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CYCLOPENTA[c,d]PYRENE

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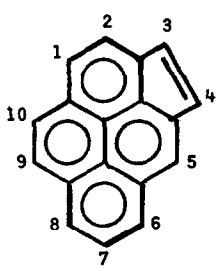
Recently we presented a theory[1] which proposed that the most chemically reactive diol epoxide on a benzo-ring of a polycyclic aromatic hydrocarbon would have the highest biological activity as a mutagen or carcinogen. Studies on benzo[a]pyrene[2], benzo[a]anthracene[3], substituted benzo[a]-anthracenes[4], chrysene[5], and dibenzo[a,h]anthracene[6], have provided support for the predictions of this theory. In addition, Eisenstadt and Gold[7] have shown that the environmental contaminant cyclopenta[c,d]pyrene (1), found in carbon black[8] and automobile exhaust[9], is highly mutagenic on metabolic activation. Our calculations of chemical reactivity[1] provide support for their suggestion[7] that an epoxide at the 3,4-position of 1 could be responsible for the mutagenicity of this hydrocarbon on metabolic activation. Because of the interest in 1, we have sought an improved synthesis[10] in order to make the hydrocarbon and its derivatives more readily available for biological studies.

Two obvious pathways for the synthesis of 1 consist of reduction of ketones 2 or 3 to alcohols followed by dehydration to 1.



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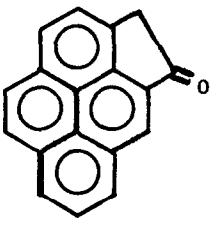

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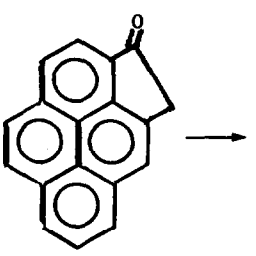

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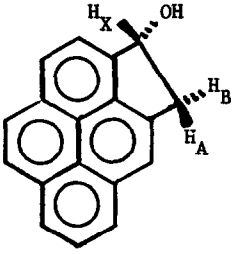

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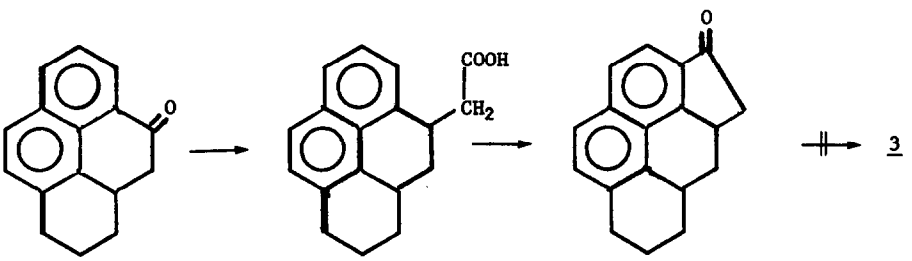
Potential precursors of these ketones are 1-pyrenylacetic acid[11] and 4-pyrenylacetic acid[12], respectively. Since 1-pyrenylacetic acid was readily accessible *via* acetylation of pyrene, cyclization of this acid was attempted first. Interestingly, treatment of 1-pyrenylacetic acid with either polyphosphoric acid at 120°C or with HF at room temperature overnight, or attempted cyclization of 1-pyrenylacetyl chloride with $SnCl_4$ in boiling benzene failed to produce 2. In

each case, dimers and higher oligomers were produced instead of the desired ketone 2. Thus, the combination of poor reactivity toward electrophiles at the K-region of the acid and the strain associated with the formation of the five-membered ring favored intermolecular reaction over cyclization.

Since pyrene itself readily undergoes electrophilic substitution at the 1-position[13], it was hoped that the less accessible 4-pyrenylacetic acid would readily cyclize to ketone 3. Cyclization of the acid or its methyl ester by treatment with liquid HF does produce modest amounts (20%) of the desired ketone 3 along with substantial amounts (45%) of dimer(s) (m/e, M^+ = 514) via intermolecular reaction. Ketone 3 forms slightly yellow crystals from ethanol (mp 201-203°; $\nu_{C=O}$ (CH_2Cl_2) 1705 cm^{-1}; $CH_2(CDCl_3)$ 3.80 ppm). Slow addition of the ester to HF followed by workup prior to complete consumption of the starting material, treatment of the acid with hot polyphosphoric acid, or attempted cyclization of the acid chloride all failed to improve the yield of 3. An alternate route was sought to improve the availability of 3. Ketone 5[14] was converted to acid 6



5 6 7

via Reformatsky reaction with ethyl α-bromoacetate, dehydration, and reduction. In contrast to 4-pyrenylacetic acid, the nonplanar and less rigid acid 6 readily cyclized to the desired ketone 7[15] in high yield (80%). Unfortunately 7 could not be aromatized to 3 either by chloranil in boiling acetic acid or by 10% Pd on carbon in boiling xylene.

Reduction of 3 to the corresponding alcohol 4 (mp 213-215°) with $NaBH_4$ in THF: CH_3OH (1:1) proceeded in essentially quantitative yield. The nmr spectrum of the protons on the five-membered ring of 4 shows a typical ABX spin system; δ($CDCl_3$), 3.59 (dd, 1H, J_{AB} = 17 Hz, J_{AX} = 2 Hz), 4.20 (dd, 1H, J_{BA} = 17 Hz, J_{BX} = 8 Hz), 6.19 (dd, 1H, J_{XB} = 8 Hz, J_{XA} = 2 Hz). Surprisingly, attempted dehydration of 4 (HCl/acetic acid at 100°, boiling formic acid, p-toluene sulphonic acid in boiling benzene invariably lead to an undesired dimer (m/e, M^+ 452) to the virtual complete exclusion of 1. Although such dehydrations are generally quite successful for polycyclic hydrocarbons[16], we have noted that attempts to dehydrate 1-(1- or 4-pyrenyl)-ethanol with acid also produces dimers, polymers, and tars.

Dehydration to 1 was achieved by heating alcohol 4 in a sublimation apparatus (210°/20 mm Hg) Although a considerable amount of dimers and polymers form, only 1 (12% after purification by tlc) along with a similar amount of starting alcohol 4 actually sublime. Storage of an nmr sample of 4 in $CDCl_3$ for several weeks resulted in almost quantitative conversion to 1, presumably due to traces of DCl. The pure hydrocarbon forms orange crystals from hexane (mp 173-175°, lit[7] 174-176°); m/e found 226.0789 calc. 226.0782. The nmr spectrum (CCl_4) of 1 shows a pair of doublets ($J_{3,4}$ = 5 Hz) at 7.36 δ and 7.55 δ due to hydrogens at C-3 and C-4 while the remaining aromatic

hydrogens appear at 8.08 - 8.61 δ. The higher field resonance of the vinyl hydrogens is indicative of the localization of the 3,4-double bond. The synthetic hydrocarbon has a UV spectrum which is essentially identical to that published for material isolated from carbon black.[17] We are presently studying 1 to determine its activity as a carcinogen on mouse skin. The high mutagenicity of 1-pyrenyloxirane[18] and the more than ten fold lower mutagenicity of 4-pyrenyloxirane[19] toward the S. typhimurium tester strain suggest that C-3 would be the primary position of attack by cellular nucleophiles on a 3,4-oxide of 1.

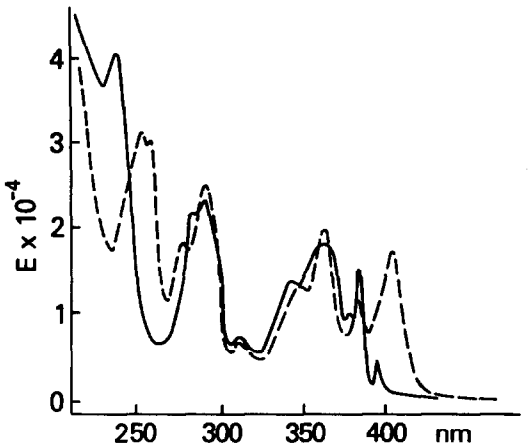


Figure 1. Ultraviolet spectra (hexane) of ketone 3 (----) and cyclopenta[c,d]pyrene (——).

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15. Since 7 could not be converted readily into 3 no effort was made to determine whether 5 (mp 228-230°) and 6 (mp 194-196°) were mixtures of diastereomers. Notably, the methyl ester of 6 can be quantitatively dehydrogenated (10% Pd on carbon, boiling xylene, 2 days) to methyl 4-pyrenylacetate thereby providing a route to this compound which avoids the difficult Wilgerodt reaction.[12]

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