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FREE RADICAL CYCLISATION OF UNSATURATED EPOXIDES

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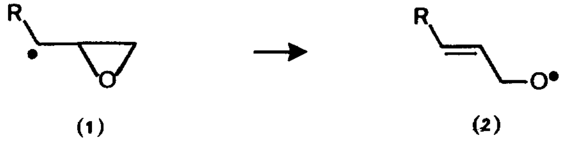
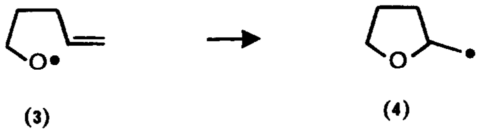
Abstract: *The e.s.r. spectra derived from 7-bromo-5,6-epoxyheptene derivatives such as epoxygeranyl bromide (7) showed that the main free radical intermediates were tetrahydrofuranylmethyl radicals (11), formed by ring opening of the epoxide and subsequent exo-cyclisation of the unsaturated alkoxyl radicals. The 7-oxabicyclo[2.2.1]heptanyl methyl radicals (12) were also formed via a double cyclisation. Products derived from both these intermediates were isolated from the reaction of (7) with tri-n-butyltin hydride.*

Introduction

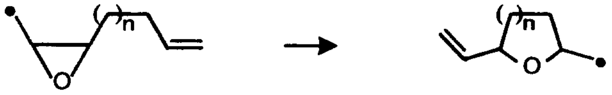
The radical chemistry of epoxides has not been very thoroughly studied, but the ring opening of 2,3-epoxyalkyl radicals (1) to unsaturated alkoxyl radicals (2) is known to occur rapidly, both from work on radicals generated from ketones [1,2] and from studies of 2-oxacyclopropylmethyl radicals[3].



The alternative β-scission of the carbon-carbon bond can occur if the resulting carbon-centred radical is stabilized by aryl or other substituents[4,5]. In addition, the *exo* cyclisation of δ, ε- unsaturated alkoxyl radicals (3) to give the THF-methyl radical (4) has been shown to occur very efficiently in several cases[6-9].

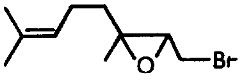


These two processes have been combined in a single case: the conversion of a *cis*-carveol derivative to a pinol[10]. Recently, Johns and Murphy showed that this combined process is of general utility for the formation of cyclic ethers (6) from unsaturated epoxides (5)[11]. We report in this paper our e.s.r. spectroscopic and product studies of some related reactions of unsaturated epoxides. Free radicals were generated from epoxygeranyl bromide (7) and epoxyneryl bromide (8)

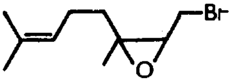


(5) (6)

by bromine abstraction with tri-n-butyltin radicals. The intermediates were identified by e.s.r. spectroscopy and the rearrangements were further studied by product analyses in closely related free radical processes.



(7)



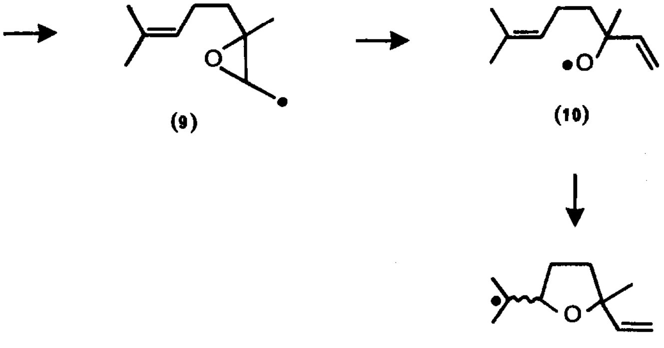
(8)

Results and Discussion

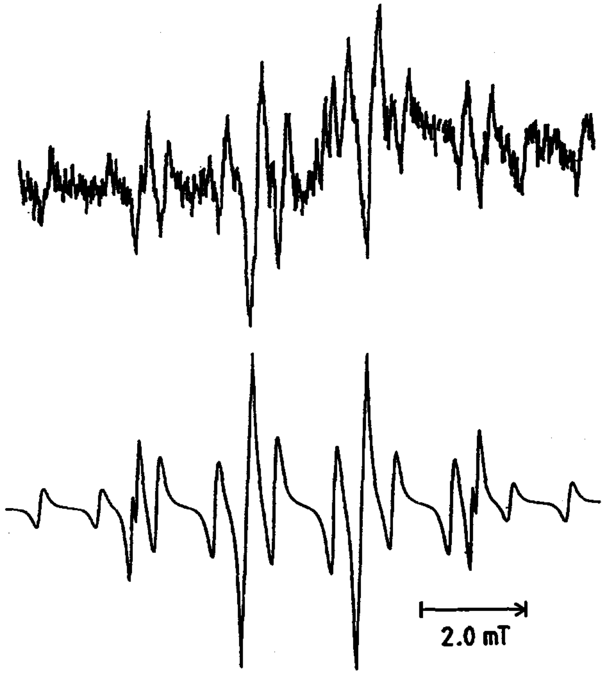
Electron Spin Resonance Study

Degassed solutions of (7) or (8), hexamethylditin and di-t-butyl peroxide in t-butylbenzene were irradiated in the cavity of the e.s.r. spectrometer. Essentially identical spectra (Figure) were obtained from both (7) and (8). The spectrum contains signals from two main radicals and the major component analyses as a heptet of doublets [*a* (6H) = 2.34, *a* (1H) = 1.17 mT at 215 K; a further hfs of *a* (2Hγ) = 0.04 mT was resolved at 150 K]. These hyperfine splittings (hfs) are very similar to those of tertiary alkyl radicals of structure $Me_2\dot{C}$-CHR_2; e.g. $Me_2\dot{C}$ $CHMe_2$ has[12] *a* (6H) = 2.29, *a* (1H) = 1.08 mT at 298 K, and hence the major component can be identified as the cyclised species (11).

(7)



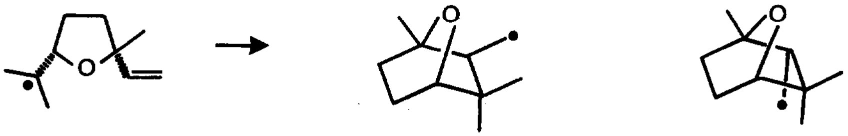
(9) (10) (11)



9.5 GHz e.s.r. spectrum of radicals derived from expoxyneryl bromide (8) in t-butylbenzene solution at 215 K. Upper spectrum; experimental, lower spectrum; computer simulation. The outer lines of radical (11) (unit intensity) are not shown.

This is formed by β-scission of the epoxymethyl radical (9) followed by *exo* cyclisation of the intermediate alkoxyl radical (10). The small β-hfs from the unique H_β indicates that radical (11) adopts a preferred conformation about the $C_\alpha Me_2$-C_β bond in which H_β lies in the nodal plane of the p-orbital containing the unpaired electron. Cyclisation of (10) is expected to produce a mixture of *cis*- and *trans*-trisubstituted tetrahydrofuranyl alkyl radicals (11). However, the *cis* and *trans* radicals will have indistinguishable e.s.r. spectra so that the spectrum of the major component probably contains exactly overlapping lines from both isomers.

The minor component consists of four lines with roughly quartet intensities, but an apparent doublet structure to the outer two lines. The e.s.r. parameters are similar to those of cyclopentylmethyl radicals$^{13-15}$ and we attribute this spectrum to the 7-oxabicyclo[2.2.1]heptanylmethyl radicals (12).


(11b) (12a) (12b)

The *cis* radical (11b) can undergo a second 1,5-exo-cyclisation to give radical (12) with the $CH_2^\bullet$ group *exo* (12a) or *endo* (12b). Small differences in the H$_\beta$ hfs are expected for these two species and the presence of both, in an approximately 1 to 1 mixture, accounts for the apparent doublet structure of the outer lines. Best simulations were achieved with the following hfs: $a\,(2H_\alpha) = 2.23$, $a\,(1H_\beta) = 2.17$; $a\,(2H_\alpha) = 2.26$, $a\,(1H_\beta) = 2.37$ mT at 215 K (see Figure); it was not possible to assign a given set of e.s.r. parameters to one or other isomer. The proportions of (11) to (12a) to (12b) were approximately 1:0.5:0.5 at 215 K, and above, as determined from the simulations. Radical (12) is formed by a complex rearrangement sequence with an unusually convoluted reaction coordinate, but the high proportion of (12) shows that this reaction is very efficient even at 215 K. At lower temperatures the proportion of (12) decreased until at 150 K in cyclopropane solvent it was virtually undetectable. Even at 150 K the cyclised radical (11) was clearly discernable in the e.s.r. spectrum, and none of the unrearranged radical (9) could be detected. It follows that the rate of *exo*-cyclisation of the alkoxyl radical (10) must be greater than that of analogous C-centred radicals, because the latter do not cyclise until much higher temperatures under e.s.r. conditions [16,17]. This inferred, fast rate of cyclisation for alkenyloxyl radicals is in agreement with other qualitative results [7,8].

Tri-n-butyltin Hydride Reductions

The reduction of bromides (7) and (8) with tri-n-butyltin hydride was carried out at different temperatures and with different tin hydride concentrations. The products and their relative yields are given in the Table.

Reduction of epoxygeranyl bromide (7) and epoxyneryl bromide (8) with tri-n-butyltin hydride †.

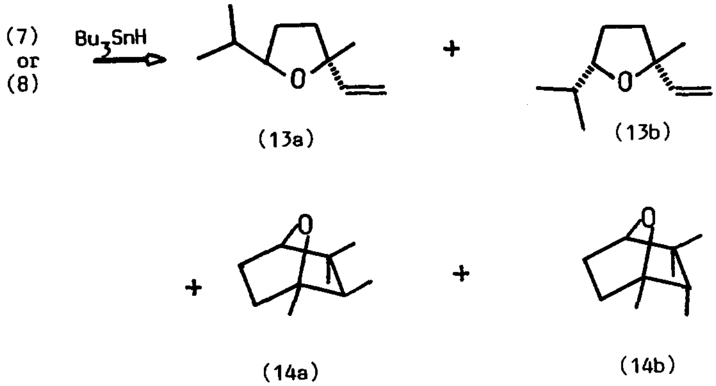
Bromide^a		Bu_3SnH^a	Temp/°C	(13a)	(13b)	(14)
(7)	2.1	2.1	5	53	47	-
(7)	2.1	2.1	20	44	54	2
(7)	2.1	2.1	55	49	47	4^b
(7)	2.1	2.1	85	51	47	~2
(7)	2.1	4.2	55	54	46	-
(7)	2.1	8.4	55	49	51	-
(7)	0.4	0.4^c	25	53	47	-
(8)	2.1	2.1	5	50	48	~2
(8)	2.1	2.1	20	53	45	~2
(8)	2.1	2.1	55	54	46	-
(8)	2.1	2.1	75	53	47	-

† Relative yields of products; overall yields were in the range 70-80 mol%.

[a] Quantities in mmol [b] Ratio (14a) : (14b) ca. 3 : 1.

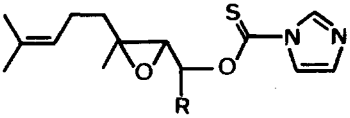
[c] Triphenyltin hydride

Both bromides gave the same mixture of products in overall yields of 70-80%. By far the major products were the *trans* (13a) and *cis* (13b) tetrahydrofuran derivatives, as expected, and these were accompanied by minor amounts of *exo*-(14a) and *endo*-(14b) 7-oxabicyclo[2.2.1]heptanes. These products are exactly as expected in the light of the e.s.r. detection of the corresponding radical intermediates. The overall yield of tetrahydrofurans is good but the ratio of *trans* to *cis* remained approximately 1 to 1 at all temperatures and reactant concentrations (Table). This inability to control the stereochemistry will limit the synthetic usefulness of this reaction.



The very low yield of (14) was surprising because the e.s.r. data indicated a relatively large amount of the precursor radicals (12). It is likely, however, that the intermediate radicals (11) abstract hydrogen so readily from Bu_3SnH that the second cyclisation stage does not compete effectively in the accessible temperature range. The yield of (14), could probably be increased by using a poorer hydrogen donor. However, use of triphenyltin hydride gave virtually the same ratio of products (Table).

Our results nicely complement those of Johns and Murphy who generated unsaturated epoxyalkyl radicals from the precursors (15)[11]. These reactions also led to an approximately 50:50 mixture of the *cis*- and *trans*- THF derivatives. None of the 7-oxabicyclo[2.2.1]heptane derivative (14) was detected for (15, R = H), but significant yields were obtained for (15, R = Me and Bu^n).



(15) R = H, CH_3, Bu^n

Experimental Section

E.s.r. spectra were recorded with a Bruker ER 200D spectrometer on degassed samples, sealed in spectrosil tubes, irradiated with light from a 500 W super-pressure Hg arc. N.m.r. spectra were obtained with Bruker WP 80 and AM 300 instruments for $CDCl_3$ solutions at ambient temperature with Me_4Si as internal standard. G.l.c. - mass spectrometric analyses were carried out with a Finnegan Incos instrument. For preparative g.l.c. a Pye-Unicam 105 chromatograph was used with 3 m x 1 cm glass columns packed with 20% FFAP on chromosorb WAW.

Epoxygeraniol and Epoxynerol[18]. To CH_2Cl_2 (50 ml) containing $4A^o$ molecular sieve (1.8 g, powdered) at 0° C under N_2 was added L-(+)-diethyltartrate (1.0 g, 4.8 mmol) followed by titanium (IV) isopropoxide (0.87 g, 3.2 mmol). The mixture was cooled to -20° C and 22 ml of a 5.8 M solution of t-butylhydroperoxide was added, the mixture was stirred for 20 min, and then E-3,7-dimethyl-2,6-octadien-1-ol (geraniol), (8.9 g, 65 mmol), or nerol, was added and stirring continued for 45 min. The mixture was warmed to 0° C and water (20 ml) was added and the mixture allowed to warm to room temperature during 60 min. The tartrate was hydrolysed by adding 6 ml of a 30% aqueous solution of NaOH saturated with NaCl. After 35 min of vigorous stirring the CH_2Cl_2 layer was separated, combined with 2 x 50 ml extracts of the aqueous phase, dried with Na_2SO_4 and distilled, b.p. 90-95° C/0.5 torr; yield 89%. The n.m.r. spectra were essentially identical to those given in the literature[18].

E- and Z-3,7-Dimethyl-2,6-octadienyl bromides (7) and (8). Epoxygeraniol (4.7 g, 28 mmol) and triethylamine (4.2 g, 41 mmol) in dry CH_2Cl_2 were cooled in an ice/salt bath under N_2 and methanesulphonyl chloride (4.12 g, 36 mmol) was added over 15 min. The solution was stirred for a further 20 min, water was added, the CH_2Cl_2 layer was separated, washed with 2 M HCl (100 ml), 5% brine (50 ml), saturated $NaHCO_3$ (100 ml), dried over Na_2SO_4 and the solvent removed at room temperature on a rotary evaporator. The crude mesylate was added to LiBr (4.8 g, 55 mmol) in dry acetone (100 ml) and the solution refluxed for 30 min. The mixture was cooled, filtered and the acetone evaporated off at atmospheric pressure. Water was added, the mixture was extracted with ether, dried (Na_2SO_4) and distilled to give (7), b.pt. 65° C/0.1 torr; yield 4.8 g, 68%, δ_H 1.32 (3H,s), 1.39-1.52 (1H,m), 1.62 (3H,s) 1.69 (3H,s), 1.68-1.78 (1H,m), 2.10 (2H, q), 3.10 (1H, dd) 3.26 (1H, dd), 3.54 (1H, dd), 5.11 (t), δ_C (75 MHz) 16.06, 17.68, 23.78, 25.67, 29.74, 38.35, 61.45, 63.04, 123.21, 132.25. The M^+ ion was absent but fragments at 153 (6), 135 (4), 123 (3), 109 (82), 95 (9), 93 (9), 81 (17), 79 (7) and 69 (100) were observed. The epoxyneryl bromide (8) was made by the same procedure, δ_H 1.36 (3H,s), 1.45-1.70 (2H,m), 1.62 (3H,s), 1.70 (3H,s), 2.17 (2H,q), 3.11 (1H,dd), 3.35 (1H,dd), 3.50 (1H,dd), 5.12 (1H,t). δ_C (75 MHz) 17.67, 21.93, 24.11, 25.68, 29.67, 32.62, 62.97, 63.45, 123.22, 132.44.

Reduction of (7) and (8) with tri-n-butyltin hydride. The bromide (0.5 g, 2.1 mmol) was placed in a quartz or pyrex tube, heated to the required temperature and degassed by bubbling N_2 for *ca* 10 min. Bu_3SnH (0.61 g) was added while the N_2 stream was maintained. The mixture was then irradiated through a pyrex filter with light from a 250 W medium pressure Hg arc for 60 min. The contents of the tube was then distilled on a vacuum line. The product was examined by g.l.c.-m.s. on an

HP 1 capillary column which showed two major products eluted close together both with molecular ions at 154 and major fragments at m/z 139, 111, 93, 81, 69, 67 and 55, i.e. these were, the THF derivatives (13a) and (13b).

These major components were accompanied by two minor peaks at slightly longer retention times, with molecular ions at 154 (5%) and virtually identical fragmentation patterns; m/z (%) 139 (12), 136 (5), 125 (30), 121 (22), 111 (18), 110 (28), 97 (54), 96 (67), 95 (33), 83 (64), 81(45), 69(42), 55(83) and 43(100) which we attribute to the 7-oxabicyclo[2.2.1]heptanes (14a) and (14b). Some additional, minor, unidentified products were observed on the chromatogram. The identity of the products was confirmed by separation of the components by preparative g.l.c. Peak 1, (∼49%), δ_H 0.87 (3H,d,J = 8Hz), 0.95 (3H,d,J = 8Hz), 1.29 (3H,s), 1.55-1.77 (4H,m), 1.78-1.92 (1H,m), 3.58 (1H,q,J = 7Hz), 4.96 (1H,dd,J = 10, 2 Hz), 5.17 (1H,dd,J = 17,2 Hz), 5.88 (1H,dd,J = 17,10 Hz). δ_C(75 MHz) 18.08 (q), 19.17 (q), 27.10 (q), 28.27 (t), 33.05 (d), 37.27 (t), 82.30 (s), 84.25 (d), 111.00 (t), 144.33 (d), i.e. the *trans* isomer (13a). Peak 2 (47%), δ_H, 0.82 (3H,d,J = 8Hz), 0.98 (3H,d,J = 8Hz), 1.29 (3H, s), 1.4-2.1 (5H,m), 5.67 (1H,q,J = 8Hz), 4.95 (1H,dd,J = 10, 2Hz), 5.20 (1H,dd,J = 17,2 Hz), 5.95 (1H,dd,J = 10,17 Hz), δ_C(75 MHz), 18.43 (q), 19.70 (q), 26.48 (q), 29.10 (t), 33.50 (d), 38.18 (t), 82.29 (s), 84.90 (d), 111.24 (t), 144.99 (d), i.e. the *cis* isomer (13b). Peak 3 (4%) was contaminated by the tail of peak 2 but, after subtraction, gave the following: δ_H 0.82 (3H,d), 1.02 (3H,s), 1.25 (3H,s), 1.32 (3H,s), 1.7-2.0 (5H,m), 3.85 (1H,d) which supports structure (14a). The second 7-oxabicyclo[2.2.1]heptane isomer (14b) was not formed in sufficient quantity for n.m.r. analysis, but its structure follows from the virtual identity of its mass spectrum to that of (14a).

Tin hydride reductions were carried out at several different temperatures and tin hydride concentrations and the results are recorded in the Table. A further reaction in which the Bu_3SnH was added slowly over 60 min to the epoxygeranyl bromide at 55^o C gave results essentially the same as those recorded for the standard conditions.

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