光學活性衍生劑之製備與混旋胺類之分割

Synthesis of A New Chiral Reagent for Resolution of Enantiomeric Amines

中文摘要

GITC (2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate) 是一種光學分割衍生劑, 曾被用於許多混旋性胺類化合物光學分割的研究. 這些硫代尿素類 (thiou- reas) 的衍生物在高效液相層析管中有很好的解析度, 並可於紫外光 254 nm 檢測. 但 GITC 生成衍生應用上最大的缺點是如果胺類化合物若不具或僅有微弱的發色團時 ,尤其是於低濃度的生物檢品, 其靈敏度不夠而無法偵測到. 本實驗室擬合成一種新的具有螢光的光學分割衍生劑 ,[6-O-(4'-methylcoumarin-7'-methoxycarbonyl)-2,3,4-triacetyl]-α- D-glucopyranosyl isothiocyanate 簡稱爲 CGIT, 本試劑是將一具有螢光的香豆素化合物(coumarin) 接到葡萄糖的分子上而形成的化合物. 即由 7-[(chlorocarbonyl)methoxy]- 4-methylcoumarin (CMMC) 與 1,2,3,4-O-tetraacetyl-β-D-glucopyranose 反應後,再與氫溴酸反應形成 glucopyranosyl bromide 衍生物,該衍生物再與 silver isothiocyanate 反應, 即可生成本試劑 CGIT. CGIT 可與第一、二級的胺類化合物在氯仿或氯甲烷溶液中反應形成衍生物, 而胺基酸則需要在百分之五十的氯甲烷水溶液及三乙胺的鹼性條件下與 CGIT 反應形成衍生物 .CGIT 與各種混旋性的第一、二級胺類或胺基酸反應, 形成 diastereoisomeric 的 thiourea 衍生物, 這些衍生物在高效液相層析管中有很好的分離度 (α), 例如混旋的 ketamine 之 CGIT 衍生物之分離度爲 α=1.47, 十七種混旋的胺基酸之 CGIT 衍生物除絲胺酸爲 α=1.05 外, 其餘十六種胺基酸衍生物之分離度都在 α=1.10-1.36 之間, 八種混旋的 adrenergic β-blockers 之 CGIT 衍生物之分離度在 α=1.19-1.38 之間 ,以及四種混旋的 phenethylamines 包括目前正在國內濫用的甲基安非他命在內的 CGIT 衍生物之分離度在 α=1.07-1.17 之間. 在純品中, 比較相同的第一、二級混旋性的胺類或胺基酸的 CGIT 及 GITC 衍生物兩者在高效液相層析管之最大靈敏度, CGIT 衍生物之靈敏度比 GITC 衍生物之靈敏度高 10-36 倍之間.

英文摘要

GITC (2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate), a chiral derivatizing agennt is widely used to resolve racemic amines. Good resolution of the

diastereoisomeric thioureas derivatives is generally achieved by HPLC via detection by UV at 254 nm. The major drawback of GITC is that its derivati- ves with amines of weak chromophores are not sensitive enough to be detected in low concentrations in biological samples. We like to report here the synthesis of a new fluorescent chiral derivatizing agent, [6-O-(4'-methylcoumarin-7'-met- hoxycarbonyl)-2,3,4-triacetyl]-α -D-glucopyranosyl isothiocyanate(10)(CGIT) by incopration of a fluorescent moeity into glucose molecule. CGIT was prepare by reaction of 7-[(chlorocarbonyl)methoxy]-4-methylcoumarin(7)(CMMC) with 1,2,3,4- O-tetraacetyl-β-D-glucopyranose (4) and then reacted with hydrobromic acid to afford the glucopyranosyl bromide (9). Subsequent reaction with silver isothio- cyanate yielded the chiral reagent, CGIT (10). Derivatization was performed by reaction of CGIT with primary or secondary amines in chloroform or acetonitrile . The amino acids were reacted in 50% aqueous acetonitrile in the presence of triethylamine. Good separation of seventeen racemic amino acids (α=1.05-1.36), ketamine (α=1.47), eight adrenergic β-blockers (α=1.19-1.38) and four phene- thylamines(α =1.07-1.17) were observed after derivatization with CGIT in liquid chromatography. Comparison of the detection limits of each enantiomeric amine after derivatization with CGIT and GITC. The detection limit of CGIT derivatives were 10-36 times more sensitive than those of GITC derivatives.