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A NEW METHOD FOR THE PREPARATION OF N-(NUCLEOSIDYL)-α-AMINO ACIDS USING TRIOCTYLMETHYLAMMONIUM SALTS OF α-AMINO ACIDS

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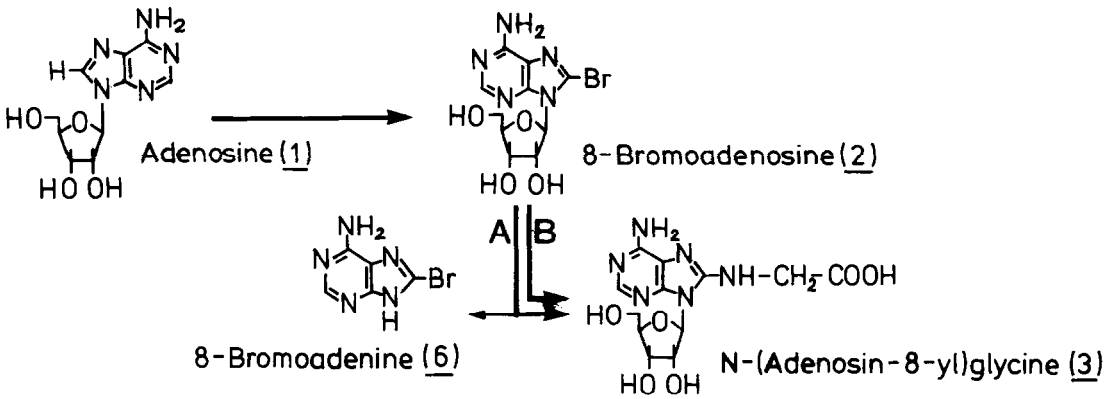
8-Bromoadenosine reacts with trioctylmethylammonium salts of α-amino acids (e.g. glycine) to yield N-(adenosin-8-yl)-α-amino acids which can be readily separated from the starting material by two subsequent extraction steps at different pH values.

N-(nucleosidyl)-α-amino acids play an important part in biological chemistry. N-(Inosin-2-yl)-L-alanine has been found in Fusarium species[1], while [N-(nebularin-6-yl)carbamoyl]--L-threonine is a constituent of the modified nucleosides in tRNA[2]. N-(Adenosin-8-yl)-L-valine acts as an α-amino acid analogue which can inhibit the binding of valine to valyl-tRNA synthetase from yeast[3].

N-(Nucleosidyl)-α-amino acids are prepared by nucleophilic attack of the α-amino group of an α-amino acid on the corresponding halogeno or methylthio substituted nucleoside[4]. The reaction product is usually isolated by anion-exchange chromatography because the recrystallization of these compounds is extremely difficult[5]. In the purine ring system a substituent with an unshared pair of electrons (electron donor) at C-6 (e.g. $-NH_2$, -NHR, $-NR_2$ with R = Alkyl) increases the electron density at C-8[6] so the H-8 can very easily be substituted by a convenient electrophile e.g. bromine. On the other hand, the velocity of a S_{NAr} reaction at this carbon atom is decreased. Therefore it has been suggested that in such ring systems a bromine atom at C-8 cannot be substituted by an α-amino acid or a similar weak nucleophile[7]. Initially we attempted such a synthesis by reaction of 8-bromoadenosine (2) with a twofold excess of sodium glycinate at 120°C in dimethylsulfoxide, for 28 h (A). The main difficulty in this step is the low solubility of sodium glycinate in dimethylsulfoxide. N-(adenosin-8-yl)glycine (3)[8] was formed in a 20% yield as estimated by thin layer chromatography[9]. Additionally unreacted 8-bromoadenosine (2) and 8-bromoadenine (6) were found, when the reaction mixture was chromatographed on a diethylaminoethyl-cellulose (DEAE A 25) column with a triethylammonium bicarbonate (TEA) gradient. N-(Adenosin-8-yl)-L-alanine (4) and N-(adenosin-8-yl)-L-valine (5) could be prepared and purified in an analogous way[10].

Trioctylmethylammonium chloride (Adogen[11]) is a potent phase transfer reagent[12]. Because of this we prepared the trioctylmethylammonium salt of glycine by extraction of a mixture of Adogen and glycine in water/n-propanol with chloroform at pH 11. The product was a yellow oil which dissolved readily in toluene and other non polar solvents. The substance gave a positive Ninhydrin test and could be used without further purification. A five fold excess of trioctylmethylammonium glycinate over 8-bromoadenosine (2) gave after 12 h in dimethylsulfoxide at 105°C N-(adenosin-8-yl)glycine (3) in 60 % yield (as estimated by thin layer

chromatography)[9] (B); no byproducts could be detected. Water was added and the trioctylmethylammonium salt of (3) could be extracted with chloroform from the aqueous phase at pH 6 when the heterocyclic amino groups are not protonated. 8-Bromoadenosine (2), the unreacted trioctylmethylammonium glycinate, which is protonated at this pH, and dimethylsulfoxide remained in the aqueous phase. The organic phase was shaken vigorously with 25% aqueous ammonia to convert the trioctylmethylammonium salt of (3) into the ammonium salt which is soluble in water. After evaporation of excess ammonia and water N-(adenosin-8-yl)glycine (3)[8] could be purified by recrystallization.



With this method even the rather unreactive 8-bromoadenosine (2) does react with the amino groups of amino acids in satisfactory yield. Thus, this method may be extended to other convenient substituted nucleosides, providing a general synthesis for N-(nucleosidyl)-amino acids.

References and Notes

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8. N-(adenosin-8-yl)glycine (3): UV spectrum λ_{max} = 278.5 nm, ε = 18214 (pH 1); elemental analysis - found : C 42.22 %, H 4.61 %, N 25.93 %, calculated for $C_{12}H_{16}N_6O_6$: C 42.20 %, H 4.7 %, N 24.6 %.
^1H NMR (100 MHz DMSO-d_6) δ 7.94, 1 H, s, 2-H; 6.52, 2 H, s, 6-NH_2; 5.9, 1 H, d, 1'-H; 4.76, 1 H, t, 2'-H; 4.14, 1 H, m, 3'-H; 4.04, 1 H, m, 4'-H; 3.66, 2 H, d, 5'-H, 3.18, 2 H, s (-CH_2- of glycine).
The compounds synthesized according to (A) and (B) were identical by thin layer chromatography, UV spectra and elemental analysis.
9. Thin layer chromatography was performed using DC-Mikrokarten SI-F purchased from RIEDEL DE HAEN, Seelze (FRG) with chloroform : methanol : 25 % aqueous ammonia (7 : 3 : 1) (v/v/v) as an eluent.
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11. Adogen was purchased from SERVA, Heidelberg (FRG), another trade name is Aliquat 336.
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