Synthesis of Cyclopenta[*cd*]pyrene-3,4-oxide, the Suspected Ultimate Carcinogenic Metabolite of Cyclopenta[*cd*]pyrene

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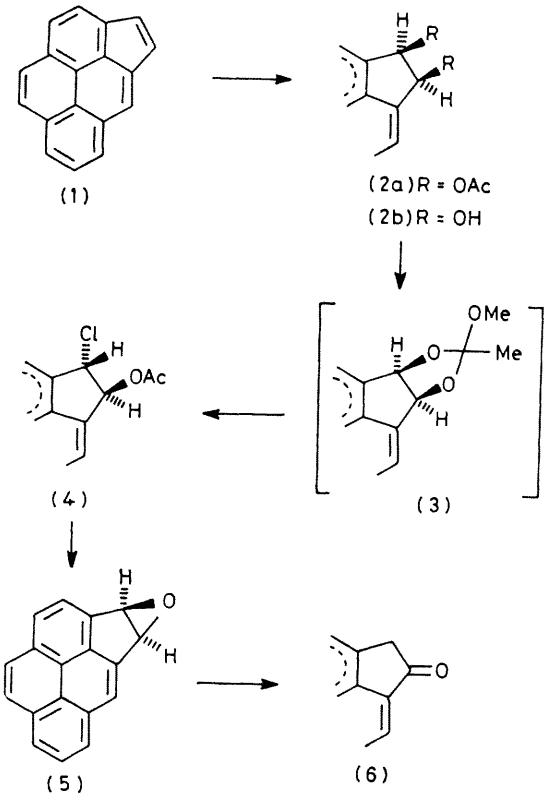
Summary A synthesis of cyclopenta[*cd*]pyrene-3,4-oxide, the suspected ultimate carcinogenic metabolite of the widely distributed environmental carcinogen cyclopenta[*cd*]pyrene, is described

EISENSTADT and GOLD[1] predicted that cyclopenta[*cd*]-pyrene-3,4-oxide (**5**) should be a highly mutagenic metabolite of the environmental carcinogen cyclopenta[*cd*]-pyrene (**1**) These authors observed that opening of the epoxide ring at C(3) would give a benzylic carbonium ion equivalent to that derived from the opening of the epoxide ring in benzo[*a*]pyrene-7,8-dihydrodiol-9,10-oxide, the metabolite which is now believed to be the ultimate carcinogenic form of benzo[*a*]pyrene To permit further exploration of this prediction and other aspects of the metabolism of (**1**), we have undertaken the synthesis of the epoxide (**5**)



The parent hydrocarbon, cyclopenta[*cd*]pyrene, (**1**) was prepared by the method previously described[2] and on treatment with osmium tetroxide in ether or benzene solution, in the presence of pyridine, provided the osmate ester. Decomposition of the ester by the method of LaBudde and Heidelberger[3] provided the *cis*-3,4-dihydrocyclopenta[*cd*]pyrene-3,4-diol diacetate (**2a**) in 65% yield as white needles (acetone); m.p. 198—200 °C; ν_{CO} (Nujol) 1,730, ν_{OCO} 1,250 cm^{-1}; ^{1}H n.m.r. (60 MHz, $CDCl_3$, Me_4Si) δ 7·7—8·2 (m, 8H, aromatic), 6·70 (ABm, 2H, 3-H and 4-H), 2·10 and 2·15 (2 unresolved singlets, 6H, OCOMe). Deacetylation of (**2a**) afforded the corresponding *cis*-3,4-dihydrodiol (**2b**) in a quantitative yield as fibrous white needles [MeOH–tetrahydrofuran (THF)]; m.p. 254—256 °C; ν_{OH} (Nujol) 3,330 and 3 180 cm^{-1}.

The remaining three steps of the synthesis followed the general method of Dansette and Jerina for the synthesis of *K*-region epoxides.[4] Conversion of the diol (**2b**) by reaction with trimethylorthoacetate–benzoic acid gave the dioxolane (**3**). This intermediate was treated directly with chlorotrimethylsilane–triethylamine (CH_2Cl_2, 4 °C, 3—18 h). Removal of solvent and chromatography of the resulting product on neutral alumina with benzene–THF (1 : 1) gave 49% (based on **2b**) of *trans*-3(4)-chloro-3,4-dihydrocyclopenta[*cd*]pyrene-4(3)-ol acetate (**4**)† as pale yellow plates (hexane–benzene); m.p. 123—126 °C; ν_{CO} (Nujol) 1,740, ν_{OCO} 1,230, and ν_{CCl} 780 cm^{-1}; ^{1}H n.m.r. (60 MHz, CCl_4, Me_4Si) δ 7·7—8·2 (m, 8H, aromatic), 6·78 (d, 1H, C*H*OAc), 5·83 (d, 1H, CHCl, $J_{3,4}$ 2 Hz), and 2·14 (s, 3H, OCOMe). Treatment of the chlorohydrin acetate (**4**) with NaOMe in dry THF gave cyclopenta[*cd*]pyrene-3,4-oxide (**5**) in 74% yield as colourless cubes (acetone); m.p. 215 °C decomp.; ^{1}H n.m.r. [200 MHz, $(CD_3)_2CO$, Me_4Si] δ 8·0—8·4 (m, 8H, aromatic) and 5·20 (s, 2H, 3-H and 4-H); *m/e* (70 eV) 242 (M^+, 100%), 226 ($M^+ - 16$, 3%), 214 ($M^+ - 28$, 89%), and 213 ($M^+ - 29$, 76%).[5]

As expected, the epoxide (**5**) was easily rearranged upon warming in benzene in the presence of alumina with opening of the C(3)–O bond to give 3,4-dihydrocyclopenta[*cd*]pyrene-4(3*H*)-one (**6**) as bronze needles (benzene); m.p. 217—219 °C; ν_{CO} 1,715 cm^{-1}.‡

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† In view of the ease of formation of the 1-pyrenyl methyl cation, cleavage of the dioxolane (**3**) at the C(3)–O bond would be expected with the formation of the 3-chloro-4-acetate. However, the alternative substitution cannot be excluded.

‡ The i.r. and u.v. spectra of this ketone (**6**) were markedly different from the known 3,4-dihydrocyclopenta[*cd*]pyrene-3(4*H*)-one. Since submission of this manuscript, an alternative synthesis of the oxide (**5**) has appeared (A. Gold, J. Brewster, and E. Eisenstadt, *J.C.S. Chem. Comm.*, 1979, 903). The reported physical characteristics of (**5**) and its rearrangement product (**6**) are in full agreement with those presented herein.

[1] E. Eisenstadt and A. Gold, *Proc. Nat. Acad. Sci. U.S.A.*, 1978, **75**, 1667.
[2] P. H. Ruehle, D. Fischer, and J. Wiley, Jr., *J.C.S. Chem. Comm.*, 1979, 302.
[3] J. A. LaBudde and C. Heidelberger, *J. Amer. Chem. Soc.*, 1958, **80**, 1225.
[4] P. Dansette and D. M. Jerina, *J. Amer. Chem. Soc.*, 1974, **96**(4), 1224.
[5] D. J. McCaustland, D. L. Fischer, K. C. Kolwyck, W. P. Duncan, J. C. Wiley, Jr., C. S. Menon, J. F. Engel, J. K. Selkirk, and P. P. Roller, *Carcinogenesis Polynuclear Aromatic Hydrocarbons: Chemistry, Metabolism, and Carcinogenesis*, vol. 1, eds. R. I. Freudenthal and P. W. Jones, Raven Press, New York, 1976, 349–411. An $M^+ - 16$ peak of intensity of 3—17%, corresponding to the loss of oxygen from the parent molecular ion, has been found to be a characteristic feature of a number of polynuclear aromatic hydrocarbon oxides. The i.r. spectrum of (**5**) was consistent with the structure. The u.v. spectrum was essentially identical to that of 3,4-dihydrocyclopenta[*cd*]pyrene.