# Synthesis, Resolution and Racemization Studies of 1,2-Epoxy-1,2-dihydrochrysene

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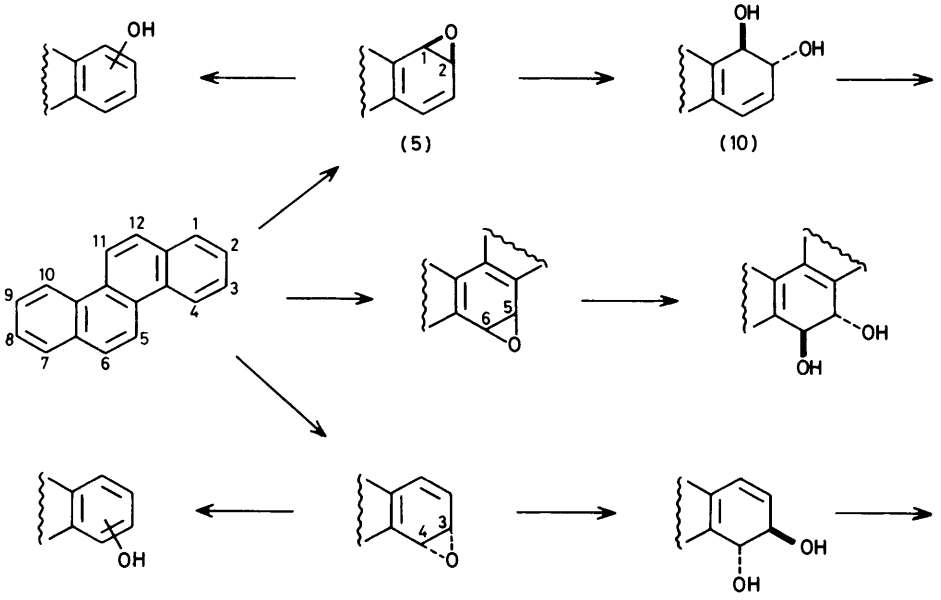
(+)-1,2-Epoxy-1,2-dihydrochrysene, a major initial mammalian metabolite of chrysene, has been synthesised and assigned the configuration (1*R*, 2*S*). Kinetic studies on the spontaneous thermal racemization of (+)-1,2-epoxy-1,2-dihydrochrysene gave a barrier to racemization ($E_a$) of 24.8 kcal mol$^{-1}$.† The kinetic results and activation parameters support a thermal racemization mechanism involving an oxepin intermediate.

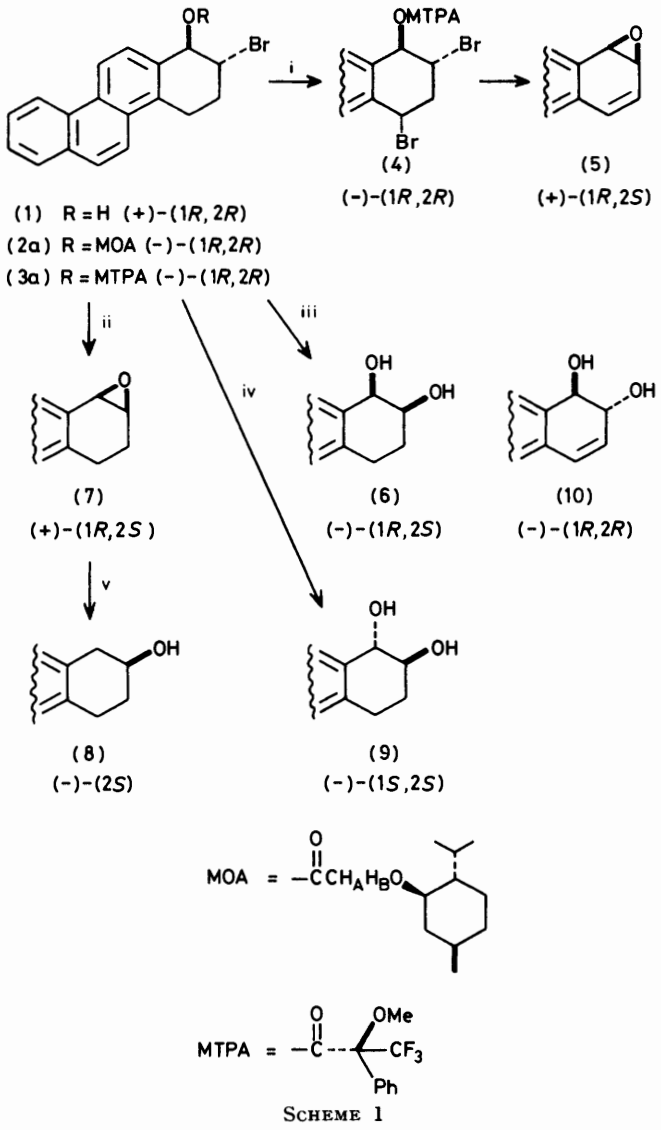
THE polycyclic aromatic hydrocarbon (PAH) chrysene is among a range of carcinogenic products found in smoke resulting from the combustion of tobacco and fossil fuels. The carcinogenicity of chrysene appears to be directly linked to the formation of epoxide metabolites in the liver systems of animals. The initially formed mammalian metabolites of chrysene are the 1,2-, 3,4-, and 5,6-epoxy-compounds which yield dihydro-diol and phenolic products by enzyme-catalysed hydration and isomerization respectively.[1-3] When the combined proportion of phenol and dihydro-diol metabolites of chrysene at the 1,2- (34—45%), 3,4- (43—53%), and 5,6- (2—6%) positions are examined it is evident that the initial enzyme-catalysed epoxidation step occurs with almost equal preference for the 1,2- and 3,4-positions. To date only 3,4- and 5,6-epoxydihydrochrysene have been synthesised in the laboratory.[4,5] The synthesis and absolute stereochemistry of the 1,2-epoxy-derivative (5) are discussed here. 1,2-Epoxy-1,2-dihydrochrysene (5) is of particular interest since the dihydro-diol and corresponding epoxy-diol metabolites derived from it cause a much higher incidence of tumours in animals than the analogous metabolites derived from the 3,4- or 5,6-epoxy-compounds. This result is in accordance with expectations based upon the bay-region theory of carcinogenicity of PAH's.[6] The synthetic route used for 1,2-epoxy-1,2-dihydrochrysene (5) is similar to that previously reported from these laboratories for optically active and racemic epoxyarenes [naphthalene (1,2-),[7] anthracene (1,2-),[7] phenanthrene (1,2-; 3,4-),[8,9] chrysene (3,4-),[5] benz[*a*]-anthracene (8,9-; 10,11-),[10,11] and benzo[*a*]pyrene (7,8-) [12]] and is outlined in Scheme 1.




The bromohydrin (1) was synthesised from 3,4-dihydrochrysene using essentially the literature route to the olefin.[13] The total resolution of compound (1) into its enantiomers was achieved indirectly by semi-preparative h.p.l.c. Thus, chromatographic separation ($\alpha$ 1.23) of the mixture of the bromo-menthyloxyacetoxy (-MOA) diastereoisomers (2) yielded a less polar isomer (2a) as crystals (high $R_F$, $[\alpha]_D$ −112°). The more polar diastereoisomer remained as a viscous oil (2b) (low $R_F$, $[\alpha]_D$ +22°). By comparison, the h.p.l.c. separation of the bromo-2-methoxy-2-phenyl-2-trifluoromethyl-acetoxy (-MTPA) diastereoisomers (3a) and (3b) was much more efficient ($\alpha$ 1.45). However, while the bromo-

† 1 kcal mol$^{-1}$ is 4.184 kJ mol$^{-1}$.

MTPA isomers, (3a and b) were more readily obtained in diastereoisomerically pure form, they also appeared to be less stable than (2a and b). Evidence of decomposition was found during attempted purification by recrystallization and compounds (3a and b) were therefore used directly after chromatography. The high $R_F$ bromo-ester diastereoisomer (3a) ($[\alpha]_D$ −19°) was converted into




SCHEME 1

*Reagents:* i, *N*-bromosuccinimide; ii, NaOMe; iii, AgOAc–HOAc–$H_2O$; iv, AgOAc–HOAC; v, $LiAlH_4$

the less stable dibromo-ester (4) ($[\alpha]_D$ −67°) with *N*-bromosuccinimide, and compound (4) was in turn directly cyclized to give (+)-1,2-epoxy-1,2-dihydrochrysene (5) by treatment with sodium methoxide at −20 °C. Purification of (+)-compound (5) was achieved by rapid recrystallization from diethyl ether–pentane at −70 °C. Owing to its spontaneous decomposition at room temperature, crystalline (+)-compound (5) was stored at −70 °C.

Chiral derivatives of compounds (2) and (3), including the tetrahydro-epoxide (7), the alcohol (8), and the cis-diol (6), were all obtained in optically pure form using steps in which the reaction mechanisms and stereochemistry were unequivocally established. Thus, a stereochemical correlation between the optically active molecules (1)—(8) was possible, as outlined in Scheme 1. The absolute stereochemistries of the diastereoisomeric pairs (2a and b) and (3a and b) were deduced from n.m.r. data. From a comparison of the n.m.r. spectra of the corresponding bromo-MOA [7-12] and bromo-MTPA [14] diastereoisomers in a range of analogous PAH systems the following general trends were established: (i) *bromo-MOA esters.* The high $R_F$ isomer in [$^2H_6$]benzene showed the exocyclic protons $H_A$ and $H_B$ of the menthyloxyester group ($H_A$,$H_B$) to be equivalent, *i.e.* a singlet. In contrast, the $H_A$ and $H_B$ protons in the low $R_F$ isomer appeared as an AB quartet with $J_{AB}$ *ca.* 16 Hz.

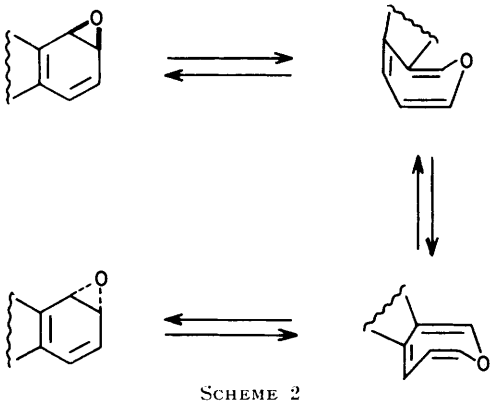
(ii) *Bromo-MTPA esters.* The high $R_F$ isomer was characterized by the fact that the 2-H and methoxy signals were upfield relative to the low $R_F$ isomer. Furthermore, the high $R_F$ isomer consistently showed smaller (negative) δ values for the $^{19}F$ chemical shifts. By the application of these comparative n.m.r. methods to the bromo-esters (2a and b) and (3a and b), the configurations of isomers (2a) and (3a) were deduced to be (1*R*,2*R*), thus showing (+)-1,2-epoxy-1,2-dihydrochrysene to have a (1*R*,2*S*)-configuration.

During the course of the present work, the resolution of the diol (9) by an independent route, the stereochemical correlation of the (−)-diols (9) and (10), and the absolute assignment of stereochemistry for compound (9) as (−) by a method using circular dichroism (c.d.) were reported.[3] A direct conversion of the (−)-fluoro-compound (3a) into the (−)-diol- (9) was carried out using the Woodward–Winstein [15] silver acetate reaction. This reaction was found to proceed with a strong preference for inversion of configuration at the C-1 position, a conclusion based upon studies of a range of analogous bromo-MTPA esters which were converted into *trans*-tetrahydro-diols of known absolute stereochemistry.[16] Thus, the formation of the (−)-isomer of (9) in 88% optical yield from the (−)-isomer of (2a) further confirms the (1*R*,2*R*)-configuration for the latter (using the absolute stereochemical assignment obtained by the c.d. method).[3] The optical rotation obtained for the (+)-isomer of (5) was found to decrease rapidly at room temperature; the value reported ([α] +76°) was the maximum observed after dissolution of the crystalline sample and does not infer enantiomeric homogeneity. It is probable that racemization occurred during the course of the synthesis despite attempts to minimize the process.

Kinetic studies were carried out using a thermostatically controlled polarimeter and cell coupled to a chart-recorder. Traces of triethylamine were introduced to the polarimeter cell in order to prevent the acid-catalysed isomerization of the epoxide (5) to chrysenols. Simultaneous n.m.r. analysis of the sample of (+)-epoxide (5) during the thermal racemization studies indi-

cated that no significant degree of decomposition had occurred.

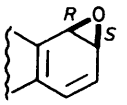
The racemization was found to follow first-order kinetics over the temperature range studied (15.7—40.5 °C). The barrier to racemization ($E_a$ 24.8 ± 0.4 kcal mol$^{-1}$) was of similar magnitude to that previously observed for the racemization of the isomeric 3,4-epoxy-3,4-dihydrochrysene ($E_a$ 25.2 ± 0.2 [5]). Perturbational molecular orbital (PMO) calculations suggested [8,17] that 1,2- and 3,4-epoxychrysenes would have comparable barriers to racemization and that these barriers would in turn be higher than those for 1,2- and 3,4-epoxyphenanthrenes. This has now been confirmed experimentally since the last named epoxy-arenes, derived from optically pure precursors, were either totally racemic or showed only a small optical rotation.[9] The value of this rotation in 3,4-epoxy-3,4-dihydrophenanthrene was found to have decreased at ambient temperature but its size precluded accurate kinetic studies.[9] The PMO calculations were based on the assumption that racemization was occurring *via* a chiral oxepin intermediate which was not detectable by n.m.r. spectroscopy. Further evidence for this assumption is provided by the small positive $\Delta S^{\ddagger}$ values observed for the racemization of the epoxide (5) ($\Delta S^{\ddagger}$ +3.7 ± 1.1 cal mol$^{-1}$ K$^{-1}$). Formation of an intermediate-valence tautomeric oxepin-form would involve a modest increase in entropy since the transition state, which would be similar to the oxepin form, should exhibit greater conformational mobility during the facile ring-inversion process (Scheme 2).



SCHEME 2

The dihydro-diol metabolite (10), isolated after liver microsomal metabolism of chrysene, was found to contain an excess of the (−)-(1*R*,2*R*)-enantiomer.[3] Previous work on the metabolism of benzo[*a*]pyrene [12,18] showed that the (+)-(7*R*,8*S*)-epoxy-arene was formed almost exclusively. Furthermore, the large enantiomeric excesses (e.e.) found in the dihydro-diols of phenanthrene (1,2- and 3,4-),[3] chrysene (3,4-),[3] and benz[*a*]anthracene (8,9- and 10,11-) [19] (>90% e.e.) are again consistent with the preferential enzymatic formation of one enantiomer of the epoxy-arene with the general configuration (A) indicated.

The major (−)-(1*R*,2*R*)-enantiomer of the dihydro-diol (10), resulting from the metabolism of chrysene by liver microsomes at the 1,2-bond, would also be obtained by enzyme-catalysed hydration of the (+)-(1*R*,2*S*)-enantiomer of 1,2-epoxy-1,2-dihydrochrysene (assuming, in all examples, exclusive attack of water at the non-benzylic oxiran ring carbon atom). It is worth noting



(+)-(*R*,*S*)

(A)

that the e.e. found in the enzymatically formed dihydro-diol (10) was dependent upon pre-treatment of the animals. The relative rates of metabolism of chrysene with liver microsomes obtained from pre-treated animals [and the corresponding e.e. of the diol (10) produced] was in the order 3-methylcholanthrene-treated (80%) > untreated (52) > phenobarbital-treated (10). However, on the basis of the present work (where spontaneous racemization of (+)-1,2-epoxy-1,2-dihydrochrysene proceeded with a half life of *ca.* 25 min at 37 °C), and on the reasonable assumption that the rate of racemization will not be significantly different under the more polar conditions of metabolism, it is highly improbable that the variation in optical yield of the (−)-diol (10) metabolite could be accounted for by differing degrees of racemization in each liver microsomal experiment.

## EXPERIMENTAL

$^1$H N.m.r. spectra were recorded at 90, 220, and 250 MHz using Bruker WH 90, Varian HR 220 and Bruker WM 250 MHz instruments, respectively, with deuteriochloroform as solvent and tetramethylsilane as reference unless stated otherwise. $^{19}$F N.m.r. spectra were recorded in deuteriochloroform on a Varian XL-100 instrument (94.2 MHz) with α,α,α-trifluorotoluene as reference. Proton noise decoupling was used to reduce the $^{19}$F line widths.

Optical rotations were measured using Perkin-Elmer automatic polarimeters (Models 141 or 241) with chloroform as solvent unless specified to the contrary. Kinetic results were obtained using the Perkin-Elmer 241 automatic polarimeter ($CDCl_3$; 546 nm) and a thermostatically controlled (±0.1 K) polarimeter cell in conjunction with a Honeywell Electronik 194 chart-recorder.

H.p.l.c. separations of the diastereoisomeric mixtures (2a and b) and (3a and b) were performed using either a Spectra-Physics 3500B Model coupled to a Cecil Instruments CE 272 u.v. detector or a Waters Associates Differential Refractometer R 401. Analytical separations were achieved using a Dupont Zorbax Sil (6.2 mm × 2.5 cm) column with cyclohexane–diethyl ether (97 : 3) as eluant. Semi-preparative separations were carried out with the same solvent system and a Whatman Magnum 9, Partisil 10, 250-mm column and a flow rate of 4—10 ml min$^{-1}$. (−)-Menthyloxyacetyl chloride and (−)-2-methoxy-2-phenyl-2-trifluoromethylacetyl chloride were obtained from the corresponding commercially available (−)-acids (Aldrich).

(±)-trans-2-*Bromo*-1-*hydroxy*-1,2,3,4-*tetrahydrochrysene*

(1).—3,4-Dihydrochrysene (2.0 g), prepared according to the literature route,[13] was treated with *N*-bromoacetamide (1.5 g) in tetrahydrofuran (THF)–water (35 ml; 4 : 3 v/v) by stirring at 0 °C for 30 min. The bromohydrin (1) (1.3 g, 46%) was obtained after the mixture had been poured into ice, filtered, dried and recrystallized from benzene, m.p. 165—167 °C (decomp.) (Found: C, 65.6; H, 4.4. $C_{18}H_{15}BrO$ requires C, 66.1; H, 4.6%); δ (90 MHz; $CDCl_3$), 2.31—2.94 (2 H, m, 3-H), 3.30—3.52 (2 H, m, 4-H), 4.37—4.63 (1 H, m, 2-H), 5.11 (1 H, d, $J_{1,2}$ 9.9 Hz, 1-H), 7.54—8.02 (6 H, m, aryl H), and 8.54—8.80 (2 H, m, aryl H).

(−)-(1R,2R)- *and* (+)-(1S,2S)-trans-2-*Bromo*-1-*menthyloxyacetoxy*-1,2,3,4-*tetrahydrochrysene* (2a and b).—(−)-Menthyloxyacetyl chloride (2 g) and racemic bromohydrin (1) (2.0 g) were stirred together at room temperature for 4 h in dry pyridine (15 ml). The mixture was extracted into diethyl ether solution, washed sequentially with 1N-hydrochloric acid and 2N-sodium carbonate solutions, dried ($MgSO_4$) and concentrated to give an oil [2.7 g, 85% (crude)]. Purification and separation by semi-preparative h.p.l.c. yielded two diastereoisomers (Found: *M*, 522.177 46. $C_{30}H_{35}BrO_3$ requires *M*, 522.177 007). Isomer (2a) (1.3 g, 41%), the high $R_F$ isomer, was eluted early from the h.p.l.c. column, m.p. 161—163 °C ($CHCl_3$–MeOH), $[\alpha]_D$ −112°; δ (220 MHz; $C_6D_6$) 4.11 (2 H, s, $H_A$ and $H_B$). Isomer (2b) (1.1 g, 36%), the low $R_F$ isomer, was eluted late from the h.p.l.c. column as a viscous, high b.p. oil, $[\alpha]_D$ +22°; δ (220 MHz; $C_6D_6$) 3.82 (d, $J_{AB}$ 16.5 Hz, $H_A$), and 3.95 (d, $J_{AB}$ 16.5 Hz, $H_B$).

(−)-(1R,2R)- and (+)-(1S,2S)-trans-2-*Bromo*-1-[2-*methoxy*-2-*phenyl*-2-*trifluoromethylacetoxy*]-1,2,3,4-*tetrahydrochrysene* (3a and b).—The racemic bromohydrin (1) (1 g) and (−)-2-methoxy-2-phenyl-2-trifluoromethylacetyl chloride (1 g) were stirred for 20 min at room temperature in dry pyridine (10 ml). The work-up procedure was identical with that used in the synthesis of compounds (2a and b) and yielded a viscous oil (1.5 g, 90%) which solidified and was recrystallized from benzene as a mixture of diastereoisomers (Found: C, 61.75; H, 4.0. $C_{28}H_{22}BrF_3O_3$ requires C, 61.9; H, 4.1%).

Preparative t.l.c. separation using silica-gel plates and diethyl ether–hexane (8 : 92) as eluant, provided pure samples of compounds (3a and b). Isomer (3a), high $R_F$ isomer, was eluted early from the h.p.l.c. column, m.p. 137—140 °C (decomp.), $[\alpha]_D$ −19°; δ (90 MHz; $CDCl_3$) 6.55 (1 H, d, $J_{1,2}$ 3.9 Hz, 1-H), 4.57 (1 H, m, $J_{1,2}$ 3.7 Hz, 2-H), and 3.51 (3 H, br s, OMe); δ($^{19}$F) (94.2 MHz; $CDCl_3$) −8.59 (3 F, s, $CF_3$). Isomer (3b), the low $R_F$ isomer, was eluted late from the h.p.l.c. column, m.p. 144—151 °C (decomp.), $[\alpha]_D$ −4°; δ (90 MHz; $CDCl_3$) 6.56 (1 H, d, $J_{1,2}$ 4.2 Hz, 1-H), 4.67 (1 H, m, $J_{1,2}$ 4.2 Hz, 2-H), 3.54 (3 H, br s, OMe). δ($^{19}$F) (94.2 MHz; $CDCl_3$) −8.65 (3 F, s, $CF_3$).

(+)-(1R,2R)-trans-2-*Bromo*-1-*hydroxy*-1,2,3,4-*tetrahydrochrysene* (1).—The bromo-MOA ester (2a) ($[\alpha]_D$ −112°) (0.1 g) in THF (2 ml) was stirred with an excess of borane–THF complex (2 ml; Aldrich) at 0 °C for 30 min and then at room temperature for 3 d under nitrogen. After addition of water (20 ml) and extraction with chloroform the (+)-bromohydrin (1) was isolated and recrystallized from benzene, m.p. 164—167 °C, $[\alpha]_D$ +28°. This chiral product was spectroscopically indistinguishable from the (±)-compound (1).

(−)-(1R,2S)-cis-1,2-*Dihydroxy*-1,2,3,4-*tetrahydrochrysene* (6).—The (−)-bromo–MTPA ester (3a) ($[\alpha]_D$ −19°) (0.2 g) was heated with silver acetate (0.4 g) in acetic acid (10 ml) and water (1 ml) at 110 °C for 24 h. The mixture was cooled, filtered, and concentrated to leave an oil which was hydrolysed with aqueous potassium hydroxide, extracted with ethyl acetate, washed with water, dried ($MgSO_4$), and concentrated. The *cis*-diol (6), which was found to be contaminated with a small amount of the *trans*-diol, was purified by preparative t.l.c. on silica gel (eluting with $CHCl_3$–MeOH, 9 : 1). Recrystallization from THF–pentane yielded colourless crystals of the diol (6) (0.037 g, 38%), m.p. 166—168 °C, $[\alpha]_D$ −26° (THF) (Found: *M*, 264.115 13. $C_{18}H_{16}O_2$ requires *M*, 264.115 02); δ (90 MHz; [$^2H_5$]-pyridine) 2.00—2.70 (2 H, m, 3-H), 2.96—3.72 (2 H, m, 4-H), 4.31—4.57 (1 H, m, 2-H), 5.21 (1 H, d, $J_{1,2}$ 3.2 Hz, 1-H), and 7.52—8.00 (8 H, m, aryl H).

(+)-(1R,2S)-1,2-*Epoxy*-1,2,3,4-*tetrahydrochrysene* (7).—The bromo–MTPA ester (3a) ($[\alpha]_D$ −19°) (0.1 g), sodium methoxide (0.11 g), and diethyl ether (100 ml) were stirred at room temperature for 2 h. Water (5 ml) was added and the ether layer was separated, dried ($MgSO_4$), and concentrated to yield a solid product which was recrystallized from ethyl acetate–pentane (0.03 g, 68%), m.p. 184—186 °C, $[\alpha]_D$ +163° (Found: *M*, 246.103 85. $C_{18}H_{14}O$ requires *M*, 246.104 46); δ (90 MHz; $CDCl_3$) 1.60—2.03 (1 H, m, 3- or 4-H), 2.51—3.65 (3 H, m, 3- and 4-H), 3.81 (1 H, m, 2-H), 4.05 (1 H, d, $J_{1,2}$ 4.4 Hz, 1-H), and 7.52—8.83 (8 H, m, aryl H).

(−)-(2S)-2-*Hydroxy*-1,2,3,4-*tetrahydrochrysene* (8).—The tetrahydro-epoxide (7) ($[\alpha]_D$ +163°) (0.02 g) was stirred at room temperature with lithium aluminium hydride (0.015 g) in diethyl ether (20 ml). The product mixture was decomposed with ethyl acetate (10 ml) and water (10 ml) added. The ether solution was separated, washed with water, and dried ($MgSO_4$). Evaporation of the solvent gave the alcohol (8) which was recrystallized from diethyl ether–pentane (0.015 g, 74%), m.p. 179—181 °C, $[\alpha]_D$ −22° (Found: *M*, 248.120 59. $C_{18}H_{16}O$ requires *M*, 248.120 11); δ (90 MHz; $CDCl_3$) 1.60—2.13 (2 H, m, 3-H), 2.50—2.80 (4 H, m, 1- and 4-H), 4.07—4.41 (1 H, m, 2-H), 7.26—8.00 (6 H, m, aryl H), and 8.66 (2 H, m, aryl H).

(−)-(1S,2S)-trans-1,2-*Dihydroxy*-1,2,3,4-*tetrahydrochrysene* (9).—Silver acetate (0.2 g) and the bromo-ester (9) ($[\alpha]_D$ −19°) (0.1 g) in dry acetic acid (10 ml) were heated at 110 °C for 24 h. A similar work-up procedure to that outlined for the *cis*-diol (6), followed by recrystallization from ethyl acetate, led to the isolation of the *trans*-diol (9) (0.025 g, 51%), m.p. 224—226 °C, $[\alpha]_D$ −68° (THF) [lit.,[3] m.p. 236 °C, $[\alpha]_D$ −78° (THF)]; δ (90 MHz; [$^2H_5$]pyridine) 1.94—2.78 (2 H, m, 3-H), 3.15—3.70 (2 H, m, 4-H), 4.33—4.61 (1 H, m, 2-H), 5.28 (1 H, d, $J_{1,2}$ 6.7 Hz, 1-H), and 7.52—8.00 (8 H, m, aryl H).

(−)-(1R,2R)-2,4-*Dibromo*-1-(2-*methoxy*-2-*phenyl*-2-*trifluoromethylacetoxy*)-1,2,3,4-*tetrahydrochrysene* (4).—The bromo-ester (3a) ($[\alpha]_D$ −19°) (0.1 g), *N*-bromosuccinimide (0.039 g), and 2,2′-azoisobutyronitrile (0.002 g) in dry refluxing carbon tetrachloride (20 ml) gave the dibromo-ester (4) as an oily solid after filtration and concentration. Attempts to purify the crude dibromo-ester (4) by either chromatography or recrystallization resulted in decomposition, and the crude form was used without purification [0.083 g, 72% (crude)], $[\alpha]_D$ −67.3°; δ (90 MHz; $CDCl_3$) 2.67—3.50 (2 H, m, 3-H), 3.54 and 3.70 (3 H, m, OMe), 4.78—5.15 (1 H, m, 2-H), 5.79—6.06 (1 H, m, 4-H), 6.76 (1 H, d, $J_{1,2}$ 10.7 Hz, 1-H), and 6.87—8.78 (13 H, m, aryl H).

(+)-(1R,2S)-1,2-*Epoxy*-1,2-*dihydrochrysene* (5).—The dibromo–MTPA ester (4) (0.063 g) ($[\alpha]_D$ −67°) and sodium

methoxide (0.03 g) in dry THF (10 ml) were stirred at −20 °C for 1 h. Diethyl ether was added, and the ether layer rapidly washed with ice-cold 1N-potassium hydroxide and water, dried ($K_2CO_3$), and concentrated under reduced pressure at 0 °C. 1,2-Epoxy-1,2-dihydrochrysene (5) was recrystallized at −70 °C from diethyl ether–pentane to yield colourless crystals (0.013 g, 55%), m.p. 130—162 °C (decomp.), $[\alpha]_D$ +76° ($CDCl_3$). The epoxy-arene was stored at −70 °C as the crystals were found to decompose to phenolic products at ambient temperaure (n.m.r. analysis); δ (90 MHz; $CDCl_3$) 4.22—4.39 (1 H, m, 2-H), 4.74 (1 H, d, $J_{1,2}$ 3.9 Hz, 1-H), 6.69 (1 H, dd, $J_{3,4}$ 11.3 Hz, $J_{2,3}$ 4.3 Hz, 3-H), and 7.44—8.95 (9 H, m, 4-H and aryl H).

*Kinetic Results.*—The racemization of (+)-compound (5) was found to follow first-order kinetics and a plot of $\log_{10}(\alpha - \alpha_a)$ against $t$ gave a straight line, the slope of which gave the rate constant $k$. A plot of $\log_{10} k$ against $T^{-1}$ gave the Arrhenius activation energy ($E_a$) and the frequency factor ($A$). The enthalpy ($\Delta H^{\ddagger}$) and entropy of activation ($\Delta S^{\ddagger}$) were obtained from the slope and intercept, respectively, of a plot of $\log_{10}(k/T)$ against $T^{-1}$. The kinetic data are given in the Table.

Kinetic data for the racemization of (+)-compound (5)

| $T$/K | $10^{-6}k$/s$^{-1}$ | $\Delta G^{\ddagger}$/kcal mol$^{-1}$ (±0.4) |
|---|---|---|
| 288.7 | 19.1 | 23.09 |
| 289.5 | 20.1 | 23.13 |
| 298.7 | 80.8 | 23.06 |
| 311.8 | 441.3 | 23.04 |
| 312.7 | 545.8 | 22.99 |
| 313.5 | 545.5 | 23.05 |

$E_a = 24.8 \pm 0.4$ kcal mol$^{-1}$; log $A = 14.0 \pm 0.2$; $\Delta H^{\ddagger} = 24.2 \pm 0.3$ kcal mol$^{-1}$; $\Delta S^{\ddagger} = +3.7 \pm 1.1$ cal mol$^{-1}$ K$^{-1}$.

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