The Absolute Configurations of *Anti*-Benzene and *Anti*-Naphthalene 1,2:3,4-Dioxides

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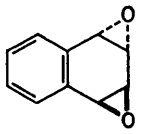
Summary Optically active *anti*-1,2:3,4-dioxides of benzene and naphthalene have been synthesized and their absolute configurations assigned using the exciton chirality c.d. method.

THE principal initial step in the metabolism of polycyclic aromatic hydrocarbons (PAHs) by mammals is the formation of their monoepoxide derivatives which are further transformed into numerous metabolites such as *trans*-dihydrodiols (epoxide hydrase) and phenols (thermal isomerisation *via* the NIH shift).[1] A recent study[2] on the metabolism of naphthalene in rats presented evidence indicating the *in vivo* intermediacy of *anti*-naphthalene 1,2:3,4-dioxide. This pathway was further implicated as a possible novel mode of metabolism of other PAHs.[2] In conjunction with our stereochemical and biological studies of the metabolites of PAHs, we have synthesized optically active *anti*-benzene and *anti*-naphthalene 1,2:3,4-dioxides[3,4] and determined their absolute configurations.

(1)



(2)

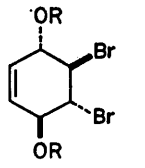
TABLE. Physical properties of optically active *anti*-benzene and *anti*-naphthalene 1,2:3,4-dioxides.[a]

	(1)	(2)
M.p./°C	53—54[b]	132—134[c]
$[\alpha]_D^{25}$/°	+170·3 (c 0·301, $CHCl_3$)	+119·7 (c 0·112, $CHCl_3$)
C.d. (cyclohexane–dioxan 49:1)	$\Delta\epsilon_{222}$ +2·14	$\Delta\epsilon_{275}$ +0·126 $\Delta\epsilon_{268\cdot5}$ +0·114 $\Delta\epsilon_{266}$ +0·112 $\Delta\epsilon_{263\cdot5}$ +0·090 $\Delta\epsilon_{257\cdot5}$ +0·088 $\Delta\epsilon_{228\cdot5}$ +3·11

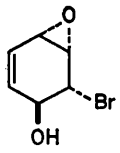
[a] > 98% optical purity based on the diastereometic purity of their (−)-MTPA ester precursors. [b] M.p. of racemic (**1**): 58—59 °C (ref. 3c). [c] M.p. of racemic (**2**): 99—100 °C (ref. 4).

The racemic all-*trans* diol dibromide (**3**), prepared from *p*-benzoquinone in 68% overall yield,[3c] was readily resolved *via* its bis-(−)-α-methoxy-α-trifluoromethylphenylacetyl [(−)-MTPA] esters[5] (**4**) (81%). Two fractional recrystallisations of the diastereomers (**4**) from ether–benzene–hexanes (5:1:1) provided the less polar isomer (**4a**), m.p. 140—142 °C, $[\alpha]_D^{25}$ + 11·7° (c 1·011, $CHCl_3$), and the more polar isomer (**4b**), m.p. 178—180 °C, $[\alpha]_D^{25}$ − 59·9° (c 1·008, $CHCl_3$), in 48 and 41% recovery, respectively. Each isomer was shown to be over 98% diastereomerically pure from its 360 MHz ^1H n.m.r. spectrum. The less polar ester (**4a**) was then hydrolysed with NaOMe in MeOH–Et_2O at 0 °C for 3 h to give the monoepoxide (**5**), m.p. 101—102 °C, $[\alpha]_D^{25}$ + 170·6° (c 0·812, $CHCl_3$), in 80% yield. Further treatment of the monoepoxide (**5**) with KOH–$MgSO_4$ in anhydrous ether gave (+)-*anti*-benzene 1,2:3,4-dioxide (**1**) (Table) in 92% yield.† Use of the same sequence of reactions on (**4b**) provided (−)-*anti*-benzene 1,2:3,4-dioxide, $[\alpha]_D^{25}$ −170·0 °(c 0·821, $CHCl_3$).

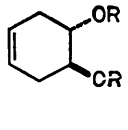
The stereochemistry of the dioxide was assigned using the exciton chirality c.d. method.[6]‡ Namely, the *trans*-diol (**6**), m.p. 86—87 °C, $[\alpha]_D^{25}$ + 43·9° (c 0·598, MeOH), obtained from the dioxide (**1**) using $LiAlH_4$ (72% yield), was converted into the bis-*p*-chlorobenzoate (**7**), m.p. 121—123 °C, $[\alpha]_D^{25}$ + 191·5° (c 0·273, $CHCl_3$). The c.d. spectrum of the dibenzoate (**7**) showed a typical set of Cotton effects [$\Delta\epsilon_{247\cdot5}$ + 32·7, $\Delta\epsilon_{236\cdot5}$ 0, and $\Delta\epsilon_{231}$ − 8·6 in MeOH–dioxan (9:1)] ascribable to the positive chirality of the two benzoyloxy-groups in (**7**), thus assigning the 1*S*,2*S*,3*S*,4*S*-stereochemistry to the dioxide (**1**).



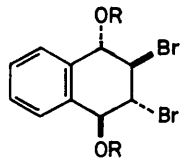
(3) R = H (racemic)
(4) R = (−)-MTPA
(diastereomeric mixture)



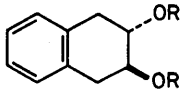
(5)



(6) R = H
(7) R = *p*-ClC_6H_4CO-



(8) R = H (racemic)
(9) R = (−)-MTPA
(diastereomeric mixture)



(10) R = H
(11) R = *p*-ClC_6H_4CO-

MTPA = α-methoxy-α-trifluoromethylphenylacetyl

Resolution of *anti*-dioxides of naphthalene and their stereochemical assignments were carried out in a similar fashion. The racemic all-*trans* diol dibromide (**8**), m.p. 186 °C, was synthesised from 1,4-naphthoquinone in 64% overall yield through a modification of the method used for the synthesis of (**3**).[3c] Thus, treatment of 1,4-naphthoquinone with excess of bromine in Et_2O yielded an extremely labile *trans*-2,3-dibromide which was immediately reduced with $LiAlH_4$ in tetrahydrofuran (THF), giving the desired all-*trans*-diol dibromide (**8**).§ The less polar (−)-MTPA ester (**9a**) [43% recovery from (**9**), > 98% diastereomeric purity], m.p. 185—187 °C, $[\alpha]_D^{25}$ + 14·0° (c 1·512, $CHCl_3$), was obtained by three fractional recrystallisations of the bis-(−)-MTPA esters (**9**) [83% from (**8**)] from Et_2O–$CHCl_3$ (1:1). The diastereomer (**9a**) was converted into (+)-*anti*-naphthalene 1,2:3,4-dioxide (**2**) (Table) in 62% yield using NaOMe in MeOH–Et_2O (room temperature, 6 h). The more polar isomer (**9b**) [obtained by fractional recrystallisations as above in 39% yield from (**9**), > 98% diastereomeric purity], m.p. 137—139 °C, $[\alpha]_D^{25}$ − 21·3° (c 1·213, $CHCl_3$), was similarly converted into (−)-*anti*-naphthalene 1,2:3,4-dioxide, $[\alpha]_D^{25}$ − 120·3° (c 0·560, $CHCl_3$). The stereochemistry was assigned based on the c.d. spectrum of the bis-*p*-chlorobenzoate (**11**), m.p. 171—173 °C, $[\alpha]_D^{25}$ + 174·8° (c 0·253, $CHCl_3$), of the *trans*-2,3-diol (**10**), m.p. 110—112 °C, $[\alpha]_D^{25}$ + 35·0° (c 0·422, $CHCl_3$). The *trans*-2,3-diol (**10**) was obtained *via* $LiAlH_4$ treatment of the dioxide (**2**) (79% yield).

† Attempts to obtain the dioxide (**1**) directly from the (−)-MTPA ester (**4a**) under a variety of conditions were unsuccessful, invariably providing only a low yield of the dioxide (**1**) and a substantial amount of its degradation products.

‡ Although some discussion of the basis of the exciton c.d. method has been stimulated by the incorrect assignment of the electric transition dipole (see J. Tanaka, C. Katayama, F. Ogura, H. Tatemitsu, and N. Nakagawa, *J. Chem. Soc., Chem. Commun.*, 1973, 21; for the correct assignment see: S. F. Mason, *ibid.*, 1973, 239), the present examples are believed to be unambiguous because of the use of the chromophore whose electric transition dipole has been well established (ref. 6).

§ Treatment of (**8**) with NaOMe in MeOH–Et_2O at room temperature for 4 h provided racemic *anti*-naphthalene 1,2:3,4-dioxide in 88% yield. This procedure, when applied to the synthesis of racemic *anti*-naphthalene dioxide, is superior, in yield and cleanness of the reaction, to the known methods (ref. 4).

The positive chirality of the two benzoyloxy-groups in (**11**), determined from its c.d. spectrum in MeOH–dioxan (9 : 1) ($\Delta\epsilon_{248}$ + 25·9, $\Delta\epsilon_{238\cdot5}$ 0, and $\Delta\epsilon_{232}$ − 12·7), proved the 1*S*,2*S*,3*S*,4*S*-stereochemistry for the (+)-dioxide (**2**).

The method described above for the synthesis of highly optically active dioxides and the determination of their absolute configuration may be applied to other *anti*-dioxides of PAHs. Preliminary studies indicate that all racemic and optically active dioxides of benzene and naphthalene are mutagenic in the Ames test; the benzene dioxides, though somewhat less active than the well known mutagen ethyl methanesulphonate, showed significantly stronger activity than the naphthalene analogues.[7]

We thank the National Cancer Institute, NIH, for financial support. The Bruker 360 MHz n.m.r. spectrometer used in this research was purchased by funds provided by the N.S.F.

(*Received*, 29*th May* 1981; *Com.* 635.)

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