Tetrahedron 1963, Vol. 19, pp. 1959 to 1953. Pergamon Press Ltd. Printed in Northern Ireland

OXIDATION REACTION OF STEROID ALCOHOLS BY RUTHENIUM TETROXIDE

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(*Received* 18 *June; in revised form* 19 *July* 1963)

Abstract—Oxidation of steroid alcohols by ruthenium tetroxide gives corresponding ketones in almost quantitative yields. The reaction provides a simple and convenient procedure for converting secondary alcohols to ketones in neutral media. The reconversion of ruthenium dioxide, produced during the oxidation, into the tetroxide with an appropriate oxygen donor such as sodium metaperiodate makes possible the oxidation of a given steroid alcohol to a ketone in the presence of a catalytic amount of ruthenium tetroxide.

As reported by Berkowitz and Rylander,[1] ruthenium tetroxide is a very powerful oxidizing agent and readily attacks a variety of functional groups. In connection with other steroid studies we had a chance to examine this oxidation reaction. Although the reagent has been known as a good oxidizing agent of ethers to esters,[1,2] and of sulfides to sulfoxides,[3] the reaction has received relatively little attention in the steroid field. We have now found that steroidal secondary alcohols are readily oxidized to ketones in excellent yields and that the reversible interconversion between ruthenium dioxide and ruthenium tetroxide makes it possible to oxidize simple steroid alcohols to ketones with sodium metaperiodate using a catalytic amount of the oxide.

The reagent, ruthenium tetroxide, was easily prepared from ruthenium dioxide and sodium metaperiodate.[4,5] As a carbon tetrachloride solution it was convenient and safe to handle for most purposes.

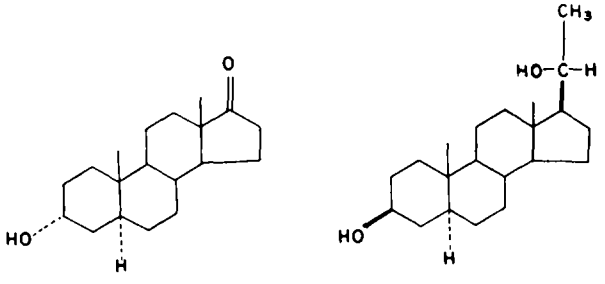
The procedure of the oxidation reaction is essentially the same as that of the previous workers.[1] When a carbon tetrachloride solution of a steroid alcohol is treated with a slight excess of the reagent solution, the oxidation reaction takes place immediately as seen by the precipitation of black ruthenium dioxide. In most cases the reaction is complete within a few minutes at room temperature. After removing the precipitated ruthenium dioxide, evaporation of the solvent gives the corresponding ketone in an excellent yield.

Thus, 5α-androstane-3α-ol-17-one (I) was oxidized to 5α-androstane-3,17-dione in 93% yield, and 5α-pregnane-3β,20β-diol (II) was oxidized to 5α-pregnane-3,20-dione in 91% yield. In a similar manner cholestane-3β,6β-diol 3-acetate (III) gave cholestane-3β-ol-6-one 3-acetate in 92% yield. The only by-product of the reaction is the unreactive, insoluble ruthenium dioxide, which is readily separable from the reaction mixture by filtration. This oxidation reaction, therefore, provides a simple and convenient procedure for converting steroid alcohols to ketones in neutral media, and

[1] L. M. Berkowitz and P. N. Rylander, *J. Amer. Chem. Soc.* **80**, 6682 (1958).
[2] J. Weinstock and M. E. Wolff, U.S. Patent 2,960,503, November 15, 1960.
[3] C. Djerassi and R. R. Engle, *J. Amer. Chem. Soc.* **75**, 3838 (1953).
[4] F. S. Martin, *J. Chem. Soc.* 2682, 3055 (1952).
[5] F. G. Oberender and J. A. Dixon, *J. Org. Chem.* **24**, 1226 (1959).

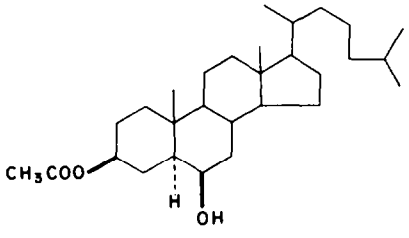
would be applicable to terpenoid alcohols as well. Other functional groups such as ketones and esters are not oxidized but unsaturated double bonds are attacked by the reagent. This might be a limitation of the reaction.

The ruthenium dioxide, produced during the oxidation reaction, can be reconverted into the tetroxide when an appropriate oxygen donor such as sodium metaperiodate is present in the reaction mixture. Therefore, steroid alcohols can be catalytically oxidized by sodium metaperiodate, which by itself does not attack isolated hydroxyl functions. For instance, 5α-androstane-3β-ol-17-one (IV) was oxidized to the corresponding 3,17-dione by a slight excess of sodium metaperiodate in the presence of a catalytic amount of ruthenium tetroxide (10 mole %). The yield was 82%. Essentially the same result was obtained when a large excess of sodium metaperiodate and a very small amount of ruthenium tetroxide (1 mole %) were employed (yield 84%). Further application of this catalytic oxidation is shown by the conversion of cholestane-3β,5α,6β-triol 3-acetate (V) to cholestane-3β,5α-diol-6-one 3-acetate in the yield of 76%.

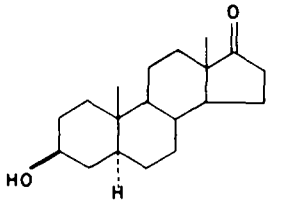


I

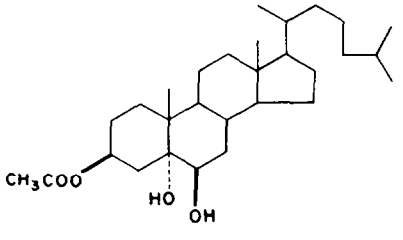
II



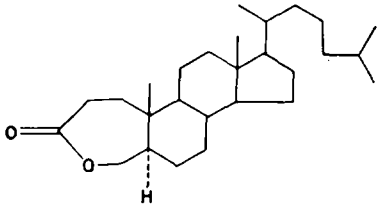
III



IV



V



VI

One of the disadvantages of this catalytic oxidation is that the reaction must be carried out under heterogeneous conditions because of the very low solubility of sodium metaperiodate in non-polar organic solvents. It was found that the sodium metaperiodate was replaceable by lead tetraacetate, and thus the reaction could be carried out in glacial acetic acid under homogeneous conditions.

In this case, however, the oxidation reaction was rather slow. For example, oxidation of cholestanol gave 30% of cholestanone with 31% recovery of the starting material. When more vigorous conditions were employed, the major product was a compound, m.p. 188–189°, which was neither cholestanone nor cholestanol acetate. The compound has a strong ester carbonyl absorption at 1724 cm^{-1} (in methylene chloride solution) and is most likely formulated either as 4-oxa-A-homo-5α-cholestane-3-one (VI) or as isomeric 3-oxa-A-homo-5α-cholestane-4-one. The production of these lactones from cholestanone by peracids has been reported[6–8] and the melting point of VI agrees well with that of the oxidation product mentioned above. It is not unlikely that the reaction of ruthenium tetroxide and acetic acid gives rise to peracetic acid which oxidizes the cholestanone, the primary oxidation product, to afford the lactone.

It has been shown[1] that when the reaction product is an aldehyde or an acid, the yield becomes very low since these products are strongly absorbed on the precipitated ruthenium dioxide. Further studies are in progress in order to see whether the above catalytic method would give any improvement on this point, and the result will be reported elsewhere.

EXPERIMENTAL

Preparation of ruthenium tetroxide solution

Ruthenium dioxide (0·4 g, Engelhard Industries, N.J., U.S.A.) was suspended in 50 ml CCl_4. A solution of 3·2 g sodium metaperiodate in 50 ml water was added and the mixture stirred 1 hr at 0°. The black ruthenium dioxide gradually dissolved.

The clear yellow CCl_4 layer was separated and filtered through glass wool to remove insoluble materials. To the solution in a separatory funnel, fresh sodium metaperiodate solution (1·0 g/50 ml) was added. The mixture was shaken until the yellow color of the CCl_4 phase persisted and then it was kept in a cold place.

Determination of ruthenium tetroxide in carbon tetrachloride solution

An aliquot (2·0 ml) of the ruthenium tetroxide solution was added to a mixture of 0·5 ml 2-propanol and 5 ml CCl_4. The black ruthenium dioxide was collected, washed with CCl_4 and with water, and dried in a vacuum desiccator.

The following data, obtained from a duplicate run, are representative, 1 mmole ruthenium dioxide corresponding to 0·1331 g.

No. 1 RuO_2: 0·009711 g (0·07296 mmole/2 ml)
Conc: 0·0365 M.

No. 2 RuO_2: 0·009877 g (0·07421 mmole/2 ml)
Conc: 0·0371 M.

Oxidation of 5α-androstane-3α-ol-17-one (I)

A solution of 0·295 g (1·02 mmoles) 5α-androstane-3α-ol-17-one (I) (m.p. 185—186°) in 30 ml CCl_4 was covered with 2 ml water and stirred. The solution of ruthenium tetroxide was added

[6] V. Burckhardt and T. Reichstein, *Helv. Chim. Acta* **25**, 1434 (1942).
[7] G. R. Pettit, B. Green, T. R. Kasturi and U. R. Ghatak, *Tetrahedron* **18**, 953 (1962).
[8] S. Hara, N. Matsumoto and M. Takeuchi, *Chem. & Ind.* 2086 (1962).

dropwise until a slight yellow color persisted in the CCl_4 layer. Most of the black ruthenium dioxide produced during the oxidation was found in the water phase. The excess ruthenium tetroxide was destroyed by addition of 1 ml 2-propanol. The mixture was then filtered and the CCl_4 layer separated, washed with water and dried (Na_2SO_4). Removal of the solvent yielded 0·285 g which recrystallized from *n*-hexane in colorless leaflets, 0·235 g, m.p. 132–134° (first crop), and 0·037 g, m.p. 132–133° (second crop), total yield 0·272 g, 93% (Found: C, 79·01; H, 9·70. Calcd. for $C_{19}H_{28}O_2$: C, 79·12; H, 9·79%). $\nu_{max}^{CH_2Cl_2}$ 1730, 1704 cm^{-1}. The reported m.p. of 5α-androstane-3,17-dione is 132–134° [9,10].

Oxidation of 5α-pregnane-3β,20β-diol (II)

A CCl_4 solution of 0·283 g (0·88 mmole) 5α-pregnane-3β,20β-diol (II) (m.p. 194–195°) was treated with slight excess ruthenium tetroxide solution and the reaction mixture worked up as in the preceding experiment. The product was recrystallized from acetone–*n*-hexane in colorless plates, 0·199 g, m.p. 200–201° (first crop), and 0·054 g, m.p. 199–200° (second crop), total yield 0·253 g, 91% (Found: C, 79·62; H, 10·11. Calcd. for $C_{21}H_{32}O_2$; C, 79·70; H, 10·19%). $\nu_{max}^{CH_2Cl_2}$ 1701 cm^{-1}. The reported m.p. of 5α-pregnane-3,20-dione is 200–201° [11].

Oxidation of cholestane-3β,6β-diol 3-acetate (III)

The ruthenium tetroxide solution was added to a stirred solution of 0·520 g (1·17 mmoles) cholestane-3β,6β-diol 3-acetate[12] (III) (m.p. 156–157°) in 30 ml CCl_4 covered with 30 ml water. The addition was stopped when the slight yellow color persisted in the CCl_4 phase. The excess ruthenium tetroxide was destroyed by addition of 2-propanol (2 ml). The black ruthenium dioxide was filtered and the aqueous phase extracted once with fresh CCl_4. The combined CCl_4 solution was evaporated under red. press. to give a white solid which recrystallized from aqueous methanol in colorless needles, 0·402 g, m.p. 130–131° (first crop), and 0·082 g, m.p. 129–130° (second crop), total yield 0·484 g, 92%. No m.p. depression was observed on admixture with authentic cholestane-3β-ol-6-one 3-acetate, m.p. 130–131°.[13] The IR spectrum of the product was superimposable on that of the authentic sample.

Catalytic oxidation of 5α-androstane-3β-ol-17-one (IV)

(a) A solution of 0·292 g (1·01 mmoles) 5α-androstane-3β-ol-17-one (IV) (m.p. 174–176°) in 50 ml CCl_4 was mixed with 15 ml (1·5 mmoles) of sodium metaperiodate aq (2·14 g/100 ml). To this mixture was added 2·70 ml of 0·037 M ruthenium tetroxide solution (0·1 mmole, 10 mole %) and the mixture shaken vigorously (3 hr at room temp). The CCl_4 layer was separated and a small amount of 2-propanol added to destroy the excess reagent. The ruthenium dioxide was removed by filtration and the solvent evaporated (red. press.). The residue was recrystallized from *n*-hexane in colorless leaflets, 0·202 g, m.p. 133–134° (first crop), and 0·036 g, m.p. 133–134° (second crop), total yield 0·238 g, 82%. No m.p. depression was observed on admixture with 5α-androstane-3,17-dione obtained from the non-catalytic oxidation of 5α-androstane-3α-ol-17-one (I) described above.

(b) In the similar manner, 0·293 g (1·01 mmoles) was oxidized with 90 ml (9·0 mmoles) sodium metaperiodate solution in the presence of 0·27 ml (0·01 mmole, 1 mole %) ruthenium tetroxide solution. The oxidation was complete after shaking for 7 hr and 0·210 g, m.p. 133–134° (first crop), and 0·035 g, m.p. 133–134° (second crop) of 5α-androstane-3,17-dione was obtained, total yield 0·245 g, 84%.

Catalytic oxidation of cholestane-3β,5α,6β-triol 3-acetate (V)

In a 200-ml separatory funnel, 60 ml of a saturated solution of sodium metaperiodate and 40 ml CCl_4 containing 3·0 ml of 0·021 M ruthenium tetroxide solution (0·036 mmole, 3·60 mole %) were added. Cholestane-3β,5α,6β-triol 3-acetate (V) (m.p. 205–206°; 0·422 g, 0·913 mmole) was dissolved in 40 ml CCl_4. A few drops of this solution was added to the separatory funnel and the mixture was

[9] C. W. Shoppee, *Helv. Chim. Acta* **23**, 740 (1940).
[10] C. Djerassi, *J. Org. Chem* **12**, 823 (1947).
[11] M. Steiger and T. Reichstein, *Helv. Chim. Acta* **21**, 161 (1938).
[12] D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.* 2459 (1949).
[13] R. M. Dodson and B. Riegel, *J. Org. Chem.* **13**, 424 (1948).

shaken vigorously until the black color of ruthenium dioxide had disappeared. This procedure was repeated many times until the whole solution of the steroid was consumed. To make the oxidation more effective, the sodium metaperiodate solution may be replaced by a fresh solution during the reaction. When the oxidation reaction was complete, the CCl_4 layer was separated and the remaining ruthenium tetroxide destroyed by addition of 2-propanol (2 ml). Precipitated ruthenium dioxide was filtered off and the slightly colored solution evaporated (red. press.). The residue was dissolved in 50 ml hot methanol and the solution treated with Norit A to remove colloidal ruthenium dioxide. Removal of the solvent and recrystallization of the product from aq methanol gave colorless plates, 0·276 g, m.p. 238–239° (first crop), and 0·044 g, m.p. 235–236° (second crop), total yield 0·320 g, 76%. No m.p. depression was observed on admixture with chloestane-3β,5α-diol-6-one 3-acetate[14]; the IR spectrum was superimposable on that of the authentic sample.

Catalytic oxidation of β-cholestanol with lead tetraacetate

(a) A solution of 1·044 g (2·686 mmoles) β-cholestanol (m.p. 137–138°) in 100 ml acetic acid was added dropwise to a stirred solution of 4·0 g lead tetraacetate in 100 ml acetic acid containing 1·0 ml of 0·042 M ruthenium tetroxide solution (0·042 mmole, 1·56 mole %). After the addition was complete the mixture was stirred for 1 hr at room temp and then diluted with 200 ml water. The solution was extracted with four 100-ml portions methylene chloride. The extracts were washed with dil. NaOH aq to remove acetic acid and the solvent evaporated (red. press.). The residue recrystallized from pet. ether in colorless prisms, m.p. 126–127°, yield 0·314 g, 30%. $\nu_{max}^{CH_2Cl_2}$ 1704 cm^{-1}. The product was identified as cholestanone by mixed m.p. and by the comparison of the IR spectrum with an authentic sample. From the mother liquor, 0·328 g starting material was obtained, recovery 31%.

(b) In the similar manner, 0·981 g (2·520 mmoles) β-cholestanol was oxidized at 40° with 10 g lead tetraacetate and 5·0 ml of 0·042 M ruthenium tetroxide solution (0·210 mmole, 8·34 mole %) in 100 ml acetic acid. After the reaction the excess lead tetraacetate was destroyed by adding 10 ml ethylene glycol. The acetic acid was removed by repeated azeotropic evaporation with CCl_4. Finally the residue was dissolved in methylene chloride and the solution washed with water to remove inorganic materials. Evaporation of the solvent gave 0·390 g of an oily residue which was chromatographed on 30 g Florisil (25 × 250-mm column) using benzene-acetone as an elution solvent. The first fraction, 0·183 g, was identified as cholestanone. The major product, which was eluted later, was colorless plates, m.p. 188–189°, 0·410 g. $\nu_{max}^{CH_2Cl_2}$ 1724 cm^{-1}. The reported m.p. of 4-oxa-A-homo-5α-cholestane-3-one (VI) is 186–187°[6] and 188–189°[7].

Acknowledgements—The author is indebted to Professor Yoshimasa Hirata of Nagoya University for his encouragement during this work. The author is also grateful for a grant from the Ministry of Education.

[14] L. F. Fieser and S. Rajagopalan, *J. Amer. Chem. Soc.* **71**, 3938 (1949).