Quantitative calculations thus indicate that an *S* configuration should be assigned to (+)-*trans*-abscisic acid, and therefore to (+)-*cis*-abscisic acid.

As exemplified in the present case, quantitative applications of the exciton chirality method should provide a useful tool for conformational analyses of natural products. An alternative application of the exciton chirality method has also indicated that the configuration of natural (+)-*cis*-abscisic acid should be represented by *S*.[19,20]

Acknowledgments. The author is indebted to Professor K. Nakanishi, Columbia University, and Dr. Y. Nakadaira, Tohoku University, for helpful discussions. This work has been supported by the Ministry of Education, Japan.

(19) M. Koreeda, G. Weiss, and K. Nakanishi, *J. Amer. Chem. Soc.*, **95**, 239 (1973).

(20) NOTE ADDED IN PROOF. Natural (+)-ABA has recently been correlated with (*S*)-malic acid and this has led to the same absolute configuration **13**: G. Ryback, *Chem. Commun.*, 1190 (1972).

Nobuyuki Harada

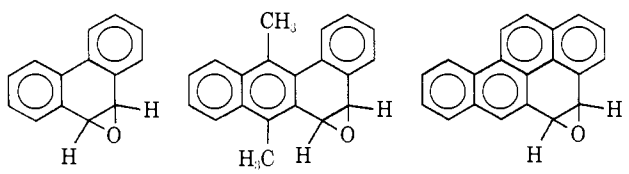
Chemical Research Institute of Nonaqueous Solutions
Tohoku University, Sendai, 980, Japan

Received September 23, 1972

K-Region Arene Oxides of Carcinogenic Aromatic Hydrocarbons

Sir:

Arene oxides have recently been implicated as primary intermediates in the metabolism of aromatic molecules,[1] and the "K-region" oxides of certain polycyclic hydrocarbons have been shown to induce "malignant transformation" of rodent cells in culture[2] and mutational changes in mammalian cells and bacteriophages.[3] This evidence would appear to support the suggestion of Boyland[4] that epoxides are responsible for the carcinogenic activity of the parent hydrocarbons. However, investigation has been hampered by the synthetic inaccessibility of many of the compounds of greatest interest, *e.g.*, 7,12-dimethylbenz[*a*]anthracene 5,6-oxide (**1b**) and benzo[*a*]pyrene 4,5-oxide (**1c**), the parent hydrocarbons of which are among the most powerful carcinogens.[5] A new general synthesis of arene oxides, and of compounds **1a–c**, in particular, is now reported.



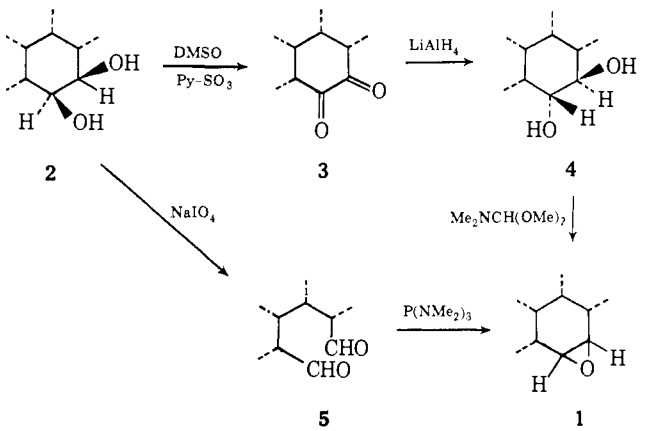
1a **1b** **1c**

The general synthetic scheme involves the following sequence: (1) generation of the "K-region" *cis*-dihydrodiols (**2**) *via* interaction of the corresponding hydrocarbons with osmium tetroxide,[6] (2) oxidation with dimethyl sulfoxide and sulfur trioxide–pyridine complex[7] to the quinones **3**, (3) reduction with lithium aluminum hydride to yield the related *trans*-dihydrodiols[8] (**4**), and finally (4) cyclization of the latter with the dimethyl acetal of dimethylformamide[9] (DMA–DMF) to afford the desired epoxide (**1**). Good yields of epoxides and intermediates were generally obtained, and the results are summarized in Table I.

Table I. Product Yields (%)[a]

Compd	a	b	c
3	96	49	98
4	87 (93)[b]	85 (55)[b]	44 (96)[b,c]
5		100	68[d]
1 from **4**	71	80	68
1 from **5**	89[e]	75	50

[a] All new compounds show consistent nmr, ir, mass spectral, and microanalytical data. [b] Percentage of trans isomer as determined by nmr on the diacetates is given in parentheses. [c] Isolated as the diacetate, since the diol is susceptible to air oxidation. [d] Lead tetraacetate was employed as the oxidant. [e] M. S. Newman and S. Blum, *J. Amer. Chem. Soc.*, **86**, 5598 (1964).



2 **3** **4** **5** **1**

Oxidation of the *cis*-diols to the corresponding 1,2-diones presented the first synthetic challenge.[10] A number of unsuccessful attempts to transform the *cis*-diol of DMBA (**2b**) to the related quinone **3b** are recorded in the literature.[11,12] Oxidation with dimethyl sulfoxide and acetic anhydride, according to the method of Newman and Davis,[12] gave fair but erratic yields of the quinones. Also, phenanthrene-9,10-dihydro-9,10-diol (**2a**) on treatment with DMSO–Ac_2O afforded principally the phenanthrene 9,10-diacetate. In contrast, the sulfur trioxide–pyridine complex in DMSO–triethylamine[7] at room temperature efficiently and

(1) D. M. Jerina, J. W. Daly, B. Witkop, P. Zaltzman-Nirenberg, and S. Udenfriend, *J. Amer. Chem. Soc.*, **90**, 6525 (1968); *Biochemistry*, **9**, 147 (1970); J. Selkirk, E. Huberman, and C. Heidelberger, *Biochem. Biophys. Res. Commun.*, **43**, 1010 (1971).

(2) H. Marquardt, T. Kuroki, E. Huberman, J. Selkirk, C. Heidelberger, P. Grover, and P. Sims, *Cancer Res.*, **32**, 716 (1972); Y. Berwald and L. Sachs, *J. Nat. Cancer Inst.*, **35**, 641 (1965); J. DiPaolo, R. Nelson, and P. Donovan, *Science*, **165**, 917 (1969).

(3) E. Huberman, L. Aspiras, C. Heidelberger, P. Grover, and P. Sims, *Proc. Nat. Acad. Sci. U. S.*, **68**, 3195 (1971); M. Cookson, P. Sims, and P. Grover, *Nature (London)*, **234**, 186 (1971).

(4) E. Boyland, *Biochem. Soc., Symp.*, **5**, 40 (1950).

(5) J. Pataki, C. Duguid, P. W. Rabideau, H. Huisman, and R. G. Harvey, *J. Med. Chem.*, **14**, 940 (1971); C. B. Huggins, J. Pataki, and R. G. Harvey, *Proc. Nat. Acad. Sci. U. S.*, **58**, 2253 (1967).

(6) J. W. Cook and R. Schoental, *J. Chem. Soc.*, 170 (1948); R. Criegee, B. Marchand, and H. Wannowius, *Justus Leibigs Ann. Chem.*, **550**, 99 (1942).

(7) J. R. Parikh and W. von E. Doering, *J. Amer. Chem. Soc.*, **89**, 5505 (1967).

(8) J. Booth, E. Boyland, and E. E. Turner, *J. Chem. Soc.*, 1188 (1950).

(9) H. Neumann, *Chimia*, **23**, 267 (1969).

(10) Controlled oxidation of aromatic 1,2-diols to 1,2-diones is complicated by the relative facility of both dehydration and oxidative cleavage of the carbon–carbon bond.

(11) H. I. Hadler and A. C. Kryger, *J. Org. Chem.*, **25**, 1896 (1960); E. Boyland and P. Sims, *Biochem. J.*, **95**, 780 (1965).

(12) M. S. Newman and C. C. Davis, *J. Org. Chem.*, **32**, 66 (1967).

rapidly oxidized all diols to quinones. On neutralization, the latter precipitated from solution in relatively pure state. It appears that the DMSO–SO_3 reagent[7] may offer broader applicability than existing methods[13] for the general oxidation of 1,2-diols to 1,2-diones.

Reduction of **3** with lithium aluminum hydride[8] proceeded smoothly and stereoselectively to furnish the expected *trans*-diols; however, **3b** was accompanied by a major proportion (45%) of the cis isomer. This diminished steric preference is likely due to the steric influence of the adjacent 7-methyl group.[14] Fortunately, the *trans*-diols may be separated from the cis isomers through conversion of the latter to acetonides with acetone in the presence of anhydrous copper sulfate.

Conversion to the epoxides was effected under conditions similar to those described in the aliphatic series[9] except that DMA–DMF was employed as reagent only (2.5 equiv) and not as solvent (in order to minimize formation of the unreactive bis adducts), and dimethylformamide or chloroform was used as the solvent.

7,12-Dimethylbenz[*a*]anthracene 5,6-oxide, obtained as almost colorless crystals from benzene–ether–hexane, exhibited the following properties: mp 148° (soften ~139°); nmr[15] (CCl_4) δ 2.78 (s, 3, 7-CH_3), 2.93 (s, 3, 12-CH_3), 4.27 (d, 1, oxirane-H, J = 4 Hz), 4.68 (d, 1, oxirane-H, J = 4 Hz), 7.2–8.1 ppm (m, 8, aromatic); ir (KBr) 11.3 μ (medium–weak); mass spectrum *m/e* 272 (parent peak). *Anal.* Calcd for $C_{20}H_{16}O$: C, 88.20; H, 5.92. Found: C, 88.07; H, 5.96. This epoxide proved considerably more sensitive than **1a** to both heat and protonic solvents. Thus, **1b** in carbon tetrachloride, though stable at 0°, decomposed completely at room temperature within 1 week. In aqueous acetone, decomposition was virtually complete in 72 hr at ambient temperature. Mild hydrolysis in aqueous acetic acid regenerated **4b** accompanied by its dehydration product, 7,12-dimethylbenz[*a*]anthracen-5-ol.

Benzo[*a*]pyrene 4,5-oxide crystallized from benzene in light straw needles: mp 150° (softens ~135°); nmr ($CDCl_3$) δ 4.70 (d, 1, J = 4 Hz), 4.80 (d, 1, J = Hz), 7.5–8.8 ppm (m, 10, aromatic); ir (KBr) 11.2 μ (medium weak); mass spectrum *m/e* 268 (parent peak). *Anal.* Calcd for $C_{20}H_{12}O$: C, 89.53; H, 4.50. Found: C, 89.32; H, 4.64. A sample of the epoxide in benzene showed only slight decomposition after 1 month at room temperature.

The observed instability of **1b** suggested that the previous failure[16] to synthesize it *via* interaction of 1,4-dimethyl- 2- phenylnaphthalene- 3,2′-dicarboxaldehyde with tris(dimethylamino)phosphine[17] was more due to its facility of decomposition than the inadequacy of the synthetic approach. Reinvestigation confirmed this suspicion, and it was found that with appropriate care the epoxides of interest were also obtainable through this method; the yields are given in Table I. At this time, the two approaches appear complementary, and since **1b** and **1c** represent probably the two most difficult to synthesize types of K-region oxide derived from highly active carcinogens, all such compounds should now be available.

It is tempting to speculate that the comparative instability of **1b** may relate to its carcinogenic activity. Structural features, electronic or steric (*e.g.*, symmetry, ring polarization, ring strain, low steric hindrance), which enhance the chemical reactivity of the oxide ring, may be expected to favor greater facility of interaction with a cellular receptor. On the other hand, excessive reactivity might lead to destruction before initiation of the carcinogenic process. Since the number of K-region oxides known is still quite limited and data on their relative reactivity are lacking, no meaningful decision regarding the relationship among arene oxide structure, chemical reactivity, and carcinogenic activity is yet possible. However, the problem is currently under active investigation.

Acknowledgment. This investigation was supported by Grant No. 71-24 from the Illinois Division of the American Cancer Society. We wish to thank Mr. R. Balick for technical assistance during the initial phase of this research.

(13) S. L. Regen and G. M. Whitesides, *ibid.*, **37**, 1832 (1972).

(14) A mixture of diols of unspecified composition was also reported to be obtained from similar reduction of 7-methylbenz[*a*]anthracene-5,6-quinone: P. Sims, *Biochem. J.*, **105**, 591 (1967).

(15) The lower field singlet is assigned to the 12-CH_3 in recognition of the anticipated steric effect of the aromatic proton in the 1 position.

(16) M. S. Newman and S. Blum, *J. Amer. Chem. Soc.*, **86**, 5598 (1964).

(17) V. Mark, *ibid.*, 1884 (1963).

(18) On leave from the Department of Chemistry, The University of Malaysia, Kuala Lumpur, Malaysia.

S. H. Goh,[18] Ronald G. Harvey*
Ben May Laboratory for Cancer Research
The University of Chicago
Chicago, Illinois 60637
Received September 16, 1972

Synthesis of Non-K-Region Arene Oxides

Sir:

Since the initial isolation of an arene oxide as an obligatory metabolite of an aromatic hydrocarbon,[1] substantial interest has developed in the biochemistry and pharmacology of arene oxides which have been identified as metabolic intermediates[2] and causative agents in studies on necrosis,[3] mutagenesis,[4] and carcinogenesis.[5] Despite their biological importance only two general synthetic routes to arene oxides have been available.[6] K-Region arene oxides have been prepared by closure of the corresponding dialdehydes with tris(dimethylamino)phosphine.[7] In spite of its wide use,[8]

(1) D. M. Jerina, J. W. Daly, B. Witkop, P. Zaltzman-Nirenberg, and S. Udenfriend, *J. Amer. Chem. Soc.*, **90**, 6525 (1968); *Biochemistry*, **9**, 147 (1970).

(2) J. K. Selkirk, E. Huberman, and C. Heidelberger, *Biochem. Biophys. Res. Commun.*, **43**, 1010 (1971); P. L. Grover, A. Hewer, and P. Sims, *Fed. Eur. Biochem. Soc. Lett.*, **18**, 76 (1971).

(3) B. B. Brodie, W. D. Reid, A. K. Cho, G. Sipes, G. Krishna, and J. R. Gillette, *Proc. Nat. Acad. Sci. U. S.*, **68**, 160 (1971).

(4) B. N. Ames, P. Sims, and P. L. Grover, *Science*, **176**, 47 (1972).

(5) H. Marquardt, T. Kuroki, E. Huberman, J. Selkirk, C. Heidelberger, P. Grover, and P. Sims, *Cancer Res.*, **32**, 716 (1972); P. L. Grover, P. Sims, H. Huberman, H. Marquardt, T. Kuroki, and C. Heidelberger, *Proc. Nat. Acad. Sci. U. S.*, **68**, 1098 (1971).

(6) The accompanying article by Goh and Harvey also represents a new synthesis of arene oxides. We thank these authors for delaying their paper in order that the present results might appear simultaneously. Other syntheses have been reported but are neither preparative nor general. Thus, naphthalene oxide has been prepared by direct oxidation of naphthalene (D. M. Jerina, D. R. Boyd, and J. W. Daly, *Tetrahedron Lett.*, 457 (1970)) and several hindered oxepins have been prepared by the dehydration of 1,4-dihydroxycyclohexadienes (S. Berger, G. Henes, and A. Rieker, *ibid.*, 1257 (1971)).

(7) M. S. Newman and S. Blum, *J. Amer. Chem. Soc.*, **86**, 5559 (1964).