Synthesis of (+)- and (−)-Naphthalene and Anthracene 1,2-Oxides

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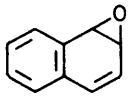
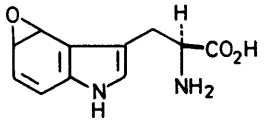
(−)-Menthyloxyacetyl derivatives of *trans*-2-bromo-1-hydroxy-1,2,3,4-tetrahydronaphthalene and *trans*-2 bromo-1-hydroxy-1, 2,3,4-tetrahydroanthracene have been synthesized and resolved into diastereoisomers by a combination of short-column chromatography and recrystallization. The chiral oxirans naphthalene 1,2-oxide, anthracene 1,2-oxide, 1,2-epoxy-1,2,3,4-tetrahydronaphthalene, and 1,2-epoxy-1,2,3,4-tetrahydroanthracene have been obtained in a high state of optical purity. The absolute stereochemistry and optical purity of these epoxides have been determined by several methods including n.m.r. analysis and correlation with alcohols of known configuration.

THE carcinogenic effects of and metabolism of polycyclic aromatic hydrocarbons (PAHs) have been extensively studied, particularly within the last decade.[1] An important contributory factor to the resurgence of interest was the identification of arene oxides as obligatory intermediates in PAH metabolism by animal liver systems.[1] Studies on the role of arene oxides during the mammalian metabolism of the lower molecular weight PAHs, naphthalene [2] and anthracene,[3,4] have been made possible by the availability of racemic samples of the 1,2-oxides of naphthalene [5] and anthracene.[4]

One aspect of PAH metabolism which, prior to the preliminary communication of the present work,[6] has received little attention [7] is the stereochemistry of the mono-oxygenase-catalysed addition of an oxygen atom to the stereoheterotopic faces of a PAH.



(A)



(B)

If the oxygen atom, in association with a mono-oxygenase, is considered as a chiral oxidant then attack would be expected to occur preferentially from one direction. Thus the probable arene oxide intermediates (A) and (B) in mammalian metabolism of the polycyclic substrates naphthalene and tryptophan may in principle be optically active as a result of selective attack at the enantiotopic and diastereotopic faces, respectively.

Optical activity in an arene oxide was first demonstrated for naphthalene 1,2-oxide where chirality was introduced at an earlier stage of the synthesis by the asymmetric oxidizing agent (+)-peroxycamphoric acid.[7] The (−)-naphthalene 1,2-oxide produced, although in low optical yield (*ca.* 10%), confirmed that at least one arene oxide of a PAH was possessed of configurational stability.

To date arene oxide metabolites of PAHs have not been isolated in sufficient quantity to permit optical rotation measurements to be made. However, a comparison of the $[\alpha]_D$ values of the isolated *trans*-dihydro-diol products obtained after incubation with liver microsomes of (i) the parent PAH and (ii) the chemically synthesized racemic arene oxide (the intermediate in the metabolism of the PAH) appears to indicate that in several cases an enantiomeric excess of arene oxide is indeed formed enzymically.[8-12]

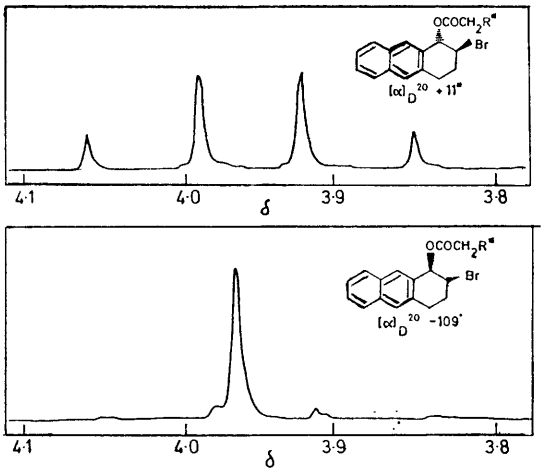
The potential biological significance of chiral arene oxides initiated the quest for a convenient synthesis of the individual enantiomers. In view of the low optical yield generally associated with asymmetric oxidations [7] the resolution of bromohydrin ester diastereoisomers was examined. (−)-Menthyloxyacetyl derivatives of 2-bromo-1-hydroxy-1,2,3,4-tetrahydronaphthalene (1a†) [and tetrahydroanthracene (1b†)] were found to be the most suitable esters for chromatographic resolution. Thus a partial separation of the diastereoisomers of *trans*-2-bromo-1-menthyloxyacetoxy-1,2,3,4-tetrahydronaphthalene (2a) was achieved by short-column chromatography [13] on silica gel using light petroleum–ether (90 : 10). The maximum numerical $[\alpha]_D$ values obtained in the initial and final chromatographic fractions were −140 and −25°, respectively. Recrystallization of these extreme fractions of (2a) to constant optical rotation yielded materials of high diastereoisomeric purity ($[\alpha]_D$ −149°, +44°). Similar treatment of the diastereoisomeric mixture of *trans*-2-bromo-1-menthyloxyacetoxy-1,2,3,4-tetrahydroanthracene (2b) gave crystalline fractions of $[\alpha]_D$ −118° and +11°.

The efficiency of this diastereoisomer separation was readily determined by n.m.r. analysis in C_6D_6 solution. The Figure (R* = menthyloxy) shows an expanded region of the 220-MHz spectrum of diastereoisomerically enriched samples of (2b) in C_6D_6. The laevorotatory diastereoisomers of (2a) and (2b) were eluted first from the chromatographic column, and showed a singlet for the exocyclic methylene protons (H_A, H_B) at δ 3.98 and 3.96, respectively. The dextrorotatory diastereoisomers showed lower R_F values on silica gel and the n.m.r. spectra contained an AB quartet with mean positions for protons A and B at δ 4.10 and 3.91 (J_{AB} 16.3 Hz) and 4.02 and 3.88 (J_{AB} 16.1 Hz), respectively. Using this n.m.r. method to distinguish between the (−)- and (+)-diastereoisomers in the two series, it was deduced that the maximum values obtained after recrystallization of (2a) ($[\alpha]_D$ −149°, +43°) and (2b) ($[\alpha]_D$ −118°, +11°) represented diastereoisomeric homogeneity. Recent extensions of this n.m.r. method to the phenanthrene,[14]

† a: naphthyl series; b: anthryl series.

chrysene,[15] benz[*a*]anthracene,[15] and benzo[*a*]pyrene [16] series of PAHs show that the present trend (high R_F implies negative $[\alpha]_D$ implies singlet for protons A and B; low R_F implies positive $[\alpha]_D$ implies quartet for protons A and B) may be general for the PAH series.

The reagents and conditions used in the conversion of the bromo-menthyloxy-acetates (2) into the optically

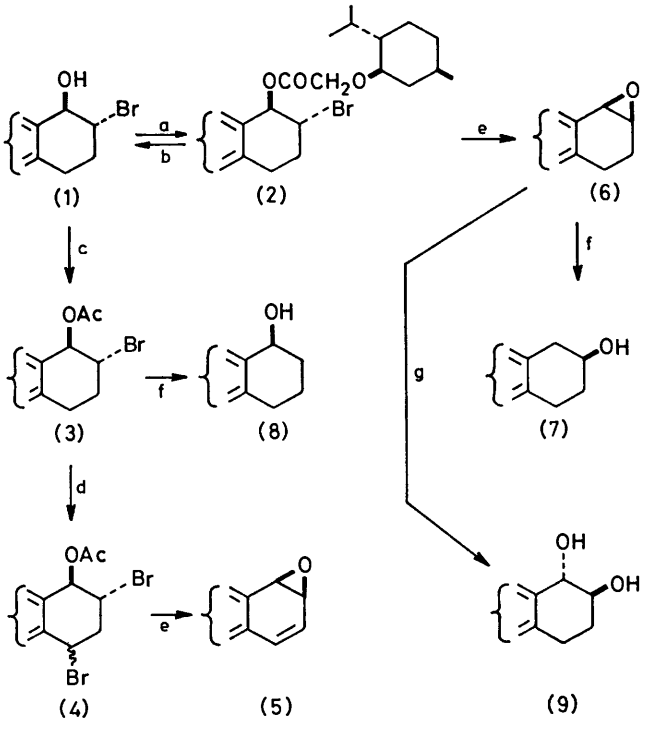


Expanded region of the 220 MHz ^{1}H n.m.r. spectra of diastereoisomerically enriched samples of (2b) in C_6D_6

active derivatives (1) and (3)—(8) are summarized in the Scheme and are given in detail in the Experimental section. The reactions in general were carried out in a similar manner to those reported for the racemic compounds.[4,17] The reduction reactions (2) ⟶ (1) and (3) ⟶ (8), using diborane and lithium aluminium hydride, respectively, demonstrate the selectivity of these reagents in the synthesis of products (1) and (8) containing an alcohol group. It was assumed (n.m.r. analysis) that diastereoisomerically pure bromo-esters (2a) and (2b) were being used in the conversion into the chiral derivatives shown in the Scheme. The reaction sequence and conditions selected should not have resulted in any significant racemization and the $[\alpha]_D$ values presented in the Table were considered to represent high optical purity. This was confirmed by comparison with the $[\alpha]_D$ values reported for the alcohols (7a),[18] (7b),[3] (8a),[19] and (8b) [20] which have been resolved by independent methods. The known absolute configurations for these alcohols were correlated with data for the related chiral molecules whose stereochemistry is presented in the Table.

The optically active epoxides (6a) and (6b) were converted into *trans*-1,2-diols (9a) and (9b) by preferential attack of hydroxide anion at the benzylic position. This correlation of absolute stereochemistry between alcohol (7b) and diol (9b) has been used [3] to determine the configuration of 1,2-dihydroanthracene-*trans*-1,2-diols obtained from mammalian metabolism of anthracene and is equally applicable in the naphthalene series [(7a) ⟶ (6b) ⟶ (9a)].

The arene oxides (5a) ($[\alpha]_D$ +149°) and (5b) ($[\alpha]_D$ +214°), derived from (2a) ($[\alpha]_D$ −149°) and (2b) ($[\alpha]_D$ −118°), provide the first examples to be reported of optically pure arene oxides. While (+)-naphthalene 1,2-oxide (5a) proved to be very unstable in the crystalline state, (+)-anthracene 1,2-oxide (5b) was relatively stable in crystalline form and remained largely unchanged after several days at ambient temperature. N.m.r. analysis showed the samples of (−)-(5a) and



SCHEME a, (−)-menthyloxyacetyl chloride–pyridine; b, diborane–THF; c, AcCl–pyridine; d, *N*-bromosuccinimide; e, NaOMe; f, $LiAlH_4$; g, KOH–aq. Bu^{t}OH

(−)-(5b) to be spectrally identical with previously synthesized racemic samples and to be in a high state of purity before and during $[\alpha]_D$ measurement. Using fractions of lower diastereoisomeric purity, (2a) ($[\alpha]_D$ −25°)and (2b) ($[\alpha]_D$ −11°), laevorotatory samples of (5a) ($[\alpha]_D$ −21°) and (5b) ($[\alpha]_D$ −203°) were obtained.

The optically active arene oxides (5a) and (5b) did not appear to be racemized in chloroform solution to any

Maximum $[\alpha]_D$ values (°); solvent $CHCl_3$

	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
a	−149 (+44) †	−144	−103	+149	+135	−58	+27	−110
b	−118 (+11) †	−129	−203	+214	+140	−47	+126	−44 ‡
	(1*R*, 2*R*)	(1*R*, 2*R*)	(1*R*, 2*R*)	(1*R*, 2*S*)	(1*R*, 2*S*)	(2*S*)	(1*R*)	(1*S*, 2*S*)

† For (1*S*, 2*S*)-diastereoisomer. ‡ In acetone solution.

measurable degree at ambient temperature over 24 h. This configurational stability contrasts with recent observations from these laboratories on the analogous phenanthrene 1,2- and 3,4-oxides [14] which, although derived from precursors of high optical purity, appeared to be optically inactive. Thus the barrier to thermal racemization of chiral arene oxides appears to be structure dependent. Further investigations of this aspect of arene oxide stereochemistry and possible biological implications will be discussed elsewhere.

The availability of enantiomerically pure arene oxides (5a) and (5b) will facilitate studies of the stereoselectivity of mammalian mono-oxygenase-catalysed oxidation of naphthalene and anthracene and the enantioselectivity of mammalian enzymes which utilize these arene oxides as substrates.

EXPERIMENTAL

M.p.s were determined using a Reichert Kofler hot-stage apparatus. N.m.r. spectra were obtained using Varian A–60, JEOL JNM–PMX60, and Varian HR–220 instruments with deuteriochloroform as solvent and tetramethylsilane as reference unless otherwise stated. Optical rotations were measured using a Perkin-Elmer 141 automatic polarimeter and $[\alpha]_D$ values were obtained for compounds in chloroform solution unless otherwise stated.

Short-column chromatography [13] was carried out using silica gel G type 60 (Merck). Light petroleum used had b.p. 40—60 °C. 2-Bromo-1-hydroxy-1,2,3,4-tetrahydronaphthalene (1a) and 2-bromo-1-hydroxy-1,2,3,4-tetrahydroanthracene (1b) were prepared according to literature methods.[5,21] The synthetic methods used in the preparation of chiral derivatives in the naphthalene series are identical with those used in the anthracene series.

(+)- *and* (−)-trans-2-*Bromo*-1-*menthyloxyacetoxy*-1,2,3,4-*tetrahydronaphthalene* (2a).—2-Bromo-1-hydroxy-1,2,3,4-tetrahydronaphthalene (1a) (20 g, 0.088 mol) was dissolved in dry pyridine (70 ml; AnalaR) and the stirred solution was cooled (0 °C). (−)-Menthyloxyacetyl chloride (24.1 g, 0.09 mol) was added dropwise at *ca.* 0 °C. The mixture was then allowed to warm up slowly to ambient temperature and then stirred overnight, poured into water, and extracted with ether (4 × 60 ml). The extracts were combined, washed with ice cold dilute aq. HCl and aq. K_2CO_3 (10%), and dried ($MgSO_4$). The residual oil obtained after concentration solidified to a diastereoisomeric mixture (2a); yield 35.7 g (96%).

This mixture was partially separated by short-column chromatography.[13] Thus the mixture (*ca.* 15 g) in a minimal quantity of solvent mixture was added to silica gel H (1 500 g) in a 14-cm diam. glass column fitted with a sintered glass disc, which had been packed previously under a pressure of 5 lb in^{-2} of nitrogen. Elution (ether–petroleum 5 : 95) yielded fractions with a range of $[\alpha]_D$ values [(2a) −140° to −25°]. Recrystallization of the middle chromatographic fractions from methanol yielded a diastereoisomeric mixture which melted over a wide range (Found: C, 62.4; H, 7.4. Calc. for $C_{12}H_{31}BrO_3$: C, 62.4; H, 7.4%). Recrystallization of terminal fractions yielded individual diastereoisomers of (2a), m.p. 62—65°, $[\alpha]_D$ −149°; m.p. 45—49°, $[\alpha]_D$ +44°.

(+)- *and* (−)-trans-2-*Bromo*-1-*menthyloxyacetoxy*-1,2,3,4-*tetrahydroanthracene* (2b).—The diastereoisomeric mixture (2b) was separated by short-column chromatography to yield liquid fractions with a range of $[\alpha]_D$ values from −160° to −10° which solidified. Recrystallization from pentane gave a diastereoisomeric mixture of indefinite m.p. (Found: C, 66.35; H, 6.8. Calc. for $C_{26}H_{33}BrO_3$: C, 66.1; H, 7.0%). Initial and final chromatography fractions upon recrystallization gave diastereoisomers of (2b), m.p. 102—104°, $[\alpha]_D$ −118; m.p. 68—71°, $[\alpha]_D$ +11°.

(−)-trans-1-*Acetoxy*-2-*bromo*-1,2,3,4-*tetrahydronaphthalene* (3a).—Diborane, generated externally by addition of sodium borohydride (1.4 g) in dry bis-(2-methoxyethyl) ether (50 ml) to a solution of freshly distilled boron trifluoride diethyl ether complex (14 ml in 50 ml of the same solvent), was passed into a stirred solution of (2a) (1.3 g, 0.003 mol; $[\alpha]_D$ −149°) in dry tetrahydrofuran (50 ml) at room temperature. The diborane-generating flask was heated for 0.5 h at 50 °C before disconnection from the reaction vessel, whose contents were then stirred at room temperature under nitrogen for 72 h. The excess of diborane was destroyed by addition of aqueous methanol. The solvents were removed under vacuum and the resulting oil was dried ($MgSO_4$). I.r. analysis showed the product to be very similar to the racemic bromohydrin (1a) which showed evidence of decomposition during attempted chromatographic purification. The optically active bromohydrin (1a) was therefore esterified without purification. 2-Bromo-1-hydroxy-1,2,3,4-tetrahydronaphthalene (1a) (1.1 g, 0.005 mol) was dissolved in dry pyridine (20 ml) and acetic anhydride (6 ml, 0.064 mol) was added dropwise with stirring at 0 °C. The solution was allowed to warm to ambient temperature overnight before being poured into water (75 ml). The product (3a) was isolated after being extracted into ether (4 × 50 ml); the extracts were washed (2N-HCl, 2N-$NaHCO_3$), dried ($MgSO_4$), and concentrated. Recrystallization from ether–petroleum yielded 1.2 g of product (3a) (91% yield), identical in spectral data with the racemic material; m.p. 102—103° (lit.,[17] racemic, m.p. 96—97°), $[\alpha]_D$ −144°.

(−)-trans-1-*Acetoxy*-2-*bromo*-1,2,3,4-*tetrahydroanthracene* (3b).—This was obtained in 89% yield; m.p. 138—139° (lit.,[4] racemic, m.p. 108—109°), $[\alpha]_D$ −129°.

(−)-1-*Acetoxy*-2,4-*dibromo*-1,2,3,4-*tetrahydronaphthalene* (4a).—This synthesis was carried out in the same manner as that reported [17] for racemic (4a), to give (−)-(4a) in 80% yield. Recrystallization from ether–light petroleum yielded (−)-(4a), m.p. 113—115° (lit.,[17] racemic, m.p. 114—115°), $[\alpha]_D$ −103°.

(−)-1-*Acetoxy*-2,4-*dibromo*-1,2,3,4-*tetrahydroanthracene* (4b).—This was obtained in 45% yield; m.p. 128—130° (lit.,[4] racemic, 128—130°), $[\alpha]_D$ −203°.

(+)-*Naphthalene* 1,2-*Oxide* (5a).—Using conditions previously reported [17] for racemic (5a), (−)-(5a) was obtained in 93% yield. Recrystallization from pentane at −78 °C gave white crystals, $[\alpha]_D$ +149°, identical in spectral characteristics with an authentic sample.[5]

(+)-*Anthracene* 1,2-*Oxide* (5b).—This was obtained in 33% yield; m.p. 130—134° (lit.,[4] racemic, m.p. 130—134°), $[\alpha]_D$ +214°.

(+)-1,2,3,4-*Tetrahydronaphthalene* 1,2-*Oxide* (6a).—(−)-*trans*-2-Bromo-1-menthyloxyacetoxy-1,2,3,4-tetrahydronaphthalene (0.69 g, 0.0016 mol) and dry sodium methoxide (0.18 g, 0.0037 mol) were dissolved in dry tetrahydrofuran (15 ml), and the solution was stirred for 24 h at room temperature. Filtration and concentration yielded a liquid which was taken up in ether, washed (2N-KOH), and

dried (K_2CO_3). Removal of solvent and recrystallization from pentane yielded 0.17 g (74%) of (6a), m.p. 45—48° (lit.,[5] racemic, b.p. 55—62° at 0.3—0.4 mmHg), $[\alpha]_D$ +135°.

(+)-1,2,3,4-*Tetrahydroanthracene* 1,2-*Oxide* (6b).—This was obtained in 33% yield; m.p. 155—156° (lit.,[3] racemic, m.p. 146—150°), $[\alpha]_D$ +140°.

(−)-2-*Hydroxy*-1,2,3,4-*tetrahydronaphthalene* (7a).—Compound (−)-(7a) was prepared from (+)-(6a) in 60% yield according to the literature method.[7] Distillation (b.p. 120—122° at 10 mmHg) yielded (−)-(7a) as a viscous oil which solidified; m.p. 30—35°, $[\alpha]_D$ −58° (lit.,[18] 41—43°, $[\alpha]_D$ −67°).

(−)-2-*Hydroxy*-1,2,3,4-*tetrahydroanthracene* (7b).—This was obtained in 56% yield; m.p. 138—139°, $[\alpha]_D$ −47° (lit.,[3] m.p. 136—138, $[\alpha]_D$ −47°).

(+)-1-*Hydroxy*-1,2,3,4-*tetrahydronaphthalene* (8a).—The (−)-1-acetoxy-2-bromo-1,2,3,4-tetrahydronaphthalene (3a) (0.15 g, 0.000 56 mol) was dissolved in ether (20 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (0.5 g, 0.013 mol). The mixture was refluxed for 12 h before water was added dropwise. The ethereal solution was filtered, dried ($MgSO_4$), and concentrated to yield an oil which was distilled to give (+)-(8a) (0.07 g, 85%), b.p. 120—130° at 10 mmHg, $[\alpha]_D$ +26.5° (lit.,[22] b.p. 132—134° at 12—13 mmHg, $[\alpha]_D^{20}$ +26.5°).

(+)-1-*Hydroxy*-1,2,3,4-*tetrahydroanthracene* (8b). This was obtained in 50% yield; m.p. 79—81°, $[\alpha]_D$ +126° (lit.,[20] $[\alpha]_D$ +138°) (Found: C, 85.1; H, 7.1. $C_{14}H_{14}O$ requires C, 84.8; 7.1%).

(−)-trans-1,2-*Dihydroxy*-1,2,3,4-*tetrahydronaphthalene* (9a).—The *trans*-diol (−)-(9a) was prepared from (+)-(6a) by the method previously reported for the conversion of (6b) into (9b).[3] The yield of (−)-(9a) was 78%; m.p. 105—107°, $[\alpha]_D$ −110° (lit.,[18] m.p. 112—113°, $[\alpha]_D$ −111°).

(−)-trans-1,2-*Dihydroxy*-1,2,3,4-*tetrahydroanthracene* (9b).—This was obtained in 82% yield; m.p. 160—162°, $[\alpha]_D$ −44° (acetone) (lit.,[21] racemic, m.p. 162—163°).

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