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论文

抗血吸虫病药物的研究 α,ω-双-(对氨基苯氧(硫)基)-烷类及其多羟基衍生物的合成

梁晓天;谢晶曦

中国医学科学院药物研究所

摘要:

1.对乙酰氨基苯酚与1,7-二溴代庚烷,在乙醇钠液中缩合,得1,7-双(对乙酰氨基苯氧基)-庚烷,经稀盐酸水解制得1,7-双(对氨基苯氧基)-庚烷二盐酸盐.2.对乙酰氨基硫酚在硷醇中分别与1,3-二溴代丙烷,1,6-二溴代己烷和1,7-二溴代庚烷缩合,水解就可以分别得到相应的α,ω-双(对氨基苯硫基)-烷二盐酸盐.3.1-氯代甘油及1,3-二溴代甘油与对乙酰氨基苯酚或硫酚缩合,再行水解后,分别获得甘油的1-(对氨基苯基)及1,3-双(对氨基苯基)-醚或其硫代醚.4.1,6-二氯代-2,3-4,5-二亚甲基-D-甘露醇与对乙酰氨基苯酚钠盐,在封闭管中长期加热,可获得2,3-4,5-二亚甲基-D-甘露醇-1,6-双(对乙酰氨基苯)-醚.5.将D-甘露醇做成1,2-3,4-5,6-三异丙基-D-甘露醇,经部分水解成3,4-异丙基化合物,再制成1,6-双(对甲苯磺酰基)-2,5-二乙酰基-3,4-异丙基-D-甘露醇,在乙醇钠溶液中,分别与对乙酰氨基苯酚或硫酚缩合,再经水解,即分别得到D-甘露醇-1,6-双(对氨基苯基)-醚或D-甘露醇-1,6-双(对氨基苯基)硫代醚的双盐酸盐.6.对硝基苯酚与1,4-二溴代-2-丁烯缩合,生成1,4-双(对硝基苯氧基)-2-丁烯,于双键上进行双羟基化,并将硝基还原,得1,4-双(对氨基苯氧基)-2,3-threo-双羟基丁烷二盐酸盐.7.本文报导中的11个化合物,其中除Ⅰ、Ⅴ外,均为未知化合物,用作动物试验,初步结果表明,这些多羟基的氨苯氧(或硫)烷类化合物,对日本住血吸虫病都无效.

关键词:

SYNTHESIS OF α,ω-BIS-(p-AMINOPHENOXY AND p-AMINO-THIOPHENOXY)-ALKANES AND THEIR POLYHYDROXY DERIVATIVES

LIANG XIAO-TIAN XIE JING-XI

Abstract:

Condensation of sodium *p*-acetaminophenoxide with 1,7-dibromoheptane and subsequent hydrolysis gave 1,7-*bis*-(*p*-aminophenoxy)-heptane dihydrochloride(Ⅰ).Condensation of sodium *p*-acetaminothiophenoxide with 1,3-dibromopropane,1,6-dibromohexane or 1,7-dibromoheptane and subsequent hydrolysis gave the dihydrochlorides of the *a,ω*-disubstituted alkanes(Ⅱ, Ⅲ,Ⅳ).Similar treatment of sodium *p*-acetaminophenoxide and its thio derivative with 3-chloro-1,2-propanediol or 1,3-dibromo-2-propanol gave the hydrochloric salts of 3-*p*-ami- nophenoxy-1,2-propanediol(Ⅴ)or 1,3-*bis*-(*p*-aminophenoxy)-2-propanol(Ⅶ)and their thio analogs(Ⅵ,Ⅷ). 1,6-Dichloro-2,3-4,5-bis-methylene-*D*-mannitol upon prolonged heating with sodium *p*-acetaminophenoxide in sealed tubes gave a small yield of the 1,6-diether(Ⅺ).A more convenient route to the 1,6-disubstituted mannitol was as follows.The triisopropylidene derivative of mannitol was partially hydrolyzed to gave the 3,4-isopropylidene derivative which was in turn tosylated at the 1,6-positions and acetylated at the 2,5-positions,giving Ⅻ. Treatment of Ⅻ with sodium *p*-acetaminophenoxide gave the 1,6-diether(ⅩⅢ),with concomittant loss of acetyl groups.Hydrolysis of ⅩⅢ gave ⅩⅣ.Similar treatment of sodium *p*-acetaminothiophenoxide gave the corresponding thio analog(ⅩⅤ). Condensation of sodium *p*-nitrophenoxide with 1,4-dibromo-2-butene gave 1,4-bis-(*p*- nitrophenoxy)-2-butene(ⅩⅥ).Hydroxylation of the double bond and then reduction of the nitro groups gave 1,4-bis-(*p*-aminophenoxy)-2,3-*threo*-dihydroxybutane dihydrochloride (ⅩⅧ). These *p*-aminophenoxy ethers and thioethers were shown to have no therapeutic value against *schistosomiasis japonica* when tested with experimentally infected animals.

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