Synthesis and Physical Properties of *N*-2-Phenylethyl- and *N*-2-(3-Indolyl)ethyl-5′-deoxy-5′-adenosineacetamides

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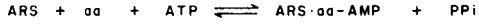
Received June 20, 1983

The synthesis and physical properties of *N*-2-phenylethyl- and N-2-(3-indolyl)ethyl-5′-deoxy-5′-adenosineacetamides (**2** and **3**), which are stable compounds of phenylalanyl- and tryptophanyl-AMPs, are described.

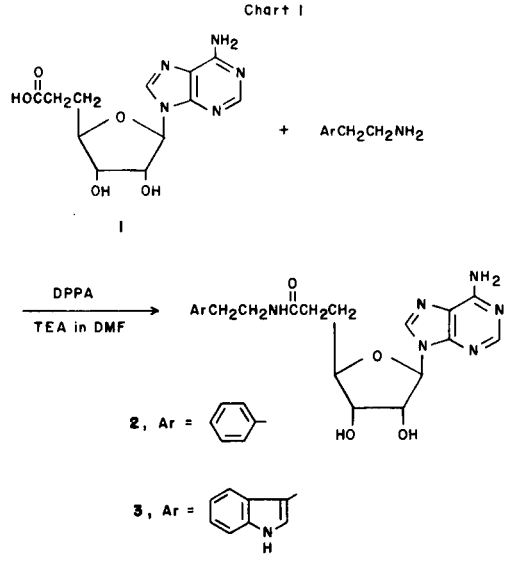
J. Heterocyclic Chem., **21**, 259 (1984).

In the synthesis of proteins the activation of amino acids (aa) is carried out by the formation of aminoacyl adenosine-5′-monophosphate (aa-AMP). This formation is catalysed by an amino-acyl tRNA synthetase (ARS) as follows:



The elucidation of the allowed conformation for each aa-AMP can lead to information on the conformation of the receiving stereochemistry in each ARS because the enzyme-substrate recognition is very specific for each aa. But, there is no experimental study for such conformation because of the high lability of the aminoacyl ester of the nucleotide linkage [1]. This paper describes the synthesis and physical properties of *N*-2-phenylethyl- and *N*-2-(3-indolyl)ethyl-5′-deoxy-5′-adenosineacetamides (**2** and **3**), which are stable compounds of phenylalanyl- and tryptophanyl-AMPs, respectively.

Chart I



5′-Deoxy-5′-adenosineacetic acid (**1**), which was first synthesized by Follmann [2], is known as a useful model nucleotide of AMP. Recently we reported an improved synthesis of this acid **1** [3] whose conformation was determined by X-ray crystal structure analysis [4]. Treatment of **1** with β-phenethylamine or tryptamine in the presence of diphenylphosphoryl azide (DPPA) [5] in dimethylformamide (DMF) followed by silica column chromatography afforded **2** and **3** in yields of 43 and 44%, respectively. The ^{1}H-nmr spectral data of these amides **2** and **3** in deuteriodimethylsulfoxide (DMSO-d_6) are summarized in Table 1.

The uv spectra of **2** and **3** in 0.25*M* potassium phosphate buffer, *p*H 6.83, are shown in Fig. 1. Larger degree of hypochromisity was observed in **3** (23%) than in the case of **2** (7%). This data revealed marked difference in stacking structure between benzene and adenine rings in compound **2** and that between indole and adenine rings in compound **3**. The elucidation of the ^{1}H-nmr spectra of **2** and **3** in deuterium oxide (deuterium oxide) at 10°, 30°, and 50° strongly supported the uv hypochromisity data, the results of which will be reported elsewhere in near future.

Table 1

^{1}H Nmr Spectral Data for Amides **2** and **3** [a] [b]

Compound No.	H_8	H_2	$H_{1'}$	$H_{2'}$	$H_{3'}$	$H_{4'}$	$H_{5'}$	$H_{6'}$	Others
2	8.23 s	8.14 s	5.84 d	4.64 t	4.04 t	3.82 m	1.89 m	2.10 t	3.21 (t, J 7.5 $ArCH_2CH_2$)
			$J_{1',2'}$ 4.8	$J_{2',3'}$ 4.7	$J_{3',4'}$ 4.8			$J_{5',6'}$ 7.5	2.66 (t, J 7.5 $ArCH_2CH_2$)
3	8.33 s	8.15 s	5.85 d	4.65 t	4.05 t	3.84 m	1.88 m	2.15 t	3.62 (t, J 7.3 $ArCH_2CH_2$)
			$J_{1',2'}$ 5.1	$J_{2',3'}$ 4.3	$J_{3',4'}$ 5.0			$J_{5',6'}$ 7.5	2.78 (t, J 7.3 $ArCH_2CH_2$)

[a] 200 MHz nmr Spectra in DMSO-d_6 solution, δ downfield from internal TMS, J in Hz.
[b] Peak multiplicities refer to observed splittings after deuterium oxide exchange.

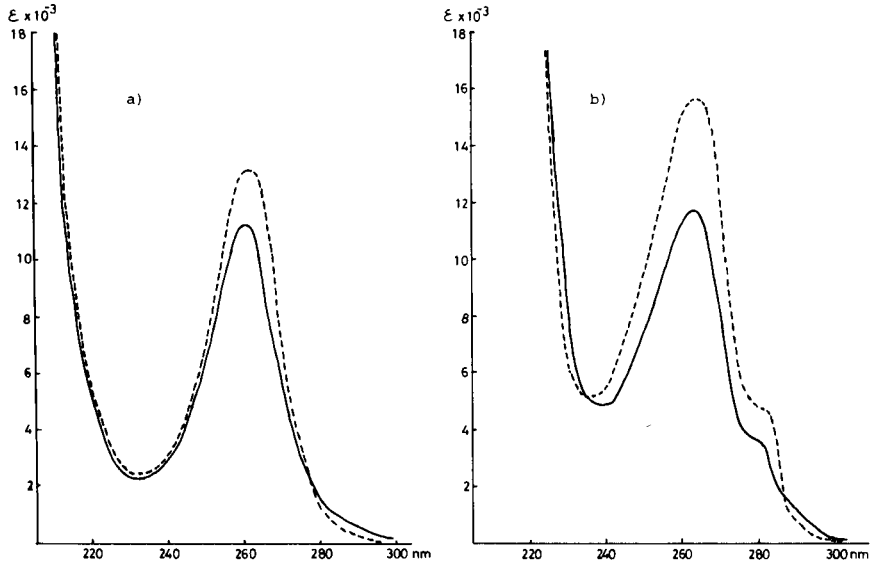


Figure 1. UV Spectra of Amides **2** and **3** in 0.25*M* Potassium Phosphate Buffer. a) —:**2** --- 1:1 mixture of ethyl 5'-deoxy-5'-adenosineacetate and β-phenethylamine. b) —:**3** --- 1:1 mixture of ethyl 5'-deoxy-5'-adenosineacetate and tryptamine.

EXPERIMENTAL

Melting points were recorded on a Yanagimoto micromelting point apparatus and are uncorrected. Infrared spectra were recorded with a JASCO model IRA-1 spectrophotometer and ultraviolet spectra with a JASCO UVIDEC-505 spectrophotometer. Nuclear magnetic resonance spectra were recorded in deuteriodimethylsulfoxide with a Varian XL-200 spectrometer with tetramethylsilane as an internal standard.

N-Phenylethyl-5'-deoxy-5'-adenosineacetamide (**2**).

To a well-stirred mixture of β-phenethylamine hydrochloride (236 mg, 1.5 mmoles) and triethylamine (155 mg, 1.5 mmoles) in dimethylformamide (3 ml) under ice cooling was added **1** (309 mg, 1 mmole), diphenylphosphoryl azide (412 mg, 1.5 mmoles) and triethylamine (155 mg, 1.5 mmoles). The mixture was then stirred at room temperature overnight. After the addition of water (1 ml), the mixture was concentrated *in vacuo*. The residue was triturated with methanol, and the resulting fine solid was removed by filtration through a Celite pad, and the pad was washed with methanol. The combined filtrates were evaporated to dryness and applied to silica gel (Merck Silica gel 60) (15 g) column chromatography. The product was then eluted with a ethyl acetate/methanol (10:1) mixture. The eluant fractions containing the product were combined and evaporated to give a white powder, yield 177 mg (43%). Recrystallization from water yielded a white powder of mp 191-194°; ir: ν cm^{-1} 1675 (CO).

Anal. Calcd. for $C_{20}H_{24}N_6O_4$: C, 58.24; H, 5.87; N, 20.38. Found: C, 58.25; H, 5.79; N, 20.66.

N-2-(3-Indolyl)ethyl-5'-deoxy-5'-adenosineacetamide (**3**).

To a well-stirred suspension of **1** (309 mg, 1 mmole) in dimethylformamide (3 ml) was added tryptamine (192 mg, 1.2 mmoles), DPPA (412 mg, 1.5 mmoles) and triethylamine (1.55 mg, 1.5 mmoles). Using the same work-up for **2**, 198 mg (44%) of **3** was obtained as a white powder of mp 115-118°, recrystallized from ethyl acetate; ir: ν cm^{-1} 1675 (CO).

Anal. Calcd. for $C_{22}H_{25}N_7O_4$: C, 58.52; H, 5.58; N, 21.79. Found: C, 58.30; H, 5.62; N, 21.47.

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