The Mechanism of the β-Acyloxyalkyl Radical Rearrangement. Part 2:[1] β-Acyloxytetrahydropyranyl Radicals

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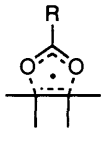
The rate of rearrangement of the 3-butanoyloxytetrahydropyran-2-yl radical (**4**) to give the product **5** of 1,2-migration of the acyloxy group has been determined by competition against the reaction of **4** with tributylstannane. The rate constant is larger than that for rearrangement of the acylic radical **18** but less than that for the substituted cholestanyl radical **19**. Experiments with ^{17}O- and ^{18}O-labelled substrates indicate that the rearrangement of **4** proceeds with *ca.* 33% transposition of the ether and carbonyl oxygen atoms, while there is also a small amount of scrambling in the product **12** formed by direct reduction of **4**. The isotope labelling studies and the Arrhenius parameters (log $[A/s^{-1}]$ = 12.7, E_{act} = 58 kJ mol^{-1}) are consistent with the view that the reaction proceeds, at least in part, *via* dissociation into a tight anion radical-cation pair **22**. A pathway *via* the three-membered transition structure **21** might also be involved.

Unlike most intramolecular radical reactions, the rearrangement of suitably constituted β-acyloxyalkyl radicals by 1,2-migration of the acyloxy group appears to have no intermolecular analogue. Earlier extensive scrutiny[2-7] of the mechanism of this unusual process led to the conclusion that it involves the redistribution of five electrons *via* a five-membered cyclic transition structure **1**. The rearrangement could therefore



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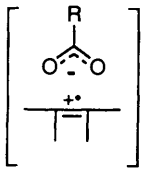

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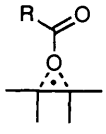

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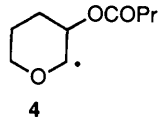
be classified as an open-shell pericyclic process, a class of reaction which possibly includes the rearrangement of allylperoxyl radicals.[8,9] However, it has recently become clear that not all rearrangements of β-acyloxyalkyl radicals proceed in this manner. Experiments with radicals derived from steroid esters enriched with ^{18}O in the ester group[1,6] have shown that the reaction in these systems proceeds, at least in part, either *via* an intermediate intimate radical-cation anion pair **2**, or *via* a three-membered cyclic transition structure **3**. Since our most recent experiments[1] favour the former mechanism, we have now carried out a study of the rearrangement of radicals substituted appropriately to facilitate the formation of the radical-cation anion pair. In this paper we describe the rearrangements of β-acyloxytetrahydropyranyl radicals **4** and **5** in which the presence of the ring oxygen is expected to stabilise an adjacent radical-cation centre.

After this work commenced it was reported that the rearrangement of the glycosyl radical **6** into **7** proceeds with complete transposition of the ether and carbonyl oxygen atoms, and must, therefore, proceed in a concerted fashion *via* a five-membered cyclic transition structure.[7] However, the experiments with isotopically enriched substrates described herein clearly demonstrate that the rearrangements of the unsubstituted species **4** and **5** proceed, at least in part, by a dissociative mechanism.



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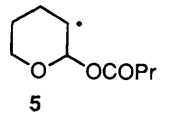

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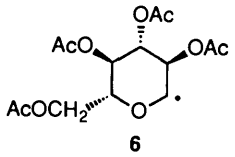

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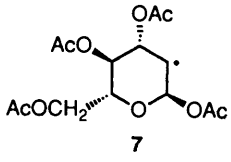

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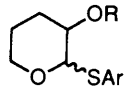
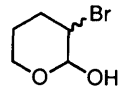
Results

Since we wished to avoid the possible incursion of ionic mechanisms, aryl sulfides were used as radical precursors rather than the more usual bromides or iodides. The 2-sulfide **9** was obtained by treatment of tetrahydropyran-2,3-diol with toluene-*p*-thiol and toluene-*p*-sulfonic acid, followed by esterification of the resultant hydroxy-sulfide **8** with butanoyl chloride and pyridine. The 3-sulfide **11** was obtained from 3-bromotetrahydropyran-2-ol, **10**, by consecutive treatment with toluene-*p*-thiol–DBU and with butanoyl chloride–pyridine. Both compounds were obtained as mixtures of *cis* and *trans* diastereoisomers, and were used as such since the stereochemistry is lost on formation of the carbon-centred radicals.



8; R = H; Ar = *p*-C_6H_4Me
9; R = COPr; Ar = *p*-C_6H_4Me



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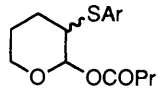
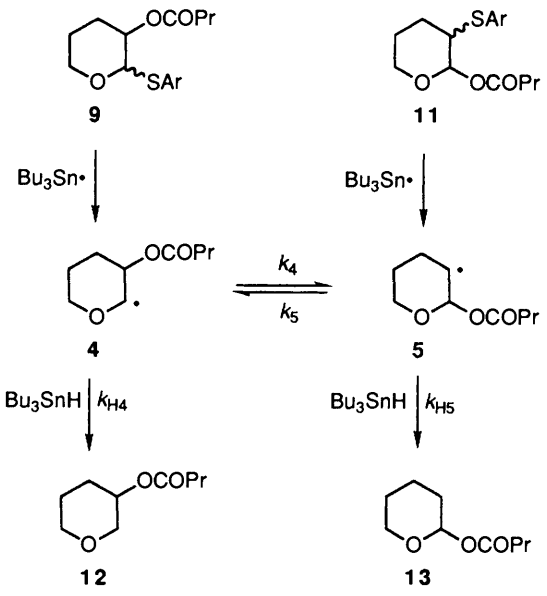


11; Ar = *p*-C_6H_4Me

The reactions expected to ensue when either the sulfide **9** or its isomer **11** is treated with tributylstannane are shown in Scheme 1. In the event, heating of a solution of **9**, tributylstannane (0.02 mol dm^{-3}) and azoisobutyronitrile (AIBN) in benzene under reflux for 2 h gave a quantitative yield of a mixture of the products **12** and **13**, the components of which

were isolated by flash chromatography and identified by comparison with authentic samples. In order to determine the kinetics of the rearrangement of **4** into **5** a series of experiments was conducted in which the sulfide **9** was treated with a large excess of tributylstannane in known concentration at various temperatures. Since the products did not separate well on gas chromatography and underwent partial hydrolysis on liquid chromatography, the product mixtures were analysed by ^{1}H NMR spectroscopy. The results are shown in Table 1.



Scheme 1

Steady state analysis of the reactions of Scheme 1 gives eqn. (1) where $[\mathbf{12}]_f$ and $[\mathbf{13}]_f$ represent the final concentrations of the two products when the tributylstannane is in large excess. When values of $[\mathbf{12}]_f/[\mathbf{13}]_f$ were plotted against $[Bu_3SnH]$ for each temperature, the straight lines of best fit were found to pass very close to the origin ($k_{H1}k_5/k_{H5}k_1 = -0.06$, -0.05 and 0.09 at 80, 100 and 120 °C, respectively). Hence the approximate expression $k_4/k_{H4} = [Bu_2SnH][\mathbf{13}]_f/[\mathbf{12}]_f$ could be used to calculate values of k_4/k_{H4}. The results are given in Table 1. Fitting of the relative rate data to the Arrhenius equation gives eqn. (2) where the activation energy is in kJ mol^{-1}.

$$[\mathbf{12}]_f/[\mathbf{13}]_f = k_{H4}k_5/k_{H5}k_4 + k_{H4}[Bu_3SnH]/k_4 \quad (1)$$

$$\log[(k_4/k_{H4})/\text{mol dm}^{-3}] = (3.36 \pm 0.5) - (34.0 \pm 3.6)/2.3\,RT \quad (2)$$

To obtain values of k_4 from eqn. (2) it is necessary to know values of k_{H4}. Unfortunately, such data have not been determined for the reaction of tributylstannane with cyclic carbon radicals with centres adjacent to oxygen. However, k_H for acyclic radicals of the type $ROCH_2$· is available from an earlier study by kinetic EPR spectroscopy of the radical **14** which gave the Arrhenius eqn. (3).[10]

$$\log(k_{H14}/\text{dm}^3\,\text{mol}^{-1}\,\text{s}^{-1}) = 9.1 - 20.8/RT \quad (3)$$

In a different approach we have now treated the glycosyl bromide **15** in the usual way with tributylstannane and AIBN at various temperatures and concentrations. The ratios of products determined by HPLC analysis are given in Table 2. With the assumption that the rearrangement is essentially irreversible the usual calculations give k_6/k_{H6} where k_6 is the rate constant for the rearrangement and k_{H6} is the rate constant for the reaction of **6** with tributylstannane. The values are given in Table 2. Because of the relative slowness of the rearrangement of **6** into **7** the yields of rearrangement product **17** were small and could not be determined very accurately. Consequently, the uncertainties of the Arrhenius parameters given in eqn. (4) are relatively large.

Table 1 Relative final concentrations of products **12** and **13** and relative rate constants for the reaction of the radical **4** with tributylstannane[a] in benzene

T/°C	$[Bu_3SnH]_m$/ mol dm^{-3}	$[\mathbf{12}]_f/[\mathbf{13}]_f$	(k_4/k_{H4})/ mol dm^{-3}
80.0	0.022	0.77	0.029
80.0	0.049	2.08	0.023
80.0	0.177	4.76	0.025
100.0	0.022	0.54	0.041
100.0	0.049	1.30	0.037
100.0	0.127	3.85	0.033
100.0	0.200	5.56	0.035
120.0	0.049	0.71	0.069
120.0	0.127	1.69	0.075

[a] The average concentration during the reaction is given.

Table 2 Relative final concentrations of products **16** and **17** and relative rate constants for the reaction of the radical **15** with tributylstannane[a] in benzene

T/°C	$[Bu_3SnH]_m$/ mol dm^{-3}	$[\mathbf{16}]_f/[\mathbf{17}]_f$	(k_{16}/k_{16H})/ mol dm^{-3}
60.0	0.005	3.64	0.0014
100.0	0.010	5.43	0.0018
100.0	0.023	8.26	0.0028
100.0	0.050	21.7	0.0023
120.0	0.010	5.0	0.0020
120.0	0.023	10.0	0.0023
120.0	0.050	19.2	0.0026

[a] The average concentration during the reaction is given.

$$\log[(k_6/k_{H6})/\text{mol dm}^{-3}] = (-1.4 \pm 1.0) - (8.8 \pm 7.5)/2.3RT \quad (4)$$

From eqn. (4) and the temperature dependence of log k_6 previously determined by EPR spectroscopy [$\log(k_6/\text{s}^{-1}) = (8.1 \pm 0.2) - (36.4 \pm 0.8)/2.3RT$][7] it follows that

$$\log[(k_{H6})/\text{dm}^{-3}\,\text{mol}^{-1}\,\text{s}^{-1}] = (9.5 \pm 1.2) - (27.6 \pm 8.4)/2.3RT \quad (5)$$

The question then arises of what values of log A and E_{act} to use for the determination of k_{H4}: those given in eqn. (3) or those in eqn. (5)? Having regard to the values of $\log(A/\text{mol dm}^{-3}\,\text{s}^{-1})$ for the reaction of tributylstannane with cyclohexyl radical (9.24) and with typical primary radicals (9.1),[11] and to the large uncertainties in the determination of values of k_6/k_{H6} it seems reasonable to assign a value of 9.3 to $\log(A/\text{mol dm}^{-3}\,\text{s}^{-1})$ for k_{H4}. For the activation energy for k_{H4} we have arbitrarily chosen a value (23.6 kJ mol^{-1}) close to the mean of those given in eqns. (3) and (5). It follows that the Arrhenius expression for k_4 is

$$\log(k_4/\text{s}^{-1}) = 12.7 - 58/2.3RT \quad (6)$$

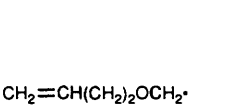
Table 3 lists values of the Arrhenius parameters and the rate constants at 80 °C for the rearrangements of **4** and **6**[7] together with those previously determined for the rearrangements of the acyclic radical **18**[4,5] and the steroid radical **19**.[1] Although the errors in all of these values are undoubtedly large it seems clear

Table 3 Arrhenius parameters and rate constants[a] for the rearrangement of β-acyloxyalkyl radicals

Radical	Solvent	log (A/s^{-1})	E_{act}/kJ mol^{-1}	k/s^{-1} at 80 °C	Ref.
4	Benzene	12.7	58	1.2×10^4	This work
6	Benzene	8.1	36.4	5.2×10^2	7
18	$Me_3CC_6H_5$	13.2[b]	70.2[b]	5.4×10^2	4
18	Water	12.3	53.1	2.8×10^4	5
19	Benzene	14.8	56.9	2.4×10^6	1

[a] Calculated from Arrhenius parameters. [b] 'Recommended values' from ref. 4; the experimental values are log (A/s^{-1}) = 13.9 ± 1.1, E_{act} = 74.9 ± 7.9 kJ mol^{-1}.

that the rearrangement of **4** is a good deal faster than that of the simple acyclic radical **18** in non-polar solvents but is still considerably slower than the rearrangement of the strained steroid radical **19**. The values of the Arrhenius parameters for the rearrangement of **6** appear to be anomalously low by comparison with the other entries in Table 3. However, since they were used to obtain acceptable values for k_{H6} they cannot be wildly in error. It appears, therefore, that the nature and stereochemistry of the other substituents present in the glycosyl radical **6** must profoundly affect the characteristics of the rearrangement reaction.



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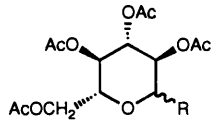
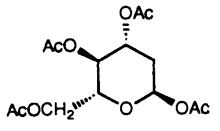


15; R = α-Br
16; R = H



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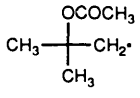

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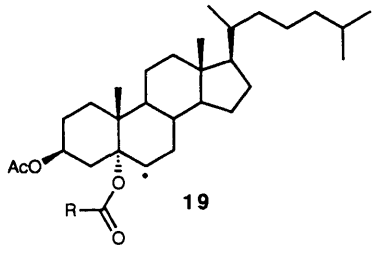

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Although fitting of the experimental data of Table 1 to eqn. (1) indicated that the value of $k_{H4}k_5/k_{H5}k_4$ is close to zero an attempt was made to estimate the value of the equilibrium constant $K(k_4/k_5)$ by treating the sulfide **11** with tributylstannane in methylcyclohexane at 110 °C, either at 0.02 mol dm^{-3} or under conditions of infinite dilution. Careful analysis of the crude product revealed the presence of a very small amount (≤5%) of the rearrangement product **12**. Thus, from eqn. (1) when [Bu_3SnH] = 0, $k_Hk_5/k_{H5}k_4 \approx 0.05$. Substitution into the latter expression of the values at 110 °C of k_{H4} (1.2×10^6 dm^{-3} mol^{-1} s^{-1}) and of k_{H5} (assumed to be the same as that for cyclohexyl radical: 9.5×10^6 dm^{-3} mol^{-1} s^{-1}) gives a value for k_4/k_5 of about 2.5. We believe that the true value of k_4/k_5 could well be a good deal higher because k_{H5} is likely to be less than $k_{H(cyclohexyl)}$. At first sight the fact that the equilibrium **4** ⇌ **5** lies in favour of the less electronically stabilised radical **5** seems surprising. However, as Giese has pointed out,[7] the overall stabilization of each species must be taken into account. The dominant effect is the anomeric stabilization[12] of **5** which outweighs the electronic stabilization of **4**.

Previous reports have demonstrated the value of experiments with ^{18}O-enriched substrates for mechanistic studies of the β-acyloxyalkyl rearrangement.[1,3,6,7] However, since the use of mass spectrometry for the accurate analysis of products often involves complicated work-up procedures an alternative isotopic label was sought. The experiments described below show that ^{17}O NMR spectroscopy is a powerful tool for the investigation of ester migration, and in many respects is often superior to mass spectrometry for this purpose. Its main limitation is that it is suitable only for compounds of relatively low molecular weight, such as those used in the present work.

Treatment of the hydroxy sulfide **8** with ^{17}O-labelled butyric acid and dicyclohexylcarbodiimide gave the radical precursor ^{17}O-**9** enriched with ^{17}O specifically in the carbonyl group. The ^{17}O NMR spectrum of the product in deuteriochloroform comprised a single resonance at 364 ppm relative to external $H_2{}^{17}O$. Treatment of ^{17}O-**9** with tributylstannane (*ca.* 0.02 mol dm^{-3}) and AIBN in benzene at reflux gave the rearranged and directly reduced products, ^{17}O-**13** and ^{17}O-**12**, respectively, which were separated by flash chromatography. The ^{17}O spectrum of the rearranged ester ^{17}O-**13** comprised resonances at 352 ppm assigned to the carbonyl ^{17}O and at 195 ppm assigned to the ether ^{17}O with relative intensities of 67:33. The directly reduced ester ^{17}O-**12** was similarly found to contain 94% of the label in the carbonyl oxygen and 6% in the ether oxygen. In order to preclude the possibility of rearrangement during the work-up procedure, one sample of the more sensitive 2-ester **13** enriched with ^{17}O specifically in the carbonyl position was passed through a flash chromatography column, while another was heated for some time in benzene under reflux. In each case the ^{17}O NMR spectrum contained only the resonance at 352 ppm.

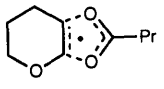
In order to validate the use of ^{17}O NMR spectroscopy as a mechanistic probe, the rearrangement of **4** was also studied by the well established mass spectrometric technique.[1,3,6,7] A sample of **9** enriched with ^{18}O (37% incorporation) specifically in the carbonyl oxygen, was treated with tributylstannane under conditions identical with those used for ^{17}O-**9**, and the products were isolated in the usual way and subjected to electron impact gas chromatography–mass spectrometry (GC–MS). Unfortunately the molecular ions at m/z 172 and 174 were too weak to be useful, but the extent of ^{18}O incorporation in the carbonyl positions of each ester could be determined from the relative abundances of the fragment ions $C_3H_7C{=}O^+$ with m/z 71 and 73. The results showed that the rearranged product ^{18}O-**13** was enriched with ^{18}O in the carbonyl group to the extent of 21%; for ^{18}O-**12** the extent of carbonyl oxygen enrichment was 24%. Reduction of ^{18}O-**12** with lithium aluminium hydride afforded an ^{18}O-enriched sample of the corresponding alcohol (tetrahydropyran-3-ol) with molecular ions at m/z 102 and 104, the relative abundances of which showed the isotopic enrichment of the ester ether oxygen in ^{18}O-**12** to be 1%. Similar reduction of ^{18}O-**13** gave isotopically enriched pentane-1,5-diol which was converted into its bisphenylcarbamate by treatment with phenyl

isocyanate. The relative abundances of the molecular ions at *m/z* 342 and 344 showed the enrichment of the ester ether oxygen in ^{18}O-**13** to be 7%.

The results of the experiments with ^{18}O-**9** indicated the ratio of the label in the ester group of the directly reduced product ^{18}O-**12** to be 96:4 for carbonyl:ethereal, and in the ester group of the rearranged product ^{18}O-**13** to be 75:25 for carbonyl:ethereal. These figures are in satisfactory agreement with those determined by ^{17}O NMR spectroscopy when the possible sources of error of both methods are taken into account. However, in view of the very low intensities of some of the mass spectral peaks used to determine the ^{18}O isotope ratios we regard the more direct NMR method as being the more reliable. A disturbing feature of the mass spectrometry results, is that the total ^{18}O incorporation was 28% in the rearranged product ^{18}O-**13** and 25% in the reduced product ^{18}O-**12** whereas it was 37% in the starting material, ^{18}O-**9**. No change was found when the products were distilled directly from the reaction mixture; exchange of the label with $H_2{}^{16}O$ in the solvent or silica during work-up was thus precluded. Nor did any exchange occur when unlabelled precursor **9** was treated with tributylstannane in the presence of $H_2{}^{18}O$ but otherwise under the usual conditions. We are, therefore, unable to account for the apparent loss of isotopic label in the reactions of ^{18}O-**9** and ^{17}O-**9** with tributylstannane.

Discussion

The observation that the rearrangement of the β-acyloxyalkyl radical **4** proceeds with only *ca.* 33% transposition of the ether and carbonyl oxygen atoms in the ester group clearly indicates that the reaction, unlike that of **18**, cannot proceed solely *via* a five-membered transition structure **20** since this would require complete transposition. Nor can it proceed solely *via* a three-membered transition structure of type **21** since this would require complete retention of the isotopic label in the carbonyl group of the rearranged product. Any scheme involving the simultaneous operation of both these mechanisms also appears to be precluded since neither can account for the observation that the product obtained by reduction of ^{17}O-**9** specifically labelled in the carbonyl group affords the direct reduction product **12** with *ca.* 6% of the label in the ether position. This result cannot be accounted for by the reversibility of the rearrangement. It clearly denotes the occurrence, at least in part, of a dissociative mechanism allowing the exchange of the carboxylate oxygens.



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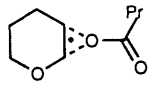

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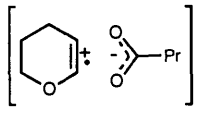

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Another plausible mechanism involves the reaction proceeding partly *via* a three-membered transition structure, **21** and partly *via* an intimate radical-cation anion pair **22**. If the dissociative pathway leads to complete scrambling of the isotopic label it follows from the experimental results that the pathway *via* the ion pair is approximately twice as fast as that proceeding *via* the three-membered transition structure. This mechanism is supported by the observation that the rate constant for the rearrangement of **4** is about 20 times greater than that for the unsubstituted acyloxyalkyl radical **18** in a similar solvent and is consistent with the view that the ring oxygen atom in the former facilitates the formation of an adjacent radical-cation function. Furthermore the value of log *A* is relatively large and is comparable to those reported for ring-opening reactions.[13] Its value accords with the view that formation of the transition structure is accompanied by considerable bond breaking. The defect of this hypotheses is that it requires the participation in part of a direct 1,2-oxygen shift, a process that has, as yet, no precedent, although it has received some theoretical support.[14]

Other possible mechanisms require that the reaction proceed either completely *via* the dissociative route, or mainly *via* dissociation with a small contribution from the five-membered cyclic concerted process. These would certainly be consistent with the kinetic data, but the observed labelling pattern can be accommodated only if the intimate radical cation-anion pair is so tight that complete scrambling cannot occur. It is relevant that some allylperoxyl radicals appear to undergo rearrangement by a dissociative mechanism without loss of stereochemistry.[9]

Conclusions

In conclusion the results reported here and elsewhere support the view that β-acyloxylalkyl radicals can undergo rearrangement by at least two and possibly three distinct pathways. One proceeds in concerted fashion and involves a five-membered cyclic transition structure (*e.g.* **1**), another involves dissociation into an intermediate radical-cation anion pair (*e.g.* **2**), while the third involves a 1,2-oxygen shift *via* a three-membered transition structure (*e.g.* **3**). The relative importance of each mode of rearrangement depends on the conditions and the nature of the radical. The rearrangement of the simple radical **18** proceeds solely *via* the concerted pathway. It involves complete transposition of the ether and carbonyl oxygens, and is relatively slow in non-polar solvents, but proceeds more rapidly in polar solvents because of the dipolar nature of the transition structure.[5] The reaction has a high value of log *A* because of the considerable degree of bond breakage at the transition structure. The rearrangement of the carbohydrate radical **6** also appears to proceed by this mechanism.[7] The reaction is slow and the Arrhenius parameters are abnormally low possibly because of the effect of the ring substituents. The rearrangement of the steroid radical **19** possibly proceeds solely *via* an intimate radical cation-anion pair. The dissociative process is aided by the relief of strain; it is relatively fast and has a very high value of log *A*.[1] Finally the radical **4** undergoes rearrangement, at least in part, by the dissociative process aided, in this case, by the electron-donating nature of the ring oxygen atom. There is also the possibility that some rearrangement occurs *via* the three-membered transition structure **21**.

Experimental

Oxygen (^{17}O) NMR spectra were recorded in deuteriochloroform on a Varian VXR-300 spectrometer operating at 40.7 MHz. They were referenced to external $H_2{}^{17}O$ (δ 0.00) contained in a Wilmad WGS-4BL capillary insert. Gas chromatography–mass spectra (GC–MS) were recorded on a Hewlett Packard 5970 mass spectrometer employing electron impact ionisation and a Hewlett Packard 5890 gas chromatograph. High performance liquid chromatography (HPLC) was conducted on a 25 cm × 10 mm P/W ALLTECH CN-bonded 10μ HPLC column. Compounds were detected in the eluates by use of a Waters R403 differential refractometer. Other general directions and procedures have been previously reported.[1]

Tetrahydropyran-2,3-diol.—3,4-Dihydro-2*H*-pyran (2.3 g, 27.4 mmol) was added dropwise to a solution of *N*-methylmorpholine *N*-oxide dihydrate (5.0 g, 27.5 mmol) and osmium tetraoxide (*ca.* 20 mg) in 30% aqueous acetone under N_2 at 0 °C.[15] The mixture was then allowed to warm gradually to room temperature, after which it was stirred overnight. A slurry of sodium sulfate (274 mg) and magnesium silicate (5 g) in water (22 cm^3) was added and the mixture was stirred for 1 h. After filtration, the pH of the solution was adjusted to *ca.* 7 with concentrated H_2SO_4 and the acetone was removed under reduced pressure. The aqueous mixture thus obtained was acidified (pH ≈ 1) and most of the water was removed on a rotary evaporator. The residue was stirred with ethyl acetate overnight and the organic phase was separated from the remaining aqueous slurry, dried, and evaporated to afford an oil from which residual ethyl acetate was distilled azeotropically with hexane. The resulting viscous oil (2.0 g, 62%) was found to be a mixture of isomers but otherwise pure by ^1H and ^{13}C NMR spectroscopy. It was used without further purification; δ_H(200 MHz) 1.40–2.14 (4 H, m, 4-H_2, 5-H_2), 3.30–4.03 (3 H, m, 3-H, 6-H_2), 4.49 (0.6 H, d, *J* 6.8, 2-H *trans*) and 4.95 (0.4 H, d, *J* 1.9, 2-H *cis*); δ_C(75 MHz) 22.1, 23.9 (C-5), 26.9, 29.1 (C-4), 61.4, 65.0 (C-6), 67.6, 70.1 (C-3) and 93.3 and 98.4 (C-2).

2-(p-*Tolylthio*)*tetrahydropyran*-3-*ol* **8**.—A solution of tetrahydropyran-2,3-diol (2.0 g, 17 mmol), *p*-methylthiophenol (4.4 g, 35 mmol) and *p*-toluenesulfonic acid (0.2 g, 1 mmol) in dry benzene (600 cm^3) under nitrogen was heated at reflux overnight. The mixture was then diluted with benzene, washed with aqueous NaOH, and dried (Na_2CO_3). Evaporation of the solvent afforded a brown oil, chromatography (ethyl acetate–hexane) of which afforded a colourless oil (2.5 g, 50%) which partially crystallised on standing (Found: M^+, 224.0870. $C_{12}H_{16}O_2S$ requires *M*, 224.0871); δ_H(200 MHz) 1.40–2.20 (4 H, m, 4-H_2, 5-H_2), 2.32 (3 H, s, $ArCH_3$), 2.50 (1 H, s, OH), 3.40–3.70 (1 H, m, 6-H), 3.85–4.20 (2 H, m, 3-H, 6-H), 4.60 (0.4 H, d, *J* 7.1, 2-H *trans*), 5.26 (0.6 H, d, *J* 3.8, 2-H *cis*), 7.08–7.17 (2 H, m, *o*-ArH) and 7.36–7.47 (2 H, m, *m*-ArH); δ_C(50 MHz) 20.9 ($ArCH_3$), 23.2, 23.3 (C-5), 29.5, 29.8 (C-4), 62.3, 66.1 (C-6), 67.7, 68.3 (C-3), 91.4, 93.0 (C-2), 129.5, 130.8, 131.9, 132.4, 137.1 and 137.9 (aromatic C); *m*/*z* 224 (M^+, 2%), 206 (2), 101 (65), 91 (22) and 84 (50).

3-*Butanoyloxy*-2-(p-*tolylthio*)*tetrahydropyran*-3-*ol* **9**.—Butanoyl chloride (1.2 cm^3, 11 mmol) was added in one portion to a solution of the alcohol **8** (1.44 g, 6.4 mmol) and pyridine (0.92 cm^3, 11 mmol) in dry ether (20 cm^3) at 0 °C. The reaction mixture was stirred for 11 h at 0 °C then tipped into ice–water. The mixture was extracted with ether and the organic layer was washed with dilute HCl and a saturated solution of $NaHCO_3$ and dried (Na_2CO_3). Evaporation of the solvent gave **9** as a colourless oil, which was purified by flash chromatography (ethyl acetate–hexane) (Found: C, 65.4; H, 7.5%. $C_{16}H_{22}O_3S$ requires C, 65.28; H, 7.53%). Partial separation of the isomers was achieved (0.48 g *cis*, 0.35 g *trans*, and 0.51 g mixture of *cis* and *trans*; total yield 70%).

trans Isomer: δ_H(200 MHz) 0.96 (3 H, t, *J* 7, $-CH_2CH_3$), 1.45–2.38 (11 H, m, $-COCH_2CH_2-$, $ArCH_3$, 4-H_2, 5-H_2), 3.52–3.68 (1 H, m, 6-H), 4.02–4.28 (1 H, m, 6-H), 4.87–4.98 (1 H, m, 3-H), 5.10 (1 H, d, *J* 4.2, 2-H), 7.10 (2 H, d, *J* 9, *o*-ArH) and 7.38 (2 H, d, *J* 9, *m*-ArH); δ_C(50 MHz) 13.6 ($-CH_2CH_3$), 18.4 ($-CH_2CH_3$), 21.1 ($ArCH_3$), 21.7 (C-5), 25.8 (C-4), 36.3 ($-COCH_2-$), 62.8 (C-6), 69.2 (C-3), 87.3 (C-2), 129.7, 130.2, 132.3 and 137.5 (ArC), 172.7 (C=O); *m*/*z* 294 (M^+, weak), 206 (weak), 171 (8%), 91 (3), 73 (0.5) and 71 (100); ν_{max}(film)/cm^{-1} 1735 (C=O).

cis Isomer: δ_H(200 MHz) 0.97 (3 H, t, *J* 7, $-CH_2CH_3$), 1.55–2.40 (11 H, m, $COCH_2CH_2-$, $ArCH_3$, 4-H_2, 5-H_2), 3.50–3.65 (1 H, m, 6-H), 4.05–4.24 (1 H, m, 6-H), 5.00–5.13 (1 H, m, 3-H), 5.36 (1 H, d, *J* 4, 2-H), 7.10 (2 H, d, *J* 9, *o*-ArH) and 7.36 (2 H, d, *J* 9, *m*-ArH); δ_C(50 MHz) 13.6 ($-CH_2CH_3$), 18.4 (CH_2CH_3), 21.0 ($ArCH_3$), 22.9 (C-5), 26.3 (C-4), 36.2 ($COCH_2$), 62.7 (C-6), 70.0 (C-3), 87.7 (C-2), 129.6, 130.6, 132.0 and 137.2 (aromatic C), and 172.9 (C=O).

3-*Bromotetrahydropyran*-2-*ol* **10**.—*N*-Bromoacetamide (330 mg, 2.4 mmol) in water (2 cm^3) was added dropwise to a solution of 3,4-dihydro-2*H*-pyran (200 mg, 2.4 mmol) in acetone (4 cm^3) at 0 °C and the mixture was stirred at 0 °C for 3 h.[16] The acetone was then evaporated under reduced pressure, the residue was taken up in CH_2Cl_2 and the solution was washed with water and dried. Evaporation of the solvent afforded (350 mg, 81%) as a pale yellow oil which solidified on standing. Recrystallisation from ethyl acetate–hexane yielded colourless platelets, m.p. 67.5–69.5 °C (Found: C, 33.35; H, 5.21. $C_5H_9BrO_2$ requires C, 33.17; H, 5.01%); δ_H(200 MHz) 1.50–2.54 (4 H, m, 4-H_2, 5-H_2), 3.50–3.72 (1 H, m, 6-H), 3.96–4.16 (2.5 H, m, –OH, 3-H, 6-H), 4.28–4.33 (0.5 H, m, 3-H) and 4.74–4.93 (1 H, m, 2-H); δ_C(50 MHz) 23.0, 25.2 (C-5), 29.7, 31.9 (C-4), 51.0, 53.9 (C-3), 63.1, 64.5 (C-6), 92.6 and 97.1 (C-2); *m*/*z* 182 (M^+, weak), 180 (M^+, weak), 136 (10%), 134 (11), 108 (15) and 106 (17); ν_{max}(film)/cm^{-1} 3400 (OH), 730 (C–Br).

3-(p-*Tolylthio*)*tetrahydropyran*-2-*ol*.—3-Bromotetrahydropyran-2-ol (4.0 g, 22 mmol) was treated with *p*-methylthiophenol (2.8 g, 23 mmol) and DBU (4.1 g, 27 mmol) in dry benzene (600 cm^3) at room temperature by means of the method described by Ono *et al.* for the preparation of butyl phenyl sulfide.[17] When the reaction was complete, the organic layer was washed with dilute HCl, water, aqueous NaOH and brine, and then dried ($MgSO_4$–Na_2CO_3). Evaporation of the solvent afforded the crude sulfide (4.7 g, 95%), purification of which was achieved by means of flash chromatography (ethyl acetate–hexane) to give a colourless oil (Found: C, 64.05; H, 7.25. $C_{12}H_{16}O_2S$ requires C, 64.25; H, 7.19%); δ_H(200 MHz) 1.50–2.25 (4 H, m, 4-H_2 and 5-H_2), 2.35 (3 H, s, $ArCH_3$), 2.73–3.06 (0.36 H, m, 3-H *trans*), 3.23–3.33 (0.64 H, m, 3-H *cis*), 3.47–3.65 (1 H, m, 6-H), 3.95–4.10 (1 H, m, 6-H), 4.72 (0.36 H, d, *J* 6.4, 2-H *trans*), 5.01 (0.64 H, d, *J* 2.4, 2-H *cis*), 7.13 (2 H, d, *J* 8, *o*-ArH), 7.35–7.45 (2 H, m, *m*-ArH); δ_C(50 MHz) 20.9 ($ArCH_3$), 24.2, 24.4 (C-5), 26.4, 27.9 (C-4), 49.8, 51.7 (C-3), 64.1, 65.7 (C-6), 92.8, 97.1 (C-2), 129.6, 129.7, 131.0, 132.3, 133.3, 137.3 and 137.4 (ArC); *m*/*z* 224 (18%), 206 (weak), 195 (4), 177 (4), 150 (15), 123 (23), 91 (32) and 71 (100); ν_{max}(film)/cm^{-1} 3400 (OH).

2-*Butanoyloxy*-3-(p-*tolylthio*)*tetrahydropyran* **11**.—Treatment of 3-(*p*-tolylthio)tetrahydropyran-2-ol (2.6 g, 11.7 mmol) with butanoyl chloride as described above gave **11** as a colourless oil (2.1 g, 61%) after flash chromatographic purification (ethyl acetate–hexane–triethyl amine) (Found: C, 65.3; H, 7.5. $C_{16}H_{22}O_3S$ requires C, 65.28; H, 7.53%); δ_H(300 MHz) 0.90 (1.7 H, t, *J* 7.5, $-CH_2CH_3$ *trans*), 1.00 (1.3 H, t, *J* 7.5, $-CH_2CH_3$ *cis*), 1.53–2.28 (7.1 H, m, 4-H_2, 5-H_2, $-CH_2CH_3$, $-COCH_2-$ *trans*), 2.32 (3 H, s, $ArCH_3$), 2.37 (0.9 H, t, *J* 7.5, $-COCH_2-$ *cis*), 3.11–3.25 (1 H, m, 3-H), 3.59–4.00 (2 H, m, 6-H_2), 5.77 (0.56 H, d, *J* 5.4, 2-H *trans*), 6.12 (0.44 H, d, *J* 3.2, 2-H *cis*), 7.09 (2 H, d, *J* 7.5, *o*-ArH) and 7.29–7.38 (2 H, m, *m*-ArH); δ_C (50 MHz) 13.5 ($-CH_2CH_3$), 18.2, 18.4 ($-CH_2CH_3$), 21.0 ($ArCH_3$), 22.6, 23.3 (C-5), 25.7, 26.8 (C-4), 36.1, 36.3 ($-COCH_2-$), 47.1, 48.8 (C-3), 60.8, 64.4 (C-6), 91.3, 95.0 (C-2), 129.6, 129.8, 130.2, 132.9, 133.0, 137.5, 137.7 (ArC) and 171.8 (C=O); *m*/*z* 294 (M^+, 5%), 223 (9), 206 (29), 177 (50) and 71 (76); ν_{max}(film)/cm^{-1} 1740 (C=O).

3-*Butanoyloxytetrahydropyran* **12**.—Treatment of tetrahydropyran-3-ol[18] (1.24 g, 12 mmol) with butanoyl chloride and

pyridine in the usual way gave **12** as a pale brown liquid, flash chromatography (ethyl acetate–petroleum ether) of which gave **12** (1.4 g, 68%) as a colourless oil (Found: C, 63.05; H, 9.45. $C_9H_{16}O_3$ requires C, 62.77; H, 9.36%); δ_H(200 MHz) 0.98 (3 H, t, *J* 7, $-CH_2CH_3$), 1.51–2.03 (6 H, m, $-CH_2CH_3$, 4-H_2 and 5-H_2), 2.34 (2 H, t, *J* 7, $-COCH_2-$), 3.58 (1 H, dd, *J* 6, 11, 2-H), 3.67 (2 H, t, *J* 5, 6-H_2), 3.80 (1 H, dd, *J* 4, 11, 2-H) and 4.84 (1 H, dd, *J* 4, 6, 3-H); δ_C(50 MHz) 13.5 ($-CH_2CH_3$), 18.4 ($-CH_2CH_3$), 22.9 (C-5), 28.1 (C-4), 36.3 ($-COCH_2-$), 67.7, 67.8 (C-2 and C-6), 69.6 (C-3) and 173.0 (C=O); *m/z* 171 (5%), 129 (6), 100 (8), 84 (70), 73 (0.2) and 71 (100); ν_{max}(film)/cm^{-1} 1735 (C=O).

2-*Butanoyloxytetrahydropyran* **13**.—Treatment of tetrahydropyran-2-ol[19] (4 g, 39 mmol) with butanoyl chloride and pyridine in dry ether in the usual way gave **13** as a colourless oil (1.7 g, 25%) after purification by flash chromatography (ethyl acetate–hexane–triethyl amine). A sample was distilled at 80 °C and 15 mmHg (Kugelrohr) (Found: C, 62.55; H, 9.15. $C_9H_{16}O_3$ requires C, 62.77; H, 9.36%); δ_H(200 MHz) 0.98 (3 H, t, *J* 7, $-CH_2CH_3$), 1.46–1.94 (8 H, m, $-CH_2CH_3$, 3-H_2, 4-H_2 and 5-H_2), 3.65–3.77 (1 H, m, 6-H), 3.86–4.00 (1 H, m, 6-H) and 6.00 (1 H, br s, 2-H); δ_C(50 MHz) 13.5 ($-CH_2CH_3$), 18.3 ($-CH_2CH_3$), 18.6 (C-4), 24.9 (C-5), 29.1 (C-3), 36.3 ($-COCH_2-$), 63.1 (C-6), 92.3 (C-2) and 172.3 (C=O); *m/z* 173 (M^+ + 1, 100%), 172 (6), 171 (42), 73 (10.7) and 71 (56.1); ν_{max}(film)/cm^{-1} 1730 (C=O).

1,5-*Diphenylcarbamoyloxypentane*.—Treatment of pentane-1,5-diol (0.5 g, 4.8 mmol) with phenyl isocyanate (1 mol cm^{-3}) in dry diethyl ether (2 cm^3) under reflux for 2 h gave the carbamate which crystallised from ethyl acetate–hexane as a white solid (1.0 g, 63%), m.p. 169–174 °C (lit.,[20] 176 °C); δ_H(200 MHz) 1.44–1.60 (2 H, m, 3-H_2), 1.66–1.84 (4 H, m, 2-H_2 and 4-H_2), 4.17 (4 H, t, *J* 7, 1-H_2 and 5-H_2), 7.02 (2 H, t, *J* 7, *p*-ArH), 7.27 (4 H, t, *J* 7, *o*-ArH), 7.47 (4 H, t, *J* 5, *m*-ArH) and 7.85 (2 H, br s, –NH); *m/z* 344 (M^+ + 2, 0.35%), 342 (M^+, 13.32), 223 (25), 119 (100) and 93 (51).

2,3,4,6-*Tetra*-O-*acetyl*-1-*deoxy*-D-*glucose* **16**.—2,3,4,6-Tetra-*O*-acetyl-α-D-glucosyl bromide, **15**, (0.50 g, 1.2 mmol) was heated with Bu_3SnH (2.0 g, 85%, 5.9 mmol) and AIBN in deoxygenated benzene (120 cm^3) at 80 °C for 1.5 h. The reaction mixture was then allowed to cool, the solvent removed and the residue purified by flash chromatography (30% ethyl acetate–hexane). The deoxy sugar (0.34 g, 81%) crystallised from pentane–diethyl ether as colourless needles, m.p. 73–75 °C (lit.,[21] 71–73 °C); δ_H(300 MHz) 2.05 (9 H, br s, 3 × $-OCH_3$), 2.11 (3 H, s, $-COCH_3$), 3.31 (1 H, t, *J* 10.8, 4-H), 3.61 (1 H, ddd, *J* 2.4, 4.5, 9.9, 5-H), 4.11–4.25 (3 H, m, 1β-H and 6-H_2), 4.98–5.07 (2 H, m, 2-H and 3-H), 5.22 (1 H, t, *J* 9.3, 1α-H).

1,3,4,6-*Tetra*-O-*acetyl*-2-*deoxy*-α-D-*glucose* **17**.—A solution of tributylstannane (0.27 g, 85%, 0.8 mmol) and AIBN (*ca.* 10 mg) in benzene (10 cm^3) was added dropwise to a deoxygenated solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl bromide (0.30 g, 0.7 mmol) in refluxing benzene (20 cm^3) over a period of 6 h. The mixture was then heated for a further 2 h, and the solvent was removed under reduced pressure. Flash chromatography of the residue afforded the desired deoxy sugar which crystallised from pentane–diethyl ether as needles (0.18 g, 74%), m.p. 107–109 °C (lit.,[22] 110 °C); δ_H(200 MHz) 1.90–2.20 (13 H, m, 2β-H and 4 × $-COCH_3$), 2.20–2.35 (1 H, m, 2α-H), 4.00–4.37 (3 H, m, 5-H and 6-H_2), 5.10 (1 H, t, *J* 10, 4-H), 5.25–5.43 (1 H, m, 3-H) and 6.36 (1 H, d, *J* 4, 1-H).

The Kinetics of the Rearrangement of the Radical **4**.—In a typical experiment, a stock solution of the sulfide *trans*-**9** (40.0 mg, 0.135 mmol), phthalide (9.4 mg, 0.070 mmol) and tributylstannane (430 mg, 82%, 1.21 mmol) in benzene was made up in a volumetric flask (25.0 cm^3 [Bu_3SnH] = 0.049 mol dm^{-3}). AIBN (*ca.* 2 mg) was placed in each of three Pierce Reacti-vials (3 cm^3), which were then filled with the benzene solution, and closed with screw-cap Teflon coated septa. A slow stream of nitrogen was bubbled through each mixture through a fine needle, for about 2 min. They were then placed close together in a 120 °C constant-temperature bath for 2 h. The solvent was removed from the combined contents of the vials, under reduced pressure and the ^{1}H NMR spectrum (200 MHz) of the residue was recorded. Integration of the resonances at 6.00 ppm (2-H, **11**) and 4.84 ppm (3-H, **12**) furnished the product ratio (**13**:**12** = 1.41:1.00), from which a value for k_4/k_{H4} was calculated by the application of eqn. (1) (see Table 1). The ratio of the combined integration of the resonances at 4.84 and 6.00 ppm to that of phthalide at 5.35 ppm (0.95:1.0) indicated the yield of the reaction was 99%.

The Kinetics of the Rearrangement of the Radical **6**.—In a typical experiment, a stock solution of glycosyl bromide **15** (50.9 mg, 0.124 mmol) and tributylstannane (354 mg, 96%, 1.17 mmol) in benzene was made up in a volumetric flask (50.0 cm^3 [Bu_3SnH] = 0.023 mol dm^{-3}). AIBN (*ca.* 2 mg) was placed in each of four Pierce Reacta-vials (3 cm^3), which were then filled with the benzene solution, and closed with screw-cap Teflon lids. A slow stream of nitrogen was bubbled through each mixture *via* a fine needle, for approx. 2 min. They were then placed close together in a 100 °C constant-temperature bath for 2 h. The combined contents of the vials were concentrated to a volume of approx. 0.5 cm^3 under reduced pressure, passed through a Waters Sep-Pak, and the eluent analysed by HPLC (20% ethyl acetate–hexane, ALLTECH 10 m CN-bonded silica column, refractive index detector, flow rate = 7.5 cm^3 min^{-1}). The detector had previously been calibrated with solutions of authentic samples of the expected products **16** (t_R = 8.1 min) and **17** (t_R = 9.3 min) of accurately known proportion. The results were recorded in terms of the ratio of rearranged **17** to unrearranged **16** product, from which a value for k_4/k_{H4} was calculated. The results are shown in Table 2.

The Reaction of the 3-*Sulfide* **11** *with Tributylstannane*.—A deoxygenated solution of the stannane (66 mg, 90%, 0.20 mmol) and AIBN (*ca.* 3 mg) in methylcyclohexane (5 cm^3) was added from a syringe pump to a deoxygenated, refluxing solution of **11** (52 mg, 0.18 mmol) in methylcyclohexane (10 cm^3) over 6 h. The mixture was then heated under reflux for a further 2 h, allowed to cool and concentrated under reduced pressure. The ^{1}H NMR spectrum of the residue showed the ratio of **12** to **13** to be approx. 0.05:1.0. A similar result was obtained when the stannane in benzene was added slowly during the reaction from a syringe pump.

Isotopically Labelled 2-*Sulfides* ^{17}O-**9** *and* ^{18}O-**9**.—In a typical experiment, butanoyl chloride (184 cm^3, 1.7 mmol) was added to a solution of $H_2{}^{17}O$ (20%, 32 cm^3, 1.7 mmol) in dry diethyl ether (4 cm^3) and the mixture was then stirred for 6 h at room temperature. It was then cooled to 0 °C and DMAP (400 mg, 3.6 mmol), **8** (600 mg, 2.7 mmol) and DCC (440 mg, 2.1 mmol) were added in one portion. The resulting reaction mixture was stirred overnight at room temperature and the urea was filtered off. The filtrate was then diluted with diethyl ether and washed with dilute HCl (2 ×) and with saturated aqueous $NaHCO_3$, dried, and concentrated. Flash chromatography (ethyl acetate–hexane) of the residue gave pure ^{17}O-**9** as a colourless oil (431 mg, 87%). The ^{17}O NMR spectra for ^{17}O-**9** contained a single peak at 364 ppm relative to external $H_2{}^{17}O$. The ^{18}O-labelled compound ^{18}O-**9** was prepared by an identical procedure with $H_2{}^{18}O$. The ^{1}H NMR spectra of

both compounds were identical with that of the unlabelled compounds **9**.

Rearrangement of the Radical ^{17}O-**4**.—The labelled 2-sulfide ^{17}O-**9** (200 mg, 0.68 mmol) was heated with tributylstannane (263 mg, 90%, 0.81 mmol) and AIBN (*ca.* 3 mg) in deoxygenated benzene (40 cm^3) under reflux. After 1.5 h the reaction mixture was concentrated under reduced pressure and the residue was then subjected to flash chromatography (4% ethyl acetate–hexane). The ^{17}O NMR spectrum of the rearranged product ^{17}O-**13** contained two peaks, one at 352 ppm and the other at 195 ppm, with relative intensities of 67:33, respectively, while the ^{17}O NMR spectrum of the reduced product ^{17}O-**12** contained two peaks, one at 347 ppm and the other at 175 ppm, with relative intensities of 94:6, respectively. A sample of the 2-ester, **13**, labelled specifically in the carbonyl oxygen with ^{17}O was prepared from tetrahydropyran-2-ol in a manner identical with that used for the preparation of ^{17}O-**9** (crude yield 30 mg, 50%). ^{17}O NMR spectra of the product were recorded before and after purification with flash chromatography, and after the purified compound was heated in benzene at 80 °C for several hours. The spectra were identical and contained a single peak at 352 ppm. The ^{1}H NMR spectra of this compound was identical with that of the corresponding unlabelled species.

Rearrangement of the Radical ^{18}O-**4**.—The labelled sulfide ^{18}O-**9** [m/z ~ 71 ($C_3H_7C{=}{}^{16}O^+$), 100%; 73 ($C_3H_7C{=}{}^{18}O^+$), 59.1%], was treated with tributylstannane as described in the preceding experiment. The GC–MS of the isolated products were recorded: ^{18}O-**13**: m/z = 71 ($C_3H_7C{=}{}^{16}O^+$), 42.1%; 73 ($C_3H_7C{=}{}^{18}O^+$), 24.7%. ^{18}O-**12**: m/z = 71 ($C_3H_7C{=}{}^{16}O^+$), 100.0%; 73 ($C_3H_7C{=}{}^{18}O^+$), 31.3%. Both esters were reduced with an excess of $LiAlH_4$ in diethyl ether. The reduction of ^{18}O-**12** gave the corresponding alcohol ^{18}O-tetrahydropyran-2-ol (10 mg, 61%) [GC–MS: m/z = 102 (M^+), 22.4%; 104 (M^+ + 2), 0.3%] [*cf.* GC–MS for the unlabelled compound: m/z = 102 (M^+), 70.4%; 104 (M^+ + 2), 0.1%]. The reduction of ^{18}O-**13** gave a mixture of products from which pentane-1,5-diol was isolated by means of flash chromatography (ethyl acetate–hexane) (3 mg, 17%). This compound was converted into the ^{18}O-labelled bisphenylurethane by a method identical with that used for the preparation of the unlabelled species [m/z = 342 (M^+), 2.72%; 334 (M^+ + 2), 0.29%].

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