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Potassium Borohydride Reductions Of Immobilised Ketosteroids†‡

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Abstract: Ketosteroids absorbed into various insoluble supports (powdered polyethylene, microporous 2% crosslinked polystyrene beads, macroporous highly crosslinked polystyrene beads, silica gel and alumina) can be reduced using aqueous potassium borohydride. The use of phase transfer catalysts generally raises yields. In the case of 6-ketosteriods the supported reactions often follow a stereochemical course significantly different from that of analogous reactions in solution. This is attributed to the adsorbtion of the steroid onto the inner surfaces of the supports. In these cases reduction of the ketosteroid by alkoxyborohydrides is substantially suppressed and thus most of the reduction is brought about by BH_4^- itself, a relatively sterically undemanding reductant. The net result is that whilst reductions of 6-ketosteroids in solution by potassium borohydride typically gives the 6α- and 6β-alcohols in the ratio 15:85, with the supported steroid the ratios can be as high as 90:10.

INTRODUCTION

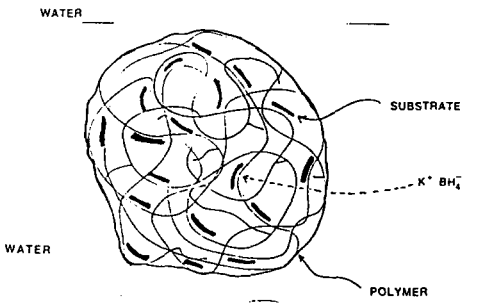
Merrifield introduced the technique of 'solid phase' peptide synthesis in 1963.[1] Since then there has been great interest in organic reactions carried out using polymer-supported (PS) species, mainly because such species can be separated simply and cleanly from non-supported species. In 1970s and 80s many studies were made of organic reactions using PS substrates, PS reagents or PS catalysts and these studies have provided an understanding of some of the most important features involved in PS reactions.[2-8] Now, in the 1990s, in connection with combinatorial syntheses there is enormous interest in the reactions of PS substrates.[9-20]

With combinatorial syntheses it is important to know whether reactions at chiral centres in PS substrates follow the same stereochemical course as analogous reactions in solution. In a previous study we investigated various reactions of PS steroids, especially the lithium aluminiumhydride and the sodium borohydride reductions of ketosterioids,[21] and found that the proportions of the stereoisomers obtained were essentially the same as in the corresponding reactions carried out in solution.[21] However, this might not always be the case. Thus, certain reaction solvents may only interact poorly with the supported substrate moieties and as a consequence the latter might interact more favourably with the support matrix. Such an effect might result in some reactions following a different stereochemical course to that they would in conventional solution reactions. We have now investigated some extreme examples of reactions involving a close interaction of the substrate and the support and here describe the results.[22] The study involves the *aqueous* potassium borohydride reduction of various PS steroidal ketones immobilised on a range of insoluble supports. Since the ketones are insoluble in water, it was not necessary to bind them covalently to the support: they were simply absorbed. This not only permits the maximum interaction of the substrate with the support matrix, it also

† Dedicated to Arthur J. Birch: an enthusiastic and inspiring researcher.
‡ This work was initiated whilst JCB and PH were at the University of Lancaster.

permits the reduction products to be recovered simply by washing the insoluble support with an organic solvent. This type of attachment-detachment procedure for PS substrates is clearly one of the simplest possible and substantially easier than procedures involving covalent linkages. It was anticipated that if diffusion of the borohydride into the support proved to be difficult, phase transfer catalysis (PTC) might be helpful.[23] The reaction system is shown schematically in Figure 1.

Figure 1:



Whilst numerous studies have been made of photochemical reactions of organic molecules adsorbed onto inorganic supports, there have been very few studies of other types of organic reactions where the organic substrates were absorbed or adsorbed either to inorganic supports or to organic polymer supports. The studies most relevant to the present work are the photochemical additions of olefins and allene to steroidal enones adsorbed onto inorganic[24] or absorbed into organic supports,[25] the lithium monoalkoxyaluminiumhydride reductions of steroidal ketones at specially prepared templated surfaces,[26] and our own work on the borohydride reduction of prochiral ketones and on the epoxidation of 2-alkyl- or -aryl-naphthoquinones absorbed into chiral supports.[27] There are several reports of lipophilic metal ion extractants being absorbed into polymer beads and then being used to extract ions from aqueous media.[28, 29] Aspects of these various studies relevant to the present work will be discussed below as and where appropriate.

RESULTS AND DISCUSSION

Absorption Studies

Initially experiments were carried out on the absorption of various steroids into microporous 2% crosslinked polystyrene beads and/or into highly crosslinked macroporous polystyrene beads (Amberlite XAD-4). The object was to identify satisfactory methods for absorption and to demonstrate that the products obtained were not simply a physical mixture of the steroid and the beads. The loadings used in these initial experiments were 8%-13% by weight.

Two methods were generally successful. In Method A the insoluble support was suspended in a solution of the steroid in tetrahydrofuran (THF). Water was then added slowly and the THF was distilled out at such a rate as to maintain the solvent volume. Thus, the polarity of the solvent increased slowly and its ability to dissolve the lipophilic steroid decreased slowly. The intention was to avoid precipitation and allow the steroid to absorb into the beads. When no THF remained, i.e. the solvent was just water, the beads were filtered off, washed with water and dried. Using this method ^{14}C-labelled cholesteryl benzoate (**1**), prepared using [*ring*-^{14}C]benzoic acid, was absorbed into Amberlite XAD-4 beads and the level of radioactivity in the solvent was monitored. This gave the results summarised in Figure 2. They show that immediately prior to filtering

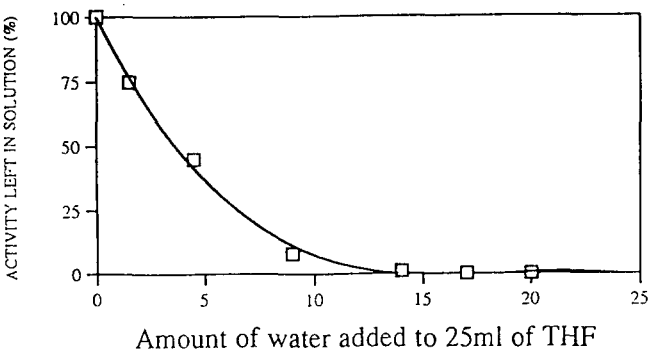
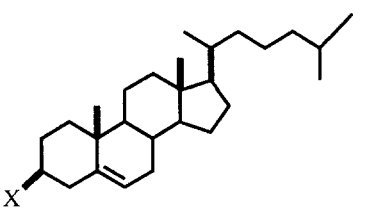
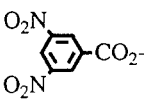


Figure 2: Level of radioactivity remaining in the solution during absorption of labelled compound (1) in Amberlite XAD-4.

off the beads <1%, if any, of the steroid remained in solution. When cholesteryl 3,5-dinitrobenzoate (**2**) was absorbed in this way onto either the microporous or the macroporous beads the products had a strong yellow colour suggesting the presence of significant π-π interactions. Inspection of these products under an optical microscope revealed that the beads were uniform in colour and that they contained only small amounts of crystalline material (<10% of that used). This was confirmed by X-ray powder photographs in comparison with those obtained for physical mixtures. A scanning electron microprobe study of cholesteryl chloride (**3**) absorbed into Amberlite XAD-4 showed that the steroid was uniformly distributed throughout the beads.



(**1**): X = $C_6H_5\ CO_2$-

(**2**): X = 

(**3**): X = Cl-

In Method B the solid support was suspended in a solution of the steroid in dichloromethane and the latter was evaporated off slowly. In this way cholesteryl benzoate (**1**) was absorbed into both the microporous and macroporous polystyrene beads. Inspection of the products under an optical microscope revealed the presence of only small amounts of crystalline material (<10% of that used) and this was confirmed by X-ray studies as before.

These two methods were used to absorb 8-13% by weight of steroids containing 3-,6-,7- or 20-keto groups [see formulae (**4**) to (**10**)] into one or more of a range of solid supports. The supports included polyethylene powder, the microporous and macroporous crosslinked polystyrene beads discussed above, silica gel and silanized silica gel, and alumina. Inspection of the products under an optical microscope revealed that in most cases the products contained little or no crystalline material (<10% of that used). In the few cases where the product did contain significant amounts of crystalline material, it was discarded. In general, Method A gave the better results with the organic supports, whilst Method B gave the better results with the inorganic supports.

Reduction and Analytical Procedures

For each ketosteroid the free or the supported material was suspended in a 2% solution of potassium borohydride in water at 60 °C for 2 h. In some cases 2.5 mole% of a PTC was added. The reduction of the free solid steroid was also studied because small amounts of solid steroid would be present in many supported samples and these reductions would provide a standard. At the end of the reaction period the mixture was cooled and the beads filtered off. The beads were washed thoroughly with water to remove any remaining reductant. The steroidal products were then washed off the beads with dichloromethane and converted into trimethylsilyl (TMS) ethers for analysis by gas chromatography (GC). Standard mixtures of the epimeric alcohols were obtained by carrying out conventional sodium borohydride and/or lithium aluminiumhydride (LAH) reductions. These products were also converted into TMS derivatives.

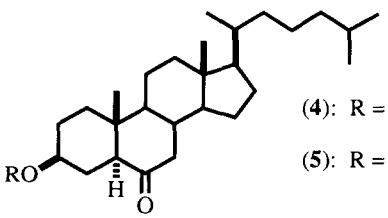
Reductions of 6-Ketosteroids

The reduction of 3β-hydroxy-5α-cholestan-6-one (**4**) was studied the most extensively. Reduction with sodium borohydride in methanol gave the 6α- and 6β-alcohols in the ratio 15:85, and reduction with LAH in ether gave the 6α- and 6β-alcohols in the ratio 11:89. These results are in excellent agreement with previous studies of hydride reductions of 6-ketosteroids of the 5α-H series.[21,30] The products were used to identify the 6α–and 6β–alcohols in the subsequent GC analyses.

Reductions were carried out with ketone (**4**) bound to the full range of supports. Several PTC were also investigated. The results are summarised in Table 1. Several points are evident. First, in all cases the supported ketosteroids reacted, though in the absence of PTC the reduction yields were usually only in the range 20%-65%. With PTC the yields were usually in the range 40%-90%. The second, and most interesting, point is that the proportion of the 6α–alcohol produced increases significantly along the series:

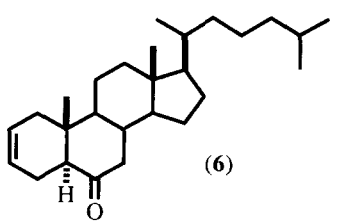
no support<polyethylene powder<2% crosslinked polystyrene beads<silica gel< Amberlite XAD-2 or XAD-4.

The proportion of the 6α-alcohol also tends to increase when PTC is used. With the Amberlite XAD-4 support and tetra-*n*-butylammonium bromide (TBAB) to provide PTC, the proportion of the 6α–alcohol was as high as 90%, representing an absolute yield of 41%. Finally, the use of alumina as a support resulted in a quantitative yield of the 6β-alcohol.

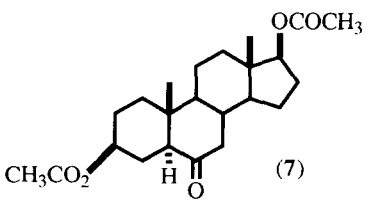


(**4**): R = H-

(**5**): R = C_6H_5CO-



(**6**)



(**7**)

Table 1: Reductions of 3β-Hydroxy-5α-cholestan-6-one(4)[a]

Entry	Support	Loading	Without Catalyst		With TBAB[c] Catalyst		With TBAHS[d] Catalyst		With DCHC[e] Catalyst	
		Method[b] by weight %	% Yield	% α-Alcohol	% Yield	% α-Alcohol	% Yield	% α-Alcohol	% Yield	% α-Alcohol
1	None	-	0	-	80	18	79	24	93	6
2	Polyethylene Powder	A;13	30	22	80	26	93	20	97	14
3	2% Crosslinked Polystyrene Beads	A;10	65	34	59	43	62	48	56	22
4	Amberlite XAD-2 †	A;8	9	-	49	81	60	60		
5	Amberlite XAD-4	A;8	20	65	46	90	18	81	41	84
6	Silica Gel	B;10	42	62	66	39	58	60		
7	Silanized Silica Gel	B;10	45	47	41	4				
8	Alumina	B;10	100	0	100	0				

a For each reaction the solid ketosteroid or the supported ketosteroid was suspended in a 2% solution of aqueous KBH_4 at 60 °C for 2h. The yields and proportions of the α- and β-alcohols were determined by GC of the TMS ethers.

b *See text for a description of Methods A and B.*

c TBAB = tetra-n-butylammonium bromide.

d TBAHS = tetra-n-butylammonium hydrogen sulphate.

e DCHC = dicyclohexano-18-crown 6.

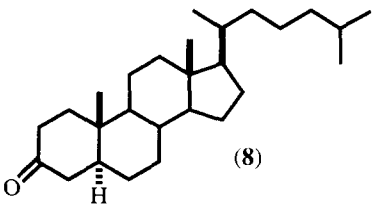
f Amberlite XAD-2 is a macroporous crosslinked polystyrene with an internal surface area of ~330m^2/g.

The reduction of three other 6-ketosteroids, namely compounds (**5**), (**6**) and (**7**), were investigated, mainly to determine whether the use of Amberlite XAD-4 as a support generally increases the proportion of the 6α–alcohol formed in the reduction. From the results summarised in Table 2 it is evident that it does.

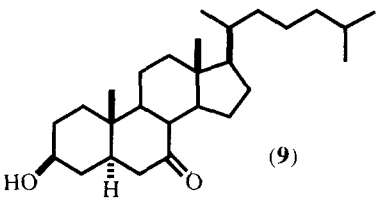
Reductions of 3-, 7-, and 20-Ketosteroids

Ketosteroids (**8**), (**9**) and (**10**) were reduced using sodium borohydride in methanol to provide samples of the mixtures of epimeric alcohols to assist in the subsequent GC analyses. The proportions of the α- and β-alcohols were, respectively, 5:95, 72:28 and 8:92. Reduction of 20-ketosteroid (**10**) with LAH in ether gave the 20α- and 20β-alcohols in the ratio 9:91. These ratios are in excellent agreement with those reported in the literature for similar ketones.[31-33]

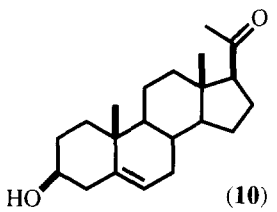
The reductions of these three ketones were then investigated using the methods discussed above for the 6-ketosteroids. The results are summarised in Table 3. Although in these cases many of the reduction yields were modest it is nevertheless clear that with the 3- and 7-ketosteroids the use of Amberlite XAD-4 *does not* bring about a major change in the proportions of the epimeric alcohols produced. With the 20-ketosteroid there is a modest, though probably significant, increase in the proportion of the 20α-alcohol produced.



(**8**)



(**9**)



(**10**)

Rationalisation of the Results

The main results to be rationalised are those concerned with the stereochemical course of the supported reductions, in particular why some of the reductions follow stereochemical courses considerably different from those observed for conventional borohydride reductions in solution. The common feature of the supports which produce the greatest stereochemical effects is that they all have very large internal surfaces. Thus, Amberlite XAD-4 and XAD-2 have ~750m^2/g and ~330m^2/g respectively and the silica gel used has a surface area of ~600m^2/g. As a consequence these supports are able to *adsorb* a significant number of steroid molecules. The surface area required to adsorb one molecule of steroid (**4**) flat to the surface is ~140$Å^2$. Thus, if all the inner surface of Amberlite XAD-4 had a close-packed monolayer of steroid (**4**) adsorbed it could, by simple calculation, adsorb ~320mg of steroid per gram of resin. This corresponds to a 32% loading by weight. Since in the present experiments loadings of 8%-13% were used, it is clear that on the basis of these simple calculations there is sufficient surface in the Amberlite XAD-4 beads for the steroid to be present entirely as a monolayer. However, it seems unlikely that the steroid would be packed so efficiently, especially as the inner

Table 2: Reductions of 6-Ketosteroids (5)-(7)[a]

Entry	Support	Loading	Without Catalyst		With TBAB[c] Catalyst	
		Method[b] by weight %	% Yield	% α-Alcohol	% Yield	% α-Alcohol
	(a) 3β-Benzoyloxy-5α-cholestan-6-one (**5**)[d]					
1.	None	A ; 8	40	6	43	24
2.	2% Crosslinked Polystyrene Beads	A ; 8	60	30	72	40
3.	Amberlite XAD-4	A ; 8	24	75	28	70
	(b) 5α-Cholest-2-ene-6-one (**6**)					
4.	None	A ; 8	63	12	73	3
5.	2% Crosslinked Polystyrene Beads	A ; 8	82	15	80	13
6.	Amberlite	A ; 10	71	53	84	45
	(c) 3β, 17β–Diacetoxy-5α-androstan-6-one(**7**)					
7.	None	A ; 10	16	28	20	25
8.	Amberlite XAD-4	A ; 10	13	51	43	91

[a] See Footnote[a] in Table 1
[b] See Footnote[b] in Table 1
[c] See Footnote[c] in Table 1
[d] Prior to GC analysis the ester groups in the products were hydrolysed by treatment with methanolic sodium hydroxide (1N) at reflux temperature for 4h.

Table 3: Reductions of Ketosteroids (8)-(10)[a]

Entry	Support	Loading	Without Catalyst		With TBAB[c] Catalyst	
		Method[b] by weight %	% Yield	% α-Alcohol	% Yield	% α-Alcohol
	(a) 5α-Cholestan-3-one (**8**)					
1.	None	-	0	-	30	5
2.	2% Crosslinked Polystyrene Beads	A ; 10	5	-	28	4
3.	Amberlite XAD-4	A ; 10	0	-	31	2
	(b) 3β-Hydroxy-5α-cholestan-7-one (**9**)					
4.	None	-	26	56	58	67
5.	Amberlite XAD-4	A ; 12	16	59	37	63
6.	Silica Gel	B ; 10	25	54	40	60
	(c) 3β, Hydroxypregn-5-en-20-one (**10**)					
7.	None	-	21	2	20	2
8.	Amberlite XAD-4	A ; 8	24	21	35	10

a See Footnote[a] in Table 1
b See Footnote[b] in Table 1
c See Footnote[c] in Table 1

surfaces will not all be planar, or that the surface area available to the steroid molecules would be quite so high as the values given since the latter were determined by the standard method using nitrogen adsorption. In practice is very likely, therefore, that with all three supports a substantial fraction of the steroid present was adsorbed as a monolayer, whilst some may have been adsorbed as a bi- or multi-layer. As a consequence of the latter not all the steroid may have been readily available for reaction.

It is tempting to seek to rationalise the stereochemical effects observed on the basis that the significantly less hindered α-face of the steroid adsorbs preferentially to the inner surfaces. This would result in the α-face being "screened" from attack so that reduction must take place by β-face attack. De Mayo *et al.* explained in this way the stereochemical outcome of some photochemical additions of olefins and allene to various steroidal enones adsorbed onto silica gel or alumina.[24] In the present systems, however, such a simple rationalisation is not plausible because the stereochemical courses of the reductions of the 3-ketone (**8**) and, more importantly since the ketone group is nearer to the 6-position, of the 7-ketone (**9**) were in each case essentially the same whether the reductions were carried out in solution, by suspending the solid steroid in aqueous potassium borohydride, or in the supported systems. Thus, the substantial stereochemical effect is only a feature of the 6-ketosteroids. Moreover, bearing in mind the results obtained with ketones (**4**)-(**7**), the nature of the groups at the 3- and 17-positions does not appear to have a very pronounced effect. As noted before, there was a smaller stereochemical effect in the reduction of the 20-ketone (**10**).

It is well known that borohydride reductions of unhindered steroidal ketones normally give the more stable equatorial alcohol rather than the less stable axial alcohol.[34] This has been called "product development control" (PDC).[35] Where, as is the case with the 6-ketones, the approach of the reagent required to give the equatorial alcohol is seriously hindered, the axial alcohol becomes the main product. This has been called "steric approach control" (SAC).[35] It is also well known that in borohydride reductions all four B-H bonds are available for reduction. The initial reagent is BH_4^-. When this brings about reduction the product is an alkoxyborohydride: see Equation 1. When this reacts the product is a dialkoxyborohydride, and so on.

Equation 1:

It is also well known that the reactivity of the reductant increases as the number of alkoxy groups increases.[36,37] Thus, in a conventional borohydride reduction in solution up to 75% of the reduction may be brought about by alkoxyborohydrides.

In the present supported reductions both the steroidal ketones and the derived alkoxyborohydrides are immobilised by adsorption and as a consequence it is difficult for them to react together. Thus, *we suggest that in the supported reductions involving Amberlite XAD-2 or -4 or silica gel most of the reduction is brought about by* BH_4^- *itself.* The latter is much less bulky than the alkoxyborohydrides and we suggest that reductions brought about by it are not subject to significant SAC, i.e. that the reductions of the 6-ketosteroids follow PDC and therefore lead to the equatorial 6α-alcohols. The proportion of 20α- and 20β-alcohols produced by the borohydride reduction of 20-ketosteroids is also usually determined by steric factors[34] and the modest shift observed in the stereochemical course of the supported reductions of ketosteroid (**10**) may also be due to a bigger contribution than usual being made towards the reducing action by BH_4^-.

The powdered polyethylene and 2% crosslinked microporous polystyrene beads do not have significant internal surfaces and the absorbed steroids cannot therefore be effectively immobilised by *adsorption*. However, diffussion within these two supports will be greatly restricted compared with that in solution and again, therefore, BH_4^- itself can be expected to contribute more to the overall reduction than it would in a solution system. Microenvironments within the supports can, in the absence of a swelling solvent, be expected to be "hexane-like" and "toluene-like" respectively and this may also influence the stereochemical course of the reductions.

Other reactions involving reagents adsorbed to alumina have been studied extensively and they are often complex.[38,39] In the present supported system the 6-ketosteroid might bind through the carbonyl oxygen to an acidic site. The binding might not only catalyse the reduction but also heavily favour reduction by the α-face approach of the reductant.

Conclusions

It has been shown that ketosteroids absorbed into various insoluble supports can be reduced using aqueous potassium borohydride. In some cases the stereochemical courses of the supported reductions differ substantially from those found for the analogous reactions in solution. The differences are particularly large for the reductions of 6-ketosteroids absorbed into three supports. These are Amberlite XAD-2 and -4 and silica gel. The common feature of these supports is that they have very large internal surfaces (~330 to ~750m^2/g). It is suggested that with each of these supports the ketosteroid and the initial reduction product, the alkoxyborohydride (see Equation 1), are immobilised by adsorption to the inner surfaces. The result is that the reduction of the ketosteroid by the alkoxyborohydrides is greatly suppressed and most of the reduction is, therefore, brought about by BH_4^- itself. This is a relatively small reagent and is not subject to "steric approach control". The net result is that whilst reductions of 6-ketosteroids in solution by potassium borohydride typically give the 6α- and 6β-alcohols in the ratio 15:85, with the supported steroid the ratios can be as high as 90:10, i.e. the stereochemical course of the reductions is essentially reversed. *These are, therefore, clear examples of where PS reactions do not follow the same stereochemical course as the analogous reactions in solution.*

The results highlight the need when discussing borohydride reductions to recognise that there can be several active reductants present, that each of these reductants may produce different stereochemical results, and that the observed stereochemical course in the weighted average of those of the various reductants. Reaction conditions that restrict the number of active reductants could lead to novel stereochemical results, especially when bulky substrates are involved.

EXPERIMENTAL

For use with lithium aluminiumhydride (LAH) ether was dried over calcium hydride, distilled, then redistilled from over LAH. Tetrahydrofuran (THF) was dried over calcium hydride, distilled, and stored over molecular sieves. Extracts were dried over magnesium sulphate. Melting points were determined with a Kofler hot-stage apparatus. Polymers were filtered off and washed using number 4 grade sintered glass filters and were dried in a vacuum oven (0.1 mmHg at 50 °C) to constant weight. Infrared spectra (IR) were generally measured for KBr discs on a Nicolet MX-1 FT-IR instrument. Proton magnetic resonance spectra (^{1}H NMR)

were recorded at 100 MHz for *ca.* 10% solution in deuteriochloroform containing tetramethylsilane as internal reference.

Source of Steroids

Steroids (**1**), (**3**), (**4**), (**8**) and (**10**) were purchased from the Sigma Chemical Company. Esters (**2**) and (**5**) were prepared from the corresponding alcohols by treating them, using standard procedures, with the appropriate acid chloride and pyridine. The 6-ketosteroid (**6**) was prepared by oxidizing steroid (**4**) using Jones' reagent, then treating the 3,6-dione produced with zinc dust and trimethylsilyl (TMS) chloride in dry THF as described previously.[40] The 6-ketosteroid(**7**) was prepared by treating commercial 3β, 17β-diacetoxyandrost-5-ene successively with borane in THF, alkaline hydrogen peroxide, and Jones' reagent using standard procedures. The 7-ketosteroid (**9**) was obtained by oxidizing commercial cholesteryl acetate with t-butyl chromate,[41] treating the product in ethanol with hydrogen at atmospheric temperature and pressure in the presence of 10% palladium on charcoal,[42] followed by ester hydrolysis using potassium hydroxide in ethanol. All the steroidal starting materials, intermediates and products had melting points in agreement with literature data and IR and H^1 NMR spectra consistent with the assigned structures.

[*Ring*-^{14}C]Benzoic acid (1.02 μCi per g) was available from an earlier study.[43] Using standard experimental procedures it was converted into the acid chloride by treatment with oxalyl chloride, then the product was used in combination with pyridine to esterify pure cholesterol (from Sigma Chemical Company). The cholesteryl benzoate (**1**) obtained had an activity of 0.26 μCi per g. Activities were determined by scintillation counting as described previously.[44]

Source of Insoluble Supports and Their Properties

Polyethylene powder was obtained from the Aldrich Chemical Company. The 2% crosslinked microporous polystyrene beads were Biobeads SX2 (200-400 mesh) from Biorad. Amberlites XAD-2 and XAD-4, produced by Rohm and Haas, were highly crosslinked macroporous polystyrene beads (20-50 mesh) with surface areas per gram of ~330m^2 and 750m^2 respectively. The silica gel, purchased from Fluka, was chromatographic grade silica gel 40 of ≥ 400 mesh with a surface area of ~600m^2/g. It was silanized as described previously.[45] The alumina, purchased from Fluka, was a neutral chromatographic grade of 100-125 mesh. The surface area per gram was not quoted.

Loading Procedures

(a) Method A: Typically the polymer support (10g) was suspended in a warm solution of the steroid (*ca.* 1.0g) in THF (25ml). Water (50ml) was added dropwise over 30 minutes as the THF was distilled out. The polymer-supported steroid was then filtered off, washed with water and dried.

(b) Method B: Typically a suspension of the inorganic support (4.50g) in a solution of the steroid (0.50g) in dichloromethane (10ml) at 20 °C was left in a fume cupboard and the solvent allowed to evaporate over several hours. The supported steroid was then collected and dried.

(c) Tracer Experiment: This was carried out as described in Method A using labelled cholesteryl benzoate and Amberlite XAD-4 beads. Periodically 0.1ml samples of the solvent were removed and the radioactivity estimated by scintillation counting using procedures described previously.[44]

Characterisation of Loaded Supports

The loaded supports were examined under a Nikon L-Ke polarising microscope at 200x magnification. The scanning electron microprobe study of the supported cholesteryl chloride was kindly made by Professor H Widdecke of the Technical University of Braunschweig, Germany. The X-ray powder photographs were taken with a Phillips PW1024 camera using Cu-K_α radiation.

Gas Chromatographic Analyses of Hydroxysteroids

Analyses of the mixtures of hydroxysteroids produced by the reactions described below were analysed as follows.[46]

A small portion (*ca.* 2mg) of the product was converted into the corresponding TMS ether(s) by treatment with a mixture of TMS chloride and N,O-bis(trimethylsilyl)acetamide (0.2ml; 1 vol: 10 vols) for a minimum of 4h at 20 °C. GC was carried out with a Perkin-Elmer 8310 gas chromatograph (flame-ionization detector) using 2-m columns containing 3% OV-1 as the stationary phase at approximately 250 °C, the precise temperature depending on the samples being analysed. Samples were analysed in duplicate.

Ester groups in products were hydrolysed by treatment with methanolic sodium hydroxide (1N) at reflux temperature for 4h prior to formation of the TMS ethers.

Reductions of Ketosteroids in Solution

These reductions were mainly carried out in order to assist with the GC analyses of the products from the reductions of the supported steroids. The results of the analyses are given in the results and discussion section. The following procedures are typical.

(a) Using sodium borohydride

6-Ketocholestanol (**4**) (0.20g, 0.50 mmol) and sodium borohydride (1.7g, 45mmol) in methanol (25ml) were heated under reflux with stirring for 4h. The reaction mixture was cooled. Saturated aqueous ammonium chloride (15ml) was added dropwise. The precipitate which formed was filtered off, washed with water, then dissolved in dichloromethane. The solution was dried. A small portion was set aside for GC analysis. On slow evaporation of the solvent colourless needles formed (90mg, 44%), m.p. 175-178 °C. By IR spectroscopy the product contained no carbonyl groups.

By GC analysis of the TMS ethers the total product contained the 6α- and 6β-alcohols in the ratio 15:85. The crystals were the 6β-alcohol.

(b) With lithium aluminiumhydride

LAH (0.50g, 27mmol) in dry ether (5ml) was added dropwise to 6-ketocholestanol (**4**) (0.20g, 0.50mmol) in ether (30ml) at 20 °C. The mixture was stirred and heated under reflux for 2h. A solution of ethyl acetate in THF (20ml; 1 vol:9 vols) was added dropwise to the cold solution followed by saturated aqueous ammonium chloride (20ml). The organic layer was separated, washed with water, and dried. Evaporation of the solvents left a white solid (0.18, 88%). By IR spectrosopy the product contained no carbonyl groups.

By GC analysis of the TMS ethers the product contained the 6α- and 6β-alcohols in the ratio 11:89.

Reductions of Supported Ketosteroids

The following procedure is typical. The results are summarised in Tables 1 to 3.

Reaction Summarised in Table 1, Entry 5 Using TBAB

6-Ketosteroid (**4**) (0.18mmol) on Amberlite XAD-4 (0.60g) was suspended in aqueous potassium borohydride (5.0 ml of a 2% solution, 1.8mmol). Tetra-n-butylammonium bromide (1.6mg, 5.0 x 10^{-3} mmol) was added as a PTC and the mixture was stirred vigorously at 60 °C for 2 h. The mixture was cooled, then the polymer beads filtered off and washed successively with dilute hydrochloric acid (2 x 5 ml, 0.1N) and water (3 x 5ml). The reduction product was extracted from the beads with dichloromethane (3 x 8 ml). The dried extracts were evaporated to leave the crude product (33 mg; 46% yield).

By GC analysis of the TMS ethers the product contained the 6α- and 6β-alcohols in the ratio 90:10.

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