Preparation of a Polymer-supported Diol and Its Use in isolating Aldehydes and Ketones from Mixtures and as a Protecting Group for Aldehydes and Ketones

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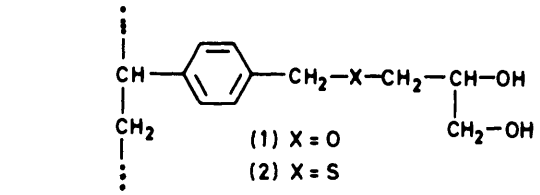
Reaction of cross-linked chloromethylated polystyrenes with 3-mercaptopropane-1,2-diol and sodium hydroxide under phase-transfer conditions gave polymers containing diol residues. A range of aldehydes and ketones were successfully bound to these polymers *via* acetal formation. The aldehydes and ketones were released by treating the products with aqueous dioxane in the presence of toluene-*p*-sulphonic acid. The polymer-supported diol could be used to isolate aldehydes or ketones from mixtures with other compounds and to separate a 3-oxosteroid from a 17- or a 20-oxosteroid. The supported diol was successfully used to protect the aldehyde group of undec-10-enal whilst the terminal vinyl group was transformed into $^{-}CH_2CH_2OCOPh$. Attempts to monoprotect dicarbonyl compounds were unsuccessful.

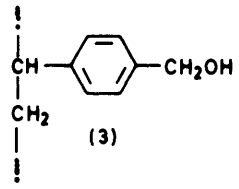
In recent years organic chemists have shown considerable interest in polymer-supported protecting groups.[1,2] Major advantages of such protecting groups are the ease with which the supported species can be separated from the non-supported species at the end of each reaction and the possibility of using excesses of soluble reagents to increase reaction yields without causing separation problems. The best known example is the use of chloromethylated cross-linked polystyrene in ' solid phase ' peptide synthesis.[3]

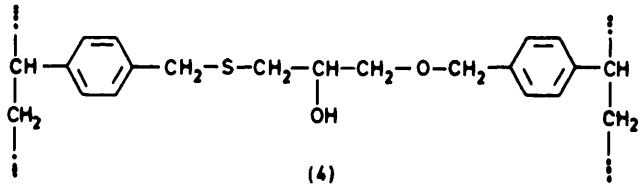
Several polymer-supported diols have been prepared and used as protecting groups for aldehydes.[4-7] The most successful of these was the diol (1), but even this only reacted satisfactorily with aldehydes, not ketones.[4,6] We report the preparation of the polymer-supported diol (2), using a phase-transfer catalysed reaction and its use both in the isolation of aldehydes and ketones from mixtures and as a protecting group for aldehydes and ketones.

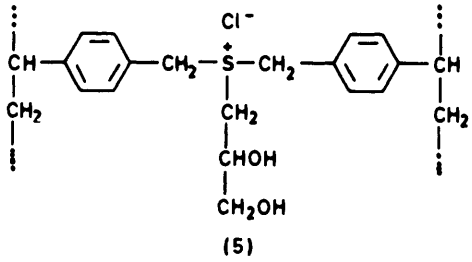
Preparation of Diol (2).—Reaction of various chloromethylated cross-linked polystyrenes with 3-mercaptopropane-1,2-diol and sodium hydroxide under phase-transfer conditions gave various polymer-supported diols (2).[8] Compared with the preparation of the diol (1), the preparation of the diol (2) has the attractive feature that it only requires one reaction step instead of two, and that this is a phase-transfer catalysed reaction (*i.e.* it uses a cheap base and the solvents need not be dry). The number of diol residues in the products, as estimated by sulphur analyses, were generally in the range 2.3—3.2 mmol per g, corresponding to reaction yields of 68—86%. Since all the chloromethyl groups reacted (i.r. spectra of products lacked the characteristic bands), other reactions were also occurring. Some chloromethyl groups may have reacted with hydroxide to give the hydroxymethyl groups (3), and some of the latter or some other polymer-bound hydroxy groups may have reacted with chloromethyl residues to give ether linkages, for example, linkage (4). A third possibility is that the residues (2) reacted with chloromethyl residues to give the sulphonium salts (5). Chloride analyses suggest that 4—10% of the chloromethyl residues may have reacted in this way.

Attachment and Detachment Reactions.—A range of aldehydes and ketones (see Table 1) reacted successfully with the polymer-supported diol (2) to give acetals. The reactions were carried out by heating the diol (2) with an excess of the carbonyl compound in benzene containing toluene-*p*-sulphonic acid as catalyst and azeotroping out the water. The products









had the expected i.r. spectra, for example, bound oxoesters displayed carbonyl bands due to the ester groups. The carbonyl compounds were successfully recovered from the polymers by treatment with aqueous dioxane containing toluene-*p*-sulphonic acid. As judged by the amounts of material recovered, 0.65—1.37 mmol of the carbonyl compounds were generally bound to 1 g of polymer. These loadings are substantially higher than those obtained by Leznoff with the diol (1) (0.3—0.4 mmol per g with aromatic aldehydes, less with other carbonyl compounds) [4,6] and comparable to

that obtained by Fréchet for the binding of terephthaldehyde to a diol-containing resin derived from a cross-linked glycidyl methacrylate.[7]

In an attempt to determine whether the polymer could be recycled successfully, *p*-bromobenzaldehyde was successively attached and then detached for five complete cycles. However, the loadings achieved varied considerably and whilst it was clear that the polymer could be re-used, it was not clear how many cycles it could withstand without serious loss of capacity. After five cycles the sulphur content of the polymer had, however, only fallen to 82% of the original value, corresponding to a loss of only 4% per cycle.

Table 1. Attachment of carbonyl compounds to 1% cross-linked polystyrenes containing the diol residues (2) and their subsequent detachment [a]

Carbonyl compound	Capacity of diol (2) (mmol per g)	Amount of carbonyl compound bound to polymer [b] (mmol per g)
p-Bromobenzaldehyde	2.27	1.22
	2.80	1.03
p-Chlorobenzaldehyde	3.19	1.37
p-Formylbenzoic acid	3.15	2.55 [c]
Terephthaldehyde	3.15	0.92 [d]
β-Naphthaldehyde	2.27	1.15
Undecanal	2.04	0.65
p-Bromoacetophenone	2.27	1.02
6-Methylhept-5-en-2-one	2.27	0.68
5α-Cholestan-3-one	3.15	1.20
Methyl 3-oxo-5β-cholanate	3.15	1.00
3β-Acetoxy-5α-androstan-17-one (7)	2.80	0.14 [c]

[a] Unless indicated otherwise, 1.9—2.5 mmol of carbonyl compound were used per mmol of diol (2). See Experimental section for details of a typical experiment. [b] Unless indicated otherwise, this is based on the amount of carbonyl compound recovered from the detachment procedure and is, therefore, a minimum value. [c] Estimated from weight gain of polymer on attachment. [d] Only 1.1 mmol of carbonyl compound used per mmol of diol (2).

Use of the Polymer-supported Diol (2) *in the Isolation of Aldehydes and Ketones.*—If compounds can be readily attached to and detached from a polymer-supported protecting group, the polymer can be used to isolate compounds containing the appropriate functional group from mixtures with other types of compounds. Such separations are a type of affinity chromatography. A recent example is the separation of *cis*-1,2-diols from other compounds using a polymer-supported phenylboronic acid.[9]

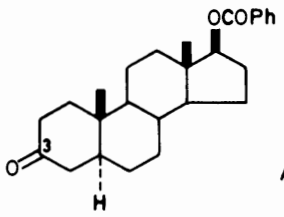
The separation of aldehydes and ketones from other compounds was investigated using the polymer-supported diol (2). The results are summarised in Table 2. The procedure used was as follows: (i) the mixture was treated with an excess of polymer under the usual conditions; (ii) the polymeric product was filtered off and washed thoroughly; then (iii) the bound material was released from the polymer in the usual way. Application of this procedure to a mixture of the ketone (6) (5%) and cholesteryl acetate (95%) gave the ketone (6) (70% of that present in the original mixture) as a crystalline solid which after one recrystallisation had a satisfactory m.p. (see entry 1). Similarly, and more usefully, 4-diphenylphosphinylbenzaldehyde was isolated (entry 2) from a crude reaction product which also contained triphenylphosphine and 4-diphenylphosphinylbromobenzene,[10] and 4-formyldibenzo-18-crown-6 was isolated (entry 3) from the crude product obtained by partial formylation of dibenzo-18-crown-6.[11]

Attempts were then made to separate pairs of carbonyl compounds from each other. To succeed one carbonyl compound must clearly bind to the polymer much more readily than the other, especially as not all the supported diol groups react with the carbonyl compounds (see Table 1). 4-Bromobenzaldehyde bound to the polymer more readily than 4-bromoacetophenone, but a clean separation was not achieved (entry 4). However, the difference between the 3-oxosteroid (6) and 17-oxosteroid (7) was such that the product isolated *via* the polymer from an equimolar mixture of the ketones

Table 2. Isolation of aldehydes and ketones using the polymer-supported diol (2)

Entry	Capacity of 1% cross-linked polymer (mmol of per g)	Amount of diol (mmol per mmol of carbonyl compound)	Components in original mixture	Molar composition of original mixture (%)	Material isolated *via* polymer: Composition (%) [a]	Material isolated *via* polymer: Recovery (%) [b]	Total recovery [c] (%)
1	1.20	2.0	3-Oxosteroid (6)	5	100	70	
			Cholesteryl acetate	95	0		
2	2.42	1.2	4-Diphenylphosphinylbenzaldehyde	55	100	66	
			4-Diphenylphosphinylbromobenzene / Triphenylphosphine	45	0		
3	2.27	1.8	4-Formyldibenzo-18-crown-6	25	100	77	
			Dibenzo-18-crown-6	75	0		
4	1.20	0.5	4-Bromobenzaldehyde	50	74	44	90
			4-Bromoacetophenone	50	26		
5	2.80	1.2	3-Oxosteroid (6)	50	96	33 [d]	84
			17-Oxosteroid (7)	50	4		
6	2.80	2.0	3-Oxosteroid (6)	50	95	35 [d]	80
			20-Oxosteroid (8)	50	5		
7	2.80	2.5	17-Oxosteroid (7)	50	64	30 [d]	86
			20-Oxosteroid (8)	50	36		

[a] Determined by ^{1}H n.m.r. spectroscopy. [b] Amount of carbonyl compound recovered as a percentage of the *total* amount of carbonyl compounds used. [c] Total amount of carbonyl compounds accounted for both bound to polymer and not bound to polymer. [d] Theoretical maximum recovery = 50%.



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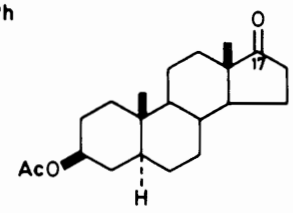

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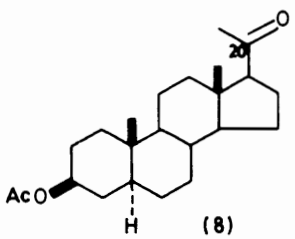

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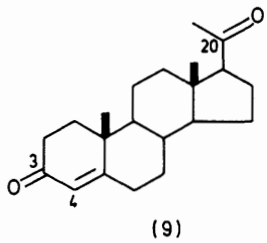

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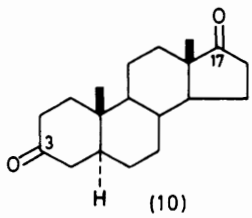

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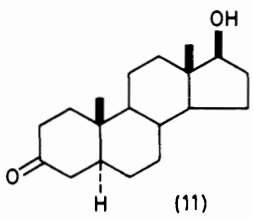

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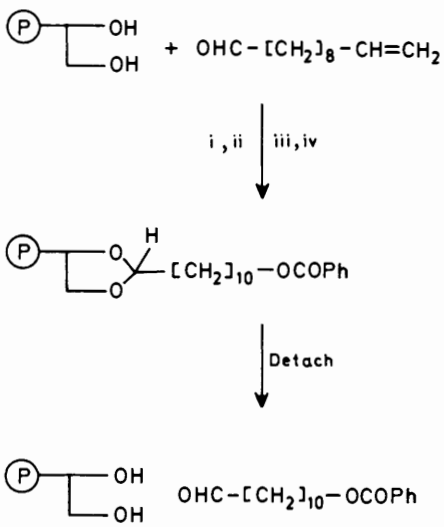

Scheme. *Reagents:* i, $-H_2O$; ii, B_2H_6; iii, $Me_3N\rightarrow O$; iv, PhCOCl–pyridine

consisted of 96% of the 3-oxosteroid (6) (entry 5). Similarly, 3-oxosteroid (6) was separated from the 20-oxosteroid (8) (entry 6). The difference between the 17- and 20-oxosteroids was, however, not sufficient for any useful separation to be achieved, though the 17-ketone bound more strongly to the polymer. The order of preference for acetal formation, *i.e.* 3-ketone ≫ 17-ketone > 20-ketone, agrees with previous work on steroidal acetals.[12] Although no systematic attempts were made to optimise the separation conditions, it is clear that polymer-supported diols of this general type have considerable potential for use in affinity chromatography.

Use of the Polymer-supported Diol (2) *as a Protecting Group.* —As an example of the use of the diol (2) as a protecting group, the reactions outlined in the Scheme were carried out. These involved protection of the aldehyde group of undec-10-enal whilst the vinyl group was hydroborated, the product oxidized with trimethylamine oxide, and the alcohol produced benzoylated. The overall yield of 11-benzoyloxyundecanal was 65% (equivalent to an average yield of *ca.* 90% for each of the four steps subsequent to attachment) and by ^1H n.m.r. spectroscopy it was 90% pure. There is little doubt that a careful study would allow the procedure to be improved considerably.

One interesting feature of polymer-supported protecting groups is the possibility of monoprotecting bifunctional compounds.[13,14] Leznoff has reported that a 2% cross-linked polystyrene containing *ca.* 0.35 mmol of the diol residues (1) per g can be used successfully to monoprotect terephthaldehyde.[4,5] We decided to investigate the monoprotection of dicarbonyl compounds using polymers containing the diol residues (2). The procedure used was as follows: (i) the dicarbonyl compound was attached to the polymer in the usual way; (ii) the free carbonyl groups of the bound substrate were reduced using a complex metal hydride; (iii) i.r. spectroscopy was used to confirm that all the free carbonyl groups had been reduced; (iv) the products were detached from the polymer in the usual way; and (v) the proportions of hydroxy-aldehyde or -ketone and dicarbonyl compound present in the product were estimated by ^1H n.m.r. spectroscopy. The results are summarised in Table 3.

It is clear (entry 1) that under the conditions we used terephthaldehyde was not successfully monoprotected. The results obtained with progesterone (9) were somewhat better (entry 2), possibly because the two carbonyl groups were not equally reactive. As expected,[12] the Δ^4-3-oxo group reacted more readily than the 20-oxo group (ratio *ca.* 4 : 1).

The 3,17-dioxosteroid (10) was studied more extensively (entries 3—9) because in all cases the i.r. spectrum of the bound steroid showed a single carbonyl band at 1 745 cm^{-1} (17-ketone), indicating that all the singly bound molecules were bound at the 3-position, and the ^1H n.m.r. spectra of the products indicated that reduction of the 17-ketone group was stereospecific. Consequently these reactions gave only one reduced product, namely 17β-hydroxy-5α-androstan-3-one (11). Several factors were investigated which were expected to lead to greater ' single binding ' than was achieved with entries 1 and 2. These were (i) the use of larger excesses of diketone; (ii) the use of polymers with lower loadings of diol groups per g; (iii) the use of a 20% cross-linked macroporous polymer; and (iv) the use of a shorter attachment time in the expectation that the 3-ketone would react more quickly. However, in no case was useful monoprotection achieved, the ' double-binding ' in all cases being in the range 23—48%. In view of our previous results indicating that a 3-ketone group binds much more readily than a 17-ketone group, the present results clearly indicate that once a molecule of the 3,17-dioxosteroid (10) is bound to the polymer *via* the 3-oxo group, the 17-oxo group reacts more readily than before and actually competes

Table 3. Estimation of ' double binding ' of various dicarbonyl compounds to the polymer-supported diols (2)

Entry	Polymer: Cross-linking (%)	Polymer: Capacity (mmol of diol per g)	Substrate	Amount of substrate (mmol per mmol of diol)	Amount of substrate bound to polymer (mmol per g) [a]	Reducing agent [b]	Percentage of substrate: Single bound	Percentage of substrate: Double bound
1	1	3.15	Terephthaldehyde	1.1	0.92	SB	52	48
2	1	3.15	Progesterone (9)	1.1	0.38	LB	72 [c]	28
3	1	3.15	3,17-Dioxosteroid (10)	0.5	0.76	LB	52	48
4	1	3.15	3,17-Dioxosteroid (10)	1.1	0.73	LB	64	36
5	1	3.15	3,17-Dioxosteroid (10)	5.0	1.24 [d]	LB	*d*	*d*
6	1	2.27	3,17-Dioxosteroid (10)	2.0	0.74 [e]	LB	77	23
7	1	1.20	3,17-Dioxosteroid (10)	2.0	0.32 [e]	LB	74	26
8	20 [f]	0.72	3,17-Dioxosteroid (10)	0.5	0.18	LB	62	38
9	20 [f]	0.72	3,17-Dioxosteroid (10)	5.0	0.26	LB	76	24

[a] Unless indicated otherwise reaction time for attachment was 11 h. Amount bound was estimated from the weight of recovered material. [b] SB = Sodium borohydride in *N,N*-dimethylformamide at 20 °C for 24 h; LB = lithium borohydride in THF at 65 °C for 2—6 days. [c] Amount of singly bound substrate bound by 3-ketone was *ca.* 4× that bound by 20-ketone. [d] Amount of bound material estimated from gain in weight of polymer. The recovery of reduced material was very low. [e] Reaction time 1 h. [f] Macroporous polymer.

effectively with the 3-oxo groups of unbound diketone. We suggest this arises because the bound steroid tends to block access to the remaining diol residues and that, at least with the low loaded macroporous polymer, the diol residues tend to be clustered.

Since this work was completed Fréchet has reported that attempts to monoprotect terephthaldehyde using a diol-containing resin derived from a cross-linked glycidyl methacrylate were similarly unsuccessful.[7]

Experimental

M.p.s were measured with a Kofler hot-stage apparatus. I.r. spectra were measured for KBr discs on a Nicolet MX-1 FT-IR instrument. ^{1}H N.m.r. spectra were measured for solutions in deuteriochloroform containing tetramethylsilane as internal standard on a Jeol FX-100 instrument operating at 99.55 MHz. Polymer samples were dried to constant weight in a vacuum oven (2 mmHg) at 60 °C. Ether refers to diethyl ether throughout.

Chloromethylation of Polystyrenes.—The 1% cross-linked polystyrene beads (Biobeads SX1) were obtained from Biorad, California. The 20% cross-linked macroporous polystyrene beads (Amberlite XAD-2) were obtained from Rohm and Haas. Chloromethylations were carried out as before.[15] The chloromethyl contents of the products were determined by treating samples with pyridine,[16] then estimating the chloride ion produced by Volhard titrations.[17] The chloromethyl contents of the various reaction products are summarised in Table 4.

Preparation of Polymer-supported Diol (2).—The following experiment is typical. The results from other experiments are summarised in Table 4.

A mixture of 1% cross-linked chloromethylated polystyrene (16.2 g, 4.84 mmol of Cl per g), *o*-dichlorobenzene (150 ml), 3-mercaptopropane-1,2-diol (18.0 g), aqueous sodium hydroxide (100 ml, 40%), and tetra-n-butylammonium hydroxide (3 ml, 40% aqueous solution) was vigorously stirred at 75 °C under nitrogen for 5 days. The mixture was then cooled and the polymer filtered off and washed successively with water, tetrahydrofuran(THF)–water (1 : 1), THF, methanol, methylene dichloride, and ether, then dried. The product (19.5 g), had S = 10.09% corresponding to 3.15 mmol of diol groups per g and a reaction yield of (19.5 × 3.15 × 100)/(16.2 × 4.80) = 79%. Volhard titrations [17] showed that the product contained 0.21 mmol of chloride per g. The i.r. spectrum of the product contained strong bands due to hydroxy groups, but none due to chloromethyl groups.

Table 4. Capacities of chloromethylated polystyrenes and the derived polymer-supported diols (2)

% Cross-linking of starting polymer	Chloromethylated polystyrenes (mmol of CH_2Cl per g)	Polymer-supported diol (2): (mmol per g)	Polymer-supported diol (2): Cl^- (mmol per g)	Yield [a] (%)
1	4.84	3.15 [b]	0.21	79
1	4.84	2.80 [b]	0.25	69
1	4.55	3.19 [b]	0.31	86
1	4.55	2.27		56
1	3.95	2.27 [b]		68
1	3.95	2.04		63
1	1.82	1.20		71
20	1.09	0.72	0.03	69

[a] Percentage of chloromethyl residues replaced by S-containing diol residues (2). [b] These products were used for all the work, except a few reactions in Tables 2 and 3.

Attachment and Detachment Procedures.—The following example is typical of the experiments summarised in Table 1.

Attachment of β-naphthaldehyde to the diol (2). A mixture of the diol (2) (1.084 g, 2.45 mmol of diol), β-naphthaldehyde (764 mg, 4.90 mmol), benzene (35 ml), and toluene-*p*-sulphonic acid (36 mg) was vigorously stirred and heated under reflux for 9 h during which time water was removed by azeotropy. The polymer was filtered off and washed successively with pyridine, water, acetone, chloroform, and ether, then dried. The product (1.325 g) had $\nu_{max.}$ 1 611 cm^{-1} (naphthalene nucleus).

Detachment of β-naphthaldehyde from the polymer. A portion of the above polymer (975 mg) and toluene-*p*-sulphonic acid (41 mg) in 20% aqueous dioxane (25 ml) was vigorously stirred at 95 °C for 10 h. The polymer was filtered off and washed with dioxane. The combined filtrate and washings were concentrated, diluted with water, and extracted with ether. The extracts were washed with sodium hydrogen carbonate solution then water and dried ($MgSO_4$). Evaporation of the

ether gave β-naphthaldehyde (143 mg, 0.92 mmol), m.p. 56 °C (lit.,[18] 59—60 °C), spectroscopically (i.r. and ^{1}H n.m.r.) identical with an authentic sample.

Recycling of polymer-supported diol (2). Using the above procedures *p*-bromobenzaldehyde was successively attached to a sample of polymer-supported diol (2) (5.00 g, 2.27 mmol of S per g) and then detached through five cycles. The loading achieved on successive cycles was 0.30, 0.22, 0.35, 0.36, and 0.13 mmol g^{-1}. The final diol had S > 5.95%, corresponding to 1.86 mmol of S per g.

Experiments Summarised in Table 2.—These were carried out using the usual attachment and detachment procedures. The following points should be noted.

Entry 1. The recovered 17β-benzoyloxy-5α-androstan-3-one (6) had m.p. 182—188 °C, $\nu_{max.}$ 1 720 cm^{-1}. After recrystallisation from acetone–hexane it had m.p. 197—199 °C (lit.,[19] 200—201 °C).

Entry 2. The Grignard reagent of *p*-diphenylphosphinylbromobenzene was prepared as described by Schiemenz,[10] then treated with an excess of *N,N*-dimethylformamide. Acidic work-up afforded a crude product which, by ^{1}H n.m.r. spectroscopy, had the composition indicated in Table 2. The *p*-diphenylphosphinylbenzaldehyde isolated had m.p. 65—68 °C (lit.,[10] 69—71 °C), $\nu_{max.}$ 1 704 cm^{-1}.

Entry 3. Dibenzo-18-crown-6 was formylated using hexamethylenetetramine and trifluoroacetic acid as described by Wada *et al.*[11] except that the reaction temperature was *ca.* 80 °C. ^{1}H N.m.r. analysis of the crude product indicated that it had the composition shown in Table 2. The 4-formyldibenzo-18-crown-6 isolated had m.p. 182—184 °C, $\nu_{max.}$ 1 691 cm^{-1}; δ 4.2 (m, $^-OCH_2CH_2O^-$, 16 H), 6.88 (s, ArH, 4 H), 6.92 (d, C_6-H), 7.38 (br s, C_3-H), 7.46 (d, C_5-H), and 9.82 (s, C*H*O) (Found: C, 64.6; H, 6.5. $C_{21}H_{24}O_7$ requires C, 64.9; H, 6.2%).

Entry 4. The analysis was based on the areas of the formyl and acetyl signals.

Entries 5, 6, *and* 7. The ^{1}H n.m.r. spectral analyses were based on the following signals: 3-oxosteroid (6), singlets at δ 0.96 and 1.04; 3β-acetoxy-5α-androstan-17-one (7), singlets at δ 0.86 and 2.02; 3β-acetoxy-5α-pregnan-20-one (8), singlets at δ 0.60, 0.82, 2.02, and 2.11. Analyses were confirmed by i.r. spectroscopy.

Conversion of Undec-10-enal into 11-Benzoyloxyundecanal.—Undec-10-enal (1.72 g) was treated with polymer-supported diol (2) (2.83 g, 7.93 mmol of diol) using the usual procedure. The product (3.423 g) had $\nu_{max.}$ 1 641 and 910 cm^{-1} (vinyl). The undec-10-enal was detached from a portion (150 mg) of the product in the usual way. By g.l.c. analysis aldehyde (15 mg) was recovered, corresponding to a loading of 0.72 mmol of aldehyde per g of original polymer.

A second portion (3.25 g) of the above polymeric product was suspended in THF at 20 °C. After 1 h trimethylamine oxide (320 mg) was added and the mixture stirred at 65 °C for 16 h. The polymer was filtered off, washed with THF, and dried (3.23 g).

The terminal hydroxy group was benzoylated by treating the polymer (3.09 g) with benzoyl chloride (2.0 ml) in pyridine (45 ml) at 75 °C for 12 h. The polymer was filtered off and washed successively with dioxane, methanol, methylene dichloride, and ether, then dried (3.37 g).

Finally, the polymer (3.07 g) was treated with aqueous dioxane and acid in the usual way. This gave a clear oil (349 mg), which was shown by ^{1}H n.m.r. analysis to consist of 11-benzoyloxyundecanal (90%) and undec-10-enal (10%). This is equivalent to 65% of the material originally bound being transformed to the ester and 7% being recovered.

Experiments Summarised in Table 3.—The following experiment is typical. 5α-Androstane-3,17-dione (10) (942 mg, 3.26 mmol) was treated with 1% cross-linked polymer-supported diol (2) (2.05 g, 6.45 mmol of diol) using the usual procedure. The product (2.48 g) had $\nu_{max.}$ 1 745 cm^{-1}. The polymer was treated with lithium borohydride (0.64 g) in THF (25 ml) at 65 °C for 136 h. It was then filtered off, washed with methanol, THF–water (1 : 1), water, THF, and acetone, then dried. The i.r. spectrum no longer displayed a band at 1 745 cm^{-1}. The steroid was detached from the polymer using the usual procedure. By ^{1}H n.m.r. analysis the recovered material (367 mg) consisted of 17β-hydroxy-5α-androstan-3-one (11) (singlets at δ 0.76 and 1.02) and dione (10) (singlets at δ 0.89 and 1.04) in the mol ratio 52 : 48.

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