斑蝥胺素及其類似衍生物合成與活性之研究

Study on the Synthesis and Bioactivities of Cantharidinimides from Cantharidin

中文摘要

斑蝥素(Cantharidin; exo,exo-2,3-Dimethyl-7-oxabicyclo [2,2,1]heptane-2,3-dicarboxylic anhydride)是一個來自昆蟲的天然物。本實驗是以斑蝥素為原料與含一級胺基取代基之化合物包括：diaminobenzene，diaminopyridine，ethanolamine 的衍生物，在鹼性條件下高溫（約 200℃）封管反應兩小時，純化後得到一系列斑蝥胺素之衍生物。

在苯環上的兩個胺基取代可以鄰、間、對的排列方式形成三種位置異構物，另外再加上其它可以對苯環上電子分佈產生不同影響的取代基，例如：拉電子的硝基取代，供電子的氫氧基取代，或產生立體障礙的甲基取代，使得兩個胺基取代的電子密度有所差異，換句話說，也就是其表現出來的鹼性不一樣，所以在反應後的產率上有所不同。首先，使用未含有其它取代的 diaminobenzene 衍生物與斑蝥素反應，結果只有在與 1,3-diaminobenzene 反應後得到有兩個斑蝥胺取代基的產物，化合物 9b (1,3-dicantharidinimidobenzene)，所以推論斑蝥胺取代基在苯環上為拉電子的取代基。另一方面，由產率上的結果來看，可以得知硝基為強力的拉電子基團，會減少鄰位和對位胺基的電子密度比間位多；而氫氧基與胺基是供電子基團，會增加鄰位和對位胺基的電子密度比間位多；甲基取代對反應則只有立體障礙的影響，而且與反應的氨基成鄰位存在下影響最大。在與 diaminopyridine 的衍生物反應時，因為 pyridine 是一個含氮的雜環，氮原子的電負度比碳原子大，會產生拉電子的效應使產率降低；，另一方面，氮原子上的未共用電子對可以經由共振效應增加第二和第四位置的電子密度。在與 ethanolamine 的衍生物反應時，因為 ethanolamine 是一個直鏈的化合物，所以產率只受到立體障礙的影響，當立體障礙越大時，產率也就越低。

合成的斑蝥胺衍生物已由核磁共振儀、紅外線光譜儀、質譜儀和高解析度質譜儀確定結構。此外也利用斑蝥胺的衍生物對人類肝癌細胞 Hep 3B 和 Hep G2，以及血癌細胞 HL-60 的細胞毒性進行測試，結果顯示化合物 20 [N-(2-amino-3-nitrophenyl)cantharidinimide]有較好的抑制作用，但是效果仍未比斑蝥素好。

關鍵字：斑蝥素，斑蝥胺素，抗腫瘤劑

英文摘要

Cantharidin (exo,exo-2,3-Dimethyl-7-oxabicyclo[2,2,1]heptane-2,3-dicar- boxylic anhydride) is an active principle of Lytta caragarae, Mylabris Phalerata and Epicauta gorhami, and exists in various other insect species. We used cantharidin as a starting material by reaction with primary amine ex: diaminobenzene, diaminopyridine, ethanolamine and their derivatives and heating ca. 200°C to give various cantharidinimide derivatives.

The two amino groups attaching to a benzene ring had three kinds of position

isomers ortho, meta, and para. After dehydration and cyclization, cantharidin was converted to cantharidinimides. The inductive effect, resonance effect and steric hindrance effect might reflect the yields. The formation of imide group had electron-withdrawing character influence on benzene ring and displayed a meta activating effect.
Furthermore we used some diaminobenzene with some functional groups, for example, the electron-withdrawing group, NO_2, the electron-donating group, OH, and the methyl group. These functional groups might exert the electron-withdrawing and electron-donating capability with resonance and displayed the different basicity to influence the reaction. Because the results obtained with diaminobenzene derivatives, strongly confirmed the influence of amine nucleophilicity and basicity compared the imide group with other functional groups on the benzene ring. We described that the nitro group is a stronger electron withdrawing and meta activating characters than the imide group, the amino and hydroxy are both electron donating groups and had ortho, para activating characters. The methyl group might have a steric hindrance effect in this reaction. Our results indicated that methyl group at the ortho position of the amino group on the benzene ring, the steric hindrance effect became stronger. Pyridine was a heterocycle compound with one nitrogen atom, and nitrogen atom was more electronegative than the carbon atom, the yields were low. In contrast, the long pair of the nitrogen might increase the electron density at the second and fourth position on pyridine ring via the resonance effect. Ethanolamine derivatives were aliphatic compounds, so the yields of cantharidinimide derivatives were only influenced by steric hindrance effect. The more steric hindrance resulted in the less yields.
All of the cantharidinimide and their derivatives were measured by 1H-NMR, IR, mass spectrometry. Besides, the series of synthetic compounds were tested for their capability to suppress growth of human hepatocellular carcinoma cell line Hep 3B and Hep G2, and myeloid leukemia cell line HL-60. The results showed compound 20, N-(2-amino-3-nitrophenyl)cantharidinimide, exhibited more potent than others, but it was still less effective than cantharidin.
Key words : cantharidin, cantharidinimide, antitumor agent