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Applications of High-potential Quinones. Convenient Syntheses of Steroidal 1,4,6-Trien-3-ones

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The exceptional oxidising properties of the high-potential quinone, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), have found useful application in the selective dehydrogenation of steroidal ketones.[1] Hydrogen transfers of this kind involve abstraction of hydride ion from the enolic form of the substrate, with enolization being the rate-determining step in the process.[2] We now show how advantage can be taken of this latter finding by applying this reaction to readily enolized $\beta\gamma$-unsaturated ketones.

Steroidal 5-en-3-ones are rapidly dehydrogenated by DDQ in refluxing benzene. Thus, androst-5-ene-3,17-dione, cholest-5-en-3-one, and pregn-5-ene-3,20-dione give the corresponding 4,6-dien-3-ones with one equivalent of the quinone in yields of 80—85%. Oxidations were carried out by refluxing solutions approximately 0·2M with respect to steroid for 90 min. After removal of precipitated hydroquinone, the solutions were passed through short columns of neutral alumina and the oxidation products were eluted with ethyl acetate. Their identity was established by comparison with authentic samples.

These 4,6-dien-3-ones undergo 1,2-dehydrogenation with DDQ,[1] and, after refluxing for 15 hr. in anhydrous benzene or dioxan with two equivalents of the quinone, the 5-en-3-ones give androsta-1,4,6-triene-3,17-dione, cholesta-1,4,6-trien-3-one, and pregna-1,4,6-triene-3,20-dione, respectively, in 68—72% yields. In our hands this procedure has given better yields of the pure trienones than other methods in the literature,[3,4] but it is limited by the inaccessibility of the starting 5-en-3-ones. In view of this, we have extended the process to the corresponding alcohols, which are oxidised by DDQ under the same conditions using prolonged reaction times.[5]

Three equivalents of quinone are required to convert 3-hydroxyandrost-5-en-3,17-one, cholesterol, and pregnenolone into their corresponding 1,4,6-trien-3-ones, which are obtained in yields of 47—54% after 20 hr. in refluxing dioxan. The solutions used were approximately 0·1M in steroid and the products were isolated and characterised in the manner described above. These yields compare favourably with those obtained in various indirect methods.[4] Examination of the reaction mixtures at intervals by thin-layer chromatography revealed the presence of the intermediate 5-en-3-ones and 1,4,6-trien-3-ones. This, together with the experiments described above, indicates that the reaction takes the expected course:

5-en-3-ol → 5-en-3-one →
4,6-dien-3-one → 1,4,6-trien-3-one.

A comparison of oxidation rates in the cholesterol series shows that the initial oxidation of the hydroxyl group is the slowest step in the sequence, being much slower than dehydrogenation of the resulting 5-en-3-one, and rather slower than the final 1,2-dehydrogenation of the 4,6-dien-3-one.

This reaction provides a convenient, direct route from common steroid alcohols to compounds which are readily transformed into œstrogens. It also highlights the remarkable difference in oxidising properties between DDQ [$E^0 = 1{\cdot}0$ (approx.)] and its close relative, chloranil [$E^0 = 0{\cdot}70$], which does not attack cholesterol under these conditions. When more vigorous conditions are used, chloranil reacts with cholesterol to give dehydrogenation products, but these do not arise by oxidation of the hydroxyl group.[6]

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