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Selective Reductions of Steroid Carbonyl Groups with Homogeneous Catalysts Containing Iridium and Rhodium

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Summary Steroid 2-, 3-, and 17-ketones can be reduced selectively with isopropyl alcohol, trimethyl phosphite, and sodium chloroiridate or tris(triphenylphosphine)-rhodium(I) chloride; stereospecific 2- and 3-reduction to the axial alcohol is best attained with the rhodium catalyst.

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THE reduction of 5α-cholestan-3-one to the axial 3α-alcohol by sodium chloroiridate, aqueous isopropyl alcohol, and trimethyl phosphite has been described by Henbest *et al.*,[1] and its remarkable selectivity for reduction of the 3-keto-group alone under the original conditions has been employed for the preparation of a number of useful 3-axial steroid alcohols.[2]

We have also observed this selectivity and examined some different aspects of the reaction. In addition, a rhodium-containing catalyst of even greater selectivity has been discovered.

The reductions were conveniently effected by maintaining a mixture of the steroid (36 μmoles, approx. 10 mg.), isopropyl alcohol (0·82 ml.), trimethyl phosphite (0·10 ml., 854 μmoles), and a solution of sodium chloroiridate (9 μmoles) in water (0·09 ml.) in a sealed tube at 82° (isopropyl alcohol–water azeotrope) for 24 hr. Preparative runs (0·1—3 g.) were also carried out in sealed tubes with relatively less solvent mixture. The reaction products were examined by t.l.c., n.m.r., and combined g.l.c.–mass spectrometry. Under these conditions the 3-keto-groups of 5α- and 5β-steroids were completely reduced, predominantly to the axial alcohols. 4-Keto-groups in steroids of both the A/B *cis* and A/B *trans* series and 17- and 20-keto-groups remained unaffected; 30% of 5α-cholestan-2-one remained unreduced. After 46 hr., approximately 20% of 19-oxocholesterol was reduced to cholest-5-ene-3β,19-diol. The reduction of 17β-hydroxy-5α-androstan-2-one was complete after 9 days at 81°, giving 99% of the axial product androstane-2β,17β-diol, and 1% of the equatorial 2α,17β-diol. The two epimers were readily separable by t.l.c.; the n.m.r. absorptions of the 19-H_3 protons and of the C-2 proton allowed clear distinction between them. Pure 3α-hydroxy-5α-androstan-17-one and 3β-hydroxy-5β-androstan-17-one were prepared directly from the corresponding diketones in 70—80% yields.

In agreement with Browne and Kirk,[3] we find that isomerization occurs at the 17-position during selective 3-reduction of 5α-pregnane-3,20-dione. The n.m.r. absorption of the 18-H_3 protons with a 17α-acetyl side-chain (0·907 p.p.m. from Me_4Si) clearly distinguishes it from the 17β-epimer (0·605 p.p.m.). The relative areas under the peaks indicate approximately 14% isomerization, less than the equilibrium value,[3] suggesting that milder conditions might cause reduction of the 3-ketone with less isomerization at C-17. Pure 3α-hydroxy-5α,17β-pregnan-20-one (m.p. 174—175°) could not be obtained from the product (m.p. 110—130°) even after eight recrystallizations from several solvents (to m.p. 164—173°), but was obtained by column chromatography on alumina.

Addition to the reaction mixture described above of acetic acid (1·75 mmoles) caused a slight decrease in the rate of reduction of the 3-keto-group of 5β-androstane-3,17-dione. Sodium hydroxide (0·1 ml. of 1N), although insufficient to neutralize the phosphorous acid, caused approximately a 3-fold increase in rate and gave, after 10 hr. at 82°, complete reduction of the 3-keto-group to the alcohols with no apparent loss of stereospecificity (3β; 3α approximately 11 : 1). In addition, the 17-keto-group had been reduced to the extent of 5%. 3β-Hydroxy-5α-androstan-17-one was treated at 100° for 7 days in the presence of sodium hydroxide. The product contained approximately 35% of unreduced 17-ketone, 60% of 5α-androstane-3β,17β-diol and 5% of the 3β,17α-diol. Separation of the diols was accomplished only by t.l.c. on alumina G (Brinkmann) with benzene : ethanol 9 : 1 and on titanium dioxide with benzene : ether 4 : 1. The isomers could be distinguished by the n.m.r. absorptions of 18-H_3 at 0·73 p.p.m. (17β-OH) and 0·64 p.p.m. (17α-OH).

The predominant formation of the ψ-equatorial 17β-alcohol indicates that formation of the axial alcohol is not obligatory. Inspection of models suggests that in each case the reducing agent approaches from the less hindered side of the carbonyl group. The reduction of the 10-formyl group indicates that the mechanism need not be *via* the hydrogenation of an enol.

Testosterone, under the chloroiridate reducing conditions in the presence of sodium hydroxide for 24 hr., gave starting material (70%), androsta-3,5-diene-17β-ol (27%) and a small amount of an allylic alcohol. The allylic alcohol was not detectable by g.l.c.–mass spectrometry, but showed on t.l.c. as a blue spot that appeared immediately on spraying the plate with sulphuric acid–ethanol.

The possibility of employing the reaction in the oxidative direction was examined. 3α-Hydroxy-5α-androstan-17-one was treated with acetone, trimethyl phosphite, water (9 : 1 : 1 by volume), and sodium chloroiridate, and after 18 hr. at 100° in a sealed tube, gave 5% yield of the dione, the remainder being unchanged. These conditions of time and temperature were sufficient for complete reaction in the reductive direction.

During the first 30 min. of heating, the chloroiridate reaction mixture turns from deep red-brown to colourless[4] (under reflux in air,[1] the solution becomes yellow); on opening the tube, gas evolution occurs. The possibility that the transfer of hydrogen from isopropyl alcohol to the steroid might be taking place through reversible homogeneous hydrogenation led us to examine the homogeneous hydrogenation catalyst tris(triphenylphosphine)rhodium(I) chloride.[5] Its substitution for sodium chloroiridate resulted in complete reduction of 5β-androstane-3,17-dione to the 3-alcohols with even greater stereospecificity (axial : equatorial 50 : 1), and with no detectable reduction of the

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17-keto-group. The rhodium catalyst caused slow (60% complete in 9 days at 82°) reduction of 17β-hydroxyandrostan-2-one entirely to the 2β,17β-diol; the iridium catalyst under these conditions also caused complete reduction but gave 1% of the equatorial 2α,17β-diol. The rhodium catalyst does not cause reduction of the 10-formyl group. The reaction rate at the 3-position with the rhodium catalyst is approximately the same as that of the chloroiridate reduction in the absence of sodium hydroxide. Without trimethyl phosphite, no reduction takes place; tris(triphenylphosphine)rhodium(I) chloride remains as deep red crystals. In its presence a yellow solid is formed and partly dissolved. The rate of the rhodium-catalysed reaction is not appreciably altered by addition of sodium hydroxide. On a preparative scale, removal of the yellow rhodium catalyst from the steroid requires chromatography on alumina;[6] the iridium catalyst can be removed merely by water–ethyl acetate partition.

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