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RELATIVE REACTIVITIES OF PYRENE RING POSITIONS: CYCLOPENTA (cd) PYRENE VIA AN INTRAMOLECULAR FRIEDEL-CRAFTS ACYLATION

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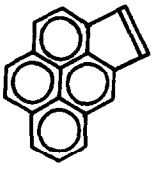
Polycyclic aromatic hydrocarbons are widespread environmental contaminants with human carcinogenic potential (1) whose biological activity requires metabolism to highly reactive epoxides (2). The structural basis for polycyclic aromatic hydrocarbon activity has been the object of intensive studies emphasizing hydrocarbons containing a "bay region" feature (3). The diol epoxides formed adjacent to the bay region appear to be the most active metabolites. We have recently reported (4) that a non-bay region polycyclic aromatic hydrocarbon, cyclopenta (cd) pyrene (I), is a potent bacterial mutagen in the presence of liver metabolizing enzymes. Our studies on the biological activity and metabolism of cyclopenta (cd) pyrene require larger amounts of the compound than are conveniently available by isolation from carbon blacks (4,5) or through the published synthesis (6). A new synthetic route was therefore desirable.

Formation of the cd-fused ring by intramolecular Friedel-Crafts acylation of suitably functionalized pyrene was selected as an approach to the synthesis. Cyclization of 1-pyrenylacetic acid, a readily available (7) candidate for internal Friedel-Crafts condensation, could not be achieved (Fig. 1). The lack of reactivity towards electrophilic substitution at C(4) and the well documented reactivity at both C(1) and C(2) (7-12) may reflect the ordering of PMO delocalization energies ($\Delta E_{deloc.}$) (13) of the carbonium ions resulting from electrophilic attack (Fig. 2).



I

The high reactivity of C(1) towards electrophilic addition leads to the prediction that 4-pyrenylacetic acid will cyclize to 3,4-dihydrocyclopenta (cd) pyren-3-one (II) (Fig. 3). 4-Pyrenylacetic acid was synthesized by a published method (13) with minor modifications. Friedel-Crafts acylation of 1,2,3,6,7,8-hexahydropyrene (9) with acetyl chloride and $AlCl_3$ in

nitromethane (3 hr. at rm. temp.) yielded 4-acyl-1,2,3,6,7,8-hexahydropyrene (84%) after chromatography of the crude reaction mixture in benzene on silica.

Dehydrogenation of 4-acyl-1,2,3,6,7,8-hexahydropyrene with chloranil yielded 4-acetylpyrene (85%) which was converted by Willgerodt oxidation to 4-pyrenylthioacetamide (12). The yield of 4-pyrenylacetic acid (83%) from the thioacetamide was improved (from 34%) by acid hydrolysis of thioacetamide recrystallized from HOAc-chlorobenzene after decolorization with activated carbon: 4-pyrenylthioacetamide (2g) was dissolved in HOAc (30 mL) and after addition of conc. HCl (15 mL), refluxed for 2 hrs. 4-Pyrenylacetic acid precipitated by cooling and dilution with conc. HCl (15 mL) was collected, partitioned between 5% KOH and CH_2Cl_2, reprecipitated by acidification of the aqueous layer and recrystallized from chlorobenzene after decolorization with activated carbon. 4-Pyrenylacetic acid did indeed cyclize to II (Fig. 3): 4-pyrenylacetic acid (0.4g), covered with $SOCl_2$ and one drop of pyridine, was stirred for 1 hr. under N_2. After removal of excess $SOCl_2$ with a stream of N_2, the residue was covered with nitromethane and $AlCl_3$ (0.24g) added. The reaction was stirred 1 hr. at room temperature and then partitioned between H_2O and CH_2Cl_2. The organic layer was extracted with 5% KOH, dried over Na_2SO_4, evaporated and the residue chromatographed on silica. A highly fluorescent yellow band, eluted with benzene, was collected and recrystallized from EtOH to yield II as pale yellow needles (0.065g, 16%), mp 214°; ν_{CO} (KBr) 1701 cm^{-1}; λ_{max} (log ε) (CH_2Cl_2) 395 (4.02), 372 (3,84), 351 (4.06), 340 (sh) (3.88), 284 (4.16), 271 (sh) (4.02), 251 (4.26) nm; mass spectrum, $M^{+\cdot}$ 242 with major fragment at m/e 214 ($M^{+\cdot}$-CO); exact mass of $M^{+\cdot}$ 242.0735 (expected for $C_{18}H_{10}O$,242.0732);NMR($CDCl_3$, 60MHz), singlet (2H) 3.83δ, aromatic multiplet (8H) 7.8-8.58. δ

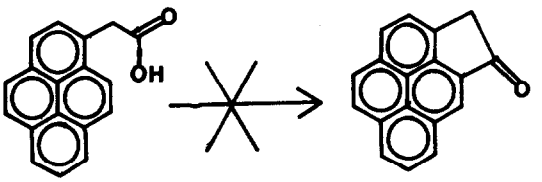


Figure 1

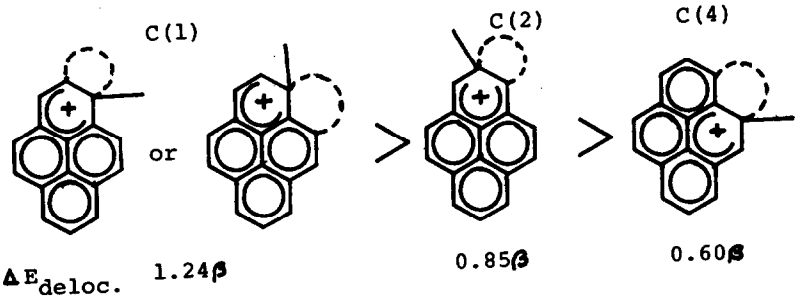


Figure 2

The ketone was quantitatively (by uv) reduced by stirring overnight in Et_2O and hydrolyzing with a small amount of 6N HCl. Pure alcohol (Fig. 3) could not be isolated by evaporation of the Et_2O (because of decomposition induced by HCl in the Et_2O?) but the mass spectrum of the slightly discolored crude alcohol was obtained: M^+ 244, with a base peak at m/e 226 (M^+-H_2O). The peak at m/e 226 is likely to be a fragment resulting from dehydration of the alcohol rather than the molecular ion I because of the absence of the doubly charged molecular ion at m/e 113 which appeared in the mass spectrum of I under identical conditions. Dehydration of the alcohol was accomplished (14) without isolation from the hydrolysis reaction. After addition of benzene to the reaction mixture, the organic layer was separated and dried over Na_2SO_4 and

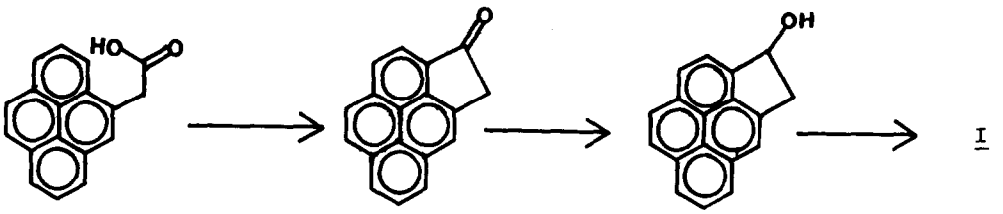


Figure 3

a 10-fold excess (by wt. of II) of 200-mesh basic alumina activity grade I (ICN Pharmaceuticals) was added. The Et_2O was removed by distillation and the reaction refluxed for 2 hrs. Filtration and evaporation of the benzene yielded I (63%) which was pure by the following criteria: mp, 176° (5,6,15); undepressed mixed mp with material from Jacob synthesis (6); uv, mass spectrum, and NMR {($CDCl_3$,60MHz), AB quartet doublets (J=5Hz) (2H) centered at 7.15 and 7.38δ, aromatic multiplet (8H) 7.9-8.3δ}. This route permits the synthesis of relatively large amounts of cyclopenta (cd) pyrene and provides access through the ketone to derivatives of cyclopenta-(cd) pyrene for further studies on the structural basis of polycyclic aromatic hydrocarbon biological activity.

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