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GENERAL SYNTHETIC ROUTES TO DIARENE OXIDES OF POLYCYCLIC AROMATIC HYDROCARBONS

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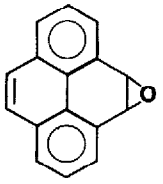
SUMMARY Diarene oxides have been synthesised by a single step oxidation of monoarene oxides using dimethyldioxirane, and by a three step cyclization sequence from the appropriate trans-tetrahydrobromoacetate precursors.

The initial step in the metabolism of polycyclic aromatic hydrocarbons (PAHs) in mammalian systems involves epoxidation to yield monoarene oxides.[1] Two separate enzyme-catalysed epoxidation steps in the same ring are involved in the metabolism of naphthalene to yield naphthalene 1,2,3,4-dioxide[2] (an arene dioxide[1]). Evidence has recently been found of epoxidation having occurred in two different rings of individual members of the PAH series to yield phenol-trans-diol,[3,4] arene oxide-phenol[5] and trans-diol-arene oxide[6] metabolites. To-date, however, diarene oxides have not yet been detected as mammalian metabolites. Their anticipated instability, coupled with the unavailability of suitable synthetic routes, have hampered the quest for diarene oxide metabolites.

The only general route to diarene oxides currently available involves ozonolysis of PAHs containing two K-regions and partial deoxygenation of the resulting tetraaldehydes in the presence of tris-(dimethylamino)phosphine to yield K-region diarene oxides[7-9] (three examples are given including the diarene oxide derivatives of pyrene (2) and dibenz[a,h]anthracene (4)).

An earlier report[10] on the use of the strong neutral oxidant dimethyldioxirane (generated in situ) to yield the K-region monoarene oxide (1) suggested to us that a purified form of this reagent[11] should also be applicable to the synthesis of diarene oxides using monoarene oxide precursors which have proved to be unstable with other types of oxidant. Thus, a series of K-region monoarene oxides (1), (3) and (5) (synthesised by dimethyldioxirane oxidation of the corresponding PAHs in acetone solution at 0-5°C over 12 h) and non-K-region monoarene oxides (8 and 10) (available from previous studies[12,13]) was treated with an acetone solution of dimethyldioxirane, 0-5°C, 12 h). The K-region diarene oxides (2) and (4) were thus obtained from partial oxidation of the corresponding monoarene oxides (1 and 3) and were identified by comparison of the n.m.r. spectral data of the



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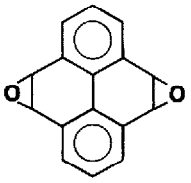

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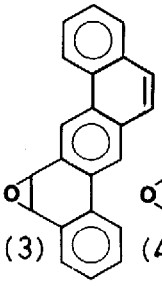

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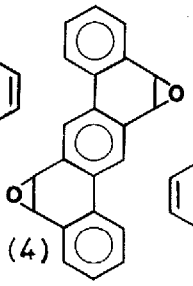

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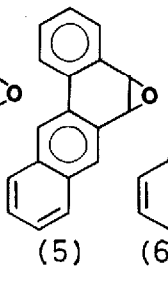

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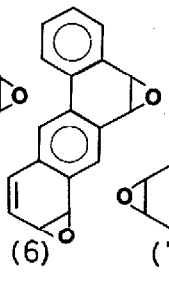

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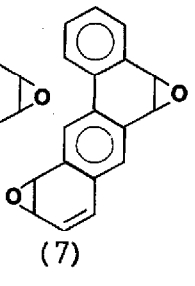

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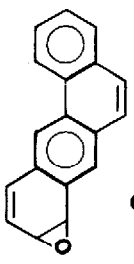

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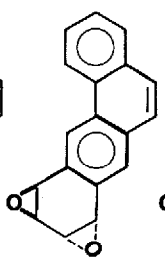

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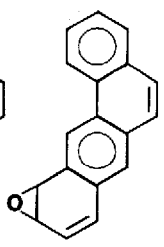

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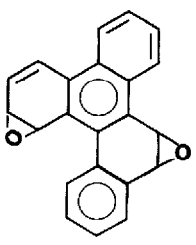

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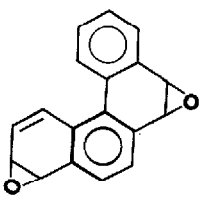

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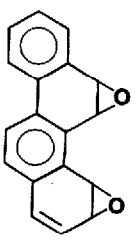

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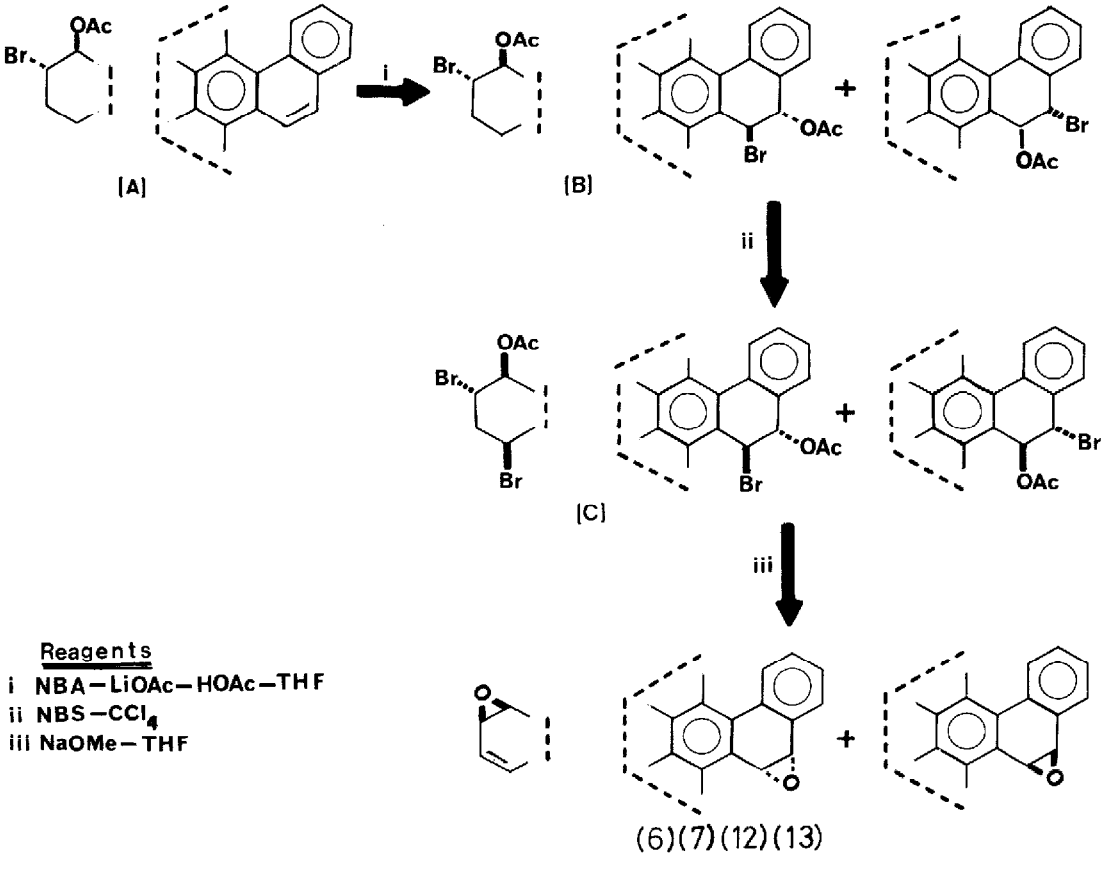

product mixture with authentic samples. Similar attempts to obtain the K-region:non-K-region diarene oxides (6) or (7) by dimethyldioxirane oxidation of K-region arene oxide (5) were unsuccessful. The attempted reverse process i.e. oxidation of non-K-region arene oxide (8) resulted in a total conversion to the arene dioxide (9). Surprisingly the monoarene oxide (10) did not appear to be oxidized to arene dioxide (9) under identical conditions but gave an incomplete oxidation to the K-region:non-K-region diarene oxide (7). Although no spectral evidence was available in confirmation, it is assumed that all the diarene oxides produced by dimethyldioxirane oxidation (2,4 and 7) of the corresponding monoarene oxides were mixtures of cis and trans isomers. The yields of diarene oxides (2), (4) and (7) shown in the Table have not been optimized.

While the oxidation route to diarene oxides is clearly more suitable for K-region diarene oxides (e.g. 2 and 4), an alternative procedure is required for other types of diarene-oxides e.g. (6),(7),(12) (K-region:non-K-region), and (13) (K-region:bay region). The serendipitous formation of the K-region:fjord region diarene oxide (11) by use of an excess of N-bromoacetamide reagent upon 3,4-dihydrobenzo[g]chrysene[14] suggests that a simple modification of this reaction should provide a general route to diarene oxides which are unavailable by earlier methods. Thus, the previously reported trans- tetrahydrobromoacetates (A) (trans-8-acetoxy-9-bromo-8,9,10,11-tetrahydrobenz[a]anthracene,[12] trans-11-acetoxy-10-bromo-8,9,10,11-tetrahydrobenz[a]anthracene,[13] trans-4-acetoxy-3-bromo-1,2,3,4-tetrahydrochrysene,[15] trans-4-acetoxy-3-bromo-1,2,3,4-tetrahydrobenzo[c]phenanthrene[16]) were each in turn treated with (i) N-bromoacetamide to yield dibromodiacetates (B), (ii) N-bromosuccinimide to yield tribromodiacetates (C) and (iii) sodium methoxide to yield diarene oxides (6),(7),(12) and (13) respectively (Scheme). The dibromodiacetates (B) and tribromoacetates (C) were found to be rather unstable mixtures of isomers which were thus converted directly to the diarene oxides (6),(7),(12) and (13) without prior separation. The latter products were purified by recrystallization and were fully characterised by spectral and other methods (Table). In common with diarene oxides (2) and (4) which were formed by oxidation, the diarene oxides (6),(7),(12) and (13) are also assumed to have been formed as a mixture of cis and trans-isomers. Using high resolution n.m.r. methods (400 MHz, $CDCl_3$) a 28:72 ratio of stereoisomers of the diarene oxide (13) was observed. Diarene oxides (6),(7),(12) and (13) are among the six possible diarene oxides in the tetracyclic series of PAHs having the general structure shown in the Scheme. Similarly, the previously reported diarene oxide (11) is but one of a much larger number of possible diarene oxides in the pentacyclic series of PAHs which emphasises the general nature of this synthetic route to diarene oxides.

The difference in reactivity between K-region and other types of monoarene oxides is well documented.[1] Thus, K-region monoarene oxides are generally more easily hydrated to yield trans-dihydrodiols and less easily aromatized to form phenols. This differential could in principle be utilized

in the synthesis of arene oxide-phenol, trans-diol phenol and arene oxide-trans-diol metabolites.

TABLE: ^{1}H N.m.r. Data (δ,250 or 400 MHz, $CDCl_3$) and Yields of Diarene Oxides (2,4,6,7,12,13) and Arene Dioxide (9)

Arene Oxide	K-region Epoxide	Non-K Region Epoxide (Bz)[a]	Non-K Region Epoxide (NBz)[b]	Olefinic (Bz)[a]	Olefinic (NBz)[b]	Yield (%)
(2)	4.64					7[c,d]
(4)	4.40[e] 4.37[e]					16[c,d]
(9)		4.54[f]	3.95[f]			97[c,d]
(6)	4.60[e] 4.56[e]	4.52[e]	4.14[e]	6.85[g]	6.50[g]	60[h]
(7)	4.56[f] 4.56[f]	4.56[e]	4.15[e]	6.81[g]	6.49[g]	18[c],
(12)	4.68[e] 4.55[e]	4.60[e]	4.30[e]	7.48[g]	6.44[g]	70[h]
(13)	4.64[e,i] 5.21[e,i] 4.54[e,j] 5.06[e,j]	5.13[e,i] 5.00[e,j]	4.22[e,i] 4.12[e,j]	6.79[g]	6.48[g]	72[h]

a: Benzylic. b: Non-benzylic. c: Dimethyldioxirane in acetone, 0-5°C, 12 h. d: Based upon n.m.r. analysis. e: Coupling constants 3.8-4.0 Hz. f: Multiplet. g: Coupling constants 9.6 Hz. h: Overall isolated yield from trans tetrahydrobromoacetate precursor. i: Major isomer. j: Minor isomer.

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REFERENCES

1. D.R. Boyd and D.M. Jerina, "Small Ring Heterocycles", Vol.42 Part 3; John Wiley, New York, 1985, 197.
2. W.G. Stillwell, O.J. Bouwsma, J.-P.Theonot, M.G. Horning, G.W. Griffin, K. Ishikawa and M. Takaku, Res. Commun. Chem. Pathol. Pharmacol., 1978, 20, 509.
3. R.M. Hodgson, A. Seidel, W. Bochnitschek, R.H. Glatt, F. Oesch and P.L. Grover, Carcinogenesis, 1985, 6, 135.
4. M. Boroujerdi, H.-C. Kung, A.G.E. Wilson and M.W. Anderson, Cancer Res., 1981, 41, 951.
5. D.R. Thakker, H. Yagi, J.M. Sayer, V. Kapur, W. Levin, R.L. Chang, A.W. Wood, A.H. Conney and D.M. Jerina, J. Biol. Chem., 1984, 260, 11249.
6. O. Ribeiro, C.A. Kirkby, P.C. Hirom and F. Oesch, Carcinogenesis, 1987, 8, 1621.
7. S.C. Agarwal and B.L. Van Duuren, J. Org. Chem., 1977, 42, 2730.
8. S.C. Agarwal and B.L. Van Duuren, J. Org. Chem., 1975, 40, 2307.
9. R.M. Moriarty, P. Dansette and D.M. Jerina, Tetrahedron Letters, 1975, 2557.
10. R. Jeyaraman and R.W. Murray, J. Amer. Chem. Soc., 1984, 106, 2462.
11. R.W. Murray and R. Jeyaram, J. Org. Chem., 1985, 50, 2847.
12. D.R. Boyd, K.A. Dawson, G.S. Gadaginamath, J.G. Hamilton, J.F. Malone and N.D. Sharma, J.C.S. Perkin Trans.1, 1980. 2112.
13. D.R. Boyd, G.S. Gadaginamath, N.D. Sharma, A.F. Drake, S.F. Mason and D.M. Jerina, J.C.S. Perkin Trans.1, 1981, 2233.
14. S.K. Agarwal, D.R. Boyd and W.B. Jennings, J.C.S. Perkin Trans.1, 1985, 857.
15. D.R. Boyd, M.G. Burnett and R.M.E. Greene, J.C.S. Perkin Trans. 1, 1983, 595.
16. S.K. Balani, D.R. Boyd, R.M.E. Greene and D.M. Jerina, J.C.S. Perkin Trans.1, 1984, 1781.

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