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PYRENE DERIVATIVES OXYGENATED AT BOTH K-REGIONS. SYNTHESIS OF A BIS-ARENE OXIDE.

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Polycyclic aromatic hydrocarbons (PAHs) probably exert their carcinogenic properties through metabolically induced binding to tissue constituents.[2] While arene oxides are attractive intermediates by which such binding may be explained,[3] recent studies have implicated more highly oxygenated metabolites. For example, 7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene 9,10-oxide[4] and 8,9-dihydroxy-8,9-dihydrobenzo[a]anthracene 10,11-oxide[5] are formed by a hepatic microsomal oxidizing system and readily bind to DNA.

As part of a study on the metabolism of carcinogenic PAHs, the non-carcinogen pyrene (1) was selected as a model system upon which routes could be developed for the synthesis of potential secondary metabolites. Since pyrene (1) posesses two K-regions, a feature common to many PAH carcinogens, we investigated sequential chemical oxidation of both these sites and report here on tetrol derivatives, an arene oxide-diol, and a bis-arene oxide. The bis-arene oxide is of especial interest as a precursor of a number of secondary metabolites which could arise from further chemical or enzymatic transformations of the oxido functionality.

The starting point for our synthetic scheme (Fig. 1) was oxidation of the K-region double bond of pyrene (1) to a cis dihydrodiol. Accordingly, pyrene (1) was converted with OsO_4/pyridine to the known cis-4,5-dihydroxy-4,5-dihydropyrene (2a) in 75% yield. The derived diacetate 2b had m.p. 147-48°, lit.[6] 146-47°, m/e 320, CH_3CO 2.06 ppm, CH-O 6.58 ppm. In order to convert the K-region double bond of pyrene (1) into a trans dihydrodiol, the cis dihydrodiol (2a) was oxidized to the ortho-quinone followed by stereospecific reduction. Although oxidation of 2a with CrO_3/pyridine[7] or with SO_3/pyridine[8] provides fair yields of pyrene 4,5-dione (3), we have found that MnO_2 is the reagent of choice for this type oxidation, in that consistently high yields were obtained (90-95%) and isolation of the desired product was greatly simplified.[9] Quinone 3 had m.p. 310°-312°, lit.[11] 303-304°. Several other dihydrodiols were oxidized with similar efficiency. Reduction of 3 with KBH_4[12] at 0° in MeOH gave trans-4,5-dihydroxy-4,5-dihydropyrene (4a), mp 222-223°, lit.[14] 222°, m/e 236; diacetate (4b), mp 216-17°, lit.[14] 218°, m/e 320, CH_3CO 2.02 ppm,

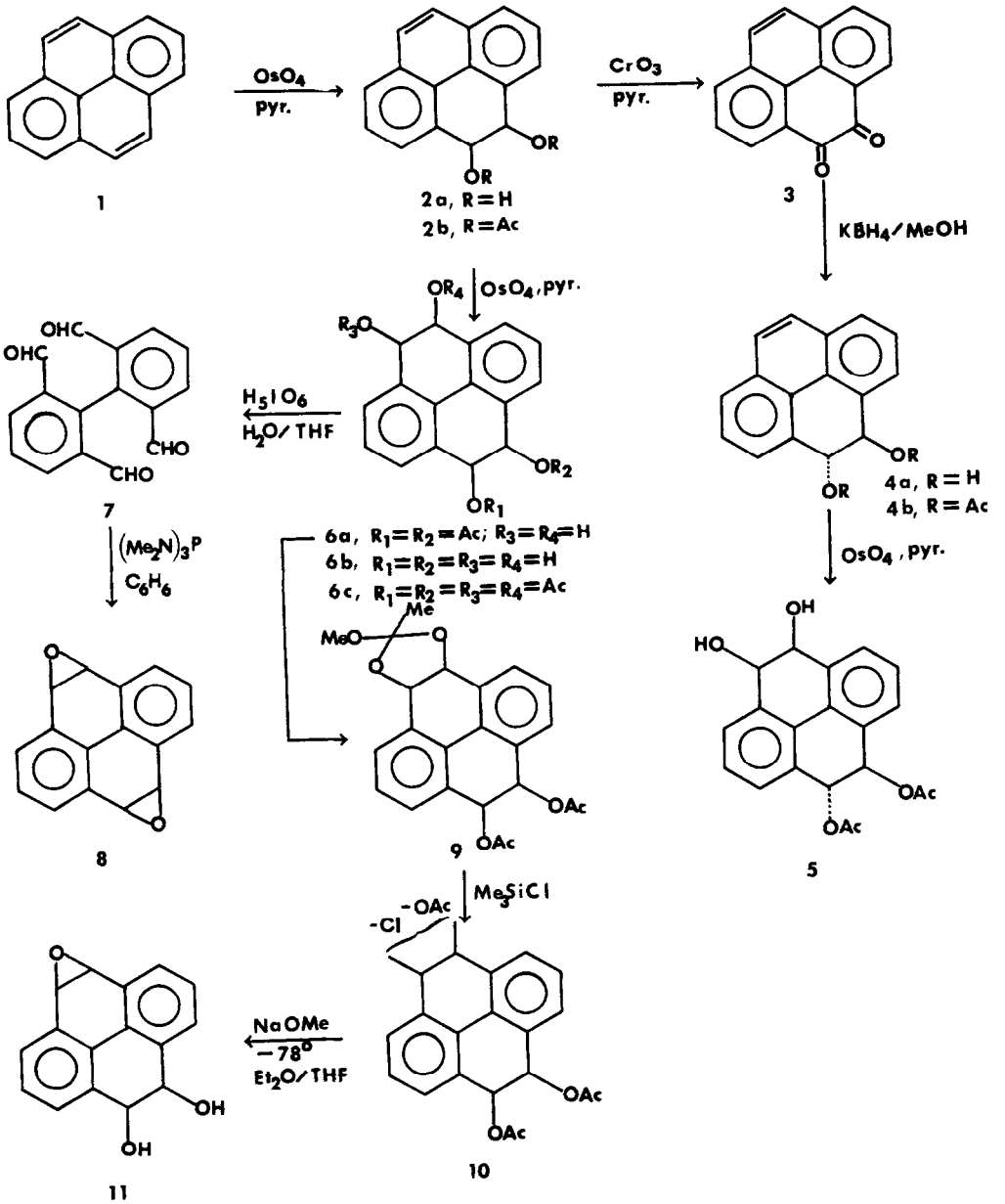
CH-O 6.20 ppm. Osmium tetroxide oxidation of 4b yielded cis-4,5-dihydroxy-trans-9,10-diacetoxy-4,5,9,10-tetrahydropyrene (5) in 60% yield; mp 169-71°, m/e 354, CH_3CO 2.00 ppm, $H_{4,5}$ 4.88 ppm, $H_{9,10}$ 6.12 ppm. cis-Diacetate 2b, upon oxidation with OsO_4, yielded cis-4,5-dihydroxy-cis-9,10-diacetoxy-4,5,9,10-tetrahydropyrene (6a) in 65% yield; mp 232-35°, m/e 354, CH_3CO 2.08 ppm, $H_{4,5}$ 4.80 ppm, $H_{9,10}$ 6.25 ppm. The derived tetraacetate 6c had mp 239-241°, CH_3CO 2.10 ppm, CH-O 6.26 ppm; the tetrol 6b had m.p. 269-70°, m/e 270, CH-O 4.60 (d) ppm, C-OH 5.00 (d, exchanges in D_2O).

The vicinal groups in 6a-6c must be mutually cis but, pairwise, they may be syn or anti with respect to each other. Because these three compounds are crystalline solids and appear individuall homogeneous in chromatographic behavior, each is probably a pure diastereomer. The actual stereochemistry has not been elucidated and this is under investigation.

The tetrol derivatives (6) were employed for the synthesis of an arene oxide-diol and a bis-arene oxide. cis-4,5-Dihydroxy-4,5-dihydropyrene 9,10-oxide (11) was prepared by the methoxydioxolane route[15]. Conversion of 6a into the methoxydioxolane 9 afforded a mixture of two diastereomers as evidenced by n.m.r. Without separation 9 was converted to a mixture of chloroacetates (10) which were not separated but subjected to intramolecular oxide formation to yield one diastereomerically pure oxide diol (11). The overall reaction, 6a→9→10→11, proceeded in 40% yield and 11 had mp 171-74°, m/e 254, $H_{4,5}$ 4.78 (d) ppm, $H_{9,10}$ 4.50 ppm.

Application of the methoxydioxolane route for the synthesis of pyrene 4,5; 9,10-bis-oxide (8) was not satisfactory. Therefore, resort to the dialdehyde → epoxide route of Newman and Blum[16] was employed. Pyrene 4,5;9,10-bis-oxide (8) was prepared starting from tetrol 6b which was cleaved with H_5IO_6-THF-H_2O to the known biphenyl-2,2'; 6,6'-tetracarboxaldehyde (7) m.p. 164-65°, lit.[17] 162-63°, CH=O 1680 cm^{-1}, CHO 9.86 ppm. Conversion of 7 to bis-arene oxide 8 was accomplished as follows:[16] 0.63 mmoles of 7 in benzene was treated with 1.4 mmoles of freshly distilled $[(CH_3)_2N]_3P$ (Mark's reagent) in benzene at 53° for 3 hr. The bis-oxide was obtained in 20% yield and had m.p. 210° [d], m/e 234, CHO 4.64 ppm. This compound is thermally stable as evidenced by the intense molecular ion (234, 100%) and a loss of oxygen (218, 15%) rather than CHO had a phenol been formed. Decomposition on t.l.c. prevented determination of whether 8 is a mixture of syn and anti diastereomers.

Bis-arene oxides could act as bifunctional binding agents within the cell while diol-arene oxides might reach more polar regions of the cell which are inaccessible to arene oxides. Chemical reactions of diol-oxide11 and bis-oxide 8 will be reported in the full paper along with data on their biological activities.


OsO4
pyr.
CrO3
pyr.
OR
OR
2a, R=H
2b, R=Ac
O
O
3
KBH4/MeOH
OR
OR
4a, R=H
4b, R=Ac
OsO4, pyr.
OH
HO
OAc
OAc
5
OR4
OsO4, pyr.
R3O
OR2
OR1
H5IO6
H2O/THF
6a, R1=R2=Ac; R3=R4=H
6b, R1=R2=R3=R4=H
6c, R1=R2=R3=R4=Ac
OHC
OHC
CHO
CHO
7
(Me2N)3P
C6H6
8
Me
MeO
OAc
OAc
9
Me3SiCl
-OAc
-Cl
OAc
OAc
10
NaOMe
−78°
Et2O/THF
OH
OH
11

REFERENCES

1. Visiting Scientist 1974-75, University of Illinois, Circle Campus, Chicago Illinois.
2. J. A. Miller, Cancer Res., 30, 559 (1970).
3. For a recent review see D. M. Jerina and J. W. Daly, Science, 185, 573 (1974).
4. P. Sims, P. L. Grover, A. Swaisland, K. Pal and A. Hewer, Nature, 252, 326 (1974).
5. A. L. Swaisland, A. Hewer, K. Pal, G. R. Keysell, J. Booth, P. L. Grover and P. Sims, FEBS Letters, 47, 34 (1974).
6. J. W. Cook and R. Schoental, J. Chem. Soc., 170 (1948).
7. Unpublished results, this Laboratory by Dr. S. Chu 1974.
8. S. H. Goh and R. G. Harvey, J. Am. Chem. Soc., 95, 242 (1973).
9. Activated MnO_2 was prepared by the method of Goldman[10].
10. I. M. Goldman, J. Org. Chem., 34, 1979 (1969).
11. J. Fatiadi, Synthesis, 4, 229 (1974).
12. A. S. Dey and J. L. Neumeyer, J. Med, Chem., 17, 1095 (1974) report the use of KBH_4 in alcohol for the reduction of phenanthrene 9,10-quinone to the corresponding trans dihydrodiol We have applied this method to several K-region quinones and have found it far superior to $LiAlH_4$.[13]
13. For typical applications of $LiAlH_4$ in this reduction see J. Booth, E. Boyland, and E. E. Turner, J. Chem. Soc., 1188 (1950) and H. Cho and R. G. Harvey, Tet. Let., 16, 1491 (1974).
14. E. Boyland and P. Sims, Biochem. J., 90 (2), 391 (1964).
15. P. Dansette and D. M. Jerina, J. Am. Chem. Soc., 96, 1224 (1974).
16. M. S. Newman and S. Blum, J. Am. Chem. Soc., 86, 5598 (1964).
17. L. F. Fieser and F. Novello, J. Am. Chem. Soc., 62, 1855 (1940).