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4-TRIFLUOROACETAMIDOBENZOTRIAZOLE N_2-2,3,4-TRI-O-ACETYL-β-D-RIBOPYRANOSIDE

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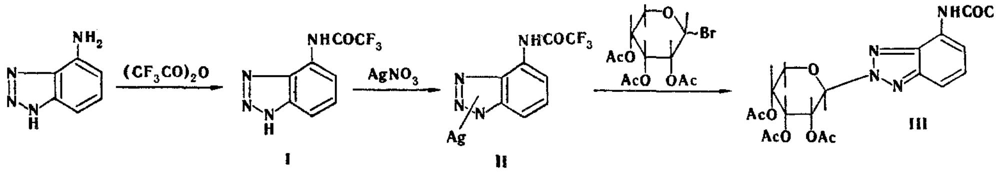
4-Trifluoroacetamidobenzotriazole (I) was synthesized by acylation of 4-aminobenzotriazole with trifluoroacetic anhydride under mild conditions in pyridine. The silver salt (II) of I was obtained by treatment of base I with an aqueous alcohol solution of $AgNO_3$. Condensation of silver salt II with 1-bromo-2,3,4-tri-O-acetyl-D-ribopyranoside leads to 4-trifluoroacetamidobenzotriazole N_2-2,3,4-tri-O-acetyl-β-D-ribopyranoside (III). The structure of nucleoside III was confirmed by its IR, UV, and PMR spectra.

Some benzotriazole derivatives – synthetic analogs of nucleosides – display antitumorigenic activity [1,2]. Up until now, 4-trifluoroacetamidobenzotriazole and nucleosides based on it were unknown.

4-Trifluoroacetamidobenzotriazole (I) was synthesized by acylation of 4-aminobenzotriazole with trifluoroacetic anhydride under mild conditions in pyridine. The silver salt (II) of base I was obtained by the action of an aqueous solution of silver nitrate on an alcohol solution of base I. Alkylation at the nitrogen atom of the 4-trifluoroacetamido group does not occur in the condensation of silver salt II with 1-bromo-2,3,4-tri-O-acetyl-D-ribopyranoside in toluene; this may evidently be due to the considerable deactivating effect of the strong electron-acceptor CF_3 group (σ_I 0.41 and σ_R 0.10) and p–π conjugation of the nitrogen atom with the oxygen atom of the adjacent carbonyl group. 4-Trifluoroacetamidobenzotriazole N_2-2,3,4-tri-O-acetyl-β-D-ribopyranoside (III) is therefore formed as a result of the reaction.



Completely protected nucleoside III gives one spot as a result of chromatography in various solvent systems and has an R_f value of 0.87 (Silufol UV-254). The IR spectrum displays the characteristic frequency of the vibration of the CF_3CONH group at 1715 cm^{-1} [3].

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Our previous study [4] showed that N_1- and N_2-methylbenzotriazoles differ substantially with respect to their UV spectra in ethanol. A substantial difference in the UV spectra in ethanol is also characteristic for N_1- and N_2-glycosylbenzotriazoles. Thus in ethanol N_1-glycosylbenzotriazoles absorb at 250-255 nm, whereas longer-wave absorption at 280-290 nm is characteristic for the N_2 isomers. The formation of N_3 isomers has not been observed [1]. The III nucleoside synthesized in the present research has an absorption maximum in ethanol at 276 nm and a small shoulder at 287 nm (log ε 4.13 and 4.06, respectively). This constitutes evidence for glycosylation at the N_2 position of 4-trifluoroacetamidobenzotriazole.

The β configuration of the glycoside residue in nucleoside III was established from the PMR spectrum, which contains a doublet of an anomeric proton with a chemical shift of δ 5.84 ppm and a J_{1a2a} constant of 8.9 Hz; this is characteristic for an axial hydrogen attached to the glycoside center of β-nucleosides [5].

EXPERIMENTAL

Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in n-butanol – ethanol – water (13 : 8 : 4) and in n-butanol saturated with water at 20°C; the chromatograms were developed in UV light.

The UV spectrum of the compound in ethanol was recorded with a Specord UV-vis spectrophotometer. The IR spectrum of a KBr pellet of the compound was recorded with a Specord 75 spectrometer. The NMR spectrum of a solution of the compound in perfluoropyridine was recorded with a Tesla BS-487B spectrometer at 40°C with tetramethylsilane as the external standard.

All of the evaporations were carried out in the vacuum provided by a water aspirator at temperatures no higher than 30°C.

4-Trifluoroacetamidobenzotriazole (I). A 0.3-ml (2 mmole) sample of trifluoroacetic anhydride was added dropwise with stirring at −15°C to a solution of 0.27 g (2 mmole) of 4-aminobenzotriazole in 7.5 ml of anhydrous pyridine, and the mixture was then allowed to warm up to 20°C and allowed to stand overnight at this temperature. The pyridine was then removed by vacuum distillation, and the residue was extracted with ether (three 30-ml portions). The ether was removed by vacuum distillation, and the residual oil was treated with 2.5 ml of cold water and triturated in a porcelain dish until it began to crystallize. The crystals were removed by filtration, washed with cold water (three 1-ml portions), and dried in vacuo over P_2O_5 to give 0.4 g (83%) of a product with mp 193-194°C (from ether with hexane). The IR spectrum displayed the frequency of the vibration of a CF_3CONH group at 1715 cm^{-1} [3]. Found: C 41.9; H 2.3; F 24.7; N 24.0%. $C_8H_5F_3N_4O$. Calculated: C 41.7; H 2.2; F 24.8; N 24.3%.

4-Trifluoroacetamidobenzotriazole Silver Salt (II). A solution of 0.34 g (2 mmole) of $AgNO_3$ in 2 ml of aqueous ethanol (1 : 1) was added with stirring at 20°C to a solution of 0.46 g (2 mmole) of base I in 5 ml of ethanol, and the mixture was allowed to stand in the dark at 10°C for 12 h. The resulting precipitate was removed by filtration and dried in vacuo over P_2O_5 at 20°C and in vacuo at 0.008 mm and 75°C for 3 h to give 0.6 g (90%) of a product with mp > 345°C. Found: F 16.5%. $C_8H_4AgF_3N_4O$. Calculated: F 16.9%.

4-Trifluoroacetamidobenzotriazole N_2-2,3,4-Tri-O-acetyl-β-D-ribopyranoside (III). A 0.34-g (1 mmole) sample of tetraacetyl-D-ribopyranoside was dissolved in 1.8 ml of a 45% solution of anhydrous HBr in anhydrous acetic acid, and the mixture was allowed to stand in the dark for 90 min with protection against the entry of air moisture by means of a calcium chloride tube filled with glass wool and P_2O_5. The acetic acid and HBr were carefully removed by vacuum distillation, and the resulting syrup was dissolved rapidly in 15 ml of anhydrous toluene, after which the solvent was removed by distillation. This operation was repeated three times to completely remove traces of acetic acid. The residue was then dissolved in 15 ml of anhydrous toluene, and the solution was added at 80°C with stirring to a suspension of 0.34 g (1 mmole) of salt II in 30 ml of anhydrous toluene. The mixture was stirred at 80°C for 2 h, after which it was cooled and allowed to stand overnight. The precipitated AgBr was removed by filtration, and the toluene was carefully removed by vacuum distillation. The residue was dissolved in dichloroethane, pentane was added, and the mixture was stirred as the solvents were removed by vacuum distillation, during which foaming of the residue was observed. The yield of III, with mp 71-72°C (from aqueous acetone), was 0.35 g (78%). IR spectrum: ν_{CF_3CONH} 1715; $\nu_{arom\ C\text{-}H}$ 3070, 2995; $\nu_{C\text{-}O\text{-}C}$ 1230 cm^{-1}. UV spectrum (in ethanol), λ_{max} (log ε): 276 (4.13) and 287 nm (4.06). Found: C 46.7; H 4.0; F 11.9; N 11.6%. $C_{19}H_{19}F_3N_4O_8$. Calculated: C 46.7; H 3.9; F 11.7; N 11.5%.

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