BOND ALTERNATION AND MUTAGENICITY OF AZULENOQUINOLINES AND DIAZULENOPYRIDINES

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Many benzenoid aza-arenes have been known to be carcigenic and mutagenic, but the bioactivity of non-benzenoid aza-arenes containing the azulene ring has been uninvestigated. Azulenobenzoquinolines (2 & 3) and diazulenopyridines (4, 5, and 6) have an isoelectronic structure with carcinogenic dibenzacridines. The synthesis, bond alternation, and mutagenicity of azulenoquinolines and diazulenopyridines will be presented. Ullmann coupling of a mixture of activated 2-chloroazulene derivative (I) and arylamines (aryl=phenyl, α- and β-naphthyl) gave the corresponding arylazuleneamines (II) in good yields. Friedel-Craft ring closure of II with PPA afforded pyridone type compounds (III). Upon heating of III with $POCl_3$, aromatization to chloropyridines (IV) was achieved. Finally, dechorination of IV with hydrazine-PtO_2 generated the target compounds (1, 2, and 3). Diazulenopyridines (4, 5, and 6) were also synthesized by using of 2-aminoazulene derivative as a starting material which was coupled with 2-, 1-, or 6-haloazulenes, respectively. The bond alternation of the azulene ring of 1~6 on the basis of the vicinal coupling constants of their NMR spectra increases in a relative order: 4 > 1 > 6 > 2,3 > 5. Mutagenicity of 2, 3, and 4 was tested in Salmonella typhimurium strains TA 98 and TA 100 with and without rat liver S9 mix. All these compounds were inactive without S9 mix. In the presence of S9 mix, 2 [revartant/μg= 8] and 3 [7] were as active as dibenz[c,h]acridine to TA 98, but 4 [19] was more active than it. Compounds 2 [58], 3 [12], 4 [31] were somewhat weaker to TA 100 than dibenz[c,h]acridine [95] and benzo[a]pyrene [80]. The difference between 2 and 3 can be explained by pi-delocalization energy calculated for substitution of CH_2^+ ion at the positions 4 (0.877 β) or 1 (0.796 β) of azulenoquinoline (1).