Decarboxylative Rearrangement of an Alkanoyl Arylcarbonyl Peroxide Involving Migration of a Primary Chiral Centre

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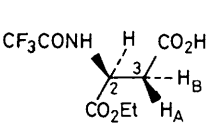
Although migration of a secondary chiral centre in the decarboxylative rearrangement of diacyl peroxides occurs with retention of configuration, this is not the case for migration of the primary chiral centre in (2*S*)-*O*-ethyl-*N*-trifluoroacetyl-β-aspartyl *m*-chlorobenzoyl peroxide (2). This result is in keeping with the suggestion that the mechanisms of the reactions are different and that the latter rearrangement proceeds *via* a radical cage process.

CARBOXYLIC acids, RCO_2H, can be degraded to the corresponding alcohols, ROH, by conversion into the peroxy-anhydrides, RCO·O·O·COR′, which undergo thermal decomposition to yield the esters $R'CO_2R$. It has been shown that when the alkyl group which migrates to oxygen in this rearrangement is secondary and chiral, then the rearrangement is stereospecific and occurs largely with retention of configuration.[1-8] Further, when the carbonyl oxygen in the secondary acyl peroxide is labelled with ^{18}O, then there is little or no scrambling of ^{18}O between the acyl and ether oxygen atoms in the product ester, the label remaining on the carbonyl oxygen. Indeed any small amount of scrambling of label seems to correspond directly with an equivalent loss of optical integrity in the product.[4,9]

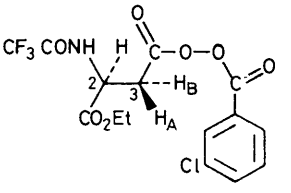
Walling [8,11] has accounted for the dichotomy between ionic and radical pathways in the decomposition of secondary and tertiary diacyl peroxides by a common mechanism, the stereospecific decarboxylative rearrangement involving polar intermediates. It has been shown,[9,10,12] however, that diacyl peroxides, RCO·O·O·COR, in which the group R is primary, decompose differently: when the carbonyl oxygen atoms are labelled with ^{18}O, then the ester product, RCO_2R, has the label ' scrambled ' between the carbonyl and ether oxygen atoms. A radical cage mechanism has been suggested to account for this finding.[9,10,12] Information about the stereochemistry of the rearrangement of a ' primary ' diacyl peroxide would evidently extend our knowledge of this process, and since we had prepared the compound (1) in which C-3 was stereospecifically labelled with deuterium,[13] we were ideally situated to examine this question.

The acid (1) would serve as the precursor for a diacyl peroxide which would have the C-3 chiral primary carboxylic acid CH_2 group adjacent to a chiral centre at C-2. The C-3 protons would thus be diastereotopic, and so the stereochemical purity of the primary centre could be assessed by ^1H n.m.r. spectroscopy. Further the product ester from the rearrangement [*e.g.* (3)] would yield serine on hydrolysis. The absolute stereochemistry of (3R)- and (3*S*)-[3-$^2H_1$]serines can easily be ascertained by ^1H n.m.r. spectroscopy,[14] so that the stereochemistry of the decarboxylative rearrangement might readily be assessed.

The acid chloride from (2*S*)-α-ethyl *N*-trifluoroacetylaspartate (1) [13] reacted with *meta*-chloroperbenzoic acid to yield the diacyl peroxide (2). The ^1H n.m.r. spectrum of this compound differentiates between the prochiral hydrogen atoms on C-3, which are part of an ABX system. Thus when the reaction was repeated using (2*S*,3*R*)-α-ethyl *N*-trifluoroacetyl[3-$^2H_1$]aspartate [13] (1; H_B = ^2H), we were able to ascertain that the product (2; H_B = ^2H) was stereospecifically labelled at C-3 by the



(1)



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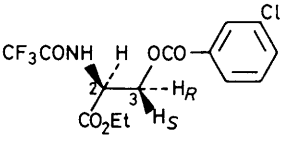

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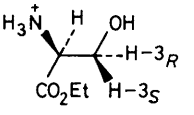
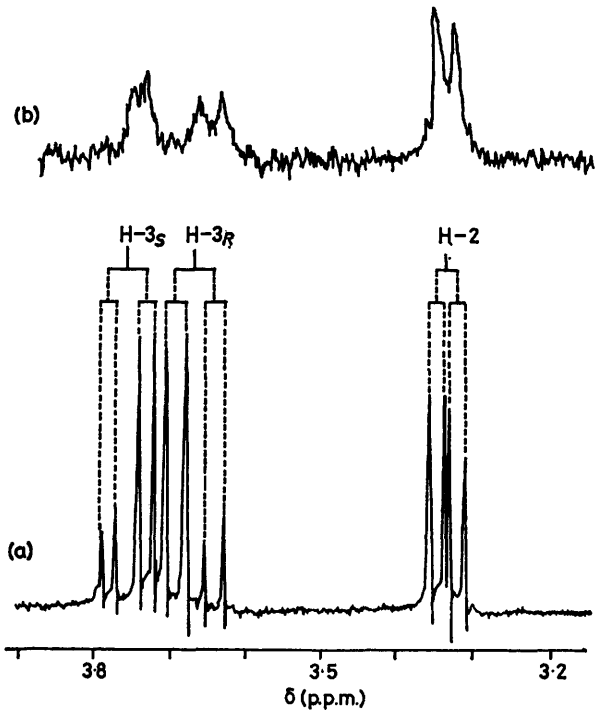


(4)

selective loss of one of the signals in the AB part of the ABX system.

The diacyl peroxides (2) and (2; H_B = ^2H) were then separately heated to reflux in toluene: they underwent decarboxylative rearrangement to the esters (3) and [3-$^2H_1$]-(3) in *ca.* 70% yield. The protons on C-2 and C-3 now appeared as an A_2X system in the ^1H n.m.r. spectrum of the non-deuteriated sample and so it was not possible to infer the stereochemistry of the deuteriated sample from its ^1H n.m.r. spectrum. Hydrolysis of the esters in hydrochloric acid, however, yielded (2*S*)-serine (4) and (2*S*)-[3-$^2H_1$]serine. The ^1H n.m.r. spectra of these samples are shown in the Figure. The occurrence of a signal corresponding to one half of a proton at the chemical shift for each of $H\text{-}3_R$ and $H\text{-}3_S$ in the deuteriated sample makes it evident that the chirally deuteriated centre C-3 is racemic. The rotation of the samples of serine obtained from these hydrolyses was in keeping with expectation for optically pure (2*S*)-serine and so elimination–addition processes are ruled out as an explanation for the racemisation.



^{1}H N.m.r. spectrum (220 MHz; solvent 10% NaOD–D_2O) of (a)(2*S*)-serine; (*b*) (2*S*,3*RS*)-[3-$^2H_1$]serine from the rearranged ester (3); assignments based on ref. 14

We conclude therefore that this, the first reported decarboxylative rearrangement of a diacyl peroxide in which a chiral primary carbon centre is migrating, proceeds non-stereospecifically. This supports a radical cage mechanism for the process and is in keeping with the ^{18}O studies.[9,10,12] It is evident that chirality cannot be maintained within the cage whereas, in the ionic mechanism,[8,11] secondary diacyl peroxides rearrange with retention of stereochemistry.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra were recorded on Perkin-Elmer 257 and 477 instruments and ^{1}H n.m.r. spectra on Perkin-Elmer R32 (90 MHz) and R12 (60 MHz) and Varian T60 (60 MHz) instruments; 220 MHz spectra were obtained from the PCMU, Harwell. Specific rotations were determined on a Perkin-Elmer 241 polarimeter using a 1 dm cell, and mass spectra were recorded on an A.E.I. MS30 instrument. Merck Kieselgel GF_{254} of thickness 0.75 mm was used for t.l.c.

(2S)-O-*Ethyl*-N-*trifluoroacetyl*-β-*aspartyl* m-*Chlorobenzoyl Peroxide* (2).—(a) *Unlabelled*. The acid chloride of (2*S*)-α-ethyl *N*-trifluoroacetylaspartate (500 mg, 1.9 mmol) [13] and 85% *meta*-chloroperbenzoic acid (376 mg, 1.9 mmol) were added to dry ether (15 ml), and the solution was stirred under nitrogen in an ice–salt bath. Pyridine (150 mg, 1.9 mmol) in dry ether (2 ml) was added slowly to the mixture and stirring was continued for 4 h at 0 °C after addition was complete. The solution was filtered, washed with water and aqueous N-sodium carbonate, and dried (Na_2SO_4). The solvent was removed *in vacuo* to yield a white solid which crystallised from diethyl ether–light petroleum (b.p. 60—80 °C) as colourless *needles* (570 mg, 72%), m.p. 112—113 and 119—121 °C (two forms), $[\alpha]_D$ +47.2° (*c* 1.8, $CHCl_3$) (Found: C, 43.6; H, 3.3; N, 3.5. $C_{15}H_{13}ClF_3NO_7$ requires C, 43.8; H, 3.2; N, 3.4%); *m/z* 411 (M^+ for ^{35}Cl); $\nu_{max.}$ (Nujol) 3 270 (NH), 1 792, 1 765 (peroxy-anhydride), 1 743 (ester), and 1 710 cm^{-1}; δ ($CDCl_3$) 1.30 (3 H, t, *J* 6.5 Hz, CH_3CH_2), 3.13 and 3.26 (2 H, *ABX*, J_{AB} 16.5, J_{AX} 4.6, J_{BX} 4.4 Hz, C-3 protons), 4.27 (2 H, q, *J* 6.5 Hz, CH_2O), 4.88 (1 H, m, C-2 proton), and 7.2—8.0 (5 H, m, NH and aromatics).

(b) *The deuteriated compound* (2; $H_B = {}^2H$). This was prepared as above using (2*S*,3*R*)-α-ethyl *N*-trifluoroacetyl-[3-$^2H_1$]aspartate (1; $H_B = {}^2H$) [13] (200 mg, 0.8 mmol). The product was obtained in 72% yield and had similar properties to the undeuteriated analogue; m.p. 110—112 and 118—119 °C, $[\alpha]_D$ +45.2° (*c* 1.59, $CHCl_3$). Mass spectroscopy indicated 78% monodeuteriation (from the $M - ClC_6H_4CO_2$ fragment ion). The n.m.r. spectrum showed δ($CDCl_3$) 1.30 (3 H, t, *J* 6.5 Hz, CH_3CH_2) 3.24 (1 H, br, s, C-3 proton), 4.27 (2 H, q, *J* 6.5 Hz, CH_2O), 4.90 (1 H, q, NHC*H*), and 7.2—8.0 (5 H, m, NH and aromatics).

(S)-*Ethyl* N-*Trifluoroacetyl*-O-(m-*chlorobenzoyl*)*serinate* (3).—The peroxy-anhydride (2) (500 mg, 1.2 mmol) was heated to reflux in toluene (12 ml) for 3 h. The solvent was removed *in vacuo* and the resultant gummy solid was taken up in hot, light petroleum (b.p. 60—80 °C). Left overnight at 4 °C, the solution deposited a white solid, which contained a small amount of impurity. Preparative t.l.c. (SiO_2; $CHCl_3$) yielded the *product* (3) (302 mg, 68%), m.p. 74—75 °C, $[\alpha]_D$ +30.8° (*c* 1.0 in $CHCl_3$) (Found: C, 45.5; H, 3.9; N, 3.8. $C_{14}H_{13}ClF_3NO_5$ requires C, 45.8; H, 3.5; N, 3.8%); *m/z* 367 (M^+); $\nu_{max.}$ (Nujol) 3 275 (NH), 1 740 (aliphatic ester), 1 728 (aromatic ester), and 1 700 cm^{-1}; δ ($CDCl_3$) 1.29 (3 H, t, *J* 7 Hz, CH_3CH_2), 4.26 (2 H, q, *J* 7 Hz, CH_3CH_2), 4.69 (2 H, d, *J* 5 Hz, C-3 protons), 4.89 (1 H, br, m, NH–C*H*), and 7.1—8.0 (5 H, m, NH and aromatics).

(2S,3RS)-*Ethyl* N-*Trifluoracetyl*-O-(m-*chlorobenzoyl*)[3-$^2H_1$]*serinate* was prepared as above from the (3*R*)-[3-$^2H_1$]-peroxy-anhydride (2; $H_B = {}^2H$) (200 mg, 0.5 mmol) in 71% yield; m.p. 73.5—75 °C, $[\alpha]_D$ +31.2 (*c* 0.98 in $CHCl_3$); *m/z* 368 shows 71% monodeuteriation; δ($CDCl_3$) 1.29 (3 H, t, *J* 7.5 Hz, CH_3CH_2), 4.26 (2 H, q, *J* 7.5 Hz, CH_3CH_2), 4.69 [1 H, br,m, C-3 proton(s)], 4.90 (1 H, m, NH–C*H*), and 7.2—8.1 (5 H, m, NH and aromatics).

(2S)-*Serine Hydrochloride*.—(2*S*)-Ethyl *N*-trifluoroacetyl-*O*-(*m*-chlorobenzoyl)serinate (3) (60 mg, 0.16 mmol) was heated to reflux in 1 : 1 conc. HCl–water (10 ml) for 2 h under nitrogen. The solution was cooled and washed with chloroform. The aqueous phase was lyophilised to yield a solid (19 mg, 84%), identical with authentic serine hydrochloride (t.l.c. and spectral data); $[\alpha]_D$ +7.5° (*c* 1.2, H_2O); *cf.* +7.2° for authentic (2*S*)-serine hydrochloride. The ^{1}H n.m.r. spectrum is shown in the Figure.

(2S,3RS)-[3-$^2H_1$]*Serine hydrochloride* was prepared from the [$^2H_1$]ester (3) as above. The ^{1}H n.m.r. spectrum is shown in the Figure. A small sample of the free base was obtained by passing an aqueous solution of the hydrochloride through a column of Amberlite IRA-400 anion-exchange resin which had been prewashed with NaOH, and lyophilising the eluate. The product, subjected to mass spectrometry, showed 75% monodeuteriation [on the basis of the $(M - CH_2OH)^+$ fragment].

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