Synthesis and Spontaneous Racemization of Benz[*a*]anthracene 3,4-Oxide: Photochemical Oxygen-walk Rearrangements of Arene Oxides of Benz[*a*]anthracene and Triphenylene to Yield Oxepines

Derek R. Boyd,[a,*] Narain D. Sharma,[a] Shiv K. Agarwal,[a] Guru S. Gadaginamath,[a] Gerard A. O'Kane,[a] W. Brian Jennings,[b] Haruhiko Yagi[c] and Donald M. Jerina[c,*]

[a] *Department of Chemistry, The Queens's University of Belfast, Belfast, BT9 5AG, Northern Ireland UK*

[b] *Department of Chemistry, University College, Cork, Republic of Ireland*

[c] *Laboratory of Bioorganic Chemistry, NIADDK, The National Institutes of Health, Bethesda, MD20892, USA*

Benz[*a*]anthracene 3,4-oxide **2**, when synthesised from optically pure dibromo ester precursors, was found to have racemized spontaneously and was accompanied by anthra[2,1-*b*]oxepine **14**. Photoisomerization of benz[*a*]anthracene 3,4-oxide **2**, triphenylene 1,2-oxide **4** and benz[*a*]anthracene 1,2-oxide **5** proceeds *via* an oxygen-walk mechanism to yield anthra[2,1-*b*]oxepine **14**, phenanthro[10,9-*b*]oxepine **16** and anthra[2,1-*f*]oxepine **17** respectively.

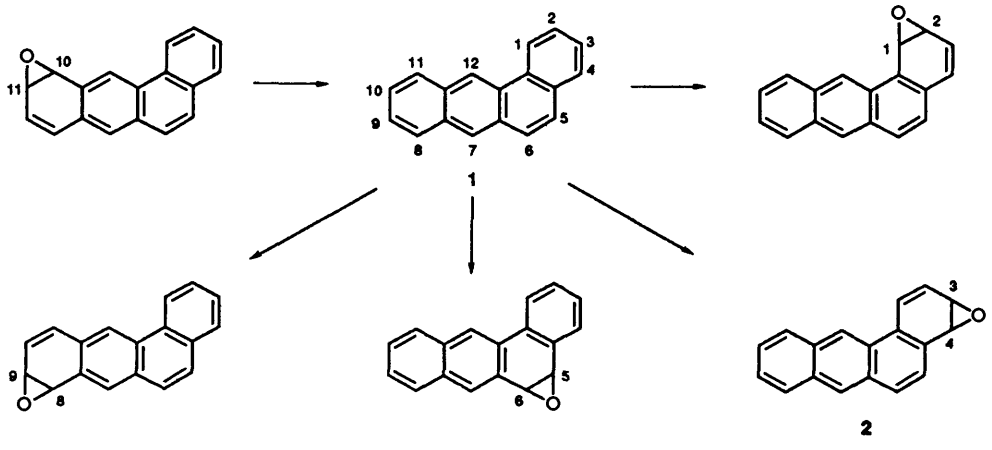
Benz[*a*]anthracene **1** [B(a)A] is both an environmental pollutant resulting from the combustion of fossil fuels, and a carcinogen. The metabolism of B(a)A in mammals resulted in the formation of arene oxides and *trans*-dihydro diols at the 1,2-, 3,4-, 5,6- 8,9- and 10,11-positions.[1-3]

The synthesis of the 1,2-,[4] 5,6-,[5] 8,9-[6] and 10,11-[5] arene oxides of B(a)A from both racemic and optically pure precursors has previously been reported from these laboratories. Of these arene oxide metabolites only the further metabolites of compound **2** such as the *trans*-dihydro diol **3** and the derived diol epoxides showed significant mutagenic and carcinogenic activity.[7] The synthesis and spontaneous racemization of benz[*a*]anthracene 3,4-oxide **2** and the photoisomerization of the arene oxides **2**, **4**[8] and **5**[4] to the corresponding isolable oxepine isomers **14**, **16**, **17** is discussed herein.

1,2-Dihydrobenz[*a*]anthracene **6** was obtained by the literature route[8] and was converted into the racemic bromohydrin (±)-**7** using *N*-bromoacetamide in aqueous tetrahydrofuran. The bromohydrin (±)-**7** was resolved *via* the bromomenthyloxyacetate (bromo MOA) diastereoisomers **8A** and **8B**. The crude mixture of bromo MOA esters **8A** and **8B** [obtained by treatment of the racemic bromohydrin (±)-**7** with (−)-menthyloxyacetyl chloride in dry pyridine] was purified by column chromatography (silica gel) and totally separated by preparative HPLC on a silica column into the early eluting, *i.e.* less polar diastereoisomer (−)-**8B** ($[\alpha]_D$ −157.5) and late eluting, *i.e.* more polar diastereoisomer (+)-**8A** ($[\alpha]_D$ +73) (Scheme 1). Similar studies of the corresponding bromo-MOA esters in the naphthalene,[9] anthracene,[9] phenanthrene,[10,11] chrysene,[12,13] benz[*a*]anthracene[4-6] and benzo[*a*]pyrene[14] series have indicated that in all cases the early eluted isomer having a negative $[\alpha]_D$ value and a smaller degree of non-equivalence for the ^1H NMR signals of the exocyclic methylene protons (H_A and H_B) will have an *R*,*R* configuration. Thus, the diastereoisomer **8B** being the early eluting isomer by HPLC analysis, having a negative $[\alpha]_D$ value and showing protons H_A/H_B in the ^1H NMR spectrum, as doublets centred at δ 4.08 and 4.11 respectively (J_{AB} 16.4 Hz) may similarly be assigned the (3*R*,4*R*) configuration. Conversely, the late eluting dextrorotatory isomer **8A** showed a larger degree of non-equivalence for H_A and H_B protons (centred at δ 4.02 and 4.12, J_{AB} 16.4 Hz respectively) consistent with the 3*S*,4*S* configuration.

The separated bromo MOA diastereoisomers **8A** and **8B** were each converted into the parent bromohydrin enantiomers [(+)-**8A** ⟶ (−)-**7**; (−)-**8B** ⟶ (+)-**7**] by treatment with diborane in THF. The magnitude and sign of optical rotation for each bromohydrin enantiomer **7** ($[\alpha]_D$ +18 and $[\alpha]_D$ −18) provides confirmation of the efficiency of separation of the diastereoisomers.

The bromohydrin enantiomers (−)-**7** and (+)-**7** were separately transformed into the corresponding tetrahydro epoxide enantiomers (−)-**9**: ($[\alpha]_D$ −214) and (+)-**9** ($[\alpha]_D$ +228) in good yields using a basic form of the ion-exchange resin Amberlite IRA-400 under anhydrous conditions. Conversion of the enantiomer (+)-**9** into the *trans*-tetrahydro diol derivative (—)-**10** was achieved using aqueous alkaline conditions



(KOH–Bu^{t}OH–H_2O). After rigorous purification by PLC and recrystallization, the *trans*-dihydro diol **10** was found to have a very small (too small for accurate measurement) but consistent negative $[\alpha]_D$ value. Attack of the hydroxide anion is known to occur exclusively at the benzylic position in epoxides of this type.

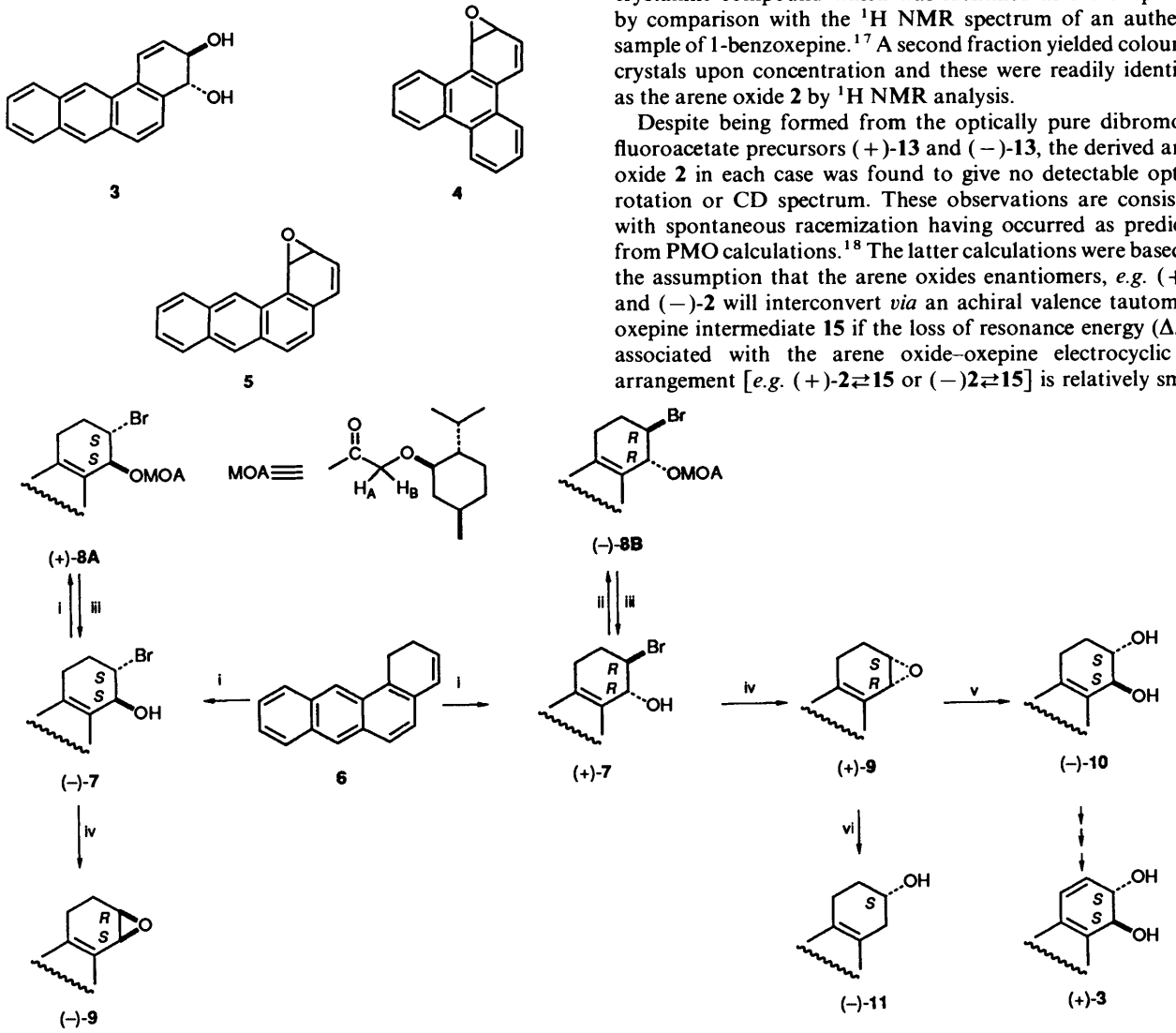
This result is in accord with that obtained by direct resolution of a racemic sample of the tetrahydro diol **10** *via* the di MOA esters which gave enantiomers **10** ($[\alpha]_D < +2$ and < -2).[15] The laevorotatory enantiomer of the diol **10** had previously been assigned the 3*S*,4*S* configuration by CD spectroscopy[16] and this is in agreement with its stereochemical correlation to the (−)-(3*R*,4*R*)-bromo MOA **8B** diastereoisomer (Scheme 1). The very small optical rotations observed for both (+)- and (−)-enantiomers of the *trans*-tetrahydro diol **10** is in marked contrast to the large $[\alpha]_D$ values observed for the derived *trans*-dihydro diols **3** ($[\alpha]_D$ +364)[15] and for the alcohol **11** ($[\alpha]_D$ −85) obtained from reduction of the tetrahydro-epoxide (+)-**9**, using $LiAlH_4$.

The bromohydrin enantiomers (−)-**7** and (+)-**7** yielded the corresponding bromotrifluoroacetate enantiomers (+)-**12** ($[\alpha]_D$ +43) and (−)-**12** ($[\alpha]_D$ −44) after treatment with trifluoroacetic anhydride (Scheme 2). Benzylic bromination of the bromo ester enantiomers (+)-**12** and (−)-**12** using *N*-bromosuccinimide in carbon tetrachloride yielded the corresponding dibromotrifluoroacetate enantiomers (+)-**13** ($[\alpha]_D$ +164) and (−)-**13** ($[\alpha]_D$ −165).

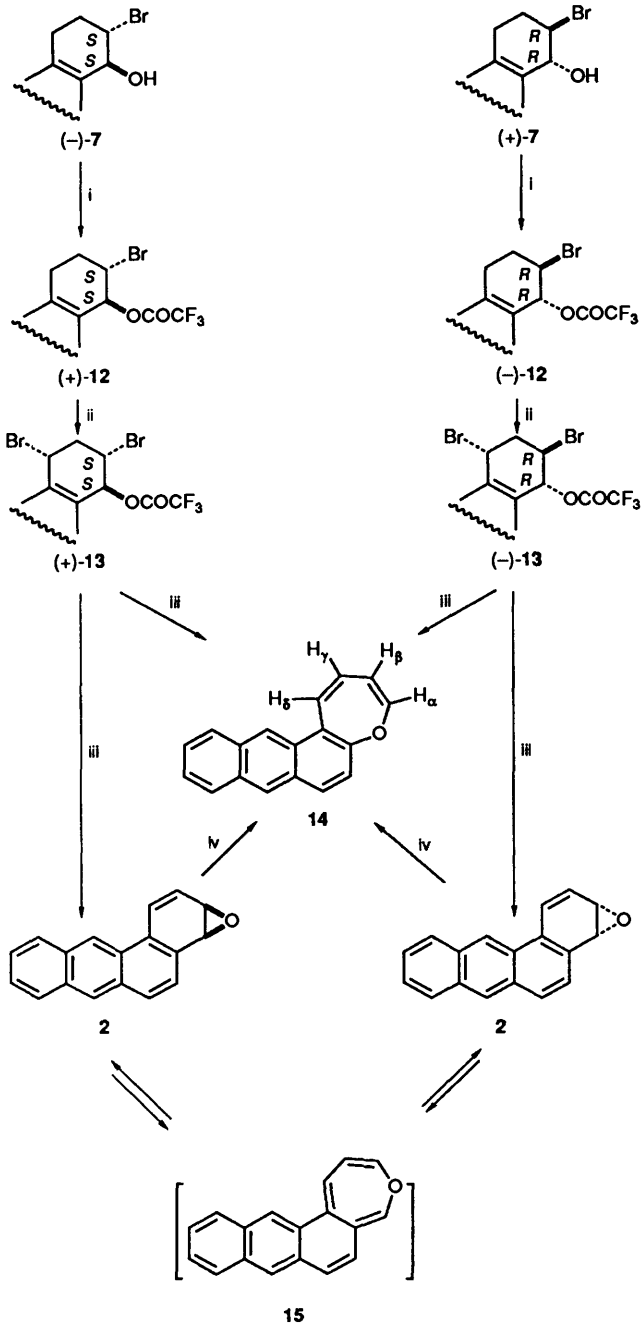
Benz[*a*]anthracene 3,4-oxide **2** was obtained by treatment of individual dibromotrifluoroacetate enantiomers (+)-**13** and (−)-**13** with sodium methoxide in dry tetrahydrofuran (THF) at *ca.* 0 °C. Despite attempts to exclude light at all stages of the conversion of the dibromo ester (+)-**13** or (−)-**13** into the arene oxide **2** and during the work-up procedure, the crude product was consistently found to be a mixture of the arene oxide **2** and the oxepine **14**. The composition of this mixture varied slightly among experiments (40–60% **2**, 60–40% **14**). When the racemic bromoacetate analogue of the bromotrifluoroacetate **12** was used, a similar ratio of the arene oxide **2** (50%) and oxepine **14** (50%) was obtained. Attempts to synthesise benz[*a*]anthracene 3,4-oxide **2** exclusively by benzylic bromination of the tetrahydro epoxide **9** and subsequent dehydrobromination were unsuccessful due to the instability of the bromo epoxide intermediate. Both the arene oxide **2** and oxepine **14** were found to aromatize to the corresponding phenols {3-hydroxy-(minor) and 4-hydroxy benz[*a*]anthracene (major)} in aqueous acetone under almost neutral (pH 7.4) or acidic conditions (pH 1.0).

The mixture of the arene oxide **2** and the oxepine **14** was successfully separated by preparative HPLC using hexane (89%), diethyl ether (10%) and triethylamine (1%) as eluent. The initial component eluted from the column was a bright yellow crystalline compound which was identified as the oxepine **14** by comparison with the ^1H NMR spectrum of an authentic sample of 1-benzoxepine.[17] A second fraction yielded colourless crystals upon concentration and these were readily identified as the arene oxide **2** by ^1H NMR analysis.

Despite being formed from the optically pure dibromotrifluoroacetate precursors (+)-**13** and (−)-**13**, the derived arene oxide **2** in each case was found to give no detectable optical rotation or CD spectrum. These observations are consistent with spontaneous racemization having occurred as predicted from PMO calculations.[18] The latter calculations were based on the assumption that the arene oxides enantiomers, *e.g.* (+)-**2** and (−)-**2** will interconvert *via* an achiral valence tautomeric oxepine intermediate **15** if the loss of resonance energy ($\Delta\Delta E$) associated with the arene oxide–oxepine electrocyclic rearrangement [*e.g.* (+)-**2**⇄**15** or (−)**2**⇄**15**] is relatively small.



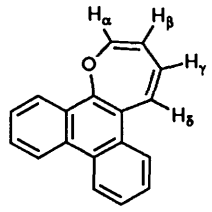
Scheme 1 i, NBA–H_2O–THF; ii, MOACl pyridine; iii, diborane–THF; iv, NaOMe–THF; v, KOH–H_2O–Bu^{t}OH; vi, $LiAlH_4$



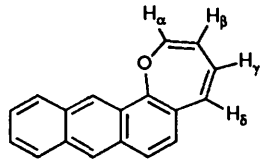
Scheme 2 *Reagents:* i, $(CF_3CO)_2O$; ii, NBS; iii, NaOMe THF; iv, UV light

Although the $\Delta\Delta E$ value calculated for the latter isomerization (**2**⇄**15**) was small (7.2 kcal mol^{-1}) in comparison with many other arene oxides,[18] the oxepine **15** should be regarded as a high energy or unstable oxepine relative to the isolated oxepine (**14**) which has a higher resonance energy. It should be noted that although oxepines of similar type to oxepine **15** have been postulated as intermediates in the racemization of many arene oxides,[4,10,12,13,18-21] they are only present as a very minor (and as yet undetected) component of the equilibrium ratio.

The formation of both arene oxide **2** and isolable oxepine **14**, during the well established dibromo ester cyclization route to arene oxides[12] was without precedent prior to the preliminary report of the present work.[23] This phenomenon has now been identified as a minor pathway during the synthesis of two further arene oxides from the tetracyclic PAH series, *i.e.* triphenylene 1,2-oxide **4** and benz[*a*]anthracene 1,2-oxide **5**.



16



17

The arene oxide **4**, obtained by the dibromo ester route,[19] was consistently found to be accompanied by a minor (*ca.* 15%) unidentified component which can now be unequivocally assigned as the oxepine **16**. In an earlier paper this minor component was reported to be present in variable proportions and was removed by fractional crystallization. As part of the present study, further work with a range of dibromo ester precursors of arene oxide **4** (acetates, trifluoroacetates and 2-methoxy-2-phenyl-2-trifluoromethylacetates) also showed a variable (15–30%) proportion of the oxepine **16** to be present with the arene oxide **4**.

In comparison with the arene oxides **2** and **4** the arene oxide **5** was much less stable and was only obtained in pure form by low temperature recrystallization.[4] A careful reexamination of the ^1H NMR spectra of the crude samples of the arene oxide **5** reported previously[4] showed the presence of a very minor (2–5%) component in several experiments, which has now been identified as the oxepine **17**.

In view of the detection of varying proportions of the oxepines **14**, **16** and **17** as minor by-products of the synthesis of the arene oxides **2**, **4** and **5**, respectively, it seemed appropriate to examine this reaction under rigorously controlled conditions. The synthesis of the arene oxide **4** from *trans*-1-acetoxy-2,4-dibromo-1,2,3,4-tetrahydrotriphenylene[19] was carried out in a standard NMR tube using $NaOCD_3$ in [$^2H_8$]-THF with pentamethylbenzene as reference. The NMR tube was maintained at *ca.* 0 °C in total darkness and the reaction progress was periodically monitored by ^1H NMR spectroscopy. The oxepine **16** was formed simultaneously with the arene oxide **4** at all stages of the reaction although the proportion of **4** to **16** appeared to decrease with time as aromatization occurred. Thus the relative ratio of compounds **4** and **16** changed from 64:15 (21% aromatization) after 5 days to 0:30 (70% aromatization) after 12 days.

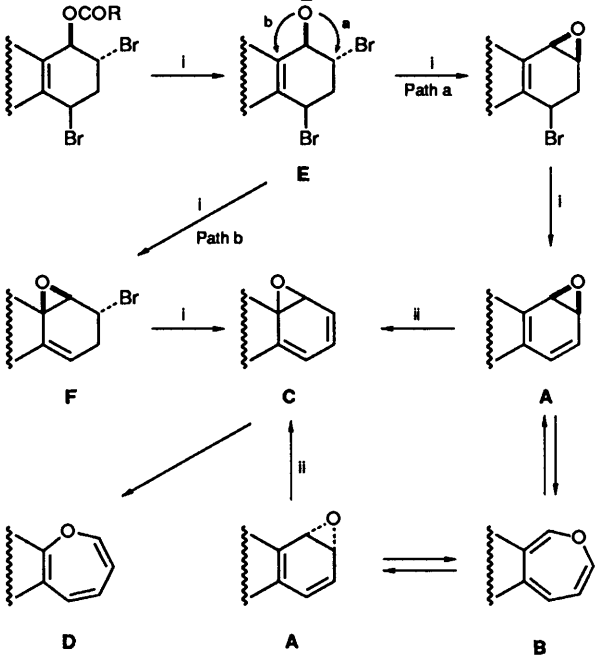
A possible mechanistic rationalization of the formation of the oxepines **14**, **16** and **17** at all stages of synthesis of the arene oxides **2**, **4** and **5** was provided in the preliminary report[23] as is outlined in Scheme 3.

Pathway a involves the normal synthetic route to arene oxides **A**, which in the cases of arene oxides **2**, **4** and **5** are found to undergo spontaneous racemization *via* the 'high energy' oxepine **B**. The alternative pathway b may proceed *via* an S_N2' (or an equivalent non-concerted)[24] mechanism to yield a 'high energy' arene oxide **C** which will spontaneously undergo an electrocyclic rearrangement to the 'low energy' oxepine **D**. Both the rate of racemization of arene oxides **A** (*e.g.* **2**, **4** and **5**) *via* the oxepine **B**, and the ease of formation of the stable oxepines **D** (*e.g.* **14**, **16** and **17**) from the dibromo ester precursors **E** *via* the arene oxide **C** will involve a roughly comparable loss of resonance energy [steps **A**→**B**→**A** (racemization) and steps **E**→**C**→**D** (oxepine formation)]. Previous PMO calculations[18] have indicated that the loss of resonance energy ($\Delta\Delta E$) associated with steps **A**→**B** is relatively low, *i.e.* 4.9–7.2 kcal mol^{-1} for arene oxides **2**, **4** and **5** and will lead to spontaneous racemization. The formation of oxepines of type **D** (**14**, **16** and **17**) will also involve a similar small loss of resonance energy in steps (**E**→**F**→**C**) and thus should occur more readily.

Table 1 Photoisomerization of the arene oxides **2**, **4** and **5** to the oxepines **14**, **16** and **17**

Arene oxide:oxepine (%)	Reaction conditions	Arene oxide (%)[a]	Oxepine (%)[a]	Phenol (%)[a]
2 100:0	(7×10^{-2} mol dm^{-3}) $CDCl_3$, sunlight, 20 min[b]	50	50	0
2 100:0	(7×10^{-2} mol dm^{-3}) $CDCl_3$, sunlight, 50 min[b]	0	80	20
2 100:0	(4×10^{-4} mol dm^{-3}) THF, fluorescent lamp,[c] 18 h	0	80	20
2 50:50	(7×10^{-2} mol dm^{-3}) $CDCl_3$, UV lamp,[d] 10 min	5	65	30
4 70:30	(7×10^{-2} mol dm^{-3}), $CDCl_3$, UV lamp,[d] 30 min	0	72	28
5 100:0[e]	(7×10^{-2} mol dm^{-3}) $CDCl_3$, UV lamp,[d] 60 min	5	55	40

[a] Determined by ^{1}H NMR analysis. [b] Reaction occurred spontaneously in Pyrex glass vessel in direct sunlight. [c] Westinghouse, 2 × 15 W cool white lamp. [d] >300 nm, Hanovia Reading Photochemical Reactor, medium pressure mercury vapour arc tube, 500 W, with broad band output peaking at 366 nm (also contributions at 313, 435, 546 and 578 nm); in a water cooled NMR tube placed in front of the lamp. [e] Traces of tetrahydro epoxide and oxepine present (<5%).



Scheme 3 *Reagents:* i, NaOMe; ii, UV light

Recent evidence from these laboratories[25] using dibromo ester precursors where the adjacent benzylic bromine atom and ester group positions have been reversed appear to support the S_N2' mechanism. Thus, in the benzo[*e*]pyrene series the 'reverse' dibromoacetate upon treatment with methoxide yielded the arene oxide **A** without evidence of the oxepine isomer **D**. The latter reaction clearly occurred *via* the bromoepoxide intermediate in pathway a since pathway b was not a possible option.

The ratio of oxepine (**14**, **16** or **17**) relative to arene oxide (**2**, **4** or **5**) respectively was found to increase in each case when the mixture, in a Pyrex glass vessel, was exposed to UV light (sunlight or a medium pressure Hg lamp). The photoisomerization of arene oxides **A** to oxepines **D** is assumed to have occurred *via* the 'high energy' arene oxide **C**, *i.e.* a circumambulatory rearrangement or oxygen-walk process followed by electrocyclization. This type of photochemical oxygen walk process to yield an oxepine has previously been observed for the K-region arene oxides of phenanthrene[26,27] and pyrene[28] using higher energy UV light (254 nm) for extended periods. The loss of resonance energy ($\Delta\Delta E$) associated with the arene oxide isomerization (**A**→**C**→**D**) is again similar to that involved in the racemization process (**A**⇄**B**⇄**A**) and the oxepine formation (**E**→**F**→**C**→**D**) which is particularly favourable to arene oxides **2**, **4** and **5** ($\Delta\Delta E$ <8 kcal mol^{-1}). The results of several photoisomerization reactions of the arene oxides **2**, **4** and **5** are summarized in Table 1. The oxepines **14**, **16** and **17** were separated from the corresponding arene oxides **2**, **4** and **5** and phenols by preparative HPLC or TLC and were fully characterized. The present report on the formation of isolable oxepines from arene oxides of benz[*a*]anthracene (1,2- and 3,4-) and triphenylene (1,2-) should be compared with similar observations in the benzo[*e*]pyrene (9,10-),[20] dibenz[*a,j*]anthracene (3,4-),[21] dibenz[*a,h*]anthracene (3,4-),[23] and dibenz[*a,c*]anthracene (1,2-)[29] series where a similar rationale can be applied.

Attempts to obtain the stable oxepine (type **D**) by photoisomerization of naphthalene 1,2-oxide ($\Delta\Delta E$ 20.0 kcal mol^{-1}),[14] anthracene 1,2-oxide ($\Delta\Delta E$ 30.5 kcal mol^{-1})[14] or chrysene 3,4-oxide ($\Delta\Delta E$ 14.1 kcal mol^{-1}),[14] under similar photochemical conditions to those successfully used for the arene oxides **2**, **4** and **5** provided no evidence of oxepine formation and instead resulted only in aromatization. While the marked differences in the UV absorption between individual arene oxides in the PAH series will clearly be a major factor in their photochemistry, the loss of resonance energy associated with the photochemically induced oxygen-walk process (**A**→**C**→**D**) may also play an important role.

Since the oxepine isomer **D** can be readily formed from the arene oxide isomer **A**, the potential role of such oxepines in metabolism should be of interest. Mutagenicity tests on the oxepines produced in the dibenz[*a,c*]anthracene series[23] have been reported.[30] In common with the range of arene oxides, *trans*-dihydro diols and phenols from the dibenz[*a,c*]anthracene series, the oxepines were again found to be less mutagenic than the parent PAH's.

The *trans*-3,4-dihydrobenz[*a*]anthracene-3,4-diol metabolite **3** of benz[*a*]anthracene in liver microsomal systems is predominantly the (−)-3*R*,4*R* enantiomer (38% e.e.).[2] The 3*S*,4*R* enantiomer of the arene oxide **2** would yield the latter metabolite (assuming that epoxide hydrolase-catalysed hydration occurs by normal attack at the non-benzylic oxirane carbon atom).

Experimental

1,2-Dihydrobenz[*a*]anthracene **6** was synthesised by the previously reported method.[8] (−)-Menthyloxyacetic acid (MOA) and diborane solution (1.0 mol dm^{-3} in THF) were purchased from the Aldrich Chemical Company. $[\alpha]_D$ Values are recorded in units of 10^{-1} deg cm^{-2} g^{-1} and *J* values in Hz.

(±)-trans-3-*Bromo*-1,2,3,4-*tetrahydrobenz*[a]*anthracen*-4-*ol* **7**.—*N*-Bromoacetamide (1.09 g, 7.9 mmol) was added slowly to a stirred solution of 1,2-dihydrobenz[*a*]anthracene **6** (1.65 g, 7.2 mmol) in THF (100 cm^3) and water (20 cm^3) and the mixture stirred overnight at 0 °C. It was then diluted with ethyl acetate (100 cm^3), washed with water, dried ($MgSO_4$) and concentrated. The resulting crude product was purified by column chromatography (silica gel) and recrystallized to give the racemic bromohydrin **7** as yellow needles (0.45 g, 19%), m.p. 171–172 °C (chloroform–pentane) (Found: C, 66.6; H, 4.65. $C_{18}H_{15}BrO$ requires C, 66.1; H, 4.6%); δ(90 MHz; $CDCl_3$) 2.31–2.91 (2 H, m, 2-H), 3.25–3.49 (2 H, m, 1-H), 4.45 (1 H, m, 3-H), 5.06 (1 H, *J* 5.9, 4-H), 7.43–8.04 (6 H, m, ArH), 8.46 (1 H, s, 7-H) and 8.50 (1 H, s, 12-H).

(−)-(3R,4R)-**8** *and* (+)-(3S,4S)-**8**-trans-3-*Bromo*-4-*menthyloxyacetoxy*-1,2,3,4-*tetrahydrobenz*[a]*anthracene*.—Treatment of the (±)-bromohydrin **7** (1.5 g, 4.6 mmol) with menthyloxyacetyl chloride (1.2 g, 5.2 mmol) in dry pyridine solution yielded a diastereoisomeric mixture of the bromo esters **8A** and **8B** which was purified by column chromatography on silica gel (1.6 g, 67%). The diastereoisomers **8A** and **8B** were separated by preparative HPLC using diethyl ether–cyclohexane (3:97) as eluent and a Waters Prep. 500 HPLC system.

(+)-(3S,4S)-**8A**: low R_f, more polar isomer (0.7 g), m.p. 111–112 °C (Et_2O–MeOH); $[\alpha]_D$ +73 ($CHCl_3$) (Found: M, 522.1775. $C_{30}H_{35}BrO_3$ requires *M*, 522.1769); δ(300 MHz, C_6D_6) 0.68–3.3 (23 H, m, menthyl-H, 2-H, 1-H), 4.02 (1 H, d, J_{AB} 16.4, H_B), 4.12 (1 H, d, J_{AB} 16.4, H_A), 4.46 (1 H, m, 3-H), 6.71 (1 H, d, $J_{3,4}$ 4.8, 4-H) and 7.3–8.3 (8 H, m, ArH).

(−)-(3R,4R)-**8B**: high R_f, less polar isomer (0.64 g), m.p. 151 °C (acetone), $[\alpha]_D$ −157.5 ($CHCl_3$) (Found: M, 522.1790. $C_{30}H_{35}BrO_3$ requires *M*, 522.1769); δ(300 MHz, C_6D_6), 0.68–3.3 (23 H, m, menthyl-H, 2-H, 1-H), 4.08 (1 H, d, J_{AB} 16.4, H_B), 4.11 (1 H, d, J_{AB} 16.4, H_A), 4.45 (1 H, m, 3-H), 6.70 (1 H, d, *J* 4.8, 4-H) and 7.3–8.3 (8 H, m, ArH).

(+)-(3R,4R)-**7***and*(−)-(3S,4S)-**7**-trans-3-*Bromo*-1,2,3,4-*tetrahydrobenz*[a]*anthracen*-4-*ol*.—A mixture of (−)-*trans*-3-bromo-4-menthyloxyacetoxy-1,2,3,4-tetrahydrobenz[*a*]anthracene **8B** (1.2 g, 2.3 mmol), THF (30 cm^3 and diborane solution (1.0 mol dm^{-3} in THF; 5 cm^3) was allowed to stand at room temperature for 6 days. The reaction mixture was then treated with cold water (10 cm^3) and the THF was removed under reduced pressure. The residue was extracted with ethyl acetate (3 × 15 cm^3) and the combined extracts were washed with water, dried ($MgSO_4$) and concentrated to give the bromohydrin **7** (0.6 g, 80%) as a colourless crystalline product. (+)-(3*R*,4*R*)-**7**, m.p. 164 °C (decomp.) (Et_2O); $[\alpha]_D$ +18 (THF); (−)-(3*S*,4*S*)-**7A** [obtained from (+)-(3*S*,4*S*)-**8A**, m.p. 164 °C (decomp.) (Et_2O); $[\alpha]_D$ −18 (THF). The two bromohydrin enantiomers **7** had ^1H NMR spectra identical with that of the racemic sample.

(−)-(3R,4S)-**9** *and* (+)-(3S,4R)-**9**-3,4-*Epoxy*-1,2,3,4-*tetrahydrobenz*[a]*anthracene*.—A mixture of (+)-(3*R*,4*R*)-bromohydrin **7** (0.12 g, 0.37 mmol) and the basic form of Amberlite resin [IRA-400 (0.5 g) dried by washing with dry THF] in anhydrous THF (5 cm^3) was stirred under argon for 18 h at room temperature. The mixture was filtered, the filtrate concentrated, and the residual crystals were recrystallized to yield (+)-(3*S*,4*R*)-**9**, m.p. 184–185 °C (Et_2O–pentane), $[\alpha]_D$ +228 (THF) (Found: C, 87.4; H, 5.9. $C_{18}H_{14}O$ requires C, 87.8; H, 5.7%); δ(300 MHz, $CDCl_3$), 1.93 (1 H, m, 2-H), 2.69 (1 H, m, 2-H), 2.90 (1 H, m, 1-H), 3.58 (1 H, m, 1-H), 3.88 (1 H, m, 3-H), 4.07 (1 H, d, $J_{4,3}$ 4.2, 4-H), 7.47 (2 H, m, Ar-H), 7.50 (1 H, d, $J_{5,6}$ 8.7, 5-H), 7.91 (1 H, d, $J_{6,5}$ 8.7, 6-H), 8.00 (2 H, m, ArH), 8.42 (1 H, s, 7-H) and 8.60 (1 H, s, 12-H); (−)-(3*R*,4*S*)-**9**, m.p. 184–185 °C, $[\alpha]_D$ −214 (THF).

(−)-(3S,4S)-trans-1,2,3,4-*Tetrahydrobenz*[a]*anthracene*-3,4-*diol* **10**.—The (+)-(3*S*,4*R*)-epoxide **9** (0.03 g, 0.12 mmol) underwent base-catalysed hydration in a refluxing mixture of aqueous potassium hydroxide (1 mol dm^{-3}; 8 cm^3) and *tert*-butyl alcohol (8 cm^3) over a period of 20 h. The *tert*-butyl alcohol was removed under reduced pressure and the aqueous portion was extracted with diethyl ether. The latter extract was washed with water, dried ($MgSO_4$) and concentrated to yield the crude diol **10** which was purified by PLC on silica gel. The diol **10** was obtained as a crystalline product (0.011 g, 34%), m.p. 178–180 °C (chloroform–methanol), $[\alpha]_D$ negative (THF) {lit.,[15] m.p. 193–194 °C (decomp.), $[\alpha]_D$ < −2}. While the sign of $[\alpha]_D$ was negative, the magnitude was too small to be measured with accuracy. The ^1H NMR spectrum of the diol **10** was found to be identical with that reported.[8]

(−)-(3S)-1,2,3,4-*Tetrahydrobenz*[a]*anthracen*-3-*ol* **11**.—A solution of the (+)-(3*S*,4*R*)-epoxide **9** (0.02 g, 0.08 mmol) in dry diethyl ether (5 cm^3) was reduced with lithium aluminium hydride (0.02 g, 0.5 mmol) by stirring at ambient temperature (0.5 h) and then refluxing for (0.5 h). The product was isolated after addition of water and extraction with diethyl ether. Concentration of the dried ($MgSO_4$) extract yielded the alcohol **11** which was purified by PLC on silica gel. (−)-(3*S*)-**11** (0.009 g, 45%), m.p. 162–164 °C (diethyl ether–hexane), $[\alpha]_D$ −85 ($CHCl_3$) (Found: C, 86.8; H, 6.8. $C_{18}H_{16}O$ requires C, 87.1; H, 6.5%); δ(300 MHz, $CDCl_3$), 1.57 (1 H, s, OH), 2.05 (1 H, m, 2-H), 2.29 (1 H, m, 2-H), 2.95 (1 H, m, 4-H), 3.27 (2 H, m, 1-H and 4-H), 3.48 (1 H, m, 1-H), 4.31 (1 H, m, 3-H), 7.17 (1 H, d, $J_{5,6}$ 8.7, 5-H), 7.47 (2 H, m, ArH), 7.81 (1 H, d, $J_{6,5}$ 8.7, 6-H), 8.00 (2 H, m, ArH), 8.37 (1 H, s, 7-H) and 8.48 (1 H, s, 12-H).

(−)-(3R,4R)-**12** *and* (+)-(3S,4R)-(**12**)-trans-3-*Bromo*-4-*trifluoroacetyl*-1,2,3,4-*tetrahydrobenz*[a]*anthracene*.—A mixture of the (+)-(3*R*,4*R*)-bromohydrin **7** (0.48 g, 1.5 mmol), chloroform (40 cm^3) and trifluoroacetic anhydride (0.6 cm^3, 4.25 mmol) was allowed to stand at ambient temperature for 1 h. Solvent and excess of reagent were removed under reduced pressure to yield a product which upon recrystallization gave colourless needles of the bromotrifluoroacetate (−)-(3*R*,4*R*)-**12** (0.48 g, 77%), m.p. 117 °C (racemic m.p. 129–130 °C) (Et_2O–pentane), $[\alpha]_D$ −44 (THF) (Found: C, 56.4; H, 3.6. $C_{20}H_{14}BrO_2F_3$ requires C, 56.7; H, 3.3%); δ(300 MHz, $CDCl_3$) 2.70 (2 H, m, 2-H), 3.39 (1 H, m, 1-H), 3.65 (1 H, m, 1-H), 4.68 (1 H, m, 3-H), 6.46 (1 H, d, $J_{3,4}$ 2.9, 4-H), 7.30 (1 H, d, $J_{5,6}$ 8.8, 5-H), 7.53 (2 H, m, ArH), 7.90 (1 H, d, $J_{6,5}$ 8.8, 6-H), 8.30 (2 H, m, ArH), 8.41 (1 H, s, 7-H) and 8.53 (1 H, s, 12-H).

(+)-(3*S*,4*R*)-**12**, m.p. 117 °C (Et_2O–pentane), $[\alpha]_D$ +43 (THF).

(−)-(3R,4R)-**13** *and* (+)-(3S,4S)-**13**-trans-1,3-*Dibromo*-4-*trifluoroacetoxy*-1,2,3,4-*tetrahydrobenz*[a]*anthracene*.—The (+)-bromotrifluoroacetate **12** (0.42 g, 1.0 mmol) underwent bromination with *N*-bromosuccinimide (0.2 g, 1.2 mmol) and α,α′-azoisobutyronitrile (0.005 g) in carbon tetrachloride (100 cm^3) at 60 °C for 0.5 h under an atmosphere of argon. The solution was cooled, filtered and concentrated to yield the dibromo ester (+)-(3*S*,4*S*)-**13** (0.45 g, 90%), m.p. 151–152 °C ($CHCl_3$–pentane), $[\alpha]_D$ +164 (THF) (Found: M, 501.9265. $C_{20}H_{13}Br_2F_3O_2$ requires *M*, 501.9214); δ(100 MHz, $CDCl_3$) 3.10 (2 H, m, 2-H and 2-H′), 5.10 (1 H, ddd, $J_{3,4}$ 9.5, $J_{2,3}$ 12.5, $J_{2',3}$ 4.0, 3-H), 6.10 (1 H, dd, $J_{1,2'}$ 3.0, 1-H), 6.70 (1 H, d, $J_{3,4}$ 9.5, 4-H), 7.00 (1 H, d, $J_{5,6}$ 9.0, 5-H), 7.40–8.20 (5 H, m, ArH), 8.40 (1 H, s, 7-H) and 8.64 (1 H, s, 12-H).

(−)-(3*R*,4*R*)-**13**, m.p. 151–152 °C, $[\alpha]_D$ −165 (THF).

(±)-*Benz*[a]*anthracene* 3,4-*Oxide* **2** *and Anthra*[2,1-b]*oxepine* **14**.—A solution of the (+)-(3*S*,4*S*)-dibromo ester **13** (0.1 g, 0.2 mmol) in dry THF (5 cm^3) was stirred with sodium methoxide (0.15 g, 2.8 mmol) at 0 °C for 18 h. The product mixture was diluted with cold diethyl ether (100 cm^3) and the resulting solution was washed with ice cold water, dried (K_2CO_3) and concentrated to yield a yellow solid (0.04 g, 82%). The latter product was purified by preparative HPLC using a Perkin-Elmer HS-3 SIL column (4.6 × 100 mm) and hexane (79%)–diethyl ether (20%)–triethylamine (1%) as eluent.

Solvent evaporation from the late fraction (k′ 2.9)† yielded benz[*a*]anthracene 3,4-oxide **2** (0.01 g), m.p. 206–207 °C (diethyl ether–hexane), $[\alpha]_D$ 0 (THF) (Found: M, 244.0894. $C_{18}H_{12}O$ requires *M*, 244.0888); δ(100 MHz, $CDCl_3$) 4.44 (1 H, m, $J_{3,4}$ 3.5, $J_{2,3}$ 3.2, $J_{1,3}$ 1.2, 3-H), 4.78 (1 H, d, $J_{3,4}$ 3.5, 4-H), 6.76 (1 H, dd, $J_{1,2}$ 9.0, $J_{2,3}$ 3.2, 2-H), 7.40–8.24 (6 H, m, ArH), 8.12 (1 H, dd, $J_{1,2}$ 9.0, $J_{1,3}$ 1.2, 1-H), 8.48 (1 H, s, 7-H) and 8.84 (1 H, s, 12-H).

Similar treatment of the dibromo ester (−)-(3*R*,4*R*)-**13** also yielded racemic benz[*a*]anthracene 3,4-oxide **2** as the late eluting compound from preparative HPLC purification. The arene oxide **2** obtained from either of the dibromo ester enantiomers **13** showed no peaks in the CD spectrum indicating that the product in each case was racemic.

Concentration of the early peak (k′ 0.8) fraction from preparative HPLC gave yellow crystals of anthra[2,1-*b*]oxepine **14** (0.15 g), m.p. 125–126 °C (diethyl ether–pentane) (Found: M, 244.0845. $C_{18}H_{12}O$ requires *M*, 244.0888); δ(250 MHz, $CDCl_3$) 5.70 (1 H, dd, $J_{\gamma,\beta} = J_{\beta,\alpha}$ 5.3, β-H), 6.34 (1 H, d, $J_{\beta,\alpha}$ 5.3, α-H), 6.47 (1 H, dd, $J_{\delta,\gamma}$ 11.2, $J_{\gamma,\beta}$ 5.3, γ-H), 7.56 (1 H, d, $J_{\delta,\gamma}$ 11.3, δ-H) and 7.38–8.70 (8 H, m, ArH).

Phenanthro[10,9-b]*oxepine* **16**.—The mixture of products previously reported [19] from the treatment of *trans*-2,4-dibromo-1-trifluoroacetoxy-1,2,3,4-tetrahydrotriphenylene with sodium methoxide was found to yield pure triphenylene 1,2-oxide **4** after low-temperature recrystallization from acetone. When the mother liquor from the latter recrystallization was concentrated a residual solid (0.06 g) remained. Using the preparative HPLC system previously employed for the separation of the arene oxide **2** and the oxepine **14** [Perkin-Elmer HS-3 SIL column and hexane–diethyl ether–triethylamine (79, 20, 1) as eluent] two major fractions were obtained.

Early fraction, phenanthro[10,9-*b*]oxepine **16** (0.012 g), k′ 1.0, m.p. 109–110 °C (diethyl ether–hexane) (Found: M, 244.0885. $C_{18}H_{12}O$ requires *M*, 244.0888); δ(250 MHz, $CDCl_3$), 5.83 (1 H, dd, $J_{\alpha,\beta} = J_{\gamma,\beta}$ = 5.1, β-H), 6.50 (1 H, d, $J_{\alpha,\beta}$ 5.1, α-H), 6.57 (1 H, dd, $J_{\gamma,\beta}$ 5.1 and $J_{\gamma,\delta}$ 11.3 γ-H) and 7.5–8.7 (9 H, m, ArH and δ-H).

The second fraction (0.01 g, k′ 3.0) was found to be indistinguishable from a sample of triphenylene 1,2-oxide **4** available from a previous study.[19]

Photoisomerization Reactions of Arene Oxides **2**, **4** *and* **5**.—The arene oxides **2**, **4** and **5** were obtained by the methods discussed previously.[4,19]

The photoisomerization studies of the arene oxide **2** were carried out using either pure arene oxide or a sample containing the oxepine **14**. Using a range of sources of UV light, the photoisomerization to the oxepine **14** and aromatization reactions in Pyrex glass vessels appeared to occur in all cases. The decrease in the proportion of the arene oxide **2** was found to be directly linked to the increased proportion of the oxepine **14** and isomeric phenol formation. The progress of the photoisomerization at ambient temperature was followed *in situ* by ^1H NMR analysis in $CDCl_3$ containing a standard reference peak (C_6Me_6) whose concentration remained constant throughout the irradiation.

A similar photoisomerization reaction on the arene oxide **4** (containing 30% of the oxepine **16**) was carried out in a Pyrex NMR tube in $CDCL_3$ solvent. After a short period of irradiation (30 min) the arene oxide **4** was found to have been totally converted into the oxepine **16** and the isomeric phenols. The oxepine product **16** was found to be spectrally indistinguishable from the previously isolated sample.

The recrystallized sample of the pure arene oxide **5** (0.015 g) was photoisomerized to the oxepine **17** and the corresponding phenolic products in a Pyrex NMR tube under conditions similar to those used for the arene oxides **2** and **4** ($CDCl_3$, > 300 nm, 1 h) (Table 1). Anthra[2,1-*f*]oxepine (**17**) was obtained as a yellow crystalline product (R_f 0.12) after PLC purification on silica gel using hexane containing a trace of triethylamine, m.p. 70 °C (decomp.) (diethyl ether–pentane) (Found: M, 244.0845. $C_{18}H_{12}O$ requires *M*, 244.0888); δ(300 MHz, $CDCl_3$) 5.71 (1 H, dd, $J_{\alpha,\beta} = J_{\beta,\gamma}$ 5.57, β-H), 6.30 (1 H, dd, $J_{\gamma,\delta}$ 10.9, $J_{\beta,\gamma}$ 5.7, γ-H), 6.43 (1 H, d, $J_{\alpha,\beta}$ 5.5, α-H), 6.89 (1 H, d, $J_{\gamma,\delta}$ 10.95, δ-H), 7.22 (1 H, d, $J_{5,6}$ 8.8, 5-H), 7.46–7.49 (2 H, m, 9-H and 10-H), 7.75 (1 H, d, $J_{6,5}$ 8.8, 6-H), 7.96–8.02 (2 H, m, 8-H and 11-H), 8.36 (1 H, s, 7-H) and 8.86 (1, s, 12-H).

† k′ = capacity factor.

Acknowledgements

We thank DENI (G. A. O'K.) and SERC (N. D. S.) and (S. K. A.) for financial support.

References

1 P. Sims, *Biochem. Pharmacol.*, 1970, **19**, 795.
2 D. R. Thakker, W. Levin, H. Yagi, S. Turujman, D. Kapidia, A. H. Conney and D. M. Jerina, *Chem.-Biol. Interact.*, 1979, **27**, 145.
3 D. R. Thakker, W. Levin, H. Yagi, D. Ryan, P. E. Thomas, J. M. Karle, R. E. Lehr, A. H. Conney and D. M. Jerina, *Mol. Pharmacol.*, 1979, **15**, 174.
4 D. R. Boyd and N. D. Sharma, *J. Chem. Soc., Perkin Trans. 1*, 1984, 839.
5 D. R. Boyd, G. S. Gadaginamath, N. D. Sharma, A. F. Drake, S. F. Mason and D. M. Jerina, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2233.
6 D. R. Boyd, K. A. Dawson, G. S. Gadaginamath, J. G. Hamilton, J. F. Malone and N. D. Sharma, *J. Chem. Soc., Perkin Trans. 1*, 1981, 94.
7 W. Levin, R. L. Chang, A. W. Wood, H. Yagi, D. R. Thakker, D. M. Jerina and A. H. Conney, *Cancer Research*, 1984, **44**, 929.
8 R. E. Lehr, M. Schaefer-Ridder and D. M. Jerina, *J. Org. Chem.*, 1977, **42**, 736.
9 M. N. Akhtar, D. R. Boyd and J. G. Hamilton, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2437.
10 D. R. Boyd, J. D. Neill and M. E. Stubbs, *J. Chem. Soc., Chem. Commun.*, 1977, 873.
11 D. R. Boyd, R. M. E. Greene, J. D. Neill, M. E. Stubbs, H. Yagi and D. M. Jerina, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1477.
12 D. R. Boyd, M. G. Burnett and R. M. E. Greene, *J. Chem. Soc., Perkin Trans. 1*, 1983, 595.
13 D. R. Boyd and R. M. E. Greene, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1535.
14 D. R. Boyd, G. S. Gadaginamath, A. Kher, J. F. Malone, H. Yagi and D. M. Jerina, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2112.
15 H. Yagi, K. P. Vyas, M. Tada, D. R. Thakker and D. M. Jerina, *J. Org. Chem.*, 1982, **47**, 1110.
16 W. Levin, D. R. Thakker, A. W. Wood, R. L. Chang, R. E. Lehr, D. M. Jerina and A. H. Conney, *Cancer Res.*, 1978, **38**, 1705.
17 F. Sondheimer and A. Shani, *J. Am. Chem. Soc.*, 1964, **86**, 3469.
18 D. R. Boyd and M. E. Stubbs, *J. Am. Chem. Soc.*, 1983, **105**, 2554.
19 D. R. Boyd, D. A. Kennedy, J. F. Malone, G. A. O'Kane, D. T. Thakker, H. Yagi and D. M. Jerina, *J. Chem. Soc., Perkin Trans. 1*, 1987, 369.
20 S. K. Agarwal, D. R. Boyd, R. Dunlop and W. B. Jennings, *J. Chem. Soc., Perkin Trans. 1*, 1988, 3013.

21 D. R. Boyd and G. A. O'Kane, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2079.
22 H. Yagi and D. M. Jerina, *J. Am. Chem. Soc.*, 1975, **97**, 3185.
23 D. R. Boyd, S. K. Agarwal, S. K. Balani, R. Dunlop, G. S. Gadaginamath, G. A. O'Kane, N. D. Sharma, W. B. Jennings, H. Yagi and D. M. Jerina, *J. Chem. Soc., Chem. Commun.*, 1987, 1633.
24 F. G. Bordwell, *Acc. Chem. Res.*, 1970, **3**, 281.
25 R. Agarwal and D. R. Boyd, unpublished work.
26 G. W. Griffin, S. K. Satra, N. E. Brightwell, K. Ishikawa and N. S. Chacca, *Tetrahedron Lett.*, 1976, **16**, 1239.
27 N. E. Brightwell and G. W. Griffin, *J. Chem. Soc., Chem. Commun.*, 1973, 37.
28 B. L. van Duuren, G. Witz and S. C. Agarwal, *J. Org. Chem.*, 1974, **39**, 1032.
29 D. R. Boyd and G. A. O'Kane, *Tetrahedron Lett.*, 1987, **28**, 6395.
30 S. Kumar, P. L. Kole and H. C. Sikka, *Mutation Res.*, 1990, **242**, 337.

Paper 2/05288A
Received 2nd *October* 1992
Accepted 16th *November* 1992