances and rearranged products.[6]

When 1-dehydrotestosterone acetate was treated with ruthenium tetroxide, crystalline acid **11a** was obtained. Its structure was determined by spectroscopic and analytical data and by its conversion to a methyl ester **11b** by diazomethane, a 17β-acetate **11c** by acetic anhydride–pyridine, and an ester acetate **11d**. Further characterization of acid **11a** was forthcoming from its decarboxylation with acid to the described[11] des-A compound **12a**. The des-A steroid **12a** was also found in the neutral fraction due to the ease with which β-keto acid **11a** underwent decarboxylation. In fact, if the work-up of the oxidation mixture was not done with care, little of the acid **11a** could be recovered. When 1-dehydrotestosterone benzoate was oxidized, the main products were in the neutral fraction and comprised the des-A benzoate[11] **12b** and an iodo compound, which is described below.

Similar results were found with 1-dehydroprogesterone. The acid **11e** obtained from the oxidation was identified by its physical data as well as by its conversion to the methyl ester **11f** and its decarboxylation to the des-A compound **12c**.

It may be mentioned that oxidation of 1-dehydrotestosterone acetate gave in addition to the expected **11a** and **12a** a smaller amount of the tertiary alcohol **13**. The alcohol was identified by elemental analysis, and an infrared spectrum which showed a relatively sharp band at 3480 cm^{-1} consistent with a tertiary hydroxyl. Presumably the product could arise *via* the intermediacy of a C-10 aldehyde (or its peroxide), which underwent a Baeyer–Villiger oxidation. Removal of the formate might have taken place in the work-up.

Further evaluation of the ruthenium tetroxide procedure involved the use of 11-oxygenated 1,4-dien-3-ones. Androsta-1,4-diene-3,11,17-trione was cleaved to the known[6c] triketo acid **11g** in good yield. Surprisingly, the neutral fraction from the oxidation contained little, if any, of the triketone **14** corresponding to a decarboxylation of the acid **11g**. It was composed mainly of the enedione **15a**. Structural assignment of **15a** was made on the basis of its characteristic ultraviolet maximum at 261 mμ and infrared peaks at 1720, 1685, 1670, and 1590 cm^{-1}. An nmr spectrum verified the proposed structure since a signal could be seen at 117.5 cps for a vinylic methyl. Final confirmation of the structure came from the reduction of **15a** by zinc–acetic acid to trione **14**.



Likewise, prednisone acetate was oxidized and found to yield acid **11h** in low yield. This poor yield was undoubtedly the result of concomitant degradation of the side chain.[14] Acid **11h** was isolated and identified as its methyl ester **11i**, which was identical in all respects with a standard sample prepared by treating an authentic sample[6d] of the acid **11h** with diazomethane. The neutral fraction again consisted mainly of an enedione **15b**. Its ultraviolet maximum at 261 mμ and infrared peaks at 3400, 1735, 1720, 1675, and 1650 cm^{-1} suggested that an enedione system existed in the molecule. A positive blue tetrazolium reaction confirmed that the dihydroxyacetone side chain was still intact. An nmr spectrum of **15b** provided further conclusive evidence since singlets were seen at 46 cps for the 18 methyl, at 113.5 cps for the vinylic methyl, and at 128 cps for the 21-acetate methyl and a pair of doublets appeared at 280 and 305 cps (J = 18.0 cps) for the C-21 protons.

Although the mechanism for the formation of enediones **15** is not fully elucidated, evidence indicates they might be formed by elimination of hydrogen iodide from a 10-iodo intermediate. Substance for this assumption is provided by the isolation of a minor amount of a compound from the 1-dehydrotestosterone benzoate oxidation whose structure is tentatively assigned as **16**. Although the product could not be analyzed due to rapid decomposition, an nmr spectrum proved to be revealing. Among others the spectrum had a signal at 120.5 cps indicative of a tertiary methyl on a carbon bearing an iodine atom. Iodine atoms on a methyl bearing carbon usually deshield the methyl by about 60 cps.[15] In addition the product **16** could be reduced by zinc–ethanol[16] to the known[11] des-A benzoate **12b**.

The introduction of the iodine group could proceed either through a hypohalite reaction of the 1-carboxylic acids analogous to the iodine–lead tetraacetate decarboxylation[17] or simply by iodination of the 5-keto compounds. Elimination of hydrogen iodide would then yield the more stable **15**. Alternatively **15** could arise by dehydration of an 11-keto analog of **13**.

In exploring the oxidation of systems other than conjugated ketones we had occasion to try the steroidal sapogenins, hecogenin acetate **17a** and tigogenin acetate **17b**. From the acid fraction of the hecogenin acetate oxidation a crystalline compound was obtained and identified as acid **18a**. In addition to infrared bands at 3220, 1735, and 1700 cm^{-1}, the product **18a** had nmr singlets at 57.5 cps for the 18 methyl, at 66 cps for the 19 methyl, and at 122 cps for the C-3 acetate methyl. A doublet for the 27-methyl was seen at 73 cps (J = 7.0 cps). The structure of acid **18a** was further verified by its conversion to ester **18b**. The nmr signals for the ester remained essentially the same except a singlet for the ester methyl appeared at 220 cps and the C-27 methyl doublet was found at 71 cps (J = 7.0 cps). Similarly, tigogenin acetate **17b** could be oxidized to acid **18c** which was methylated to ester **18d**.

Experimental Section[18]

General Procedure for Oxidation.—A solution of the conjugated steroid[19] in acetone (50–70 ml/g of steroid) is added dropwise to the yellow ruthenium tetroxide solution generated by stirring ruthenium dioxide (100–200 mg/g of steroid) suspended in acetone (50–70 ml/g of steroid) with sodium periodate (400–800 mg/100 mg of RuO_2) in water (minimum amount). A sodium periodate solution[20] prepared by dissolving sodium metaperiodate (3–7 g/g of steroid) in water (15–21 ml/g of steroid) and adding an equal volume of acetone is used to regenerate the ruthenium tetroxide. As the mixture turns from yellow (RuO_4) to black (RuO_2) during the addition of the steroid and during the reaction time, portions of the periodate solution are introduced. After 4–5 hr of stirring at room temperature the reaction is terminated by the addition of a few milliliters of isopropyl alcohol. The solids are collected on Celite by filtration, and the acetone in the filtrate removed *in vacuo*. The steroids are then dissolved in ether–ethyl acetate and partitioned into neutral and acidic fractions with either sodium bicarbonate or sodium hydroxide.[21] The acidic fraction is recovered by extraction of the acidified solution with ether. The various products obtained are listed below.

17β-Hydroxy-3,5-seco-4-nor-5-oxoandrostan-3-oic Acid (1).—Testosterone acetate (1.0 g) was oxidized to yield keto acid **1** (880 mg), mp 192° (lit.[10,11] mp 195–197 and 204–205.5°).

17β-Hydroxy-1,3-seco-2-nor-5α-androstane-1,3-dioic Acid (2).—Oxidation of 17β-acetoxy-3-oxo-5α-androst-1-ene (200 mg) gave diacid **2** (170 mg): mp 257–260° (from ethyl acetate); ν_{max} 3430, 3100, 1715, 1670 cm^{-1}.

Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.98; H, 8.70.

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(18) Melting points were taken on a micro hot stage and are corrected. Infrared spectra were recorded on solids incorporated in a KBr wafer. Ultraviolet spectra were taken on methanol solutions. Unless otherwise stated, deuteriochloroform was used for nmr spectra which were recorded with a Varian HA-60 instrument. Silica gel HF_{254} was used for thin layer chromatograms (tlc) with the developing solution as stated. Analyses were performed by I. Beetz, Kronach, Germany. The reported yields refer to chromatographically homogeneous solids whose infrared spectra were identical with those of analytical samples. Known products were identified by comparison of melting points, chromatographic mobilities and infrared spectra with those of authentic samples.

(19) Quantities of reagents are listed in ranges. The simple α,β-unsaturated ketones take the smaller amount, while the cross-conjugated systems take the larger amount.

(20) This solution should be made up fresh for each experiment. Prolonged storage results in deterioration of the solution.

(21) Use of sodium hydroxide for the recovery of acids generally resulted in hydrolysis of any acetate moieties present.

Methyl 3α-Acetoxy-12-carboxyl-9,12-seco-11-nor-9-oxo-5β-cholan-24-oate (4).—The ring C unsaturated ketone **3** (530 mg) was converted by ruthenium tetroxide into 400 mg of keto acid **4**. Repeated recrystallization from ethyl acetate–pentane gave colorless crystals: mp 122°; ν_{max} 3070, 2630, 1730, 1700, 1685 cm^{-1}.

Anal. Calcd for $C_{26}H_{40}O_7$: C, 67.21; H, 8.68. Found: C, 67.49; H, 8.49.

3β-Hydroxy-17,20-dioxo-16,17-seco-5β-androstan-16-oic Acid (6).—The 5β-diketo acid **6** (380 mg) was obtained from the oxidation of **5** (500 mg). A sample of **6** was recrystallized from ethyl acetate to mp 152–153°; ν_{max} 3360, 3150, 1720, 1700 cm^{-1}.

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; Found: C, 68.76; H, 8.65.

3β-Acetoxy-16,17-seco-5α-androsta-16,17-dioic Acid (8).—The diacetate[12] **7** (1.0 g) was oxidized to the 5α-diacid **8** (550 mg): mp 237–242° (from ethyl acetate); ν_{max} 3060, 2640, 1730, 1685 cm^{-1}.

Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.30; H, 8.48. Found: C, 65.88, 65.54; H, 8.45, 8.62.

17β-Hydroxy-2,5-seco-3,4-bisnor-5-oxoandrostan-2-oic Acid (10).—The acid fraction from the cleavage of acetoxymethylene **9** (1.0 g) was methylated with diazomethane and chromatographed repeatedly on silica tlc plates [ethyl acetate–chloroform (3:7)] to yield 300 mg of the ester acetate of **10**. The ester acetate was saponified to acid **10**, which was identical with a previously prepared sample.[10]

17β-Hydroxy-1,5-seco-2,3,4-trisnor-5-oxoandrostan-1-oic Acid (11a).—1-Dehydrotestosterone acetate (10.0 g) gave crystalline keto acid **11a** (1.85 g). The product was recrystallized from methanol–water to mp 144–148°; ν_{max} 3450, 1720, 1700 cm^{-1}.

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.39; H, 8.86.

Methyl 17β-Hydroxy-1,5-seco-2,3,4-trisnor-5-oxoandrostan-1-oate (11b).—Acid **11a** (100 mg) obtained above was methylated with ethereal diazomethane to ester **11b**: mp 153–158° (from methanol); ν_{max} 3530, 1730, 1075 cm^{-1}.

Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.34; H, 8.62.

17β-Acetoxy-1,5-seco-2,3,4-trisnor-5-oxoandrostan-1-oic Acid (11c).—The hydroxy acid **11a** (200 mg) was acetylated with acetic anhydride–pyridine as usual to acetoxy acid **11c**. Repeated recrystallization from ethyl acetate–pentane gave colorless crystals: mp 102–104°; ν_{max} 3170, 1730, 1710, 1685 cm^{-1}.

Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 66.73; H, 8.21.

Methyl 17β-Acetoxy-1,5-seco-2,3,4-trisnor-5-oxoandrostan-1-oate (11d).—The ester acetate **11d** was formed by treating a sample of acetoxy acid **11c** with diazomethane. The sample melted at 119–123° (from methanol), ν_{max} 1735, 1730, 1695 cm^{-1}.

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.95; H, 8.22.

17β-Hydroxy-10α-des-A-androstan-5-one (12a). A.—The neutral fraction from the oxidation of 10 g of 1-dehydrotestosterone acetate was chromatographed on silica tlc plates [chloroform–ethyl acetate (9:1)], then saponified to yield **12a** (650 mg), mp 93–94° (lit.[11] mp 94–95°).

B.—Acid **11a** (100 mg) was decarboxylated by hot phosphoric acid–acetic acid to **12a** and found to be identical with the above sample.

17β-Benzoyloxy-10α-des-A-androstan-5-one (12b).—1-Dehydrotestosterone benzoate (600 mg) was oxidized as described. The neutral fraction was chromatographed on a silica gel tlc plate (chloroform–ethyl acetate 19:1) to give **12b** (381 mg), mp 126–128° (lit.[11] mp 125–126°).

17β-Benzoyloxy-10-iodo-10-des-A-androstan-5-one (16).—The most mobile tlc zone in the above chromatography was eluted to yield **16** (262 mg, crude) which could be recrystallized from methylene chloride–methanol. A melting point could not be taken due to gradual decomposition of the sample while being heated.

17β-Acetoxy-10α-hydroxy-1,5-seco-2,3,4-trisnorandrostan-5-one (13).—Oxidation of 1-dehydrotestosterone acetate (10 g) gave a neutral residue (1.46 g). The residue was dissolved in dioxane (20 ml)–ethanol (85 ml), then zinc dust was added and the mixture was refluxed for 7 hr. The recovered products were resolved on tlc [chloroform–ethyl acetate (9:1)] into four fractions. Fraction 3 was further purified on tlc [ethyl acetate–chloroform (3:7)] and gave 61 mg of **13**.

The product was crystallized from ethyl acetate: mp 65° (waxy appearance), 91–101°; ν_{max}^{KBr} 3480 (fairly sharp), 1730, 1715, 1250 cm^{-1}.

Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 68.95; H, 8.92.

5,20-Dioxo-1,5-seco-2,3,4-trisnorpregnan-1-oic Acid (11e).—Crystalline 20-keto acid **11e** (175 mg) was obtained from the oxidation of 1-dehydroprogesterone (1.0 g). Repeated recrystallization of **11e** from ethyl acetate gave colorless crystals: mp 134°; ν_{max} 3210, 1730, 1700, 1675 cm^{-1}.

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.16; H, 8.26.

Methyl 5,20-Dioxo-1,5-seco-2,3,4-trisnorpregnan-1-oate (11f).—Methylation of a portion of acid **11e** with diazomethane gave ester **11f**: mp 158° (from methanol); ν_{max} 1730, 1700 cm^{-1}.

Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.33; H, 8.54.

10α-Des-A-pregnane-5,20-dione (12c).—A solution of acid **11e** (80 mg) in glacial acetic acid (5.0 ml) containing 1 *N* phosphoric acid (1.0 ml) was heated at reflux for 2 hr. The steroids were dissolved in ethyl acetate and washed with sodium bicarbonate, then water. Removal of the solvent *in vacuo* gave 45 mg of **12c**. Repeated recrystallization from methanol gave a pure sample: mp 108–110°; ν_{max} 1700 cm^{-1}.

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.30; H, 10.03.

1,5-Seco-2,3,4-trisnor-5,11,17-trioxoandrostane (11g).—By degrading 3,11,17-trioxoandrosta-1,4-diene (1.0 g) with ruthenium tetroxide the known triketo acid **11g** (400 mg) was obtained. The material was identical in all aspects with an authentic sample.[6c]

Des-A-androst-9(10)-ene-5,11,17-trione (15a).—The neutral fraction (130 mg) from the above oxidation of androsta-1,4-diene-3,11,17-trione was chromatographed on a silica tlc plate [ethyl acetate–benzene (1:1)] to yield enedione **15a**: mp 186–188°; λ_{max} 261 mμ (ε 9700); ν_{max} 1735, 1690, 1675 cm^{-1}; nmr 61.0 (18 methyl), 117.5 cps (vinylic methyl).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.90; H, 7.44.

10α-Des-A-androsta-5,11,17-trione (14).—The enedione **15a** (40 mg) was dissolved in glacial acetic acid (1.0 ml) and heated to reflux. Zinc dust (80 mg) was refluxing solution over 25 min. The reaction was cooled, diluted with ethyl acetate, and filtered through Celite. The filtrate was washed with sodium bicarbonate and water. The residue remaining after removal of the solvent was chromatographed on a tlc silica plate (ethyl acetate–benzene, 1:1) to yield 20 mg of triketone **14**, mp 134–136°, which was identical with an authentic sample[6c] (mp 135–137°).

Methyl 21-Acetoxy-17α-hydroxy-1,5-seco-2,3,4-trisnor-5,11,20-trioxopregnan-1-oate (11i). A.—The known[6c] keto acid **11h** was methylated by diazomethane to ester **11i**: mp 223–226° (from acetone); ν_{max} 3510, 1740, 1730, 1700, 1680 cm^{-1}.

Anal. Calcd for $C_{21}H_{28}O_8$: C, 61.75; H, 6.91. Found: C, 61.87; H, 7.05.

B.—Prednisone acetate (1.0 g) was oxidized with RuO_4 as usual. The acidic fraction was methylated and chromatographed on tlc plates to yield **21-acetoxy-17α-hydroxydes-A-pregn-9(10)-ene-5,11,20-trione (15b).** The neutral fraction (150 mg) from the prednisone acetate oxidation was recrystallized from ethyl acetate to give an analytical sample of **15b**: mp 183–185°; λ_{max} 261 mμ (11,000); ν_{max} 3400, 1735, 1720, 1675, 1650 cm^{-1}; nmr 46 (18 methyl), 113.5 (vinylic methyl), 128 (20 acetate methyl), 280 and 305 cps (pair of doublets; J = 18 cps C-21 proton).

Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.60; H, 6.94. Found: C, 65.48; H, 7.02.

3β-Acetoxy-12,16,22-trioxo-5α-cholestan-26-oic Acid (18a).—Hecogenin acetate (**17a**, 500 mg) gave acid **18a** (150 mg) by RuO_4 oxidation. Recrystallization of a portion from ethyl acetate gave a sample with mp 193–195°; ν_{max} 3220, 1735, 1700 cm^{-1}; nmr 57.5 (18 methyl), 66 (19 methyl) 73, (doublet; J = 7.0 cps; 27 methyl), 122 cps (3 acetate methyl).

Anal. Calcd for $C_{29}H_{42}O_7$: C, 69.29; H, 8.42. Found: C, 69.15; H, 8.31.

Methyl 3β-Acetoy-12,16,22-trioxo-5α-cholestan-26-oate (18b).—The acid **18a** (100 mg) was methylated with diazomethane to ester **18b**: mp 139°; ν_{max} 1730, 1700 cm^{-1}; nmr 57.5 (18 methyl), 65 (19 methyl), 71 (doublet, J = 7.0 cps; 27 methyl), 122 (3 acetate methyl), 220 cps (ester methyl).

Anal. Calcd for $C_{30}H_{44}O_7$: C, 69.74; H, 8.58. Found: C, 69.81; H, 8.29.

3β-Acetoxy-16,22-dioxo-5α-cholestan-26-oic Acid (18c).—Acid **18c** was formed by the oxidation of tigogenin acetate (**17b**). Recrystallization of the material from ethyl acetate–pentane gave crystals: mp 145–147°; ν_{max} 3230, 1740, 1705 cm^{-1}.

Anal. Calcd for $C_{29}H_{44}O_6$: C, 71.28; H, 9.08. Found: C, 71.21; H, 8.97.

Methyl 3β-Acetoxy-16,22-dioxo-5α-cholestan-26-oate (18d).—By methylation with ethereal diazomethane acid **18c** was converted into ester **18d**: mp 103–105° (from ethyl acetate–pentane); ν_{max} 1730, 1710 cm^{-1}.

Anal. Calcd for $C_{30}H_{46}O_6$: C, 71.68; H, 9.22. Found: C, 71.31; H, 8.82.

Registry No.—**2**, 17955-23-6; **4**, 17955-24-7; **6**, 17955-25-8; **8**, 17955-26-9; **11a**, 17955-27-0; **11b**, 17955-28-1; **11c**, 15266-99-6; **11d**, 15267-00-2; **13**, 17955-31-6; **11e**, 17955-33-8; **11f**, 17955-32-7; **12c**, 17955-34-9; **15a**, 17955-35-0; **11i**, 17955-36-1; **15b**, 17955-37-2; **18a**, 17955-38-3; **18b**, 17955-39-4; **18c**, 17955-40-7; **18d**, 17955-41-8; RuO_4, 12036-58-7.

Steroids Containing Ring A Aromatic. XIV. The Ruthenium Tetroxide Oxidation of Aromatic Steroids[1,2]

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Received June 25, 1968

The use of ruthenium tetroxide for degrading aromatic steroids has been explored. An interesting double allylic oxidation of ring A phenols has been observed with this reagent.

We have been interested in the degradation of aromatic steroids as a means for elucidating the mechanistic pathway of the dienone–phenol and dienol–benzene rearrangements[5] and as a possible route for the preparation of intermediates required for the synthesis of heterocyclic steroids. Several oxidative methods for the selective degradation of ring A were investigated.[5c,6]

In continuing the search for better oxidative methods we turned our attention to ruthenium tetroxide, a powerful oxidant, which has attracted limited attention.[7] The reports that the reagent reacts vigorously with aromatic solvents led us to try ruthenium tetroxide for the cleavage and degradation of aromatic steroids. The reagent was found to be superior to ozonization but, in one instance, gave unexpected and interesting results.

The procedure finally adopted was easy to control and involved the use of acetone–water mixtures. The ruthenium tetroxide was generated *in situ* from ruthenium dioxide and sodium periodate. Rather than to generate large amounts of tetroxide initially, it was found practical to reoxidize the dioxide formed during the reaction with additional sodium periodate. Since the dioxide was black and the tetroxide yellow, the progress of the reaction could be followed visually.

When estrone was oxidized, a good yield of the diacid **1** was obtained. The product was identified by comparison with an authentic specimen.[6] The same acid **1** was also formed by the oxidation of the 1-hydroxy-4-methyl-1,3,5(10)-triene **2a**, obtained from the dienone–phenol rearrangement of 1-dehydrotestosterone. In this instance the 17-hydroxyl was also oxidized. Oxidation of the 4-methyl-1,3,5(10)-triene **2b** similarly gave acid **1** (Chart I).

In the above cases the degradation of ring A terminated at carbons 5 and 10, as expected. It was anticipated that oxidation of a 6-keto analog would yield diacid **4**. Indeed, when the 6-keto-4-methyl-1,3,5-(10)-triene **3** was treated with ruthenium tetroxide keto diacid **4** was produced. The product was identical with a previously prepared sample.[5c]

With estradiol diacetate the reaction took an unexpected, and totally different course. In this instance diacid **6a** was formed in a small amount, and a large neutral fraction was recovered. From this neutral fraction 9α-hydroxy-6-ketotriene **5a** was isolated in about 40% yield, with the remainder being unchanged estradiol diacetate. Product **5a** was identified on the basis of its elemental analysis, spectroscopic properties, and its structure was confirmed by chemical transformations. Ketotriene **5a** was analyzed for $C_{22}H_{26}O_6$ indicating the introduction of two additional oxygen atoms into estradiol diacetate. A sharp peak at 3490 cm^{-1} in the infrared spectrum suggested that one of these oxygens may be a tertiary hydroxyl, while a band at 1680 cm^{-1} indicated that the other oyygen was probably a ketone

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(2) This work was supported by Public Health Service Grants A-5326 and CA-07137. To simplify discussion the steroid numbering is employed.

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