Chemical Resolution and Racemization of 1,2- and 3,4-Epoxydihydrophenanthrene

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Summary 1,2- and 3,4-epoxy-1,2,3,4-tetrahydrophenanthrene were each separable into enantiomers while the corresponding 1,2- and 3,4-epoxydihydrophenanthrene (derived from identical chiral precursors) showed evidence of spontaneous racemization; preliminary PMO calculations indicate that oxepin intermediates could account for this configurational instability.

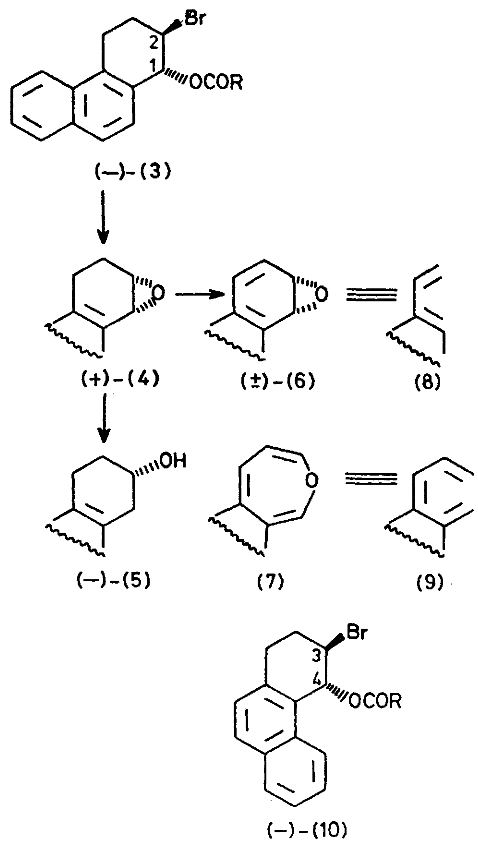
The metabolism of phenanthrene by mammals, in common with other polycyclic aromatic hydrocarbons (PAH), is initiated by the formation of epoxides.[1] This mono-oxygenase-catalysed addition of an oxygen atom may occur preferentially to one stereoheterotopic face of a PAH. The configurational stability of such optically active epoxide has previously been demonstrated for 1,2-epoxydihydro-naphthalene[2,3] (**1**) and -anthracene (**2**).[3]

The optically active *trans*-1,2-, 3,4-, and 9,10-dihydrodiols isolated from mammalian metabolism of phenanthrene[1,4] are thus derived from the corresponding 1,2-, 3,4-, and 9,10-epoxy compounds. A similar synthetic route[3,4] to that used for the resolution of (**1**) and (**2**) was employed for 1,2-epoxydihydro- (**6**) and 3,4-epoxydihydro-phenanthrene (**13**). The efficiency of the chromatographic separation of the diastereoisomeric pairs of (**3**) [or (**10**)] was readily determined from the n.m.r. signals of the exocyclic methylene protons (R = 2-isopropyl-5-methylcyclohexyloxymethyl, C_6D_6, 220 MHz).

The stereochemical relationships between (**3**) and other chiral derivatives are shown in the Scheme. The corresponding chiral tetrahydro-3,4-epoxide (**11**) and tetrahydro-3-alcohol (**12**) derived from (**10**) have $[\alpha]_D$ signs and absolute configurations identical to those shown in the partial structures of (**4**) and (**5**). Thus, $[\alpha]_D$ values obtained (and diastereoisomeric excess) for two typical chromatography fractions (in $CHCl_3$) are:

$$\underset{+70^\circ\ (>95\%)}{(\mathbf{3})} \longrightarrow \underset{-140^\circ}{(\mathbf{4})} \longrightarrow \underset{+88^\circ}{(\mathbf{5})} \quad \text{and}$$

$$\underset{-115^\circ\ (ca.\ 66\%)}{(\mathbf{10})} \longrightarrow \underset{+95^\circ}{(\mathbf{11})} \longrightarrow \underset{-30^\circ}{(\mathbf{12})}$$



Scheme

The absolute stereochemistry of structures (**3**) and (**4**) [or (**10**) and (**11**)] was related to that of the alcohols (**5**) [or (**12**)] whose configurations (as derivatives) have been determined by a range of techniques including c.d.,[5] chemical shift non-equivalence in the presence of $Eu(fod)_3$,[6] and chemical correlation of ozonolysis products.[5]

The relatively high $[\alpha]_D$ values observed for (**4**) and (**11**) are of a similar magnitude to those of the corresponding 1,2,3,4-tetrahydro-naphthalene and -anthracene epoxides.[3] In contrast, however, the $[\alpha]_D$ values of (**6**) and (**13**) are, respectively, negligible† and low at all wavelengths even when these epoxides are prepared from precursors of high optical purity. The sign and magnitude of optical rotation of (**13**) ($[\alpha]_D$ −20°, +4°, 0°) varies with the precursor (**10**) ($[\alpha]_D$ + 26°, −80°, −124°) and experimental conditions, but in each case falls spontaneously toward zero during 12 h at 25 °C; n.m.r. analysis shows no detectable amount of impurity or decomposition which could account for the above observations. Taken with the large $[\alpha]_D$ values of 1,2-epoxydihydro-naphthalene (**1**) (+149°) and -anthracene (**2**) (+214°)[2] we conclude that the present results can most easily be explained by a spontaneous racemisation of the epoxides (**6**) and (**13**).‡

Such a racemisation might proceed by epoxide–oxepin valence tautomerism (though no oxepin was detectable in the n.m.r. spectra of the epoxides). The possibility of this explanation was tested by Perturbational Molecular Orbital (PMO) calculations. The epoxides and oxepins were modelled on the isoconjugate hydrocarbons (**8**) and (**9**), respectively, since the oxiran system is localised and since the semi-empirical calculations[7] (on benzo-condensed oxepins) show the resonance energy of the oxepin to be very small and additive throughout the series to better than 2 kcal mol^{-1}. The appropriate resonance energy differences were calculated by Dewar's method[8] for the bislocalisation formally converting (**9**) into (**8**) [method (i)], and by two new methods [(ii) and (iii)], which give better correlations with full calculations[7] (to be described in forthcoming paper[9]).

TABLE

Epoxide	(i) $\Delta\Delta E^a/\beta$	(ii) $\Delta\Delta E^a/\beta$	(iii) $\Delta\Delta E^a$/kcal mol^{-1}
(**1**)	1·00	0·66	20·0
(**2**)	1·46	0·86	30·5
(**6**)	0·69	0·40	10·5
(**13**)	0·71	0·40	10·5

[a] $\Delta\Delta E = E$(substituted oxepin) − E(epoxy compound) − E(oxepin) + E(1,2-epoxydehydrobenzene).

The Table shows our results for (**1**), (**2**), (**6**) and (**13**) referred to the closely balanced oxepin–1,2-epoxydihydro benzene equilibrium as zero. Assuming that racemization barriers for the epoxides are in the same order as the $\Delta\Delta E$ values for oxepin formation, it is reasonable that (**1**) and (**2**) should be configurationally stable, while (**6**) and (**13**) are not. Since (**13**) appears to be a borderline case, we may use our calculations to predict the configurational stability of other systems. Thus, of the 1,2-, 4,5-, 7,8-, 9,10-, and 11,12-epoxydihydrobenzo[*a*]pyrenes and 1,2-, 3,4-, 5,6-, 8,9-, and 10,11-epoxydihydrobenz[*a*]anthracenes all should be resolvable, with the exception of 1,2-epoxydihydrobenzo[*a*]pyrene and 1,2- and 3,4-epoxydihydrobenz[*a*]-anthracene, which should racemize more rapidly than (**6**) or (**13**).

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† A value of $[\alpha]_D$ + 3° rotation for (**6**) remained unchanged after 12 h at 25 °C and was quantitatively attributed by n.m.r. spectroscopy to traces of (**4**).

‡ The remote possibility that (**6**) (in an optically pure state) will have no measureable $[\alpha]_D$ value cannot yet be totally excluded.

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