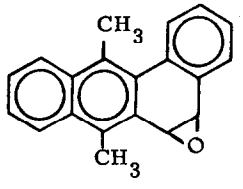
Tetrahedron Letters No. 16, pp 1491 - 1494, 1974. Pergamon Press. Printed in Great Britain.

# SYNTHESIS OF "K-REGION" QUINONES AND ARENE OXIDES OF POLYCYCLIC AROMATIC HYDROCARBONS

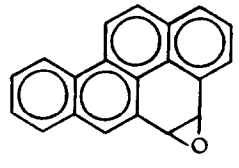
Hee Cho and Ronald G. Harvey*
Ben May Laboratory, University of Chicago
Chicago, Illinois 60637

(Received in USA 19 December 1973; received in UK for publication 5 March 1974)

A new general synthesis of arene oxides recently reported[1] from this laboratory has allowed the synthesis of the previously inaccessible "K-region" oxides (1a, b) of the potent carcinogens 7, 12-dimethylbenz[a]anthracene (7, 12-DMBA) and benzo[a]pyrene[2]. This approach, however, still suffers from the limitation of requiring the use of osmium tetroxide in the initial step. This reagent is both costly and hazardous, affords only moderate yields, and necessitates time-consuming operations in handling the air sensitive products[6]. As a consequence, the quantities of the oxides available for biological studies remain severely limited.



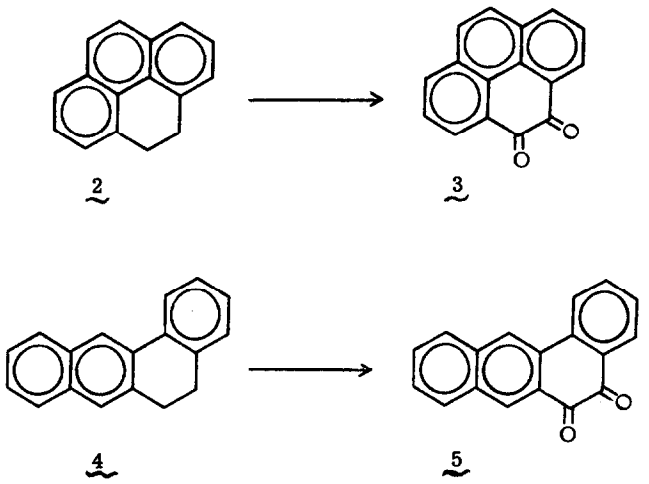

1a




1b

We now report a new synthesis of o-quinones which affords K-region quinones directly from dihydroaromatic precursors, utilizing sodium dichromate in acetic acid-acetic anhydride under mild conditions[7].

Pyrene 4, 5-quinone (3) and benz[a]anthracene 5, 6-quinone (5) were selected for this study because direct oxidation of the corresponding parent hydrocarbons generally affords primarily products of attack elsewhere in the molecule[8]. Also, the previously unknown pyrene 4, 5-oxide is of considerable interest for comparative biochemical studies in vivo and in vitro, because of its close structural relationship to 1b and the noncarcinogenicity of pyrene.



2 3



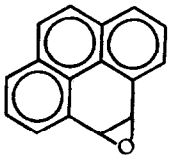
4 5

In a typical procedure, 4, 5-dihydropyrene (2) (2.04g, 10 mmol) dissolved in 50 ml of acetic anhydride-acetic acid (1:1) at 0° was added to a stirred solution of sodium dichromate dihydrate (8g, 26.7 mmol) in an equal volume of the same solvent. The resulting solution was stirred at ambient temperature for 24 hr, then poured into 500 ml of water. The dark greenish brown precipitate was collected on Celite by filtration, washed thoroughly with water, and extracted with hot chloroform (600 ml). The chloroform solution was dried over magnesium sulfate, evaporated to dryness, and chromatographed on silica gel (50g). Elution with $CH_2Cl_2$ gave a red band which afforded 0.58g of essentially pure 3 which upon recrystallization from ethanol-chloroform yielded dark red needles (0.50g), mp 318-320° (lit.[9,11] 310°, 304.5-306.4°), nmr[12] ($CDCl_3$) $\delta$ 7.68 (t, 2, $H_{2,7}$, $J$=7.5 Hz), 7.77 (s, 2, $H_{9,10}$), 8.11 (d of d, 2, $H_{1,8}$, $J$=7.5 Hz and $J$=1.8 Hz), and 8.41 ppm (d of d, 2, $H_{3,6}$, $J$=7.5 Hz and $J$=1.8 Hz). Further elution with 20% ethyl acetate in $CH_2Cl_2$ gave a mixture of the 1, 6- and 3, 6-quinones, as indicated by tlc and nmr analysis in comparison with the authentic compounds. Analogous reaction of 5, 6-dihydrobenz[a]anthracene was conducted in similar manner except that a smaller ratio of the oxidizing agent (4.4g, 14.7 mmol) was employed in order to minimize excessive oxidation. Chromatography afforded 5, 0.56g (22%), red needles from chloroform, mp 260-2° (lit.[10] 260-2°), nmr ($CDCl_3$) singlets at $\delta$8.37 and 8.72, assigned to $H_7$ and $H_{12}$, respectively.

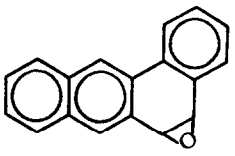
In comparison, direct oxidation of pyrene with the same reagent under comparable conditions afforded principally the 1, 6- and 3, 6-quinones (2:1 by nmr) accompanied by only a minor amount of 3 ( $<$ 2%). Similar direct oxidation of benz[a]anthracene gave the 7, 12-quinone without any detectable quantity (by nmr or tlc) of 5. Thus, pyrene and benz[a]anthracene are not intermediates in the oxidation of their K-region dihydro derivatives to the corresponding o-quinones.

The requisite dihydro compounds 2 and 4 were obtained from the parent aromatic molecules by metal-ammonia reduction[13] and catalytic hydrogenation, respectively. The K-region selectivity of the catalyst employed (6% palladium on strontium carbonate) is quite remarkable and confirms the earlier report[14] of similar regioselectivity in hydrogenation of 7,12-DMBA. Hydrogenation of benz[a]anthracene in ethyl acetate (room temperature, 20-35 psig) for 24 hr gave 4 accompanied by a minor amount of 7,12-dihydrobenz[a]anthracene which was readily removed by taking advantage of its greater ease of oxidation with sodium dichromate. Chromatography on alumina afforded pure 4 as white crystals, mp 96.0-96.5, 75%, nmr ($CCl_4$) $\delta$3.9 (apparent s, 4, benzylic), 7.1-8.1 ppm (m, 10, aromatic)[12].

Finally conversion of the quinones 3 and 5 to the corresponding K-region oxides 6 and 7 was achieved through reduction with $LiAlH_4$ to the related transdiols and cyclization by means of the dimethyacetal of dimethylformamide according to the general procedure[1]. Pyrene 4,5-oxide, obtained as pale yellow crystals from methylene chloride-cyclohexane, exhibited the following properties: mp 180-183° (soften ~139°; decomp); nmr ($CDCl_3$) $\delta$4.83 (s, 2, oxirane-H), 7.8-8.3 ppm (m, 8, aromatic). The physical properties of 7 were in essential agreement with those reported earlier[15].



6



7

Attempts of other investigators to synthesize 6 via the alternative approach of Newman and Blum[15] have been frustrated by failure to obtain the reportedly unstable[16] precursor, phenanthrene 4,5-dicarboxaldehyde in adequate quantity and purity.

The general synthetic approach described herein appears potentially applicable to the majority of polycyclic hydrocarbons having a K-region. This view has thus far been confirmed by related studies currently in progress with other ring systems.

Acknowledgement: Support of this investigation by grants from the American Cancer Society (BC-132 and IN-41) and the US Public Health Service (CA-11,968) are gratefully acknowledged. We also wish to thank Ms. Cecilia Cortez and Leticia Nazareno for valuable technical assistance during the course of this research.

## REFERENCES


1. S.H. Goh and R.G. Harvey, J. Amer. Chem. Soc., 95, 242 (1973).
2. The "K-region", defined as a bond such as the 9, 10-bond of phenanthrene is a common structural feature of carcinogenic polycyclic hydrocarbons. The K-region oxides, suspected to be the metabolically activated form of the carcinogenic hydrocarbons, have been shown to induce "malignant transformation" of cells in culture[3], mutational changes in mammalian cells, bacteriophages, and bacteria, and to bind covalently to nucleic acids and proteins in vivo and in vitro.
3. 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).
4. 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); B.N. Ames, P. Sims, and P.L. Grover, Science, 176, 47 (1972).
5. T. Kuroki, E. Huberman, H. Marquardt, J. Selkirk, C. Heidelberger, P. Grover, and P. Sims, Chem.-Biol. Interactions, 4, 389 (1971-1972); P. Grover, J. Forrester, and P. Sims, Biochem. Pharmacol., 20, 1297, 1302 (1971).
6. Both the intermediate osmate esters and the crude cisdiol products derived from 1a, b decompose in the presence of air. Purification of the latter requires conversion to the more stable diacetates, chromatography, and deacetylation with methanolic ammonia.
7. The established procedure for selective oxidation of alkyl side chains on polycyclic hydrocarbons employs neutral aqueous dichromate at high temperature (250-275°) in an autoclave, D. Lee in "Oxidation", Vol. 1, R.L. Augustine, Ed. Marcel Dekker, Inc., New York, 1969.
8. Only ozone[9] and osmium tetroxide[10], reagents known to proceed via cyclic intermediates, oxidize the "K-region" of pyrene; other agents attack the 1, 3, 6, or 8-positions. Benz[a]anthracene undergoes attack in the 7 and 12 positions by all oxidants except $OsO_4$.
9. H. Vollman, H. Becker, M. Correll, and H. Streeck, Ann., 531, 1 (1973).
10. J. Cook and R. Schoental, J. Chem. Soc., 170 (1948).
11. F. Oberender and J.A. Dixon, J. Org. Chem., 24, 1226 (1959).
12. Proton nmr spectra were obtained on Varian T-60 and Brucker 270 spectrometer; chemical shifts are reported relative to TMS. All new compounds gave satisfactory microanalysis.
13. R.G. Harvey and P.W. Rabideau, Tetrahedron Lett., 3695 (1970).
14. H. Hadler and A. Kryger, J. Org. Chem., 25, 1896 (1960).
15. M.S. Newman and S. Blum, J. Amer. Chem. Soc., 86, 5598 (1964).
16. R. Criegee, E. Hogen, G. Huber, P. Kruck, F. Marktscheffel, and H. Shellenberger, Ann., 599, 81 (1956); M.G. Sturrock and R.A. Duncan, J. Org. Chem., 33, 2149 (1968).