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论文

肿瘤的化学治疗 XXXII.N-乙酰基-N-{3-[双-(β-氯乙基)-氨基]-6-甲基(或氢)-苯基}-甘氨酸的合成

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摘要:

从3-硝基-6-甲基-苯胺为原料经过六步反应合成了N-乙酰基-N-{3-[双-(β-氯乙基)-氨基]-6-甲基-苯基}-甘氨酸(III_2),并从硝基苯胺以制备III_a相似的步骤合成N-乙酰基-N-{3-[双-(β-氯乙基)-氨基]-苯基}-甘氨酸(III_b)和N-乙酰基-N-{4-[双-(β-氯乙基)-氨基]-苯基}-甘氨酸(III_c).药理试验表明:化合物III_a对小白鼠肉瘤-180有显著的抑制作用,但化合物III_b和III_c无明显作用.III_{a-c}对体外组织培养的Hela瘤细胞都无抑制作用.

关键词:

TUMOUR CHEMOTHERAPY SYNTHESES OF N-ACETYL-N-{3-[BIS-(β-CHLOROETHYL)-AMINO]-6-METHYL-PHENYL}-GLYCINE AND ITS DEMETHYL ANALOGUES

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Abstract:

In a previous paper, it was reported by one of us that bis-[(β-chloroethyl)-amino]- indole-2-carboxylic acids (I_{a-c}) were found to have pronounced antitumour activity. For the purpose of studying the relationships between chemical structures and antitumour acti- vities of I_{a-c} and also of searching for new antitumour agents, in the present paper, N- acetyl-N-{3-[bis-(β-chloroethyl)-amino]-6-methyl-phenyl}-glycine (III_a) has been pre- pared. III_a may be considered as the ring-cleft product of the 6-[bis-(β-chloroethyl)- amino]-indole-2-carboxylic acid (I_b) at the position a. Two demethyl analogues, N-acetyl-N- {3-[bis-(β-chloroethyl)-amino] -phenyl}-glycine (III_b) and N-acetyl-N-{4-[bis- (β-chloroethyl)-amino] -phenyl}-glycine (III_c) have also been prepared and they can also be regarded as the ring-cleft products at the positions a and b of I_a and I_b respectively. Compounds III_{a-b} were prepared by a six-step synthesis, the sequence of reactions is described in the Chinese text. The starting meterials of III_{a-c} employed were ethyl N-(nitro-phenyl)-glycinates (VI_{a-c}) which were conveniently prepared by the condensa- tion of the corresponding nitro-anilines and ethyl chloroacetate or ethyl bromoacetate in the presence of sodium carbonate and sodium iodide in dimethylformamide. VI_{a-c} were acylated with acetic anhydride to give VII_{a-c}, which were subjected to catalytic hydrogena- tion in the presence of Raney-Ni or Pd-C to give N-acetyl-N-(amino-phenyl)-glycinates ($VIII_{a-c}$). The latters were treated with a solution of ethylene oxide in dilute acetic acid to yield N-acetyl-N-[bis-(β-hydroxyethyl)-amino-phenyl]-glycinates (IX_{a-c}) which afforded III_{a-c} on chlorination with phosphorus oxychloride, hydrolysis with 6 N hydro-chloric acid, and acetylation. Pharmacological studies showed that compound III_a possessed marked antitumour activity against Sarcoma-180, but neither III_b nor III_c showed any significant activity against the same tumour.

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