FORMATION OF (9-ADENINYL)-ω-CYANOALKANES FROM (9-ADENINYL)-α-AMINO ACIDS

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Elimination of CO_2 and oxidation of the amino group of the amino acid to give the corresponding (9-adeninyl)-ω-cyanoalkanes occur under the conditions of bromination of (9-adeninyl)-α-amino acids in both alkaline and buffer solutions.

In the development of our research on the chemical properties of nucleoamino acids [1] it seemed of interest of obtain (8-bromo-9-purinyl)-α-amino acids, which would subsequently make it possible to synthesize a number of 8-substituted (9-purinyl)-α-amino acids with various substituents in the 8 position of the purine ring, including 8-mercapto and 8-amino derivatives.

The literature contains data on the successful bromination of adenosine derivatives in the 8 position with bromine in glacial acetic acid [2], with bromine water in an alkaline medium or in a buffer solution [3,] and with N-bromoacetamide in chloroform [2].

We have established that a compound that does not give the color reaction with ninhydrin that is characteristic for amino acids is formed after a few minutes at room temperature in the bromination of (9-adeninyl)-α-amino acids [4] with bromine water in an acetate buffer solution or in an alkaline medium.

The same compounds are obtained in the bromination of (9-adeninyl)-α-amino acids with bromine in glacial acetic acid, except that the reaction is considerably slower. Absorption at 258 and 260 nm, respectively, which is characteristic for 9-substituted adenines, is observed in the UV spectra of the compounds that we obtained (in 0.1 N HCl and 0.1 N NaOH solution), but the absorption at 262-265 nm that is characteristic for 9-substituted 8-bromoadenines is absent. The IR spectra do not contain a band of asymmetrical stretching vibrations of the carboxylate ion at 1590 cm^{-1}, but an absorption band at 2250 cm^{-1}, which is characteristic for the stretching vibrations of C≡N bonds, does appear. An analysis of the PMR spectra confirms retention of the purine ring. A singlet signal at 8.3 ppm, which, according to the integral curve, corresponds to two protons (2- and 8-H), is observed in the PMR spectra of the compounds obtained. This constitutes evidence that the 8-H proton was not replaced by halogen. A singlet signal, which is related to two protons of the 6-amino group, is observed at 7.4 ppm. A multiplet due to a CH_2—CH_2 fragment is observed at 2-4.5 ppm.

Starting from these facts, it may be assumed that 9-ω-cyanoalkyl derivatives of adenine are formed from (9-adeninyl)-α-amino acids under the given bromination conditions.

To confirm this assumption we also obtained 9-(β-cyanoethyl)adenine by alternative synthesis by the addition of acrylonitrile to adenine by the method described in [5] and compared the chromatographic and spectroscopic properties with those of IIb: The IR spectra of the two compounds are identical, the chromatographic data in five systems coincided, and the mass spectra of both compounds contain a peak of molecular ions with m/z 188, the fragmentation of which proceeds with splitting out of the aliphatic chain. Subsequent fragmentation leads to destruction of the adenine ring with the elimination of three molecules of HCN, as in [6].

The structure of II was also proved by acid hydrolysis; the IR spectra of the hydrolysis products do not contain an absorption band at 2250 cm^{-1}, but an absorption band at 1720 cm^{-1}, which is characteristic for the stretching vibrations of the carbonyl group of carboxylic acids, does appear in the spectra.

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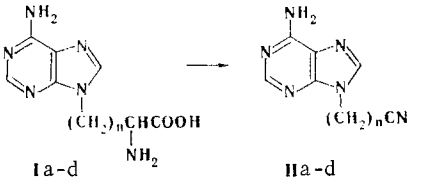
Thus we have established that (9-adeninyl)-α-amino acids readily form the corresponding 9-(ω-cyanoalkyl) derivatives of adenine under the conditions of bromination in both buffer solutions and in an alkaline medium.



Ia-d IIa-d

a n=1; b n=2; c n=3; d n=4

The literature contains data that indicate that α-amino acids give the corresponding nitriles when they are treated with N-bromosuccinimide (NBS) in aqueous solution [7]; in addition, it is known that histidine forms cyanomethylimidazole when it is treated with sodium hypochlorite [8].

Our studies showed that α-amino acids such as tryptophan, α-alanine, and histidine do not form nitriles when they are treated with bromine water in an acetate buffer or with bromine in glacial acetic acid, i.e., under the conditions of bromination of 9-adeninyl-α-amino acids. Under similar conditions 1-uracilyl-α-alanine is brominated in the 5 position of the uracil ring [9]. In the case of 9-adeninyl-α-amino acids under the influence of brominating agents oxidation of the amino group of the amino acid to the nitrile with splitting out of the carboxy group occurs more rapidly than bromination in the 8 position.

It should be noted that in the bromination of (9-adeninyl)propionic acid under similar conditions the reaction proceeds smoothly, and the previously undescribed (8-bromo-9-adeninyl)-propionic acid (III) is formed in good yield.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in 0.1 N HCl and 0.1 N NaOH were recorded with a Spectramom-204 spectrophotometer. The PMR spectra of solutions of the compounds in d_6-DMSO were recorded with a Bruker spectrometer (90 MHz) with hexamethyldisiloxane as the internal standard. The mass spectrum was recorded with an MS-50 AEI spectrometer with direct introduction of the sample into the ion source at an ionizing-electron energy of 70 eV and an ionization-chamber temperature of 300°C. The individuality of the compounds obtained was monitored by means of thin-layer chromatography (TLC) on Silufol UV-254 plates in the following systems: 1) butanol—acetic acid—water (6:2:2), 2) 2-propanol—25% ammonium hydroxide—water (7:1:2), and 3) water. The substances were detected on the chromatograms from the absorption in UV beams.

9-(Cyanomethyl)adenine (IIa). A solution of 0.1 ml of bromine in 10 ml of water was added with stirring at 20°C to a solution of 0.24 g (0.001 mole) of β-(9-adeninyl)-α-alanine in 7 ml of 0.5 M acetate buffer, and the resulting precipitate was removed by filtration and recrystallized from water to give 0.15 g (86%) of a product with mp >350°C and R_f 0.47 (system 1), 0.83 (system 2), and 0.47 (system 3). UV spectrum, λ_{max}: 258 (pH 1) and 260 nm (pH 13). PMR spectrum: 8.23 (2H, s, 2-H, 8-H), 7.38 (2H, s, 6-NH_2), and 5.43 ppm (2H, s, CH_2). Found: C 48.5; H 3.7; N 47.8%; M^+ 174. $C_7H_6N_6$. Calculated: C 48.3; H 3.5; N 48.2%; M 174.

9-(β-Cyanoethyl)adenine (IIb). This compound was obtained in 63% yield by the method used to prepare IIa and had mp 245-247°C [5] and R_f 0.38 (system 1), 0.81 (system 2), and 0.32 (system 3). UV spectrum, λ_{max}: 257 (pH 1) and 261 nm (pH 13). PMR spectrum: 8.16, 8.19 (2H, s, 2-H, 8-H), 7.26 (2H, s, 6-NH_2), 4.43 (2H, t, CH_2), 3.09 ppm (2H, t, CH_2). Found: C 50.9; H 4.2; N 44.0%; M^+ 188. $C_8H_8N_6$. Found: C 51.1; H 4.3; N 44.7%; M 188.

9-(γ-Cyanopropyl)adenine (IIc). This compound was obtained in 61% yield from amino acid Ic by the method used to prepare IIa and had mp 197-199°C [10] and R_f 0.34 (system 1), 0.86 (system 2), and 0.20 (system 3). UV spectrum, λ_{max}: 257 (pH 1) and 260 nm (pH 13). PMR spectrum: 8.12 (2H, s, 2-H, 8-H), 7.18 (2H, s, 6-NH_2), 4.24 (2H, t, CH_2), 2.53 (2H, t, CH_2), and 2.12 ppm (2H, dd, CH_2). Found: C 53.9; H 5.0; N 41.8%. $C_9H_{10}N_6$. Calculated: C 53.4; H 5.0; N 41.6%.

9-(δ-Cyanobutyl)adenine (IId). This compound was obtained in 70% yield from amino acid Id by the method used to prepare IIa and had mp 185°C and R_f 0.54 (system 1), 0.86 (system 2),

and 0.15 (system 3). UV spectrum, λ_{max}: 258 (pH 1) and 262 nm (pH 13). Found: C 55.8; H 5.6; N 39.3%. $C_{10}H_{12}N_6$. Calculated: C 55.5; H 5.6; N 38.9%.

8-Bromo-9-(β-carboxyethyl)adenine (III). A 0.21-g (0.001 mole) sample of 9-(β-carboxylethyl)adenine was dissolved by heating in 20 ml of 0.5 M acetate buffer, and the solution was cooled to 20°C and treated with stirring with a solution of 0.3 ml of bromine in 30 ml of water. The precipitate was removed by filtration and recrystallized from dilute ammonium hydroxide to give 0.15 g (52%) of a product with mp >350°C and R_f 0.58 (system 1), 0.68 (system 2), and 0.83 (system 3). UV spectrum, λ_{max}: 264 (pH 1) and 268 nm (pH 13). PMR spectrum: 8.12 (1H, s, 2-H), 7.38 (2H, s, 6-NH_2), 4.32 (2H, t, CH_2), and 2.81 ppm (2H, t, CH_2). Found: C 33.9; H 3.0; N 24.7%. $C_8H_8BrN_5O_2$. Calculated: C 33.6; H 2.8; N 24.5%.

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SYNTHESIS OF BIFUNCTIONALLY MODIFIED HEXOFURANOSIDES OF THYMINE AND URACIL

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The glycosylation of bis(trimethylsilyl) derivatives of uracil and thymine by bifunctionally modified derivatives of D-glucofuranose in the presence of $SnCl_4$ as the condensing agent was studied. It is shown that the β anomers of D-glucofuranose derivatives with a 1,2-trans orientation of the OAc groups undergo condensation more readily than the α anomers. Both anomers give a mixture of α and β nucleosides with significant preponderance of the latter due to the primary formation of a 1,2-acetoxonium ion. It is assumed that the formation of α nucleosides is due to the competitive coparticipation of other groups and/or more remote acetyl groups.

It has been previously shown that the introduction of a reactive functional group (a halogen atom [1, 2] or a p-tolylsulfonyl group [3]) in the carbohydrate fragment of a nucleoside molecule opens up great possibilities for the preparation of diverse modified nucleosides. In the present research we studied the glycosylation of bis(trimethylsilyl) derivatives of uracil (Ia) and thymine (Ib) by means of bifunctionally modified D-glucofuranose derivatives in the presence of $SnCl_4$ as the condensing agent.

We selected 5-O-acetyl-6-chloro-6-deoxy-1,2-O-isopropylidene-3-O-(p-tolylsulfonyl)-α-D-glucofuranose (II) [4] as a readily accessible bifunctionally modified carbohydrate component. Azide IIIa was obtained in 66% yield by treatment of II with sodium azide in anhydrous dimethylformamide (DMF) at 100°C for 35 h. According to the results of thin-layer chromato-

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