

Novel Products from the Oxidation of Δ^5 Steroids with Potassium Permanganate in Pyridine¹

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The oxidation of pregnenolone acetate with potassium permanganate in pyridine yields pregnane-3 β ,5,6-triol-7,20-dione 3-acetate (**3a**) (ketotriol) and other products. Similar oxidation of 7-ketopregnenolone acetate also gave **3a**. Similar results were obtained with cholesteryl acetate and with androst-5-ene-3 β ,17 β -diol diacetate. The respective ketotriols were dehydrated to diosphenols **5**, and also were oxidized to give unusual seven-membered ring anhydrides **7**.

An attempt to prepare a 5,6-*cis*-diol of pregnenolone acetate (**1a**) was made by treating it with a modification of the potassium permanganate-periodic acid reagent of Lemieux and von Rudloff.² However, instead of the desired diol, a number of unusual and interesting oxidation products were obtained. The structures and some of their chemistry are described in this and subsequent papers.

The reaction was conducted in pyridine-water solution, but for solubility reasons, the ratio was changed from the usual 1:3 pyridine-water² to approximately 5:1. It is not known at present whether this change is responsible for the different results obtained. In addition to an acid fraction which has not yet been studied, a complex neutral fraction was obtained from which so far three compounds have been isolated and identified. They are 5 β ,6 β -oxidopregnan-3 β -ol-20-one 3-acetate (**2**) ("5,6-oxide") (3-14%), pregnane-3 β ,5,6,7-tetrol-20-one 3-acetate (5-15%), and pregnane-3 β ,5,6-triol-7,20-dione 3-acetate (**3a**) (7-ketotriol) (10-24%) (Chart I).

The 5,6-oxide was identical with an authentic sample prepared as reported by Akhtar and Barton,³ and appears to be the first reported example of the formation of an oxide from an olefin with the permanganate-periodate reagent.

The structure and chemistry of the 7-ketotriol is the subject of this paper. Microanalysis indicated the presence of six oxygen atoms, and the infrared spectrum showed hydroxyl absorption and the presence of three carbonyl groups. The peak at 7.99 μ indicated that one of these was an acetate carbonyl (assigned to C-3) and a second carbonyl group was assigned to C-20. The nmr spectrum showed peaks at δ 1.98 (21-CH₃), 2.09 (3-acetate methyl), and 5.05 (at least six peaks, one proton, 3 α -H on carbon carrying an acetate group) in confirmation of these assignments. There was no significant ultraviolet absorption.

It therefore appeared that there remained two hydroxyl groups and one carbonyl group to be characterized. The nmr spectrum also showed two doublets, δ 3.80 ($J = 3$ Hz) and 3.89 ($J = 2.5$ Hz) which integrated for two protons. When D₂O was added to the sample, the doublets disappeared and a one-proton singlet appeared at δ 4.09. The same behavior was observed when D₂O-pyridine or D₂O-sodium methoxide-methanol was added. These doublets have been assigned to coupling of the 6-hydrogen and the 6-hy-

droxyl hydrogen, and further evidence for this assignment is given below.

Acetylation of the ketotriol with acetic anhydride in pyridine introduced one more acetyl group, and the infrared spectrum of this compound **3b** showed the presence of three carbonyl groups, two acetate groups, and still showed hydroxyl absorption. Therefore, one of the hydroxyl groups must be tertiary, since it did not acetylate, and most probably is at C-5. The nmr spectrum had peaks at δ 2.02, 2.10, and 2.17 (3- and 6-acetoxy and 21-methyl groups). The two doublets in the parent compound were gone, and in addition to the broad complex absorption at δ 5.0 to 5.8 for the 3 α -hydrogen, there was a single sharp one-proton peak at δ 5.17, assigned to the 6-hydrogen.

Confirmation of the structure of the ketotriol was obtained by the permanganate-periodate oxidation of 7-ketopregnenolone acetate (**4a**) which gave the ketotriol in 32% yield. None of the other oxidation products obtained from pregnenolone acetate could be isolated from this reaction mixture.

In order to gain further information about the oxidation reaction, various modifications were tried. When the oxidation was conducted under an atmosphere of nitrogen, the same products were obtained and there was no significant variation in the yields, indicating that atmospheric oxygen was not involved.

When the oxidation of pregnenolone acetate was conducted with potassium permanganate in pyridine-water, without the periodate, the ketotriol was obtained in 26% yield, and none of the other products could be isolated. When 7-ketopregnenolone acetate (**4a**) was oxidized with potassium permanganate in pyridine-water, again only the ketotriol was obtained, in 20% yield.⁴

From these results, it appears that the permanganate-periodate reagent² is not necessary for formation of the ketotriol and that permanganate is effecting both hydroxylation of the 5,6 double bond and allylic oxidation at the 7-carbon atom.

Studies currently in progress in this laboratory (R. Hanninen and G. Starkey) indicate that the conformation of the 5- and 6-hydroxyl groups is α .

When cholesteryl acetate was oxidized with the permanganate-periodate reagent, results similar, but not identical, with those from pregnenolone acetate were obtained. From the complex neutral fraction was isolated cholestane-3 β ,5,6-triol-7-one 3-acetate (**3c**) ("7-ketotriol") (8%) and cholestane-3 β ,5,6,7-tetrol 3-ace-

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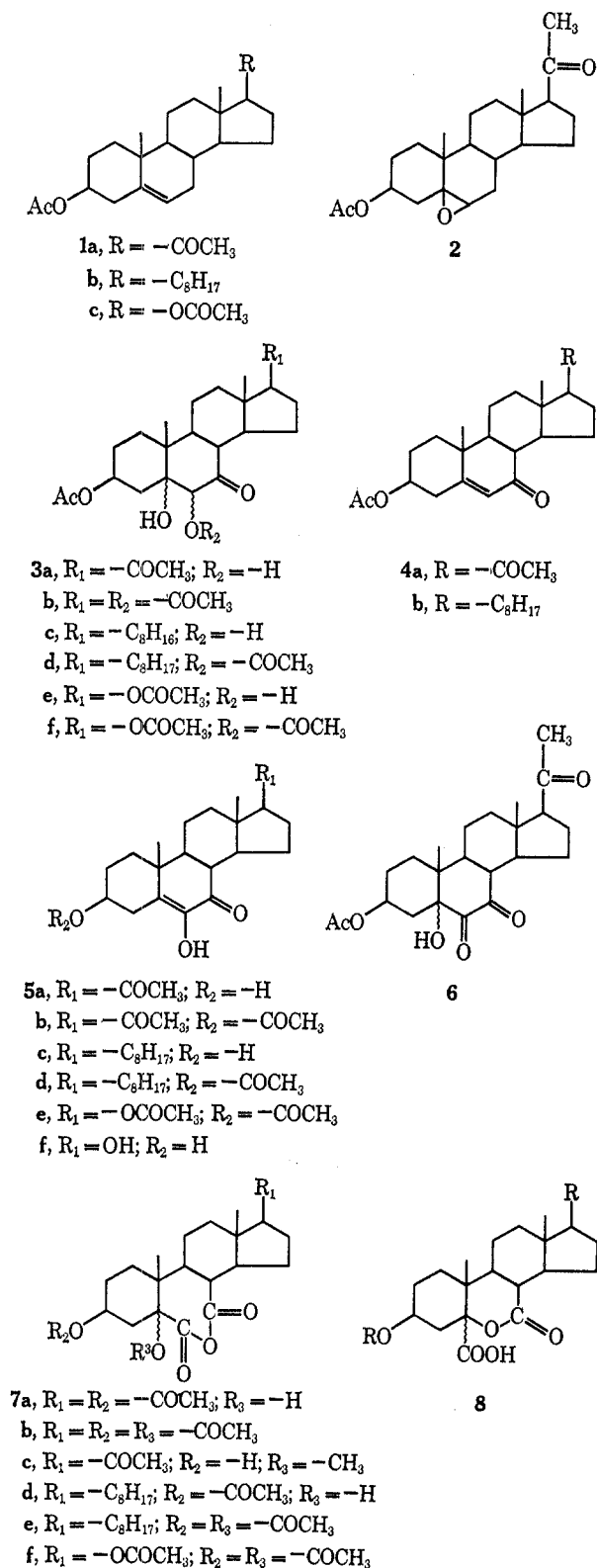
(1) Grateful acknowledgment is made to the W. S. Merrell Co. for financial support of this work.

(2) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701, 1710, 1714 (1955).

(3) M. Akhtar and D. H. R. Barton, *J. Amer. Chem. Soc.*, **86**, 1528 (1964).

(4) The oxidation has also been carried out with periodic acid alone, and none of the ketotriol was formed. The products will be described in a subsequent paper.

CHART I



tate (4%). None of the 5,6-oxide, observed with pregnenolone acetate, could be isolated.

The structure of the 7-ketotriol was established in the same manner as in the pregnane series (see Experimental Section).

Again, confirmation of the structure of the 7-ketotriol was obtained by permanganate-periodate oxidation of 7-ketocholesteryl acetate (**4b**), which gave the 7-ketotriol in 36% yield.

When cholesteryl acetate was oxidized with permanganate only in pyridine, the 7-ketotriol was obtained in 18% yield, and 7-ketocholesteryl acetate under the same conditions gave the 7-ketotriol in 23% yield.

In view of the above findings, the permanganate-periodate reagent was not used in the androstane series. Instead, androst-5-ene-3 β ,17 β -diol diacetate (**1c**) was treated with potassium permanganate in pyridine-water and androstrane-3 β ,5,6,17 β -tetrol-7-one 3,17-diacetate (**3e**) was isolated from the neutral fraction in 23% yield.

Reactions of the 7-Keto Compounds.—Hydrolysis of pregnane-3 β ,5,6-triol-7,20-dione 3-acetate (**3a**) with potassium hydroxide in aqueous methanol was carried out with the intention of removing the 3-acetate group. However, elemental analysis of the product indicated that dehydration had also occurred. The infrared spectrum was characteristic of a diosphenol, as was the ultraviolet spectrum, with a peak at 274.2 m μ (ϵ 16,700).^{5,6} The product, obtained in 64% yield, was therefore assigned the structure pregn-5-ene-3 β ,6-diol-7,20-dione (**5a**) and must have arisen by β elimination of the 5-hydroxyl group, which is β to the 7-carbonyl group. The diosphenol gave a positive ferric chloride test and application of Woodward's rules⁷ to the ultraviolet spectrum gave a calculated value of 279 m μ , compared to the observed value of 274.2 m μ .

The nmr spectrum showed a broad poorly defined multiplet centered at approximately δ 3.34 which was assigned to the 3 α -hydrogen and the allylic 4-hydrogens, and a one-proton singlet at δ 6.13 which was assigned to the hydrogen of the 6-hydroxyl group, since it disappeared in the presence of deuterium oxide (see below).

When the 7-ketotriol was treated with thionyl chloride in pyridine a product was obtained which differed from the starting material by one less molecule of water and which still contained the acetate group. The infrared and ultraviolet (maximum at 274.7 m μ , ϵ 9920) spectra and a positive ferric chloride test again indicated a diosphenol,^{5,6} to which the structure pregn-5-ene-3 β ,6-diol-7,20-dione 3-acetate (**5b**) was assigned. When the diosphenol acetate was hydrolyzed with potassium carbonate in aqueous ethanol a diosphenol was obtained which was identical with the one described above.

The same reactions were carried out with the 7-ketotriol in the cholestane series and the same results were obtained. Basic hydrolysis gave cholest-5-ene-3 β ,6-diol-7-one (**5c**) in 32% yield and the infrared, ultraviolet, and nmr spectra showed the same characteristic features. Thionyl chloride in pyridine again gave the 3-acetate (**5d**) of the diosphenol, identical with the one reported in the literature.⁵ This identity thus provides good evidence for the structures of the diosphenols in the pregnane and androstane series, and provides additional evidence for the structure of the 7-ketotriol, since it is difficult to visualize any other structures which would give the diosphenol and also be in accord with the other evidence. The nmr spectrum of the acetylated diosphenol showed two doublets centered at δ 3.33 assigned to the 4-hydrogens, a single proton as a broad

(5) H. R. Nace and M. Inaba, *J. Org. Chem.*, **27**, 4024 (1962).

(6) H. R. Nace and D. H. Nelander, *ibid.*, **29**, 1677 (1964).

(7) R. B. Woodward, *J. Amer. Chem. Soc.*, **64**, 72 (1942); see also L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 17.

(8) I. M. Heilbron, E. R. H. Jones, and F. S. Spring, *J. Chem. Soc.*, 801 (1937).

multiplet centered at 4.78, assigned to the 3 α -hydrogen, and a single-proton singlet at 6.30, assigned to the hydrogen of the 6-hydroxy group, since it disappeared in the presence of deuterium oxide. Spin decoupling experiments on this compound gave further evidence for the assignments, since irradiation in the δ 4.78 region caused marked changes in the appearance of the two doublets assigned to the C-4 hydrogens.

In the androstane series the dehydration with thionyl chloride in pyridine was carried out and the acetylated disphenol **5e** was obtained in 64% yield. It showed the same characteristics as the two described above.

In an attempt to gain additional information about the 7-ketotriol (pregnane series) it was subjected to Jones oxidation.⁹ However, instead of the expected 6,7- α -diketone **6** (or its diosphenol isomer), a compound was obtained which gave a negative ferric chloride test, a weak ultraviolet spectrum, and contained one more oxygen atom. The infrared spectrum had bands at 5.52 and 5.74 μ , characteristic of a cyclic anhydride,¹⁰ and accordingly, the compound, formed in 66% yield, has been assigned structure **7a**. In the nmr spectrum, in addition to the various methyl peaks, a sharp one-proton singlet was present at δ 4.74 which disappeared on the addition of D₂O. This peak has been assigned to the hydrogen atom on the 5-hydroxyl group.

Such an anhydride could be formed from the 6,7-diketone **6** by cleavage to the secodicarboxylic acid and subsequent formation of the anhydride. The seven-membered ring anhydride exhibited unusual stability in that it would not dissolve in sodium bicarbonate or sodium hydroxide solution, and no carbon dioxide was liberated when it was dissolved in aqueous methanol containing sodium bicarbonate. It did dissolve in ammonium hydroxide solution but apparently with decomposition since no discrete compounds could be recovered.

When the anhydride was treated with acetic anhydride and pyridine, one more acetate group was introduced, as shown by microanalysis and the nmr spectrum. Since the one-proton singlet at δ 4.74 had disappeared, the new acetate group was assigned to the 5-hydroxyl group to give **7b**. The hydroxyl absorption was no longer present in the infrared spectrum, but the two anhydride bands were still present.

When the anhydride was treated with methanol containing a small amount of concentrated hydrochloric acid, methanolysis of the tertiary 5-hydroxyl group apparently occurred, and the corresponding 5-methyl ether **7c** was obtained in 25% yield. In the process, the 3-acetate group was also hydrolyzed. The infrared spectrum showed hydroxyl absorption and in the nmr spectrum, the 3 α -hydrogen was shifted upfield to δ 3.63. The methoxyl methyl group appeared at δ 3.42, and the anhydride bands were still present in the infrared spectrum.

Jones oxidation⁹ of the ketotriol **3c** in the cholestane series gave similar results. The anhydride **7d**, obtained in 39% yield, showed the same type of infrared and nmr spectra and the same type of behavior on acetylation (methanolysis was not attempted). In the androstane series, Jones oxidation of the ketotriol **3e** also gave an

anhydride **7f** with similar properties but only stable when the 5-hydroxyl group was acetylated.

In all three series, an isomeric lactone structure can be written instead of the anhydride. The structure, **8**, can be ruled out, however, on the basis of the infrared spectra, since it would contain a free carboxyl group which should show O-H absorption at 3.33–4.00 μ (KBr), and which should liberate carbon dioxide from sodium bicarbonate. It also seems unlikely that it would behave in the observed manner on acetylation (although rearrangement to the hydroxy anhydride is possible) and it would not show infrared absorption in the 5.5–5.7 μ region. Although the structures of the anhydrides have not been unequivocally established by relating them to known compounds they are quite reasonable on the basis of the evidence at hand.

Experimental Section¹¹

Potassium Permanganate-Periodic Acid Oxidation of Pregnenolone Acetate (1a).—A solution of 6.0 g (0.18 mol) of pregnenolone acetate in 400 ml of pyridine, a suspension of 5.60 g (0.035 mol) of potassium permanganate in 80 ml of water, and a solution of 18.0 g (0.079 mol) of periodic acid in 50 ml of water were prepared. The permanganate suspension was added to the pyridine solution and any remaining permanganate was washed in with the periodic acid solution. The reaction mixture was stirred at room temperature for 43 hr and then filtered through an asbestos pad, and the pad was washed thoroughly with hot methanol. The combined filtrate and washings were cooled in an ice bath and acidified with hydrochloric acid. (In a separate experiment the filtrate and washings were treated separately and no significant difference in product ratios in the two fractions was noted.) The acid solution was decolorized with sodium bisulfite and then extracted thoroughly with ether. The extract was washed with water, 5% sodium bicarbonate solution, and water and dried (MgSO₄), and the ether was evaporated to give 4.17 g of solid neutral fraction. The sodium bicarbonate wash was acidified with hydrochloric acid and extracted with ether. The extract was washed with water, dried (MgSO₄), and evaporated to give 0.403 g of a complex mixture of acids which was not investigated further.

The neutral fraction was chromatographed on a column of silica and the various fractions eluted were checked for purity and identity by tlc. The first fraction, eluted with 10:1–9:1 benzene-ether, was a mixture of unreacted pregnenolone acetate and an as yet unidentified compound.

The next fraction, eluted with 9:1–8:1 benzene-ether, was 5 β ,6 β -oxidopregnan-3 β -ol-20-one acetate (**2a**): yield 0.25 g (3.8%) (in other experiments, 3–14%); mp (after recrystallization from aqueous methanol) 136–137°; ir (KBr) 5.80, 5.90, 8.04 μ ; homogeneous to tlc; mp (with an authentic sample,³ mp 136–137.5°), 136–137°.

The next fraction, eluted with 8:1–7:1 benzene-ether, gave 0.984 g (13.4%) (in other experiments, 5–15%) of pregnane-

(11) Melting points were determined with a Hershberg apparatus and Anschutz thermometers and are corrected. Analytical samples were recrystallized to constant melting point and then dried at 100° (0.3 mm) unless stated otherwise. Analyses by Dr. S. M. Nagy and Associates, Micro-Chemical Laboratories, Massachusetts Institute of Technology, Micro-Tech Laboratories Inc., Skokie, Ill., and by the Analytical Research Department, The Wm. S. Merrell Co., Cincinnati, Ohio.

Thin layer chromatography (tlc) was carried out with glass plates coated with silica gel (Brinkman silica gel G) 0.025 mm thick. The plates were eluted with various solvent systems and developed with a spray of 2,4-dinitrophenylhydrazine in phosphoric acid and ethanol, followed by heating at 80–100°.

Column chromatography was done with Baker's analyzed silica, packed in benzene, and the samples were put on the column in benzene. Anhydrous magnesium sulfate was used as a drying agent.

Infrared spectra were determined with a Perkin-Elmer InfraCORD or with a Perkin-Elmer Model 337 spectrophotometer. Ultraviolet spectra were determined with a Bausch and Lomb Spectronic 505. Nmr spectra were obtained with a Varian HA-60A or A-60 spectrometer, using 12–30-mg samples in 0.4 ml of deuteriochloroform with TMS as an internal standard.

The infrared and nmr spectrometers were purchased with funds granted to the chemistry department by the National Science Foundation, and grateful acknowledgment is hereby made.

(9) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 128.

3 β ,5,6,7-tetrol-20-one 3-acetate, which will be described in a subsequent paper.

The last fraction, eluted with 5:1 benzene-ether, gave 0.907 g (12%) (in other experiments 10-24%) of pregnane-3 β ,5,6-triol-7,20-dione 3-acetate (**3a**). The analytical sample was prepared by recrystallization from benzene-petroleum ether, and had mp 189-189.5°: ir (KBr) 2.85, 5.75, 5.82, 5.92, and 7.99 μ ; homogeneous to tlc; nmr δ 0.61 (18-CH₃), 1.27 (19-CH₃), 1.98 (21-CH₃), 2.09 (3-acetate CH₃), 2.17 (s, 1, disappears on addition of D₂O), 2.37 (center of quartet, 17 α -hydrogen), two doublets, which integrate for two protons at 3.80 ($J = 3$ Hz), and 3.89 ($J = 2.5$ Hz) (disappear on addition of D₂O or D₂O-pyridine, or D₂O-sodium methoxide-methanol, and a one-proton singlet appears at 4.09), and 5.05 (m, 1, 3 α -H).

Anal. Calcd for C₂₃H₃₄O₆: C, 67.95; H, 8.43. Found: C, 67.98; H, 8.64.

Pregnane-3 β ,5,6-triol-7,20-dione 3,6-Diacetate (3b).—A solution of 0.406 g (0.974 mmol) of the ketotriol in 8 ml of pyridine and 8 ml of acetic anhydride was heated on a steam bath for 2 hr and then poured onto ice. The white solid was collected and weighed 0.417 g (95%), mp 267-269 dec. The analytical sample was prepared by chromatography on silica, elution with 4:1 benzene-ether and recrystallization from aqueous methanol, and had mp 271-272°: ir (KBr) 2.94, 5.68, 5.77, 5.91, 8.00, and 8.07 μ ; homogeneous to tlc; nmr δ 0.65 (18-CH₃), 1.32 (19-CH₃), 2.02 (21-CH₃), 2.10 (3-acetate CH₃), 2.17 (6-acetate CH₃), 2.37 (center of quartet, 17 α -H), 5.17 (s, 1, 6-H), 5.0-5.8 (m, 3 α -H).

Anal. Calcd for C₂₅H₃₆O₇: C, 66.94; H, 8.09. Found: C, 67.13; H, 8.38.

Potassium Permanganate-Periodic Acid Oxidation of 7-Ketopregnenolone Acetate (4a).—To a solution of 1.00 g (2.68 mmol) of 7-ketopregnenolone acetate in 100 ml of pyridine was added 3.00 g (13.1 mmol) of periodic acid in 15 ml of water and 0.60 g of potassium permanganate in 30 ml of water. The reaction mixture was stirred at room temperature for 48 hr and then worked up as in the previous oxidation to give 0.788 g of solid neutral material and 0.255 g of acidic material, not further investigated.

Tlc of the neutral material showed that it contained four components, with the major one having the same R_f value as the ketotriol. Chromatography on silica and elution with 5:1 benzene-ether gave small amounts of a mixture of two unidentified compounds, and finally elution with 5:1-4:1 benzene-ether gave 0.35 g (32%) of the ketotriol **3a**. Its identity with the ketotriol described above was established by melting point, mixture melting point and comparison of the infrared spectra and tlc R_f values.

Potassium Permanganate-Periodic Acid Oxidation of Pregnenolone Acetate under a Nitrogen Atmosphere.—Purified nitrogen was bubbled through a solution of 3.88 g (10.8 mmol) of pregnenolone acetate in 350 ml of pyridine for 1 hr. A suspension of 2.34 g (1.48 mmol) of potassium permanganate in 75 ml of water was added and any remaining permanganate was rinsed in with a solution of 12.74 g (5.58 mmol) of periodic acid in 50 ml of water. Nitrogen was bubbled through the solution for 30 min, the flask was stoppered, and the solution was stirred for 40.5 hr. The reaction was then worked up as above and a neutral fraction of 2.69 g and an acid fraction of 0.483 g were obtained. Chromatography of the neutral fraction as above gave starting material, 0.093 g of unidentified material, 0.244 g (6.0%) of the 5,6-oxide **2a**, 0.361 g (8.2%) of the tetrol, and 0.805 g (18.5%) of the ketotriol **3a**.

Potassium Permanganate in Pyridine Oxidation of Pregnenolone Acetate.—To a solution of 10 g (27 mmol) of pregnenolone acetate in 600 ml of pyridine was added a suspension of 10 g of potassium permanganate in 150 ml of water, and the mixture was stirred for 47 hr and then worked up as in the previous oxidations. A neutral fraction of 5.7 g and an acid fraction of 1.4 g were obtained. The neutral fraction was chromatographed on 200 g of silica and 100-ml eluates were collected. Nothing was eluted with 700 ml of benzene and 500 ml of 20:1 benzene-ether. The next 500 ml of the latter solvent gave 1.87 g of starting material. The next 200 ml, followed by 400 ml of 10:1 benzene-ether eluted nothing, and then 400 ml gave 49 mg of impure material. The next 2500 ml gave 2.85 g (26%) of the ketotriol **3a**, which had mp 185.5-187° after one recrystallization from benzene-petroleum ether.

Potassium Permanganate in Pyridine Oxidation of 7-Ketopregnenolone Acetate (4a).—To a solution of 1.13 g (3.00 mmol) of 7-ketopregnenolone acetate in 75 ml of pyridine was added a suspension of 0.515 g of potassium permanganate in 15 ml of water

and the mixture was stirred for 52.5 hr and then worked up as above to give 0.61 g of neutral material and 0.11 g of acid material. Chromatography of the neutral material on silica and elution with 8:1 benzene-ether gave 0.13 g of starting material. Elution with 6:1 benzene-ether gave 0.25 g (20%) of the ketotriol **3a**.

Potassium Permanganate-Periodic Acid Oxidation of Cholesteryl Acetate (1b).—To a solution of 7.0 g (16.3 mmol) of cholesteryl acetate in 450 ml of pyridine was added a suspension of 5.6 g of potassium permanganate in 80 ml of water and a solution of 18 g of periodic acid in 40 ml of water. The reaction mixture was stirred for 39.5 hr and then worked up as for the previous oxidations to give 3.23 g of neutral material and 0.44 g of acidic material.

The neutral fraction was chromatographed on silica gel and elution with 10:1 benzene-ether gave 0.46 g of starting material, mp 111-112.5° after two recrystallizations from methanol; ir spectrum identical with that of starting material. Elution with 9:1 benzene-ether gave 0.47 g of a mixture of starting material, an unknown material, and cholestane-3 β ,5,6,7-tetrol 3-acetate, as determined by tlc. Further elution with the same solvent gave 0.34 g of the latter compound. Finally, elution with 8:1-6:1 benzene-ether gave 0.65 g (7.7%) of cholestane-3 β ,6,7-triol-7-one 3-acetate (**3c**), whose physical constants and analysis are given below.

Potassium Permanganate-Periodic Acid Oxidation of 7-Ketocholesteryl Acetate (4b).—To a solution of 6.0 g (14 mmol) of 7-ketocholesteryl acetate in 600 ml of pyridine was added a suspension of 5.6 g of potassium permanganate in 120 ml of water, followed by 18 g of periodic acid in 60 ml of water, and the mixture was stirred for 67 hr and then worked up as above to give 3.98 g of neutral material and 0.49 g of acidic material.

The neutral fraction was chromatographed on silica and elution with 9:1-7:1 benzene-ether gave 2.23 g (36%) of cholestane-3 β ,5,6-triol-7-one 3-acetate (**3c**), mp 181-182° after one recrystallization from methanol. Recrystallization from ether and then methanol gave an analytical sample: mp 180-181°; ir (KBr) 3.11, 3.03, 5.81, 5.83, and 8.04-8.1 μ ; nmr δ 0.64 (18-CH₃), 0.79 (20-CH₃), 0.89 (25-methyls), 1.27 (3-acetate CH₃), 2.23 (s, 1, which disappears on the addition of D₂O), 3.83 (d, $J = 2.4$ Hz), 4.04 (d, $J = 4$ Hz) (the pair of doublets disappeared on the addition of D₂O and a one-proton singlet appeared at 4.08), and 5.00 (m, 3 α -H).

Anal. Calcd for C₂₉H₄₈O₆: C, 73.06; H, 10.10. Found: C, 72.40; H, 10.33.

Cholestane-3 β ,5,6-triol-7-one 3,6-Diacetate (3d).—A solution of 0.21 g (0.44 mmol) of the ketotriol **3c** in 4 ml of anhydrous pyridine and 4 ml of acetic anhydride was heated on a steam bath for 2 hr and then poured on ice. The precipitate was collected to give 0.22 g (95%) of the diacetate. A sample was recrystallized from methanol for analysis to mp 221-222°: ir (KBr) 2.88, 5.78, 5.80, and 7.98 μ ; homogeneous to tlc; nmr δ 0.67 (18-CH₃), 0.82 (20-CH₃), 0.92 (25-methyls), 1.32 (19-CH₃), 2.04, 2.18 (3- and 6-OCOCH₃), 2.35 (s, 1), 5.15 (s, 1, 6-H, and a broad multiplet, 3 α -H).

Anal. Calcd for C₃₁H₅₀O₆: C, 71.78; H, 9.74. Found: 72.14; H, 9.77.

Potassium Permanganate in Pyridine Oxidation of Cholesteryl Acetate.—To a solution of 6.0 g (14 mmol) of cholesteryl acetate **1b** in 350 ml of pyridine was added 6.0 g of potassium permanganate in 40 ml of water, and the resulting mixture was stirred for 65.5 hr. After the usual work-up, 4.32 g of neutral material and 0.65 g of acidic material were obtained.

The neutral fraction was chromatographed on 200 g of silica and 100-ml eluates were collected. Elution with 1000 ml of benzene gave 1.04 g of starting material, mp 114-115° after recrystallization from benzene. Nothing was eluted with 700 ml of 20:1 benzene-ether. Elution with 900 ml of 15:1 benzene-ether gave 0.19 g of impure material. Elution with 700 ml of 8:1 benzene-ether gave 1.37 g (21%) of ketotriol **3c**, mp 181-182° after one recrystallization from methanol.

Potassium Permanganate in Pyridine Oxidation of 7-Ketocholesteryl Acetate.—To a solution of 6.0 g (13.6 mmol) of 7-ketocholesteryl acetate **4b** in 250 ml of pyridine was added 5.60 g of potassium permanganate in 100 ml of water and the resulting mixture was stirred for 88 hr. After the usual work-up, 2.47 g of neutral material and 0.92 g of acidic material were obtained.

The neutral material was chromatographed on silica, and elution with 9:1 benzene-ether gave small amounts of impure fractions and, finally, 1.50 g (23%) of the ketotriol **3c**, mp 180-181°.

Potassium Permanganate in Pyridine Oxidation of Androst-5-ene-3 β ,17 β -diol 3 β ,17-Diacetate (1c).—To a solution of 4.10 g (10.9 mmol) of the androstene 1c in 400 ml of pyridine was added 4.6 g of potassium permanganate in 65 ml of water and the resulting mixture was stirred for 19 hr. Work-up in the usual manner gave 2.84 g of neutral material and 0.62 g of acidic material.

The neutral fraction was chromatographed on silica and elution with 10:1 benzene-ether gave 1.25 g of starting material. As the proportion of ether was gradually increased a number of impure fractions were collected, and finally 5:1 benzene-ether gave 1.04 g (23%) of androstane-3 β ,5,6,17 β -tetrol-7-one 3,17-diacetate (3e). Two recrystallizations from benzene-petroleum ether gave an analytical sample: mp 158.5–159°; ir (KBr) 2.82, 2.92, 5.73, 5.75, 5.81, 7.96, and 8.06 μ ; nmr δ 0.78 (18-CH₃), 1.27 (19-CH₃), 1.98 and 1.99 (3- and 17-OCOCH₃), 2.35 (s, 1 disappears on the addition of D₂O), 3.78 (d, J = 3 Hz), and 4.03 (d, J = 3 Hz) (the two doublets disappear on the addition of D₂O, and a sharp s, 1, appears at 4.01, 6-H), and 4.83 (m, 3 α - and 17 α -H's).

Anal. Calcd for C₂₈H₄₀O₄: C, 65.38; H, 8.11. Found: C, 65.40; H, 8.11.

Androstane-3 β ,5,6,17 β -tetrol-7-one 3,6,17-Triacetate (3f).—A solution of 114 mg (0.27 mmol) of the above compound 3e in 3 ml of pyridine and 3 ml of acetate anhydride was heated on a steam bath for 4 hr and then poured over ice. The precipitate was recrystallized from methylene chloride-petroleum ether to give an analytical sample: mp 127–128.5°; ir (KBr) 2.90, 5.73, 5.75, 7.93, and 8.12 μ .

Anal. Calcd for C₂₈H₃₆O₆: C, 64.87; H, 7.81. Found: C, 64.46; H, 7.85.

Pregn-5-ene-3,6-diol-7,20-dione (5a).—To a solution of 0.704 g (1.73 mmol) of the ketotriol 3a in 55 ml of methanol was added a solution of 0.85 g of potassium hydroxide in 20 ml of water and 25 ml of methanol, and the resulting solution was allowed to stand for 18 hr. It was then poured into ice water, the resulting mixture was acidified with hydrochloric acid, sodium chloride was added, and the mixture was refrigerated for 12 hr. The resulting white solid, 0.338 g (64%) was recrystallized from methanol to give an analytical sample of the diosphenol 5a: mp 252–255°; ir (KBr) 2.90 (broad), 5.89, 5.98, and 6.11 μ ; uv max (CH₃OH) 209 m μ (ϵ 15,400), 224 (10,900), and 274.2 (16,700); homogeneous to tlc, strong positive ferric chloride test; nmr δ 0.65 (18-CH₃), 1.12 (19-CH₃), 2.12 (21-CH₃), 2.34–2.50 (q, 17 α -H), 3.00–3.42 (m, 3 α - and 4-H's), and 6.13 (s, 1, 6-OH).

Anal. Calcd for C₂₁H₃₀O₄: C, 72.79; H, 8.73. Found: C, 72.89; H, 8.75.

Pregn-5-ene-3 β ,6-diol-7,20-dione 3-acetate (5b).—A solution of 0.405 g (1.00 mmol) of the ketotriol in 4 ml of anhydrous pyridine was cooled to 0° and 4 ml of thionyl chloride was added dropwise with swirling. The reaction mixture was kept in an ice bath for 15 min and then added slowly to an ice and water mixture. The resulting tan solid was chromatographed on a column of silica, and elution with 10:1 benzene-ether gave 0.062 g (16%) of diosphenol 5b, which had mp 184–185.5° after recrystallization from methanol, was homogeneous to tlc, and gave a positive ferric chloride test.

An analytical sample was obtained by recrystallization from methanol: mp 193–193.5°; ir (KBr) 2.89, 5.74, 5.90, 5.95, 6.07, and 7.98 μ ; uv max (CH₃OH) 206.8 m μ (ϵ 1350) and 274.7 (9920); nmr δ 0.67 (18-CH₃), 1.17 (19-CH₃), 2.03 and 2.11 (3-OCOCH₃ and 21-CH₃), 2.89–3.49 (eight peaks, 4-H's), 5.33 (m, 3 α -H), and 5.33 (6-OH).

Anal. Calcd for C₂₃H₃₂O₅: C, 71.10; H, 8.30. Found: C, 70.92; H, 8.92.

A solution of 20 mg of the diosphenol 5b and 31 mg of potassium carbonate in 5 ml of 95% ethanol and 1 ml of water was allowed to stand for 16 hr and then was acidified with concentrated hydrochloric acid. The white solid was collected and had mp 232–235°. Tlc gave the same R_f value as the diosphenol 5a. One recrystallization from methanol gave mp 245–247°, mmp (with diosphenol 5a) 253–254°, ir spectra superimposable.

Cholest-5-ene-3 β ,6-diol-7-one (5c).—To a solution of 0.480 g (1.0 mmol) of the ketotriol 3c in 90 ml of methanol was added a solution of 0.511 g of potassium hydroxide in 10 ml of methanol and 10 ml of water and the resulting solution was allowed to stand for 14 hr and then poured into 100 ml of water. The mixture was acidified with hydrochloric acid and extracted with ether, and the ether extract was washed with water, dried (MgSO₄), and evaporated. The residue, 0.343 g, was chromatographed on silica, and elution with 9:1 benzene-ether gave 0.142

g (32%) of the diosphenol 5c. Recrystallization from methanol gave an analytical sample: mp 155–156°; homogeneous to tlc; ir (KBr) 2.94, 5.97, and 6.07 μ ; uv max (MeOH) 213.2 m μ (ϵ 5920) and 273.5 (15,600) [lit.⁸ mp 156–157°; uv max 274.5 m μ (ϵ 19,956)]; nmr δ 0.69 (18-CH₃), 0.81 (20-CH₃), 0.91 (25-CH₃'s), 1.17 (19-CH₃), four d at 3.10 (J = 9.6 Hz), 3.27 (J = 2 Hz), 3.42 (J = 2 Hz), 3.50 (J = 2.5 Hz) (C-4 H's coupled to the 3 α -H). Spin decoupling experiments with irradiation at 4.78 caused marked changes in the appearance of the doublets, with some coalescing to singlets: 4.78 (m, 3 α -hydrogen) and 6.3 (s, 1, 6-OH, disappears on the addition of D₂O).

Androst-5-ene-3 β ,6,17 β -triol-7-one 3,17-Diacetate (5e).—A solution of 0.153 g (0.36 mmol) of the ketotriol 3e in 2 ml of anhydrous pyridine was cooled in an ice bath and 2 ml of thionyl chloride was added dropwise over a period of 5 min. The solution was allowed to warm to room temperature and poured onto crushed ice and the precipitate collected to give 0.128 g which was chromatographed on silica. Elution with 20:1 benzene-ether gave 93 mg (64%) of the diosphenol 5e. An analytical sample was obtained by recrystallization from benzene-petroleum ether, and had mp 216.5–217°: uv max (MeOH) 274.5 m μ (ϵ 16,900); positive ferric chloride test; nmr δ 0.85 (18-CH₃), 1.22 (19-CH₃), 2.05 (six protons, 3- and 17-OCOCH₃), four doublets at 3.14 (J = 2 Hz), 3.22 (J = 2 Hz), 3.37 (J = 2 Hz), 3.45 (J = 2.5 Hz) (1.8 protons, 4-H's), 4.45 (m, 2, 3 α - and 17 α -H), and 6.18 (s, 1, disappears when D₂O is added, 6-OH).

Anal. Calcd for C₂₃H₃₂O₆: C, 68.29; H, 7.98. Found: C, 68.56; H, 7.98.

Androst-5-ene-3 β ,6,17 β -triol-7-one (5f).—To a solution of 177 mg (0.419 mmol) of androstane-3 β ,5,6,17 β -tetrol-7-one 3,17-diacetate (3e) in 35 ml of methanol was added a solution of 758 mg of potassium hydroxide in 2 ml of water. The resulting solution was heated on a steam bath for 2 hr and then allowed to stand at room temperature for 12 hr. After acidification with concentrated hydrochloric acid the solution was extracted with ether, the extract was dried (MgSO₄), and the solvent was evaporated to give 92 mg of solid which gave a positive ferric chloride test. The solid was taken up in benzene and chromatographed on 20 g of silica. Nothing was eluted with eleven 50-ml fractions of benzene, six 50-ml fractions of 10:1 benzene-ether, and three 50-ml fractions of 5:1 benzene-ether. One more 50-ml fraction of the latter gave 8 mg of impure material and the next five fractions gave 88 mg (69%) of homogeneous (tlc) diosphenol 5f (positive ferric chloride test). Recrystallization from benzene-petroleum ether gave mp 220–232°: ir (KBr) 2.91, 5.97 (sh), 6.05 (sh), and 6.06 μ ; uv max (MeOH) 215 m μ (ϵ 7000) and 269.5 (21,600).

Anal. Calcd for C₁₉H₂₈O₄: C, 71.21; H, 8.81. Found: C, 71.39; H, 9.44.

Jones' Oxidation of the Ketotriol 3a in the Pregnane Series.—To a solution of 302 mg (0.742 mmol) of the ketotriol in 20 ml of dry acetone was added 1.2 ml of Jones' reagent over a period of 2.5 min. The solution was stirred for 20 min, 10 ml of methanol was added, stirring was continued for 20 min, and then the solution was diluted with water and extracted thoroughly with chloroform. The extract was washed with water, dried (MgSO₄), and the solvent was evaporated under reduced pressure to give 207 mg (66%) of the anhydride 7a. The analytical sample, prepared by chromatography on silica, elution with 4:1–2:1 benzene-ether, and two recrystallizations from benzene-petroleum ether, had mp 199–200°: ir (KBr) 2.90–3.05, 5.52, 5.74, 5.84 (sh), 5.94 and 8.03 μ ; a complex but weak uv spectrum; a negative ferric chloride test; nmr δ 0.69 (18-CH₃), 1.13 (19-CH₃), 2.04 (21-CH₃), 2.10 (3-OCOCH₃), and 4.74 (s, 1, lost on addition of D₂O, 5-OH, and a broad multiplet, 3 α -H).

Anal. Calcd for C₂₃H₃₂O₇: C, 65.69; H, 7.67. Found: 65.22; H, 7.68.

Acetylation of the Anhydride 7a in the Pregnane Series.—A solution of 66 mg (0.15 mmol) of the anhydride in 2 ml of dry pyridine and 2 ml of acetic anhydride was heated on a steam bath for 1.75 hr and then poured onto cracked ice. The resulting solid, 52 mg, was collected and chromatographed on 8 g of silica. Elution with 8:1 benzene-ether gave 59 mg (67%) of the acetylated anhydride 7b. The analytical sample was obtained by recrystallization from acetone-water containing 1 drop of concentrated hydrochloric acid, or from methanol, and had mp 191–192°: ir (KBr) 5.52, 5.62, 5.75, 5.87, and 7.89–7.99 μ ; nmr δ 0.72 (18-CH₃), 1.12 (19-CH₃), 2.03 (21-CH₃), 2.14 (six protons, 3- and 5-OCOCH₃), 5.16 (m, 1, 3 α -H).

Anal. Calcd for $C_{25}H_{34}O_8$: C, 64.95; H, 7.41. Found: 65.51; H, 7.50.

Acid Hydrolysis of the Anhydride 7a in the Pregnane Series.—A solution of 190 mg (0.45 mmol) of the anhydride 7a in 40 ml of methanol containing 25 drops of concentrated hydrochloric acid was boiled under reflux for 1 hr, allowed to cool, and poured into 200 ml of water. The resulting solution was saturated with salt, and the white precipitate which formed was collected and recrystallized from methanol to give 42 mg, (25%) of 7c: mp 180–182°; ir (KBr) 2.80, 2.90, 5.54, 5.84, and 5.90 μ ; nmr δ 0.69 (18-CH₃), 1.12 (19-CH₃), 2.12 (21-CH₃), 3.42 (s, 3, 5-OCH₃), and 3.63 (m, 3 α -H).

Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.54; H, 8.31.

Jones Oxidation of the Ketotriol 3c in the Cholestane Series.—To a solution of 408 mg (0.855 mmol) of the ketotriol in 35 ml of dry acetone was added dropwise with stirring 1.2 ml of Jones' reagent. The reaction mixture was stirred for 8 min and then 50 ml of methanol was added and the reaction mixture was worked up as above to give 315 mg of an oily solid. The solid was chromatographed on 30 g of silica and elution with 10:1 benzene-ether gave 160 mg (39%) of anhydride 7d: mp (after recrystallization from benzene-petroleum ether) 185.5–187°; ir (KBr) 3.01–3.03, 5.54, 5.62, 5.73, 5.87, and 8.11–8.18 μ ; nmr δ 0.73 (18-CH₃), 1.12 (19-CH₃), 2.04 (3 β -OCOCH₃), and 3.89 (5-OH, disappears on the addition of D₂O).

Anal. Calcd for $C_{25}H_{40}O_6$: C, 70.82; H, 9.45. Found: C, 70.58; H, 9.23.

Acetylation of the Anhydride 7d in the Cholestane Series.—A solution of 58 mg (0.012 mmol) of 7d in 2 ml of acetic anhydride and 2 ml of pyridine was heated on a steam bath for 3.5 hr and poured onto ice. The resulting precipitate was collected and chromatographed on silica. Elution with benzene gave 41 mg of 7e which was recrystallized from aqueous methanol and then had mp 147–148°; ir (KBr) 5.52, 5.63, 5.71, 8.04, and 8.07 μ ; nmr

δ 0.74 (18-CH₃), 1.12 (19-CH₃), 2.05 and 2.12 (3- and 5-OCOCH₃'s), and 5.00 (m, 1, 3 α -H).

Anal. Calcd for $C_{31}H_{48}O_7$: C, 69.90; H, 9.08. Found: C, 70.26; H, 9.14.

Jones Oxidation of the Ketotriol 3e in the Androstane Series.—To a solution of 243 mg (0.575 mmol) of the ketotriol in 25 ml of dry acetone was added dropwise with stirring over a period of 5 min 1 ml of Jones reagent. After an additional 15 min of stirring 10 ml of methanol was added and the solution was allowed to stand for 2 hr more and worked up as above to give 232 mg of oily solid. Earlier experiments indicated that partial deacetylation had occurred, so the material was dissolved in 5 ml of pyridine and 5 ml of acetic anhydride and heated on a steam bath for 14.5 hr. The solution was then poured into water and the resulting solid was collected to give 144 mg, mp 209–210.5°, homogeneous to tlc. The solid was chromatographed on 20 g of silica. Nothing was eluted with twelve 50-ml fractions of benzene and two 50-ml fractions of 20:1 benzene-ether. Elution with four more fractions of the latter solvent gave 107 mg which was recrystallized from methanol to give 61 mg (22%) of 7f: mp 215–215.5°; ir (KBr) 5.53, 5.62, 5.75, 7.95, and 8.03 μ ; nmr δ 0.85 (18-CH₃), 1.13 (19-CH₃), 2.03 (nine protons, 3-, 5-, and 17-OCOCH₃'s), 4.48 (t, 1 17 α -H), and 5.08 (m, 3 α -H).

Anal. Calcd for $C_{25}H_{34}O_9$: C, 62.77; H, 7.18. Found: C, 63.22; H, 7.18.

Registry No.—Potassium permanganate, 7722-64-7; 3a, 26145-85-7; 3b, 26145-86-8; 3c, 26145-87-9; 3d, 26145-88-0; 3e, 26145-89-1; 3f, 26145-90-4; 5a, 26145-91-5; 5b, 26210-96-8; 5c, 26145-92-6; 5e, 26145-93-7; 5f, 26210-97-9; 7a, 26145-94-8; 7b, 26145-95-9; 7c, 26145-96-0; 7d, 26145-97-1; 7e, 26145-98-2; 7f, 26145-99-3.

Synthesis and Photocycloadditions of Compounds Related to 3-Carboxycyclohexenone¹

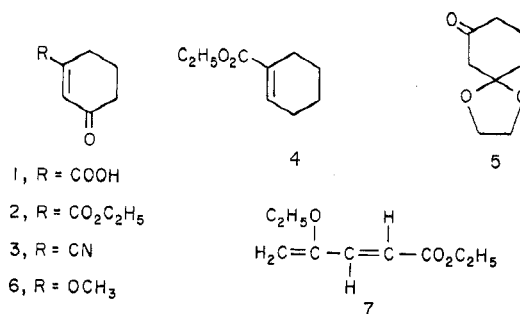
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Irradiation of 1, 2, and 3 in the presence of ethylene, acetylene, and 2-butyne leads to formation of cycloaddition products 22–26. Bromination-dehydrobromination of 23 yields the cyclooctadienone 27. The 3-carboxycyclohexenones 16 and 17 are prepared from the Diels-Alder adduct 13 of maleic anhydride with the new diene 7. Reaction of 3-methoxycyclohexenone (6) with diethylaluminum cyanide gives the corresponding nitrile 3 in a single step.

We have explored the chemistry of derivatives of 3-carboxycyclohex-2-enone (1) as synthetic intermediates and as models for more highly substituted compounds. Some of our observations appear to be of general interest, and we record these below. They include the smooth photochemical cycloaddition of ethylene, acetylene, and 2-butyne to three of the simplest examples of this system, 1, 2, and 3; a one-step preparation of nitrile 3 which may be broadly applicable; and a new route to ring-substituted derivatives of 1 employing the Diels-Alder reaction. Previous preparations of simple derivatives of 1 have involved either chromic acid oxidation of the unsaturated ester 4 to give 2,³ or addition of hydrogen cyanide to the ketal (5) of dihydroresorcinol, followed by hydrolysis and dehydration to 3.⁴ The exact conditions in the former reaction are critical and the



method is inherently limited in applicability. The cyanide addition gives only moderate overall yields but presumably could be applied to substituted cyclohexane-1,3-diones. In our hands the published procedures for both these reactions were not wholly satisfactory, and in the Experimental Section we report details of improved conditions.

(1) A portion of this work has been published in preliminary form: W. C. Agosta and W. W. Lowrance, Jr., *Tetrahedron Lett.*, 3053 (1969).

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