Aspects of Catalysis. Part III.[1] Soluble Iridium-containing Catalysts for the Reduction of Cyclohexanones by Propan-2-ol and for the Formation of Ethers from Cyclohexanones (or Enol Ethers) and Alcohols

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Transfer of hydrogen from propan-2-ol (containing water) to relatively unhindered cyclohexanones is catalysed by some soluble iridium compounds. Stereoselectivity in the reduction of a substituted cyclohexanone depends on the ligands associated with the iridium. The proportion of axial alcohol from the reduction of cholestan-3-one or 4-t-butylcyclohexanone ranges from 30—23% (piperidine present) to 66—78% (dimethyl sulphoxide present). Preformed iridium–sulphoxide complexes also give the latter degree of stereoselectivity. In the absence of water these complexes catalyse another reaction between cyclohexanones and alcohols, ethers being formed by reductive etherification of the ketones. The reaction favours the production of axial ethers and higher yields of ether can be obtained by starting with the ketone in the form of an enol ether.

Conversion of Cyclohexanones into Cyclohexanols.— In continuation of our previous studies on the effects of remotely placed substituents on the stereochemistry of addition reactions [2-5] we looked for soluble species that would catalyse the donation of hydrogen to carbonyl compounds in solution. This paper first summarises exploratory work that included the discovery of a soluble iridium-containing hydrogen transfer system.

The conversion of cyclohexanones into cyclohexanols is a convenient reaction for study, the right-hand side of the following system being favoured at equilibrium: [6]

cyclohexanone + acyclic >CH·OH ⇌ cyclohexanol + acyclic >CO

Many salts of the higher Group VIII elements are reduced to metals when they are heated in solution in ethanol or, more rapidly, in propan-2-ol. These metals sometimes function as heterogeneous catalysts for the reduction of ketones by alcohols.[7] Suitable ligands must therefore be present if a compound derived from one of these Group VIII elements is not to be reduced to metal in an alcoholic solvent. At the same time the compound must retain sufficient reactivity to act as a catalyst for the required reaction.

Addition of a suitable amount of hydrochloric acid sufficed to prevent the precipitation of metal when hexachloroiridic acid, or ammonium or potassium hexachloroiridate-(III) or -(IV), was heated in aqueous ethanol. [Under these conditions the violet-red colour of the solution of a hexachloroiridate(IV) salt first changed to the yellow-green colour of solutions containing trivalent iridium.] In this homogeneous medium 5α-cholestan-3-one was reduced (after the solution had been heated for 15—20 h) to a 36 : 64 mixture of axial and equatorial (3α- and 3β-) alcohols. Similar treatment of 4-t-butylcyclohexanone gave a 40 : 60 mixture of axial and equatorial alcohols. In both cases the percentage of axial alcohol produced is higher than that present under equilibrium conditions (16·5 and 21, respectively). Hydrobromic acid also prevented the separation of iridium from solution, but acetic acid did not. An acyclic ketone, nonadecan-2-one, was reduced (HCl present), but the reaction was slower than those of the cyclohexanones.

Under the foregoing conditions, with HCl present, cholestanone was not reduced when salts of most other Group VIII elements (Ru, Pd, Os, Pt) were used in place of an iridium salt. These solutions remained clear during the experiments. By contrast, a black precipitate soon began to separate when a rhodium salt was used; with cholestanone present some reduction of the carbonyl group occurred but part at least of this reaction may occur by heterogeneous catalysis.[7]

Cholestanone was slowly reduced in boiling aqueous ethanol containing (initially) ammonium hexachloroiridate(IV) and piperidine. The solution remained clear and a 29 : 71 mixture of axial and equatorial alcohols was produced. Other added amines behaved differently: morpholine and piperazine also stabilised the iridium but little reduction of the cholestanone occurred, whereas the solutions did not remain clear when various other amines were tried (diethylamine, *NN*-dimethyl-t-butylamine, t-butylamine, 2-amino-2,4,4-trimethylpentane, 4-hydroxy-1-methylpiperidine, and 1,10-phenanthroline).

Although hydrochloric acid stabilised iridium in solution in hot ethanol, a black precipitate separated when ethanol was replaced by the more powerful reductant, propan-2-ol. Other ligands are therefore required to retain iridium in solution in this solvent. Sulphoxides were effective in this respect and the reduction of cholestanone in propan-2-ol containing (initially) ammonium hexachloriridate(IV) and dimethyl sulphoxide was additionally interesting in that it gave more axial than equatorial alcohol product. The proportion of axial alcohol from cholestanone was *ca.* 65%, and that from 4-t-butylcyclohexanone was 77—78%. This latter value is very similar to the highest

[1] Part II, Y. M. Y. Haddad, H. B. Henbest, and J. Trocha-Grimshaw, preceding paper.
[2] M. G. Combe and H. B. Henbest, *Tetrahedron Letters*, 1961, 404.
[3] H. B. Henbest, *Proc. Chem. Soc.*, 1963, 159.
[4] H. B. Henbest and W. R. Jackson, *J. Chem. Soc.* (*C*), 1967, 2459.
[5] M. G. Combe, H. B. Henbest, and W. R. Jackson, *J. Chem. Soc.* (*C*), 1967, 2467.
[6] W. D. Cotterill and M. J. T. Robinson, *Tetrahedron Letters*, 1963, **26**, 1833.
[7] Part V, H. B. Henbest and A. Zurqiyah, *J.C.S. Perkin I*, 1974, 604.

proportion (78%) of axial alcohol obtained from 4-t-butylcyclohexanone by reduction under heterogeneous-three phase conditions (hydrogen and platinum in acetic–hydrochloric acid),[8] but lower than that produced by phosphite reduction using an iridium–phosphite catalyst.[9]

Crystalline iridium–dimethyl sulphoxide complexes were subsequently isolated from reactions of chloroiridic acid with dimethyl sulphoxide: two isomeric acids, $H[IrCl_4(Me_2SO)_2]$, and a neutral complex, $IrCl_3(Me_2SO)_3$, each of these being reduced by propan-2-ol to hydrides, $IrHCl_2(Me_2SO)_3$.[1] Reduction of cholestan-3-one and 4-t-butylcyclohexanone by propan-2-ol occurred when any of these four complexes was added initially to the reaction mixture, the ratio of axial to equatorial alcohol product being similar to that obtained using hexachloroiridic acid and dimethyl sulphoxide. Hydrides, *e.g.* $IrHCl_2(Me_2SO)_3$, are likely to be the species involved directly in the catalysis cycle; such a hydride probably adds to the carbonyl group and is later regenerated.[1,9]

A side reaction in the reduction of ketones to alcohols using propan-2-ol and an iridium–sulphoxide catalyst is reductive etherification (see later), but this can be prevented by using slightly aqueous propan-2-ol. Another complication is that the life of the catalyst diminishes fairly rapidly unless some additional sulphoxide is present in solution. (In the absence of added sulphoxide less soluble complexes are formed.) However, with sufficient water and free sulphoxide present more than 550 mol of cyclohexanone can be reduced per mol of catalyst. The reaction is susceptible to steric hindrance: the reduction of the 4,4-dimethyl-3-oxosteroid, lanost-8-en-3-one, was considerably slower than that of cholestan-3-one, under the same conditions. The ratio of axial to equatorial alcohol product (73 : 27) from lanostenone was slightly higher than that from cholestanone (65 : 35).

As mentioned already, the stereoselectivity of the reduction reaction depends on the ligands available for iridium. The results of using various ligands, summarised in Table 1, indicate that other factors are less important. However, stereoselectivity is affected to some extent by changes of structure in one type of ligand, diphenyl and dibenzyl sulphoxides giving less selective reduction than dimethyl and tetramethylene sulphoxides. Reductions of cholestanone in racemic and in optically active octan-2-ol gave the same ratio of axial to equatorial alcohol product. Thus asymmetric induction did not occur but this is not unexpected if reaction proceeds *via* an intermediate hydride with a plane of symmetry, *cf.* the hydride (I) in the preceding paper.[1]

Dimethyl sulphone did not stabilise iridium as a complex; a black precipitate formed.

The reaction in the cholestanone section of Table 1 where an iridium salt was not added refers to the acid-catalysed reduction of cholestanone to 65—70% of the axial alcohol which occurs in propan-2-ol but not to an appreciable extent in ethanol (under the conditions used in this study). Deno[10] has reported the use of 60% sulphuric acid for promoting the reaction between cyclohexanone and propan-2-ol, but the reduction of cholestanone proceeds at an appreciable rate in boiling propan-2-ol containing 10% concentrated hydrochloric acid, 27% of the ketone being reduced after 24 h. Repetition of this experiment with a small amount of the *trans*-acid, $H[IrCl_4(Me_2SO)_2]$, present led to 45% of the ketone being reduced after only 0·5 h. The rate ratio is of course larger in the absence of mineral acid, as hydrogen transfer requires a catalyst.

TABLE 1

Stereoselectivity of the reduction of ketones by alcohols (water, M_2IrCl_6, and potential ligand added initially)

Alcohol (solvent and reductant)	M	Ligand	Temp. (°C)	Time (h)	Axial alcohol (%) in total alcohol product
		Cholestanone			(16·5) *
EtOH	NH_4	$[CH_2]_5NH$	78	10	30
EtOH	NH_4	HBr	78	17	33
EtOH	K	HCl	78	24	35
EtOH	NH_4	HCl	78	46	37
(±)-Octan-2-ol	NH_4	Me_2SO	116	24	58
(−)-Octan-2-ol	NH_4	Me_2SO	116	24	58
Pr^iOH	H	$(MeO)_2SO$	83	20	59
Pr^iOH		HCl	83	24	65—70
EtOH	NH_4	Me_2SO	78	41	66
EtOH	H	Me_2SO	78	36	66
$[CH_2]_4CH{\cdot}OH$	H	Me_2SO	84	42	67
Pr^iOH	NH_4	Me_2SO	83	42	69
		4-t-Butylcyclohexanone			(21) *
Pr^iOH	H	$[CH_2]_4SO_2$	83	24	†
EtOH	NH_4	$(CH_2)_5NH$	78	14	23
EtOH	NH_4	HCl	78	19	40
$[CH_2]_4CH{\cdot}OH$	NH_4	$(PhCH_2)_2SO$	119	16	50
$[CH_2]_4CH{\cdot}OH$	NH_4	Ph_2SO	119	16	55 †
Pr^iOH	H	$[CH_2]_4S$	83	23	57
EtOH	NH_4	Et_2SO	78	16	66 †
$[CH_2]_4CH{\cdot}OH$	NH_4	Et_2SO	100	16	67 †
$[CH_2]_4CH{\cdot}OH$	NH_4	$EtSOBu^t$	111	16	71
Pr^iOH	NH_4	Me_2SO	83	16	77
Pr^iOH	H	$(MeO)_2SO$	83	23	72
$[CH_2]_4CH{\cdot}OH$	NH_4	$[CH_2]_4SO$	112	16	76
Pr^iOH	NH_4	Me_2SO	83	16	77
$[CH_2]_4CH{\cdot}OH$	NH_4	Me_2SO	106	16	78
EtOH	NH_4	$[CH_2]_4SO$	78	16	78

* Axial alcohol % at equilibrium. † Black precipitate.

Cholestanone and 4-t-butylcyclohexanone gave *ca.* 35 and 30% axial alcohol, respectively, on reduction with propan-2-ol using precipitated iridium,[7] and cholestanone gave *ca.* 16% axial alcohol on Meerwein–Ponndorf–Verley reduction.

Conversion of Cyclohexanones into Alkyl Cyclohexyl Ethers.—Reference was made earlier to the observation that ether formation becomes an alternative reaction when less aqueous propan-2-ol is used to reduce cyclohexanones to cyclohexanols. When very dry propan-2-ol is employed the production of cyclohexyl isopropyl

[8] E. L. Eliel and R. S. Ro, *J. Amer. Chem. Soc.*, 1957, **79**, 5991.
[9] Part I, H. B. Henbest and T. R. B. Mitchell, *J. Chem. Soc.* (*C*), 1970, 785.
[10] N. C. Deno, H. J. Peterson, and G. S. Saires, *Chem. Rev.*, 1960, **60**, 7.

ethers becomes the main reaction. The dichotomy of behaviour can be summarised as follows:

$$>C{=}O + Pr^iOH \xrightarrow{H_2O} >CHOH + Me_2CO$$
$$>C{=}O + 2Pr^iOH \longrightarrow >CHOPr^i + Me_2CO + H_2O$$

Reductive etherification occurs in the latter reaction, and this is a process that often takes place to some extent in the hydrogenation of a mixture of a ketone and an alcohol over a solid catalyst in the presence of (strong) acid:[11,12]

$$R^1R^2CO + R^3OH + H_2 \xrightarrow[H^+]{\text{solid catalyst}} R^1R^2CHOR^3 + H_2O$$

By-products in this heterogeneous reaction include alkanes, $R^1R^2CH_2$, and alcohols, R^1R^2CHOH, the combined yields of which can range from 9 to 88%.[13]

To return to the use of soluble iridium-containing catalysts, the results in Table 2 were obtained when 5α-cholestan-3-one was heated in propan-2-ol containing an iridium–sulphoxide acid (0·03 mol per mol of ketone) and various quantities of water. The data show (*a*) how an increase in the dryness of the propan-2-ol causes an increased proportion of cyclohexyl isopropyl ether to be formed, and (*b*) that ether production under the dry conditions is faster than reduction of the ketone to cyclohexanol when water is present (*e.g.* 0·6%).

Reductive etherification also occurred when 5α-cholestan-3-one was similarly treated with other alcohols (Table 3), but not t-butyl alcohol. The proportion of

TABLE 2

Water (% w/w) added to dried propan-2-ol	Product yields (%) * Cholestanols	Isopropoxy-cholestanes	Reaction time (h)	Cholestanone recovered (%)
0	39·5	60·5	1·5	3
0·004	71·5	28·5	1·5	11
0·008	82	18	1·5	23
0·6	97	3	16	1

* Percentages of the combined yield of cholestanols and ethers (some cholestanone was recovered, see final column).

axial ether (second column of Table 3) increases as the degree of hindrance to the approach of a reactant to the C–O bond of the alcohol increases.

TABLE 3

Alcohol (solvent and reactant)	Ratio of axial to equatorial ether products from cholestanone + alcohol	from enol ether (3-ethoxycholest-2-ene)
EtOH	62 : 38	62 : 38
Pr^nOH	64 : 36	
$[CH_2]_4CH{\cdot}OH$	72 : 28	74 : 26
Pr^iOH	83 : 17	
Bu^sOH	87 : 13	

Experiment confirmed the hypothesis that the yield of ether is limited by the water formed in the reaction; the ratio of ether to alcohol product diminished during reaction of the ketone (and then remained constant). Higher yields of ethers were obtained starting with enol ethers, for example, a 92% combined yield of 3α- and 3β-ethoxycholestanes from 3-ethoxycholest-2-ene:

$$EtO{-}\dot{C}{=}CH{-} + EtOH \longrightarrow EtO{-}\dot{C}H{-}CH_2{-} + MeCHO$$

The formation of a mixture of 3α- and 3β-cyclopentyloxycholestanes from reaction of 3-ethoxycholest-2-ene in an excess of cyclopentanol shows that alkoxy-exchange can occur:

$$EtO{-}\dot{C}{=}CH{-} + [CH_2]_4CH{\cdot}OH \longrightarrow [CH_2]_4CHO{-}\dot{C}H{-}CH_2{-} + MeCHO/[CH_2]_4CO$$

Exchange of alkoxy-groups probably takes place *via* acetals and oxacarbonium ions because the reaction solutions are acidic when either an acidic or a neutral iridium–sulphoxide complex, $IrCl_3(Me_2SO)_3$, provides the catalyst; in the latter case the solution becomes acidic owing to the formation of hydrogen chloride as the hydride, $IrHCl_2(Me_2SO)_3$,[1] is formed.

A previous paper[9] reported the reduction of unhindered cyclohexanones to give 97% or more axial alcohol, the process being carried out in an aqueous alcohol solvent containing an iridium–phosphite catalyst. When water was omitted from the reaction mixture ether formation became pronounced (up to 40—60%) and, as in the sulphoxide complex series, more axial than equatorial ether was formed. The selectivity of the accompanying 4-t-butylcyclohexanol formation was much lower (axial : equatorial *ca.* 60 : 40) than when water was present (97 : 3), whereas with the iridium–sulphoxide catalyst the selectivity of cholestanol production was less dependent on the proportion of water present.

EXPERIMENTAL

Optical rotations are for solutions in chloroform.

Formation of Cyclohexanols

(A) *Exploratory Experiments with Metal Salts.—Reduction of cholestan-3-one by ammonium hexachloroiridate–ethanol–hydrochloric acid–water.* Cholestanone (390 mg, 1·01 mmol) was added to a solution of ammonium hexachloroiridate (113 mg, 0·25 mmol) in a mixture of ethanol (60 ml), water (8 ml), and conc. hydrochloric acid (5 ml), and the solution was boiled under reflux for 46 h. The steroid (390 mg), isolated with ether, was adsorbed from benzene on deactivated alumina (50 g). Elution with pentane (200 ml) gave an oily mixture of 3α- and 3β-ethoxycholestanes (45 mg). Further elution with the same solvent (600 ml) gave cholestanone (126 mg), m.p. 129—130°, $[\alpha]_D$ +43°. Elution with pentane–ether (19 : 1; 1 l) afforded cholestan-3α-ol (80 mg), m.p. 185—186°, $[\alpha]_D$ +24°. Elution with ether (300 ml) afforded cholestan-3β-ol (138 mg), m.p. 142—143°, $[\alpha]_D$ +24°.

When the reduction of cholestanone was attempted in the absence of hydrochloric acid, the metal precipitated and the ketone was recovered unchanged.

Heating cholestanone (272 mg) under reflux with ethanol (50 ml), water (8 ml), and conc. hydrochloric acid (4 ml) for 14 h led only to the recovery of starting material.

[11] J. C. Babcock and L. F. Fieser, *J. Amer. Chem. Soc.*, 1952, **74**, 5472.

[12] M. Verzele, M. Acke, and M. Antennis, *J. Chem. Soc.*, 1963, 5598.

[13] M. Acke and M. Antennis, *Bull. Soc. Chim. belges*, 1965, **74**, 41.

Reduction of cholestanone by ammonium hexachloroiridate–ethanol–piperidine–water. Cholestanone (380 mg, 0·98 mmol) was added to a solution of ammonium or potassium hexachloroiridate (141 mg, 0·32 mmol) in a mixture of ethanol (60 ml), water (10 ml), and piperidine (2 ml) and the solution was boiled under reflux for 10 h. Chromatography of the steroid product on deactivated alumina (40 g) afforded cholestanone (211 mg), cholestan-3α-ol (49 mg), and cholestan-3β-ol (115 mg).

Reduction of cholestanone by ammonium hexahloroiridate–propan-2-ol–dimethyl sulphoxide–water. A solution of cholestanone (515 mg), ammonium hexachloroiridate (404 mg), dimethyl sulphoxide (8 ml), and water (12 ml) in propan-2-ol (50 ml) was boiled under reflux for 42 h. Chromatography of the steroid product on deactivated alumina (60 g) gave cholestanone (123 mg), cholestan-3α-ol (266 mg), and cholestan-3β-ol (117 mg).

Heating cholestanone (565 mg) under reflux with propan-2-ol (50 ml), hexachloroiridic acid (293 mg), water (12 ml), and dimethyl sulphoxide (8 ml) for 42 h followed by work-up and chromatography as before gave cholestanone (175 mg), cholestan-3α-ol (266 mg), and cholestan-3β-ol (119 mg). Less of the ketone was reduced (25%) when this experiment was repeated with ethanol in place of propan-2-ol.

When the reduction in propan-2-ol was attempted at 65°, almost all the ketone was recovered.

Reduction of 4-t-butylcyclohexanone by ammonium hexachloroiridate–ethanol–hydrochloric acid–water. 4-t-Butylcyclohexanone (160 mg) was added to a solution of ammonium hexachloroiridate (242 mg) in a mixture of ethanol (40 ml), water (8 ml), and conc. hydrochloric acid (4 ml), and the solution was boiled under reflux for 19 h. The reflux condenser was replaced by a fractionating column (30 cm) and the mixture was slowly distilled until most of the ethanol (30 ml) had been removed. The residue was diluted with sodium chloride solution and the product was extracted with ether in the usual way. Removal of most of the ether by distillation gave a residue which was analysed by g.l.c. (96°; Celite with 7% polyphenyl ether) giving unreduced ketone (4%), 1-ethoxy-4-t-butylcyclohexanes (4%), and a mixture of 4-t-butylcyclohexanols (92%) (40% *cis*- and 60% *trans*-alcohol).

Reduction of 4-t-butylcyclohexanone by ammonium hexachloroiridate–ethanol–piperidine–water. 4-t-Butylcyclohexanone (114 mg) was added to a solution of ammonium hexachloroiridate (167 mg) in a mixture of ethanol (20 ml), water (7 ml), and piperidine (3 ml), and the solution was boiled under reflux for 14 h. The reaction was worked up as before; the residue, analysed by g.l.c. at 96°, contained a 23 : 77 mixture of *cis*- and *trans*-alcohols (100% based on ketone reduced) and unreduced ketone (12%).

Reduction of nonadecan-2-one by ammonium hexachloroiridate–ethanol–piperidine–water. The ketone (410 mg), was added to a solution of ammonium hexachloroiridate (212 mg) in ethanol (50 ml) containing piperidine (5 ml) and water (10 ml) and the mixture was boiled under reflux for 23 h. Work-up in the usual way and chromatography on deactivated alumina (40 g) gave nonadecan-2-one (390 mg) and nonadecan-2-ol (20 mg), which on crystallisation from pentane had m.p. and mixed m.p. 52—53° [the authentic *sample* (Found: C, 80·2; H, 14·4. $C_{19}H_{40}O$ requires C, 80·2; H, 14·2%) was made by reducing the ketone with lithium aluminium hydride in ether].

Reduction of nonadecan-2-one by ammonium hexachloroiridate–ethanol–hydrochloric acid–water. The ketone (320 mg) was added to a solution of ammonium hexachloroiridate (223 mg) in a mixture of ethanol (45 ml), conc. hydrochloric acid (6 ml), and water (15 ml) and the mixture was boiled under reflux for 17 h. Isolation of the product in the usual way followed by chromatography on deactivated alumina (40 g) gave nonadecan-2-one (270 mg) and nonadecan-2-ol (40 mg), m.p. 52—53° (from pentane).

Comparative experiments. (a) *With sulphoxides.* A mixture of the sulphoxide, cyclopentanol (20 ml), bis-(2-methoxyethyl) ether (5 ml), water (10 ml), 4-t-butylcyclohexanone (100 mg), and ammonium hexachloroiridate (187 mg) was kept between 111 and 119° for 16 h. The results (Table 1) were as follows (amount of sulphoxide; mmol alcohol formed per mol of iridium salt; % axial alcohol): Me_2SO (5 ml; 1·0; 78%); $[CH_2]_4SO$ (1 ml; 1·4; 77%); Et_2SO (2 ml; 1·4; 66%); $MeSOBu^t$ (1 ml; 1·5; 71%); Pr^n_2SO (0·7 ml; no reduction); Ph_2SO (0·5 g; 5·0; 55%); $(PhCH_2)_2SO$ (0·3 g; 6·0; 50%).

(b) *With metal salts.* The preceding experiment was repeated with dimethyl sulphoxide (5 ml) and amounts of the following salts equivalent to the ammonium hexachloroiridate used before: $(NH_4)_2FeCl_5,H_2O$, $(NH_4)CoCl_3$, $4H_2O$, $Co(H_2O)_6Cl_2$, $Ni(H_2O)_6Cl_2$, $(NH_4)_2RuCl_6$, $(NH_4)_3$-$RhCl_6$, $(NH_4)_2PdCl_6$, $PdCl_2$, $(NH_4)_2OsCl_6$, $(NH_4)_2PtCl_6$. The ketone was not reduced in any of these experiments. Black precipitates formed when $(NH_4)_3RhCl_6$ and $(NH_4)_2$-$PdCl_6$ were used. The experiments were repeated keeping the temperature within the range 137—143°. A trace (<1%) of reduction occurred in each case.

(B) *Reactions using Sulphoxide Complexes.—Cholestanone.* (*a*) A solution of this ketone (222 mg), the complex [1] $IrCl_3(Me_2SO)_3$ containing one *O*-bonded ligand (50 mg), and dimethyl sulphoxide (70 mg) in propan-2-ol (30 ml, containing *ca.* 1% of water) was heated under reflux for 17 h. Evaporation, followed by chromatography of the product over deactivated alumina (22 g), gave 3α-isopropoxy-5α-cholestane (see later) (40 mg), m.p. 43—45°, 3β-isopropoxy-5α-cholestane (see later) (8 mg), m.p. 82—83°, cholestan-3α-ol (118 mg), and cholestan-3β-ol (60 mg), eluted in this order.

If some dimethyl sulphoxide was not added to the reaction mixture (with or without the ketone present) a white, sparingly soluble complex slowly separated from solution.

(*b*) A solution of cholestanone (600 mg) and *cis*-iridium–sulphoxide acid [1] (60 mg) in propan-2-ol (30 ml, containing *ca.* 1% of water) was heated under reflux, the yellow solution becoming almost colourless after 4·5 h (conversion into hydrides). Heating was continued for a further 12·5 h. The product was separated by chromatography into 3α-isopropoxycholestane (120 mg), 3β-isopropoxycholestane (17 mg), cholestan-3α-ol (303 mg), and cholestan-3β-ol (174 mg).

(*c*) A mixture of the ketone (284 mg) and *trans*-iridium–sulphoxide acid (15 mg) in propan-2-ol (2·5 ml) was kept in a sealed ampoule at 75—80° for 22 h. The seal was broken and the solvent was distilled out into 2,4-dinitrophenylhydrazine reagent. Acetone 2,4-dinitrophenylhydrazone (138 mg, 78%) was obtained.

4-t-Butylcyclohexanone. A solution of the ketone (0·1 g) and the hydride [(I) in ref. 1] (16 mg) in propan-2-ol (10 ml) and water (0·1 ml) containing hydrochloric acid (2 mol per mol of hydride) was heated under reflux under nitrogen for 2 h. G.l.c. analysis (2 m column Antarox at 130°) showed

that the ketone was completely reduced to a 76 : 24 mixture of the axial and equatorial alcohols.

When the experiment was conducted at 20° for 7 days, 87% of the ketone was reduced to a 73 : 27 alcohol mixture.

When the first experiment was repeated with *trans*-iridium–sulphoxide acid (16 mg) in place of the hydride, 71% of the ketone was reduced to a 73 : 27 axial : equatorial alcohol mixture.

Lanost-8-en-3-one. A solution of lanostenone (500 mg) and *cis*-iridium–sulphoxide acid [1] (70 mg) in propan-2-ol (25 ml) was refluxed for 29 h. Chromatographic separation of the product gave unchanged ketone (267 mg), m.p. 119—120°, lanost-8-en-3α-ol (163 mg), m.p. 138—139°, α_D +48°, and lanost-8-en-3β-ol (62 mg), m.p. 145—146°, α_D +61°.

Cyclohexanone. A solution of cyclohexanone (2·45 g, 25 mmol), dibenzyl sulphoxide (28 mg, 0·12 mmol), and *trans*-iridium–sulphoxide acid [1] (28 mg, 0·043 mmol) in propan-2-ol (25 ml) containing extra water (0·5 ml) was heated under reflux. The solution remained clear and after 63 h the ketone (>550 mol per mol of *trans*-acid) was completely reduced to cyclohexanol.

Benzophenone. Attempted reduction of benzophenone (2 g) in boiling propan-2-ol (30 ml) containing the *cis*-iridium acid (50 mg) for 60 h gave only starting ketone.

(C) *Other Methods of Reduction.—Acid-catalysed reduction of cholestanone.* (*a*) A solution of the ketone (344 mg) in propan-2-ol (50 ml) containing perchloric acid (5 ml; 72% solution; *d* 1·7) was refluxed for 24 h. Chromatography gave 3α- and 3β-isopropoxycholestanes (40 mg), cholestanone (103 mg), cholestan-3α-ol (132 mg), and cholestan-3β-ol (70 mg).

(*b*) A similar experiment with ketone (290 mg), propan-2-ol (50 ml), and concentrated hydrochloric acid (5 ml) gave unchanged ketone (212 mg), cholestan-3α-ol (52 mg), and cholestan-3β-ol (25 mg).

Experiment (*b*) was repeated with the *trans*-iridium acid (30 mg) present and a shorter reaction time (0·5 h). The product was a mixture of ethers (18 mg), cholestanone (159 mg), and cholestanols (112 mg).

Meerwein–Ponndorf–Verley reduction of cholestanone. The ketone (3 g) in dried propan-2-ol (300 ml) containing aluminium isopropoxide (3 g) was heated under reflux for 6 h. The mixture was slowly distilled until the distillate was acetone-free. Chromatography over alumina (100 g) gave cholestanone (1·89 g), cholestan-3α-ol (176 mg), and cholestan-3β-ol (896 mg).

Formation of Ethers

Ethanol was dried by distillation from magnesium ethoxide, and propan-2-ol was dried by the succinate ester method.

Reductive Etherification of Cholestanone.—A solution of the ketone (0·6 g) in dry propan-2-ol (30 ml) containing the *cis*-acid, $H(Me_2SO)_2[IrCl_4(Me_2SO)_2]$, (30 mg) was heated under reflux for 1·5 h. The steroids were isolated and separated by chromatography over neutral alumina (60 g). Elution with pentane gave 3α-*isopropoxycholestane*, m.p. 44—45° (from acetone), α_D +19° (Found: C, 83·8; H, 12·7. $C_{30}H_{54}O$ requires C, 83·65; H, 12·6%), and then 3β-*isopropoxycholestane*, m.p. 82—83° (from acetone), α_D +21° (Found: C, 83·5; H, 12·4%). Further elution (pentane–ether, 19 : 1) gave a mixture of cholestanone and cholestanols. Yields in this and in similar experiments in which water was added initially are given in Table 2. In one experiment the final solution was distilled and the distillate was treated with 2,4-dinitrophenylhydrazine reagent to give acetone 2,4-dinitrophenylhydrazone.

The authentic ethers were separately prepared by heating cholestan-3α- or 3β-ol (1·13 g), silver oxide (5 g), calcium sulphate (5 g), and 2-iodopropane (30 ml) under reflux for 18 h. Each ether was obtained in *ca.* 30% yield by chromatography and crystallisation.

Under the same (dry) reaction conditions, very similar proportions of ethers and alcohols were obtained starting with the *trans*-acid, $H(Me_2SO)_2[IrCl_4(Me_2SO)_2]$, or the complex $IrCl_3(Me_2SO)_3$ with one *O*-linked ligand, as catalyst (or precursor). All of these compounds are reduced to hydridoiridium species in propan-2-ol solution.[1]

Each ether and each alcohol (cholestan-3α- and 3β-ol) was recovered unchanged when submitted to the reductive etherification conditions (no cholestanone present) showing that interconversion of these compounds does not occur under the reaction conditions.

The same procedure was used to prepare other ethers from cholestanone, (Table 3). The following compounds were obtained (each crystallised from acetone).

(*a*) In ethanol: 3α-ethoxycholestane, m.p. 63·5—64·5°, α_D +22° (lit.,[14] m.p. 63—63·5°), and 3β-ethoxycholestane, m.p. 82—83°, α_D +22° (lit.,[15] m.p. 77—79°, α_D +20·8°; lit.,[16] m.p. 81—83°, α_D +23·8°).

(*b*) In propan-1-ol: 3α-*propoxycholestane*, m.p. 36—39°, α_D +18° (Found: 83·6; H, 12·5. $C_{30}H_{54}O$ requires C, 83·65; H, 12·6%), and 3β-*propoxycholestane*, m.p. 63—65°, α_D +17° (Found: C, 83·4; H, 12·6%).

(*c*) In cyclopentanol: 3α-*cyclopentyloxycholestane*, m.p. 78—79°, α_D +19° (Found: C, 84·4; H, 12·55. $C_{32}H_{56}O$ requires C, 84·15; H, 12·4%), and 3β-*cyclopentyloxycholestane*, m.p. 125—126° α_D +18° (Found: C, 84·4; H, 12·6%).

(*d*) In butan-2-ol: 3α-*s-butoxycholestane*, a liquid, α_D +22° (Found: C, 83·9; H, 12·5. $C_{31}H_{56}O$ requires C, 83·7; H, 12·7%) and 3β-*s-butoxycholestane*, m.p. 80—82°, α_D +20° (Found: C, 84·0; H, 12·6%).

Reduction of 3-Ethoxy-5α-cholest-2-ene.—(*a*) A solution of this enol ether (520 mg) in dry ethanol containing the complex $IrCl_3(Me_2SO)_3$ with one *O*-bonded ligand [1] (0·1 g) was heated under reflux for 15 h. The product was chromatographed on alumina (60 g). Elution with pentane (6 × 50 ml) gave 3α-ethoxy-5α-cholestane (303 mg), m.p. 63—64°, α_D +22°. Further elution with pentane afforded 3β-ethoxy-5α-cholestane (185 mg), m.p. 82—83°, α_D +22°. Elution with ether gave a mixture (24 mg) of cholestanone and cholestan-3α- and 3β-ols.

(*b*) The enol ether (500 mg) in cyclopentanol (25 ml) containing the same catalyst (100 mg) was kept at 95° for 16 h. Removal of the solvent followed by chromatography on alumina gave (with 8 × 50 ml pentane) 3α-cyclopentyloxycholestane (256 mg), m.p. 78—79°, α_D +19°. More pentane (6 × 50 ml) eluted 3β-cyclopentyloxycholestane (89 mg), m.p. 125—126°, α_D +18°. Elution with ether gave a mixture (165 mg) of cholestan-3α-ol and cholestan-3β-ol.

Reductive Etherification of 4-t-Butylcyclohexanone using the Iridium–Phosphite Catalyst.—(a) *In ethanol.* A solution

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of the ketone (231 mg, 1·5 mmol), iridium tetrachloride (205 mg, 0·55 mmol) and phosphorous acid (1 g, 12·5 mmol) in ethanol (20 ml; distilled from magnesium ethoxide) was heated under reflux for 18 h. Most of the ethanol was distilled off and the organic product was isolated with ether. G.l.c. analysis (1·3 m column containing polyphenyl ether at 100°) gave unchanged ketone (24%), 4-t-butylcyclohexanol (18%) (*cis* : *trans* 50 : 50), and 4-t-butylcyclohexyl ethyl ether (58%) (*cis* : *trans* 58 : 42). Authentic samples of the two ethers were made by the silver oxide method [17,18] with calcium sulphate present.[19]

An earlier experiment, in which the reagents were less dry, gave the ketone (24%), 4-t-butylcyclohexanol (46%) (*cis* : *trans* 75 : 25), and the ether (30%) (*cis* : *trans* 70 : 30).

(b) *In propan-2-ol.* The above experiment was performed with propan-2-ol in place of ethanol. The products were unchanged ketone (3%), 4-t-butylcyclohexanol (62%) (*cis* : *trans* 54 : 46), and t-butylcyclohexyl isopropyl ether (35—40%) (*cis* : *trans* 85 : 15). An authentic sample of each ether was made from the corresponding alcohol by a literature method.[14] The cis-1-*isopropoxy*-4-t-*butylcyclohexane* had b.p. 98° at 15 mmHg, n_D^{19} 1·4445 (Found: C, 79·0; H, 13·15. $C_{13}H_{26}O$ requires C, 78·7; H, 13·2%), and the trans-*isomer* had b.p. 108° at 15 mmHg, n_D^{20} 1·4443 (Found: C, 78·45; H, 13·15%).

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