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METABOLITES OF POLYCYCLIC AROMATIC HYDROCARBONS. II. SYNTHESIS OF 7,8-DIHYDROBENZO[a]PYRENE-7,8-DIOL AND 7,8-DIHYDROBENZO[a]PYRENE-7,8-EPOXIDE

Daniel J. McCaustland* and James F. Engel
Midwest Research Institute, Kansas City, Missouri 64110

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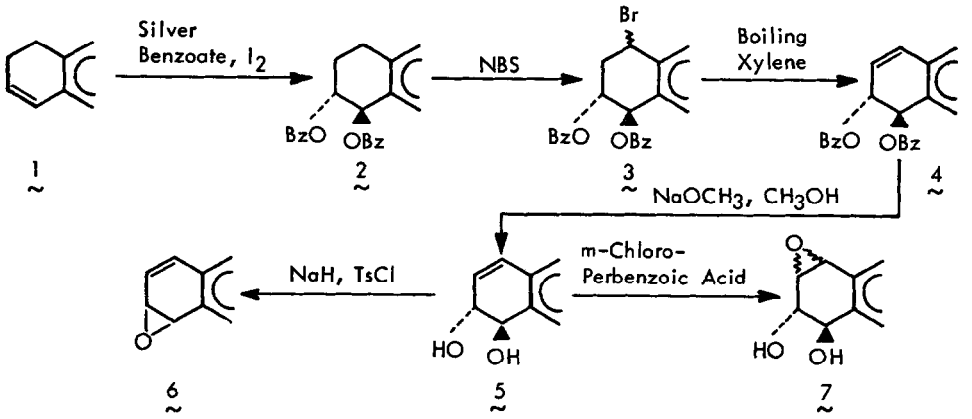
Several lines of evidence exist which implicate arene oxides as the "activated" metabolites responsible for carcinogenesis by polycyclic aromatic hydrocarbons (PAH).[1] However, the picture is not without contradictory aspects and to clarify the relationship between the formation of specific metabolites and the induction of cancer it is desirable to determine a metabolic profile for each PAH and ascertain the biological activity of the respective products. The availability of authentic samples of probable PAH metabolites would seem to be imperative for the success of such studies.

With the exception of K-region derivatives, there is a general lack of methods for the preparation of the interesting but elusive arene oxides and their related trans-dihydrodiols. Therefore, we report a four-step synthesis of trans-7,8-dihydrobenzo[a]pyrene-7,8-diol and a novel preparative conversion of this substance to 7,8-dihydrobenzo[a]pyrene-7,8-epoxide. We believe that this synthesis will be applicable to the preparation of other PAH trans-dihydrodiols and their related epoxides.

7,8-Dihydrobenzo[a]pyrene-7,8-diol and 9,10-dihydrobenzo[a]pyrene-9,10-diol are formed on incubation of benzo[a]pyrene with rat liver homogenate[2] and hamster liver microsomes.[3] Their identity was inferred from their chromatographic behavior, UV spectra, conversion to known phenolic products and mass spectral analysis. The question of their stereochemistry was not addressed. The corresponding 7,8- and 9,10-epoxides have been prepared by Waterfall and Sims[4]

using the dehydrohalogenation route of Vogel and Klärner.[5] The products proved to be too sensitive to permit purification and analytical characterization. They were tentatively identified by their UV spectra, acid-catalyzed rearrangement to the known 7- and 9-hydroxybenzo[a]pyrenes and hydration to dihydrodiols by liver microsomes.

The present synthesis, depicted below, uses the known 9,10-dihydrobenzo[a]pyrene (1) obtained in 65% overall yield from commercially available[6] 9,10-dihydrobenzo[a]pyrene-7(8H)-one by the method of Sims.[7]



This olefin, when reacted with silver benzoate and I_2 in refluxing benzene, gave a 55% yield of a dibenzoate, mp. 215-6° (white needles from acetone). Methanolysis of this diester ($NaOCH_3$ in THF-methanol, 10 min, 60°) afforded the known trans-7,8,9,10-tetrahydrobenzo[a]pyrene-7,8-diol, mp. 237-9° (reported 234-5°). The ir spectrum was identical with that of authentic material.[4] The diester was identified thereby as the trans-7,8,9,10-tetrahydrobenzo[a]pyrene-7,8-diol dibenzoate (2). This diester readily underwent bromination (NBS) to give 70% of trans-10-bromo-7,8,9,10-tetrahydrobenzo[a]pyrene-7,8-diol dibenzoate (3) as yellow needles (benzene), mp. 118° (decomp.). Dehydrobromination of the bromodibenzoate (3) was affected by heat alone. Thus, a solution of (3) in xylene was heated at reflux for 10 min and diluted with acetone. There was obtained a 97% yield of pure trans-7,8,-dihydrobenzo[a]pyrene-7,8-diol dibenzoate (4) as ivory needles, mp. 196-8°. Methanolysis of (4), in the manner described above, yielded 91% of trans-

7,8-dihydrobenzo[a]pyrene-7,8-diol (5) as off-white plates (THF-methanol) mp. 216-7°; ir (nujol) 2.95 μ, 3.10 μ, mass spectrum (70 ev) m/e 286 (parent peak). Anal. Calcd. for $C_{20}H_{14}O_2$ C, 83.90; H, 4.93. Found: C, 83.99; H, 4.88.

The dihydrodiol (5) was converted to the 7,8-epoxide (6) by in situ formation of a monotosylate and cyclization in the presence of NaH in aprotic medium.[8] Thus, a N_2-purged THF solution of the dihydrodiol (5) was added to NaH (4 equiv.) followed by slow addition, at 60°, of tosyl chloride (1 equiv.) in benzene. The product was separated by passing the reaction mixture through a short column of deactivated basic alumina and eluting with THF. 7,8-Dihydrobenzo[a]pyrene-7,8-epoxide (6) was thereby obtained in 52% yield after evaporation of solvent and recrystallization from acetone: buff plates, mp. > 360° (evacuated capillary); Anal. Calcd. for $C_{20}H_{12}O$: C, 89.53; H, 4.51. Found: C, 89.51; H, 4.66; ir (nujol) 8.1 μ, 11.3 μ, 12.0 μ; mass spectrum, (70 ev) m/e 268 (parent peak); nmr (pyridine-d_5) δ4.18 (1, ABMX,H_8), δ4.76 (1, AX,H_7), δ6.54 (1, AMX,H_9), δ7.72 (1, AMX,H_{10}), δ7.82-8.44 (8, m, aromatic H); $J_{7,8}$=4 Hz, $J_{8,9}$=4 Hz, $J_{8,10}$=1.5 Hz, $J_{9,10}$=10 Hz.

The UV spectrum of the epoxide (6) as well as that of the dihydrodiol (5) corresponded closely in peak position and intensity with that of 7,8-dihydrobenzo[a]pyrene. A solution of the epoxide (6) in 50% aq.THF decomposed (36 hr, 25°) to give exclusively 7-hydroxybenzo[a]pyrene (UV,TLC). The same behavior was observed when the solvent medium was adjusted to pH 12.

On treatment with excess m-chloroperbenzoic acid in THF-benzene (36 hr, 25°), the dihydrodiol (5) consumed one equivalent of the reagent with a resulting change of the UV spectrum to one typical of 7,8,9,10-tetrahydrobenzo[a]pyrene. Excess per-acid and m-chlorobenzoic acid were removed by percolating the reaction mixture through a column of silica gel and elution with triethylamine-THF (1:19). On evaporation of the eluate trans-7,8-dihydrobenzo-[a]pyrene-7,8-diol-9,10-epoxide (7) was obtained in 56% yield as fine off-white needles, mp. 214° (evacuated capillary); Anal. Calcd. for $C_{20}H_{14}O_3$; C, 79.45; H, 4.67. Found: C, 79.42; H, 4.76; ir (nujol) 2.88 μ, 2.96 μ, 3.10 μ, 8.0 μ, 11 μ, 12.0 μ; mass spectrum (70 ev) 302

(parent peak); TLC: SiO_2/triethylamine-THF (1:19), R_f 0.5. The stereochemical identity of this material is being investigated. A similar synthesis of this diol-epoxide (^{3}H-labeled) has been described using ^{3}H-labeled 7,8-dihydrodiol prepared by incubation of radiolabeled benzo[a]pyrene with rat liver homogenate.[9] The material was found to bind to DNA in a manner similar to metabolically-activated benzo[a]pyrene. Since no characterization data was given for this material, a comparison with the diol-epoxide reported herein is not possible.

The analogous synthesis of 9,10-dihydrobenzo[a]pyrene-9,10-diol and the corresponding 9,10-epoxide is in progress.

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