[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, EMORY UNIVERSITY]

The Mechanism of the Wettstein–Oppenauer Oxidation

BY LEON MANDELL

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Specific steric requirements with respect to the unsaturated alcohol being oxidized and the quinone acting as the hydrogen acceptor, have been shown to obtain in the Wettstein–Oppenauer oxidation. On this basis a mechanism for the transformation is put forth.

Although the mechanism of the Oppenauer oxidation has been extensively studied,[1,2] the mechanism by which Δ^5-3-hydroxysteroids are oxidized, under the Oppenauer conditions with *p*-quinone as the hydrogen acceptor, to $\Delta^{4,6}$-3-keto-steroids, has not been elucidated. This reaction, first discovered by Wettstein,[3] is extremely useful in that it affords a one-step preparation of $\Delta^{4,6}$-3-keto-steroids, giving yields as high as 50%.[3–8]

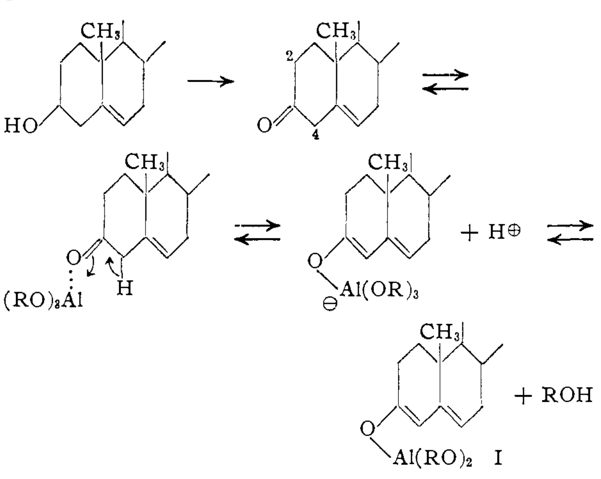
In his original work, Wettstein[3] was able to demonstrate that a Δ^5-3-keto-steroid is the probable intermediate in this reaction, since it, on treatment with *p*-quinone and aluminum alkoxide, could be converted to a $\Delta^{4,6}$-3-keto-steroid, whereas the corresponding Δ^4-3-keto-steroid remained unaffected.

In order to gain further insight into the mechanism by which this reaction proceeds, cholesterol was allowed to react with various quinones, namely, *o*-quinone, 1,2-naphthoquinone and 1,4-naphthoquinone, in the presence of aluminum alkoxide, to see if the varying oxidation potentials of the quinones[9] used would alter, in any way, the outcome of the oxidation. The reactions were carried out under conditions where cholesterol, in the presence of *p*-quinone and aluminum isopropoxide, gave a 41% yield of $\Delta^{4,6}$-3-keto-cholestadienone.[6] The reaction products were analyzed by examining the ultraviolet absorption spectra of the total crude material obtained after the usual work-up procedure (see Experimental) which separates the quinone and its reduction products from the steroidal material.[10]

It was found that *o*-quinone evidently decomposed too rapidly under the reaction conditions (refluxing toluene) and thus led to the recovery of starting material. However, 1,2-naphthoquinone gave a 40% yield of **Δ^4-3-keto-cholestenone** and no $\Delta^{4,6}$-3-ketocholestadienone, while 1,4-naphthoquinone led to the formation of 23% of **$\Delta^{4,6}$-3-keto-cholestadienone.** Further, it was shown that aluminum alkoxide had to be present for oxidation to occur, since both cholesterol and Δ^5-cholestene-3-one ethylene ketal were recovered unchanged when refluxed with *p*-quinone in toluene for prolonged periods.[11]

These important findings, coupled with the work of Wettstein[3] (*vide supra*), show that the Δ^6-double bond is not introduced *via* a "gross" dehydrogenation since the oxidation potential of 1,2-naphthoquinone is greater than that of 1,4-naphthoquinone. The facts do imply a necessity for a 1,4-relationship of the two quinone carbonyl groups in the hydrogen acceptor.

With this demonstrated it now becomes possible to write a logical path for the Wettstein–Oppenauer oxidation. The first step consists of a normal Oppenauer oxidation leading to the formation of Δ^5-3-keto-cholestenone. In the presence of aluminum alkoxide, the Δ^5-3-keto-steroid should enolize to give $\Delta^{3,5}$-enolate as



That this situation indeed obtains is evidenced by the fact that from the ordinary Oppenauer oxidation of Δ^5-3-hydroxysteroids, Δ^4-3-keto-steroids are always isolated,[1] thus inferring a transition through the enolate represented by I. If we now allow a quinone carbonyl to coördinate with the aluminum atom of the enolate I, and place the electrophilic quinone nucleus directly under the nucleophilic double bonds of the enolate I, it may be seen from molecular models that the uncoördinated *p*-carbonyl is then within bonding distance of the C-7 hydrogen atom, as pictured in the representation

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[1] For an excellent review of the Oppenauer oxidation with leading references see: C. Djerassi, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 207.

[2] W. von E. Doering and T. C. Aschner, THIS JOURNAL, **75**, 393 (1953).

[3] A. Wettstein, *Helv. Chim. Acta*, **23**, 388 (1940).

[4] M. I. Ushakov and N. F. Kosheleva, *J. Gen. Chem. U.S.S.R.*, **14**, 1138 (1944); from *C. A.*, **40**, 4071 (1946).

[5] A. Wilds and C. Djerassi, THIS JOURNAL, **68**, 1713 (1946).

[6] C. Djerassi, *ibid.*, **71**, 1009 (1949).

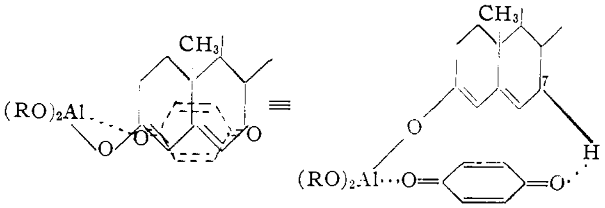
[7] R. E. Marker and D. L. Turner, *ibid.*, **63**, 767 (1941).

[8] W. G. Dauben, J. F. Eastham, R. A. Micheli, K. H. Takemura, L. Mandell and J. Chemerda, *ibid.*, **75**, 3255 (1953).

[9] *p*-Quinone, $E_0^{aq.}$ 0.699 v.; *o*-quinone, $E_0^{aq.}$ 0.792 v.; 1,2-naphthoquinone, $E_0^{aq.}$ 0.555 v.; 1,4-naphthoquinone, $E_0^{aq.}$ 0.470 v.; L. F. Fieser and M. Fieser, "Organic Chemistry," 2nd ed., D. C. Heath and Co., Boston, Mass., 1950, p. 754.

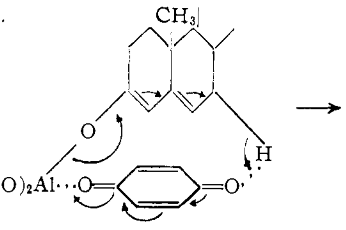
[10] This procedure was first tested by applying it to the case mentioned above.[6] Ultraviolet analysis indicated the presence of 52% of the dienone in the total crude product.

[11] These reactions served also as a further check on the analytical procedure since ultraviolet examination of the total crude showed the material to be essentially transparent toward ultraviolet light in the 215 mμ-300 mμ region.

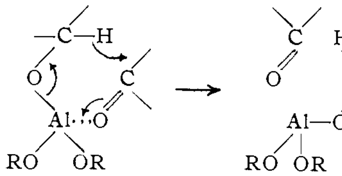


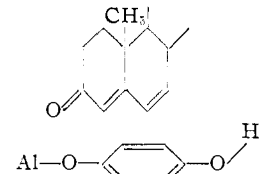
One may now envisage a cyclic rearrangement, completely analogous to that put forth for the Oppenauer oxidation,[12] differing only in that the hydride ion transferred does not come from the carbon atom bearing the initial hydroxyl group and is in turn not transferred to the carbon atom of the carbonyl coördinated with the aluminum atom.

i.e.



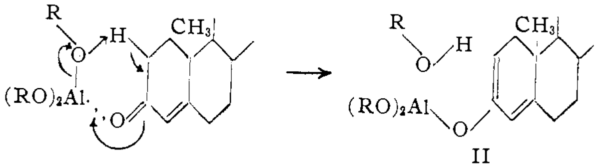
cf.[12]





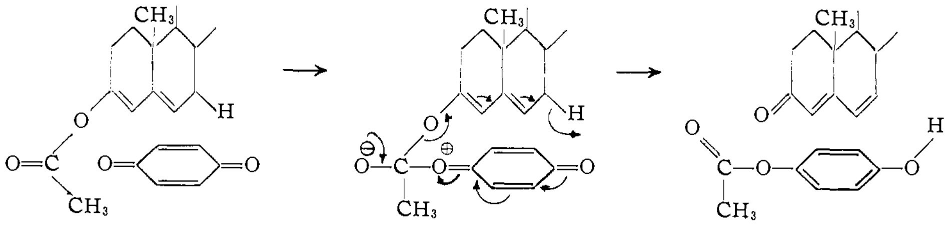
This cyclic process may also be written *via* a series of single electron transfers, but that this is unlikely may be inferred from the work of Doering[2] on the mechanism of metal–alkoxide oxidation–reduction systems.

The fact that Δ^4-3-keto-steroids will not undergo this transformation implies that the enolate formed by their interaction with aluminum alkoxide is not the $\Delta^{3,5}$-enolate, but rather the $\Delta^{2,4}$-enolate. The reason for this may be seen when it is realized that in the formation of the $\Delta^{2,4}$-enolate, aluminum alkoxide may function as an internal base, thus forcing the reaction to give the less stable $\Delta^{2,4}$-dienic system II.[13] In this enolate II the stereochemical requirements put forth above cannot obtain and therefore the reaction does not proceed.



II

Additional verification of the above postulated mechanism for the Wettstein–Oppenauer oxidation was sought by endeavoring to obtain reaction between *p*-quinone and $\Delta^{3,5}$-3-acetoxycholestadiene. The steric picture for this reaction would be identical to that hypothesized as being necessary above.



Although no reaction occurred when the two compounds were refluxed in toluene for four hours,[14] the addition of an acid catalyst (aluminum chloride) resulted in 46%[14] conversion to $\Delta^{4,6}$-3-ketocholestadienone.[15] This would appear to conclusively confirm the reaction path of the Wettstein–Oppenauer oxidation.

Experimental

Wettstein–Oppenauer Oxidation of Cholesterol with *p*-Quinone[6].—Two grams of cholesterol and 12 g. of *p*-quinone were dissolved in 150 ml. of toluene. One-third of the toluene was distilled off to ensure anhydrous conditions and then 1.7 g. of aluminum isopropoxide was added and this mixture refluxed 45 minutes. One hundred ml. of water was added and the toluene steam distilled. To this cooled mixture was added 100 ml. of 1 *N* sulfuric acid and this solution thoroughly extracted with ether. The ether layer was washed with dilute sulfuric acid and finally water.

Without shaking, 100-ml. portions of 5% potassium hydroxide were then added and separated until the color of the aqueous layer was orange. The ether layer was then thoroughly washed with 5% potassium hydroxide, finally with water and dried over sodium sulfate.

The ether extract was taken to dryness under reduced pressure and allowed to stand under high vacuum for one hour to remove any last traces of toluene.

The ultraviolet spectrum, in absolute ethanol, was taken on the total crude material which weighed 2.01 g., $\lambda^{\text{alc}}_{\text{max}}$

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[12] R. B. Woodward, N. L. Wendler and F. J. Brutschy, This Journal, **67**, 1425 (1945).

[13] Note that this type of internal base-catalyzed enolization may also take place in the formation of enolate I, where either the C-2 or C-4 proton may be removed by the alkoxide moiety of the coördinated aluminum alkoxide. In the case of the Δ^5-system, the lower energy of a $\Delta^{3,5}$-heteroannular diene over that of a non-conjugated $\Delta^{2,5}$- or homoannular $\Delta^{2,4}$-diene would furnish the driving force for the preferred loss of the C-4-proton. A similar type of process has been put forth in the study of enol-acetylation by A. Crawshaw, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 731 (1954), and also reference 8.

[14] From ultraviolet analysis of the total crude material.

[15] An alternative path suggested by one referee, namely, "acyl transfer to quinone with intermediate formation of the Δ^5-3-ketone" is unlikely, since were this the path followed one could not then rationalize the necessity for aluminum alkoxide in the Wettstein Oppenauer oxidation which was shown above.

284 mμ, E_{mol} 13,750; reported[5] $\lambda_{\max}^{\mathrm{alc}}$ 284 mμ, E_{mol} 26,300. Thus, a yield of 52% was indicated.[16]

The above procedure was repeated for *o*-quinone, 1,2-naphthoquinone and 1,4-naphthoquinone. With *o*-quinone there was no absorption in the ultraviolet (215–300 mμ) and the material recovered was shown to be cholesterol by melting point and the lack of depression in a mixture melting point. The total crude from 1,2-naphthoquinone had an absorption maximum at $\lambda_{\max}^{\mathrm{alc}}$ 239 mμ,[17] E_{mol} 9300, and no absorption at 284 mμ. In the case of 1,4-naphthoquinone the total crude exhibited absorption at $\lambda_{\max}^{\mathrm{alc}}$ 284 mμ, E_{mol} 6200.

Attempted Oxidation of Cholesterol and Δ^5-Cholestene-3-one Ethylene Ketal in the Absence of Aluminum Isopropoxide.—The above experiment was repeated on both cholesterol and Δ^5-cholestene-3-one ethylene ketal except the addition of aluminum isopropoxide was omitted. In both cases the ultraviolet analysis indicated the lack of diene system (215–300 mμ) and the starting materials were recovered unchanged.

Reaction of $\Delta^{3,5}$-3-Acetoxycholestadiene with *p*-Quinone. a. In the Absence of Acid Catalyst.—Two hundred mg. of $\Delta^{3,5}$-3-acetoxycholestadiene was heated in 15 ml. of dry toluene for four hours with 1.2 g. of *p*-quinone. The quinone was washed out of the reaction mixture as described above and, after concentration of the organic layer under reduced pressure, the ultraviolet absorption spectrum (215–300 mμ) run in absolute alcohol on the total crude material; $\lambda_{\max}^{\mathrm{alc}}$ 235 mμ, E_{mol} 18,500, no absorption in the 284 mμ region.

b. In the Presence of an Acid Catalyst.—Two hundred mg. of $\Delta^{3,5}$-3-acetoxycholestadiene, 1.2 g. of *p*-quinone and 100 mg. of anhydrous aluminum chloride were refluxed 45 minutes in 15 ml. of dry toluene. The reaction mixture was worked up as described above in the Wettstein–Oppenauer oxidation of cholesterol and the ultraviolet absorption spectrum (215–300 mμ) was run in absolute alcohol on the total crude material; $\lambda_{\max}^{\mathrm{alc}}$ 235 mμ, E_{mol} 10,400; $\lambda_{\max}^{\mathrm{alc}}$ 284 mμ, E_{mol} 11,600.

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[16] Small amounts of the quinones used, in the total crude product, would not interfere with this determination, since none of their absorption maxima, given below, appear in the 284 mμ region where $\Delta^{4,6}$-3-keto-steroids absorb. *p*-Quinone: $\lambda_{\max}$ 210, 220, 232 and 243 mμ, all having log E_{mol} *ca.* 1.3; λ_{inf} 330 mμ, log *E* 2.5; $\lambda_{\max}$ 410 mμ, log *E* 4.4 (L. C. Anderson and M. B. Geiger, THIS JOURNAL, **54**, 3064 (1932)). 1,2-Naphthoquinone: $\lambda_{\max}^{\mathrm{alc}}$ 250 mμ, log *E* 4.4; $\lambda_{\max}^{\mathrm{alc}}$ 340 mμ, log *E* 3.4, $\lambda_{\max}^{\mathrm{alc}}$ 405 mμ, log *E* 3.4 (S. Goldschmidt and F. Graef, *Ber.*, **61**, 1858 (1928)). 1,4-Naphthoquinone: $\lambda_{\max}^{\mathrm{alc}}$ 246 mμ, log *E* 4.37; $\lambda_{\max}^{\mathrm{alc}}$ 330 mμ, log *E* 3.44 (R. A. Morton and W. T. Earlam, *J. Chem. Soc.*, 159 (1941)).

[17] This is in good agreement for Δ^4-3-ketocholestenone; L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed., Reinhold Publishing Corp., New York, N. Y., 1949, p. 190.

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Reduction of Enols. New Synthesis of Certain Methoxybenzsuberenes via Hydrogenation of Dehydroacetic Acids

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Hydrogenation of dehydroacetic acid in the presence of 10% palladium–charcoal in ethyl acetate at 80° permits selective reduction of the acetyl group and affords 3-ethyl-4-hydroxy-6-methyl-5,6-dihydro-2-pyrone. Stepwise hydrogenation of veratrylidenedehydroacetic acid similarly affords 3-[γ-(3,4-dimethoxyphenyl)-propyl]-4-hydroxy-6-methyl-5,6-dihydro-2-pyrone, which is cyclized by polyphosphoric acid to 2,3-dimethoxy-5-(β-hydroxypropyl)-6-carboxybenzsuber-5-ene lactone. Evidence is presented confirming the structures of these and related products. *o*-Hydroxyacetophenone also may be reduced to *o*-ethylphenol by the same method.

A recent paper by Wiley and his students[1] showed that veratraldehyde and other aldehydes condense with the acetyl group of dehydroacetic acid and give chalcone-like compounds (III). This paper describes selective reduction of III and cyclization of the product (V) to a benzsuberene (VII).

Preliminary reduction studies were carried out with dehydroacetic acid (I). A method disclosed earlier[2] gave good results. It was found that compound I absorbed somewhat more than three moles of hydrogen in the presence of 10% palladium–charcoal in ethyl acetate at 80°. The crystalline product (56% yield) was the enolic keto-lactone II. Structure II was proven correct by hydrolysis and decarboxylation, which gave 2-hepten-4-one, and hydrogenation of this product, which led to formation of di-*n*-propyl ketone.

Experiments with veratrylidenedehydroacetic acid (III) which were carried out next, showed that it was possible, and in fact best, to reduce III in two stages. In the first stage, one mole of hydrogen was absorbed rapidly and the 3-[β-(3,4-dimethoxyphenyl)-propionyl]-pyrone (IV) was obtained in 86% yield. Structure IV was substantiated by similarity of the infrared spectra of IV and I in the carbonyl region, and by alkaline cleavage to β-(3,4-dimethoxyphenyl)-propionic acid. A mono-2,4-dinitrophenylhydrazone was prepared from IV. The infrared spectrum of this derivative showed that two carbonyl groups (5.80 and 5.87 μ) and conjugated unsaturation (6.07 μ) were present, as well as the usual N–H (3.02 μ) and C=N (6.17 μ) groups. The second reduction stage, from IV to V, involved absorption of three moles of hydrogen, as in reduction of I to II, and was slower than the first step. Compound V was obtained in 80% yield. The infrared spectrum of V in the carbonyl region was like that of II, having a double peak at 5.69 and 5.81 μ. Structure V was confirmed by cleavage with 5% alkali to ketone VI. In contrast to IV, compound V reacted very slowly with 2,4-dinitrophenylhydrazine. Evidently the 4-keto (or enol) group in I and IV is much less reactive than the acetyl group, an observation which is in keeping with properties of other cyclic 1,3-dicarbonyl compounds. The selective reduction of the acetyl sidechain in these compounds may depend upon this difference in char-

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[1] R. H. Wiley, C. H. Jarboe and H. G. Ellert, THIS JOURNAL, **77**, 5102 (1955).

[2] G. N. Walker, *ibid.*, **77**, 3844, 6699 (1955).