Absolute Configurations of (+)- and (−)-1,2,3,4-Tetrahydroanthracen-2-ol

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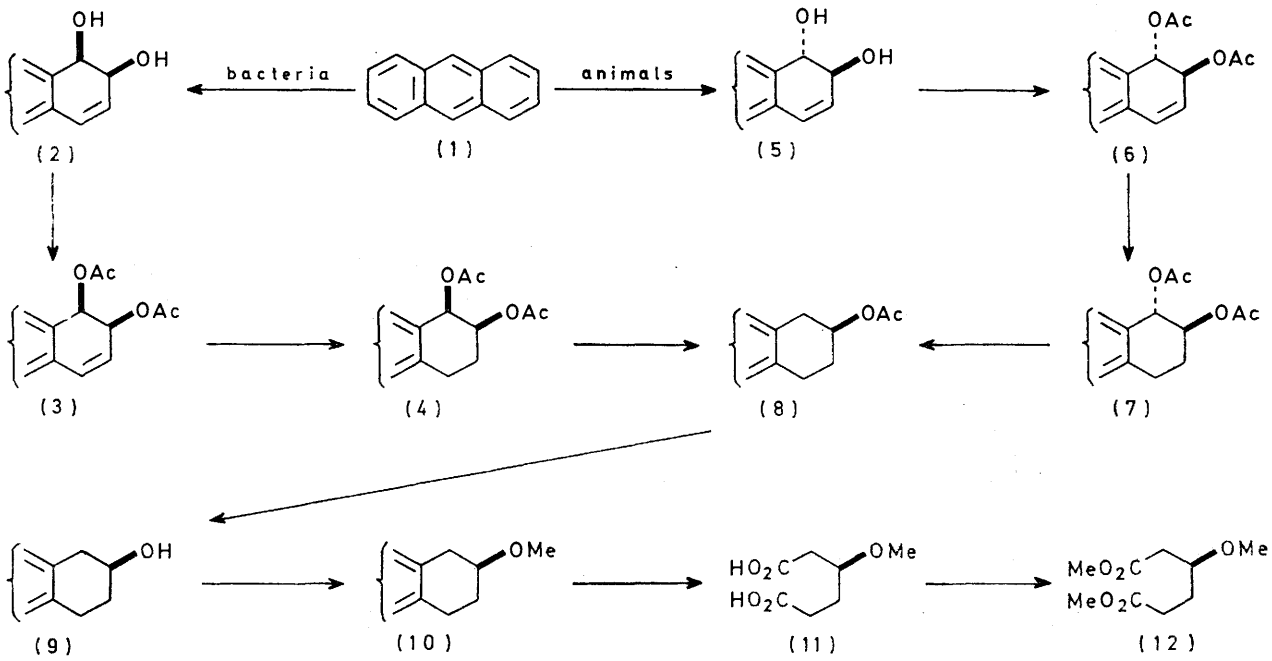
The absolute stereochemistry of the title compounds was determined by sequential methylation, ozonolysis, oxidation with peroxyformic acid, and esterification to form (+)- and (−)-dimethyl β-methoxyadipate of known configuration. From the optical rotation of the latter methoxyadipate, the optical purity of the previously resolved (+)- and (−)-1,2,3,4-tetrahydroanthracen-2-ols could be determined.

ANTHRACENE may be removed from the environment by the action of dioxygenase enzymes which are present in bacteria;[1] subsequent reduction results in *cis*-1,2-dihydroanthracene-1,2-diol.[2] Similarly, anthracene may be metabolised by animals to form mainly *trans*-1,2-dihydroanthracene-1,2-diol as a result of mono-oxygenase enzyme activity followed by enzyme-catalysed hydration[3] (see Scheme). Both dihydro-diols (2) and (5) have been isolated previously in optically active form from the enzymic transformations of anthracene {maximum observed $[\alpha]_{589}$ values +250° and +140° for (2) and (5), respectively}; both diols were then converted, *via* acetylation, catalytic reduction, hydrogenolysis, and finally hydrolysis into the common product (−)-1,2,3,4-tetrahydroanthracen-2-ol (9).[2]



SCHEME Absolute stereochemistry of bacterial and mammalian metabolism of anthracene

The alcohol (9) is thus a key compound in the determination of the absolute stereochemistry of the metabolites. We have previously[2] described a resolution procedure for the (+)- and (−)-enantiomers of (9). The efficiency of resolution was determined by n.m.r. analysis; the absolute stereochemistry of each enantiomer was also proposed on the basis of data from kinetic resolution, asymmetric synthesis, chromatographic retention of diastereoisomers, and circular dichroism. Although it was concluded from all these techniques that the (−)-enantiomer of the alcohol (9) had the *S*-configuration, each method depended upon a comparison with similar diols of known configuration. The present report provides an unequivocal method for the determination of absolute configuration of (−)- and (+)-1,2,3,4-tetrahydroanthracen-2-ol (9) by direct chemical correlation with (−)- and (+)-dimethyl β-methoxyadipate of known configuration;[4] the stereochemical assignment agrees with the earlier conclusion.[2]

Partially resolved samples of (±)-1,2,3,4-tetrahydroanthracen-2-ol (9) were methylated with sodium hydride

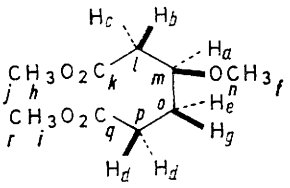
[1] D. T. Gibson, *Crit. Rev. Microbiol.*, 1973, **1**, 199.
[2] M. N. Akhtar, N. J. Thompson, D. R. Boyd, M. Koreeda, D. T. Gibson, V. Mahadevan, and D. M. Jerina, *J.C.S. Perkin I*, 1975, 2506.
[3] J. W. Daly, D. M. Jerina, and B. Witkop, *Experientia*, 1972, **28**, 1129.
[4] M. Viscontini and P. Miglioretto, *Helv. Chim. Acta*, 1955, **38**, 930.

and methyl iodide in benzene. The resulting methyl ether, (—)- or (+)-(10) was subjected to exhaustive ozonolysis in chloroform–methanol followed by oxidation with peroxyformic acid. On cooling and concentrating, phthalic acid crystallized out. The residual dark oil was then treated with diazomethane in ether without further purification. Distillation of the product yielded a colourless oil whose b.p. and i.r. spectrum, which showed the characteristic carbonyl stretching absorption, were consistent with the anticipated product, dimethyl β-methoxyadipate (12). However, in view of the relative importance of compound (12) in the unequivocal determination of absolute stereochemistry of metabolites from naphthalene,[5] anthracene, and other polycyclic aromatic hydrocarbons,[6] and the possibility of obtaining a range of ozonolysis products, it was important to examine rigorously the evidence for purity and structure.

The product oil resulting from methylation of the intermediate diacid (11) was further purified by preparative g.l.c. The collected product appeared to be homogeneous to g.l.c. analysis with various column packings, and gave correct microanalytical data for the structure (12). The ^{1}H n.m.r. spectral data are summarized in Table 1. With exception of the H_a signal, which showed extensive coupling and was located under

TABLE 1

^{1}H N.m.r. (220 MHz) and ^{13}C Fourier transform data for dimethyl β-methoxyadipate (solvent $CDCl_3$; reference Me_4Si)



Proton	δ_H	J/Hz	Carbon	δ_C
H_a	3.68—3.70 (1 H, m)		C_k	173.7
H_h	3.68 (3 H, s)		C_q	171.7
H_i	3.70 (3 H, s)		C_m	76.6
H_f	3.33 (3 H, s)		C_n	57.1
H_b	2.60 (1 H, dd)	J_{bc} 15.2, J_{ab} 17.0	$C_j + C_r$	51.5
$H_e + H_d$	2.34—2.45 (3 H, m)	J_{bc} 15.2, J_{ac} 6.0, $J_{de} = J_{dg}$ = 7.8	C_o	38.9
$H_c + H_g$	1.75—1.95 (2 H, m)	$J_{de} = J_{dg}$ = 7.8	C_l	29.7
			C_p	29.1

the large H_h and H_i signals, all the peaks were distinguishable in an expanded spectrum. The ^{13}C Fourier transform spectral data are also given in Table 1; discrete singlets (after proton noise decoupling) were observed for all the carbon atoms in structure (12) except

molecules.[7] The mass spectrum showed a molecular ion at m/e 204.099 95 ± 0.000 4, in agreement with the constitution $C_9H_{16}O_5$). Fragments resulting from electron impact were observed at m/e 131 (100%, $M - CH_3OCO\dot{C}H_2$), 173 (45%, $M - CH_3\dot{O}$), 117 (35%, $M - CH_3OCOCH_2\dot{C}H_2$), and 59 [20%, $M - CH_3OCOCH_2CH(OMe)CH_2\dot{C}H_2$].

Thus the structure and purity of the major esterified ozonolysis–oxidation product (12) was clearly established. It was then possible to assign absolute stereochemistry to both (—)- and (+)-1,2,3,4-tetrahydroanthracen-2-ol by direct chemical correlation with the known[4] configurations of (—)- and (+)-dimethyl β-methoxyadipate. The sign of specific rotation remained constant in the sequence (9) ⟶ (10) ⟶ (12) and the results are given in Table 2.

TABLE 2

Chemical correlation by the signs of specific rotation in the sequence (9) ⟶ (10) ⟶ (12)

Specific optical rotation [absolute configuration] (c 5.0 in $CHCl_3$)

Compd.	$[\alpha]_{589}$ (°)	$[\alpha]_{435}$ (°)
(9)	−34.0 [*S*]	
	+17.5 [*R*]	
(10)	−14.0 * [*S*]	
	+15.0 [*R*]	
(12)	−5.1 [*S*]	−9.5 [*S*]
	+3.2 [*R*]	+6.7 [*R*]

* Lower than the value for (+)-(10) since this intermediate was purified by distillation only.

This sequence of signs confirms the earlier conclusion that (—)-(9) has the (2*S*)-configuration. On the basis of the more recent literature values for optically pure samples of (+)- and (—)-dimethyl β-methoxyadipate ($[\alpha]_{589}$ −8.3°[8] and −8.8°[5] in $CHCl_3$) the specific rotation for optically pure (+)- or (—)-1,2,3,4-tetrahydroanthracen-2-ol should be on average + or −51.9°, in excellent agreement with the maximum rotation obtained after chemical resolution[2] (±52°). The present procedure thus provides both a check on the optical purity of the resolved alcohol (9) and an unequivocal assignment of absolute stereochemistry in full agreement with the earlier work.[2]

EXPERIMENTAL

Optical rotations were obtained with a Perkin-Elmer 141 automatic polarimeter. N.m.r. spectra were determined with Varian HA-100 and HR-220 instruments. The ^{13}C Fourier transform spectrometer used was a Bruker model HX-90. Analytical g.l.c. of compound (12) was carried out with a Pye–Unicam 104 instrument and a 2½% silicone gum rubber column at 150 °C. An identical type of column and temperature was used in conjunction with a modified

Samples of (+)- and (−)-methoxyadipate (12) were obtained by partial resolution of the racemate.[2]

(+)- *and* (−)-1,2,3,4-*Tetrahydro*-2-*methoxyanthracene*.—1,2,3,4-Tetrahydroanthracen-2-ol {(+)- ($[\alpha]_{589}$ +17.5°) or (−)- ($[\alpha_{589}]$ −34.0°)} (1.4 g, 0.0007 mol) in dry benzene (50 ml) was added dropwise to a stirred suspension of sodium hydride (50% dispersion in oil; 1.5 g) in benzene (50 ml) under nitrogen. The mixture was refluxed for 1 h and cooled before slow addition of methyl iodide (25.0 g, 0.18 mol) with stirring. The mixture was refluxed (21 h), cooled, and poured into ice-cold water. The benzene layer was separated, combined with light petroleum extracts (b.p. 40—60°) of the lower aqueous layer, and dried ($MgSO_4$). Concentration yielded a red oil which was distilled and chromatographed on silica gel [(+)-isomer only] to give a colourless *oil*, b.p. 70—75° at 0.01 mmHg; yield 1.1 g (76%), $[\alpha]_{589}$ +15.0° or −14.0° (*c* 5.0 in $CHCl_3$) (Found: C, 85.2; H, 7.4. $C_{15}H_6O$ requires C, 84.9; H, 7.5%), δ($CDCl_3$) 7.1—7.8 (6 H, m), 3.3—3.8 (1 H, m), 3.3 (3 H, s), 2.3—3.1 (4 H, m), and 1.6—2.2 (2 H, m).

Ozonolysis of (+)- *and* (−)-1,2,3,4-*Tetrahydro*-2-*methoxyanthracene*.—Ozone–oxygen (BOC cryoproducts Mark II ozonizer) was passed for 3 h into a solution of (−)-1,2,3,4-tetrahydro-2-methoxyanthracene (1.1 g; $[\alpha]_{589}$ −14.0°) or the (+)-form ($[\alpha]_{589}$ +15.0°) in chloroform–methanol (1 : 1; 50 ml) maintained at −50 to −60 °C. Evaporation under vacuum produced a colourless oil which was refluxed with 98% formic acid (5 ml) and 30% hydrogen peroxide for 6 h. Concentration of the solution to half its bulk produced crystals of phthalic acid. The mother liquor was mixed with ether (25 ml). Further concentration produced more phthalic acid, which was again removed. The residual oil (0.8 g), which showed both OH (3 500 cm^{-1}) and C:O (1 720 cm^{-1}) i.r. peaks, was then esterified with diazomethane generated from Diazald [5 g in ether (40 ml)], potassium hydroxide (0.8 g), and ethanol (20 ml). The crude product was distilled to give a viscous oil (0.5 g 44%), b.p. 110° at 11 mmHg, which g.l.c. showed contained minor impurities (2½% silicone gum rubber; 190 °C). Preparative g.l.c. yielded dimethyl β-methoxyadipate as an oil. Specific rotations of the product were $[\alpha]_{589}$ −5.1° and $[\alpha]_{435}$ −9.5°; and $[\alpha]_{589}$ +3.2° and $[\alpha]_{43}$ +6.7°, for the samples of (−)- and (+)-material, respectively (Found: C, 53.0; H, 7.9. Calc. for $C_9H_{16}O_5$: C, 52.9; H, 7.9%).

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