

because of the short lifetime of $^1(\pi, \pi^*)$ state of BPE and no exciplex is formed between BPE and tetramethylethylene and noncyclic photoaddition product is obtained when BPE is irradiated in tetramethylethylene through an allylic hydrogen atom abstraction of tetramethylethylene by $^1(n, \pi^*)$ state of BPE.¹³

Because of four nitrogen atoms in pyrazine rings of BPE, no ground state charge transfer complex is formed between *t*-BPE and tetracyanoethylene in contrast to stilbene and tetracyanoethylene case. Thus, stilbene undergoes photodehydrocyclization to phenanthrene when irradiated with tetracyanoethylene but BPE forms a singlet exciplex which leads to a $2\pi+2\pi$ C₄-photocycloadduct on irradiation with tetracyanoethylene in acetonitrile.

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Synthesis of N⁶-Aminoalkyl-5'-adenylic Acid Derivatives

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Seventeen new N⁶-aminoalkyl derivatives of 5'-adenylic acid and adenosine 5'-triphosphate (Compound I-XVII) were synthesized from 6-chloropurine ribonucleoside by reaction with appropriate diamines. This paper discusses the procedure of synthesis and the identification of the derivatives by ultraviolet spectra, high voltage electrophoresis, paper chromatography, elemental analyses, and other chemical methods.

Introduction

Both of the 5'-adenylic acid (adenosine 5'-monophosphate, AMP) and adenosine 5'-triphosphate (ATP) which is a carrier of phosphate and pyrophosphate in several important enzymatic reactions involved in the transfer of chemical energy, are substrate of a large portion of known enzymes and are utilized frequently in metabolism as allosteric regulators of enzyme activity.^{1,2} Most analogs of adenosine used in the

neoplastic chemotherapeutic agents may react with the enzyme of adenylic pyrophosphorylase, whereas hypoxanthine and guanine analogs are substrates for the enzyme inosinic-guanylic pyrophosphorylase.³ Antimetabolites, as the anticancer agents, are structural analogs of physiologically occurring substances which can produce evidence of deficiency of the metabolites in a biological system.⁴ Since the pioneering studies of Hitchings and his associates, a large number of

analogs of natural purine bases, nucleosides, and nucleotides have been synthesized and studied in a wide variety of biological and biochemical systems.³

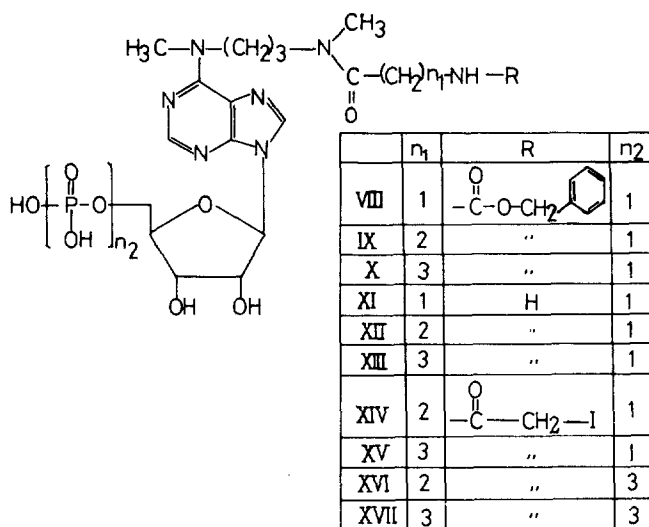
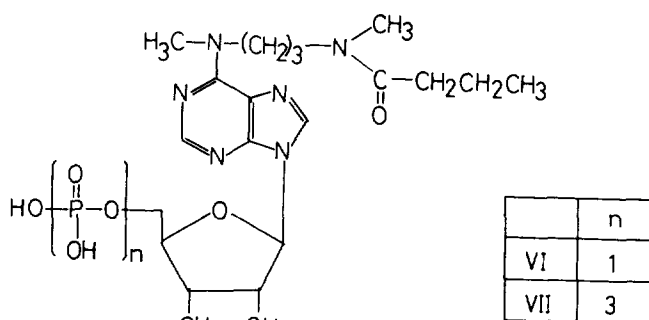
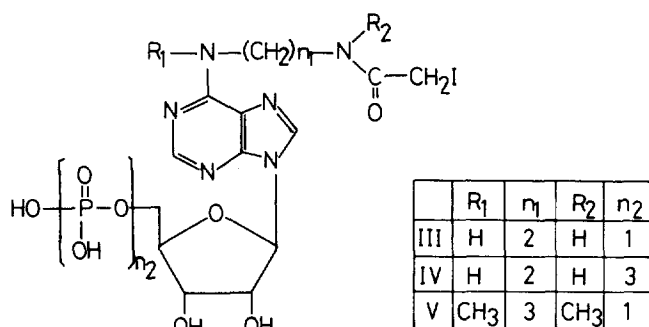
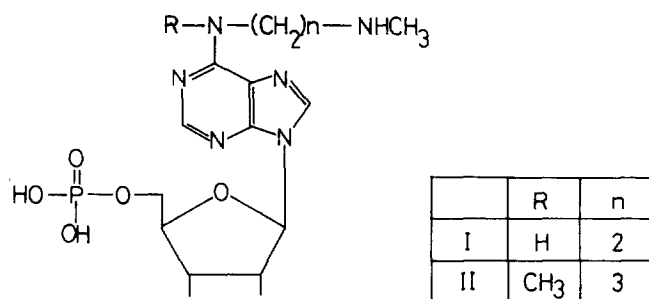
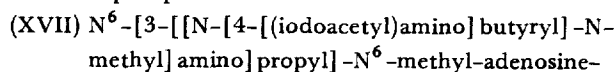
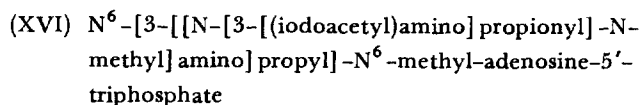
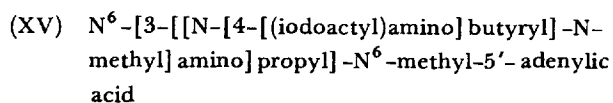
Many N⁶-aminoalkyl derivatives of AMP and ATP have been synthesized from 6-chloropurine ribonucleoside (6-CPR) as potential active site directed inhibitors of adenylate kinases. The N⁶-aminoalkyl AMP's shown in the following were prepared by using the starting material of 6-CPR which was phosphorylated with partially hydrolyzed phosphorous oxychloride in triethylphosphate.⁵ Following careful hydrolysis and neutralization of the reaction mixture, nucleophilic displacement of the 6-chloro was affected by heating the nucleotide at 80 °C. The iodoacetyl functions were introduced by the reaction of the iodoacetic acid or N-succinimidyl iodoacetate with the N⁶-aminoalkyl AMP, and the carbobenzyloxy (CBZ) functions were introduced by the reaction of CBZ-amino carboxylic acid with the N⁶-aminoalkyl AMP. The homogeneity of these products was shown by the methods of paper chromatography, high voltage electrophoresis, uv extinction coefficient and phosphate analysis.

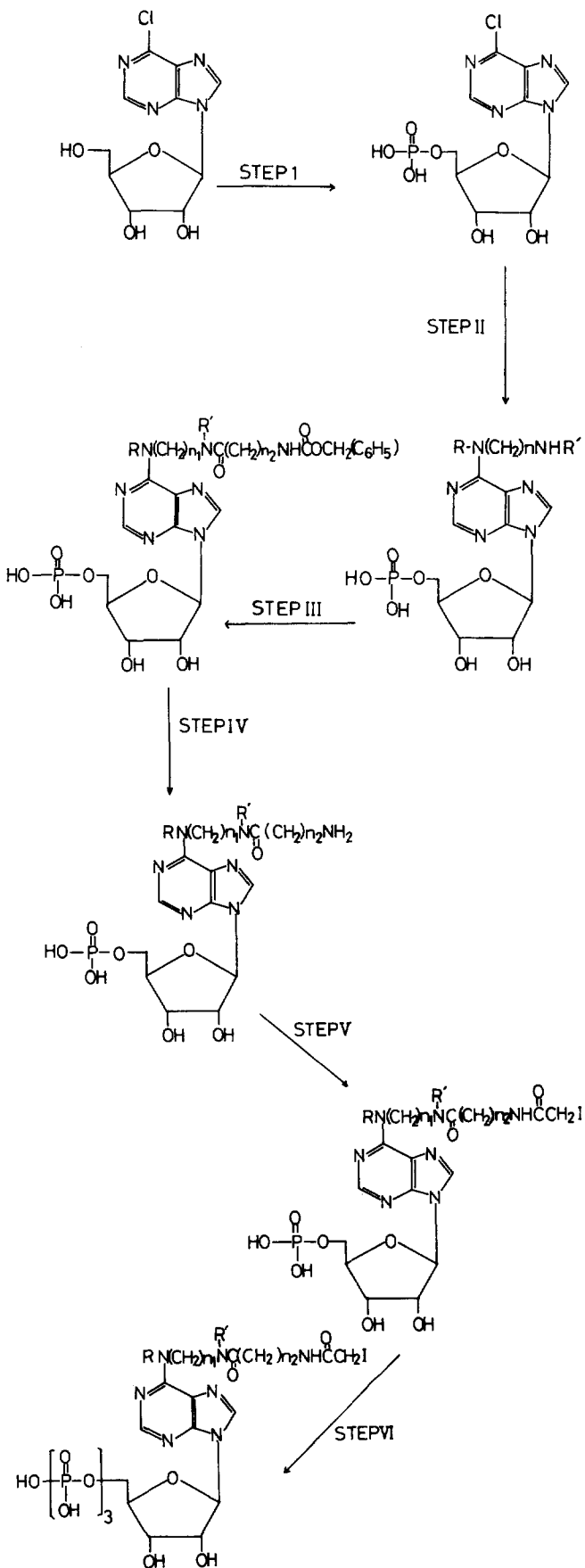
Experimental

The names, structural formula and each steps in the synthesis of the 17 N⁶-aminoalkyl derivatives of AMP and ATP from 6-CPR are given in the followings.

- (I) N⁶-[2-(methylamino)ethyl]-5'-adenylic acid
 (II) N⁶-methyl-N-[3-(methylamino)propyl]-5'-adenylic acid
 (III) N⁶-[2-[(iodoacetyl)amino]ethyl]-5'-adenylic acid
 (IV) N⁶-[2-[(iodoacetyl)amino]ethyl]-adenosine-5'-triphosphate
 (V) N⁶-[3-[N-iodoacetyl-N-methyl]amino]propyl]-N⁶-methyl-5'-adenylic acid
 (VI) N⁶-[3-[(N-n-butyl-N-methyl)amino]propyl]-N⁶-methyl-5'-adenylic acid
 (VII) N⁶-[3-[(N-n-butyl-N-methyl)amino]propyl]-N⁶-methyl-adenosine-5'-triphosphate
 (VIII) N⁶-[3-[(N-[(carbobenzyloxy)amino]acetyl)-N-methyl]amino]propyl]-N⁶-methyl-5'-adenylic acid
 (IX) N⁶-[3-[[N-3-[(carbobenzyloxy)amino]propionyl]-N-methyl]amino]propyl]-N⁶-methyl-5'-adenylic acid
 (X) N⁶-[3-[[N-4-[(carbobenzyloxy)amino]butyryl]-N-methyl]amino]propyl]-N⁶-methyl-5'-adenylic acid
 (XI) N⁶-[3-[(N-aminoacetyl-N-methyl)amino]propyl]-N⁶-methyl-5'-adenylic acid
 (XII) N⁶-[3-[[N-(3-aminopropionyl)-N-methyl]amino]propyl]-N⁶-methyl-5'-adenylic acid
 (XIII) N⁶-[3-[[N-(4-aminobutyryl)-N-methyl]amino]propyl]-N⁶-methyl-5'-adenylic acid
 (XIV) N⁶-[3-[[N-3-[(iodoacetyl)amino]propionyl]-N-methyl]amino]propyl]-N⁶-methyl-5'-adenylic acid

acid





1. Synthesis of N^6 -Aminoalkyl AMP (Step I & II: Compound I, II)

6-CPR (0.5g, 1.75 mmoles) was treated with cold

phosphorous oxychloride (0.6ml), triethylphosphate (5ml), and water (40 μ l), and the mixture was allowed to stand at -10°C for 3 hrs with occasional shaking. An additional 0.6ml of cold phosphorous oxychloride and 40 μ l of water were added and the reaction was continued over night with stirring at 4°C . The mixture was then added dropwise to 50 ml of 0.05 M sodium phosphate buffer, adjusted at pH 7.5 with 4 N NaOH. Upon completion, the solution was allowed to rise slowly to 25°C , while still watching the pH closely. The aqueous solution was extracted with ether (50 ml \times 3 times) to remove triethylphosphate, and reducing the solution to 1/3 its volume.

The mixture was then filtered and the washings were added to an aqueous solution (35 ml) of 35 mmoles of alkyl diamine (in the case of Compound I, 2.6g of *N*-methylethylenediamine was used; and 3.58g of *N,N'*-dimethyl propylenediamine was employed in Compound II which had been carefully neutralized with conc. HCl. The solution was heated at 80°C for 6 hrs. The reaction mixture was then cooled to 25°C and the volume of solution was increased to 200 ml by addition of water. The pH of this solution was then adjusted to 12.4 with 4 N NaOH and the solution was diluted to 1l. This volume was applied to Dowex-1 (acetate, 5 \times 30 cm, 200g) column and eluted with a linear gradient of water: 1N acetic acid = 1:1, and 12 ml of fractions were collected. The product appeared in the 0.2-0.3 M acetic acid range as detected by ultraviolet, was concentrated to a small volume and kept in a refrigerator over night, forming a white solid. The solid could be recrystallized from water or ethanol.

2. Synthesis of CBZ-Derivatives of N^6 -Aminoalkyl AMP (Step III)

Method A: Use of *N*-Ethoxycarbonyl-2-Ethoxy-1,2-Dihydroquinone (EEDQ) (Compound VIII, X). To the Compound II, dispersed into 3ml of water, were added 2 drops of conc. NH_4OH until the nucleotide was dissolved. The solution was evaporated to remove the excess of NH_4OH , and gained a gummy residue. A solution of EEDQ (0.5g, 2 mmoles) and *N*-CBZ-amino acetic acid (0.42g, 2 mmoles; in the case of the Compound X, there was 0.475g, 2 mmoles of *N*-CBZ- γ -amino butyric acid) in 2 ml of 2-methoxyethanol was added to a stirred solution of the gummy residue (diammonium salt of Compound II, 0.23g, 0.5 mmole) in 2-methoxyethanol:water = 8:1 (4.5 ml). The reaction solution was stirred at 25°C for 2.5 hrs. The solution was then evaporated to dryness in vacuo and the residual oil was extracted with ether (20 ml \times 5 times). The residue was then dissolved in 2-methoxyethanol (4 ml) and to this, was added a solution of EEDQ (2 mmoles) and *N*-CBZ- γ -amino compound (2 mmoles) in 2 ml of 2-methoxyethanol. The reaction was continued for an additional 4 hrs and then concentrated in vacuo. The resulting syrup was extracted with ether (20 ml \times 5 times).

Compound VI, started from triethylammonium salt of Compound II by passing through the diethylaminoethyl (DEAE) cellulose (triethylammonium bicarbonate form) column, was carried out the same as above with *n*-butyric acid as the CBZ-function.

Method B: Use of N-Succinimidyl-N-CBZ-Alanine Ester (Compound IX). To a stirred solution of the diammonium salt of Compound II (0.3 g, 0.64 mmole) in 10 ml of 2-methoxyethanol and 6 ml of water, were added N-succinimidyl-N-CBZ- γ -alanine ester (0.41 g, 1.28 mmoles) and excess of sodium bicarbonate (0.108 g, 1.28 mmoles). The reaction mixture was stirred for 16 hrs at 25 °C. Soon, all solids were dissolved, the solution was evaporated in vacuo and extracted with ether (20 ml \times 5 times).

3. *Synthesis of N⁶-Aminoacyl Derivatives from the Corresponding Compound VIII, IX, X (Step IV; Compound XI, XII, XIII)*

To an aqueous solution (25 ml) of 4 mmoles of the diammonium salt of CBZ-derivative (2.63 g of Compound VIII; 2.69 g of Compound IX; 2.74 g of Compound X) were added 1 drop of acetic acid, 1 g, of 10% palladium charcoal (Pd-C) and the mixture was hydrogenated at 25–30 psi at 25 °C for 2.5 hrs. The reaction mixture was filtered and the charcoal was washed well with 200 ml of ethanol:water:c-NH₄OH = 1:1:0.3, and repeated. The filtrate and washings were combined and concentrated in vacuo.

4. *Synthesis of N⁶-Iodoacetamido Alkyl, Derivatives of AMP (Step V; Compound III, V, XIV, XV)*

The corresponding N⁶-aminoalkyl derivative of AMP (0.42 mmole: in the case of Compound III, 0.178 g of diammonium salt of N⁶-(2-aminoethyl)-5'-adenylic acid was used as the starting material; Compound V was 0.267 g of triethylammonium salt of II; Compound XIV was 0.226 g of diammonium salt of XII; Compound XV was 0.232 g of diammonium salt of XIII) was suspended in a solution of 2-methoxyethanol:water = 5:3 (80 ml) in which had been dissolved the N-hydroxysuccinimidyl iodoacetate (0.14 g, 0.5 mmole) and sodium bicarbonate (0.04 g, 0.5 mmole). After stirring at 25 °C over night, complete dissolution was occurred and the volatiles were then removed in vacuo below 30 °C. The residue was washed with acetone and purified by recrystallization from water. In the case of Compound III, XIV, and XV, crystallization did not occur, so a sample for analysis was prepared by converting each to its disodium salt *via* the triethylammonium salt using DEAE cellulose followed by addition of 1 M NaI to an anhydrous methanol solution.

5. *Preparation of Disodium Salt of Compound III.*

The Compound III (0.078 g, 0.14 mmole) in 10 ml of water was applied to DEAE cellulose column (2.5 \times 20 cm), eluted with 100 ml of water and the 150 ml of 0.3 M triethylammonium bicarbonate aqueous solution. The triethylammonium bicarbonate fractions were collected and concentrated to dryness in vacuo. The syrupy residue was dissolved in 10 ml of anhydrous methanol, and 3 ml of 1 M NaI in acetone was added to the dissolved methanol solution.

And then, an excess of acetone was added and kept in a refrigerator for 1 hr. The white precipitate in the solution was filtered and washed well with acetone, and the obtained solid was dried over P₂O₅ in vacuo at 25 °C.

6. *Synthesis of N⁶-Aminoalkyl Derivatives of ATP from*

the Corresponding AMP (Step VI; Compound IV, VII, XVI, XVII).

The N⁶-substituted AMP (0.2 mmole; in the case of Compound IV, 0.112 g of Compound III was used and Compound VII was 0.1 g of VI, Compound XVI was 0.13 g of XIV, and Compound XVII was 0.137 g of XV) was dried by repeated evaporation of anhydrous dimethylformamide (DMF, 10 ml \times 3 times). To the residue were added DMF (10 ml) and 1,1'-carbonyldiimidazole (0.162 g, 1 mmole), and the mixture was stirred at 25 °C for 2 hrs. During the time, complete dissolution was occurred and the result of electrophoresis at pH 3.5 was shown only monoanionic material present. Methanol (65 μ l, 1.6 mmoles) was added and the solution was stirred at 25 °C for 0.5 hr. Tri-*n*-butylammonium pyrophosphate (0.92 g, 1 mmole) in 3 ml of DMF was added and the solution was stirred vigorously for 24 hrs at 25 °C. The mixture was centrifuged and the precipitated imidazolium pyrophosphate was washed with DMF. The supernatant and washings were combined, diluted 2-fold with methanol and concentrated to dryness in vacuo below 30 °C. The residue was dissolved in water and chromatographed on a DEAE cellulose (bicarbonate form) column (2 \times 30 cm) at 0 °C using a linear gradient of water (1 l): triethylammonium bicarbonate (0.3 M, pH 7.5, 1 l). The fractions at a certain part of triethylammonium bicarbonate were contained the nucleoside triphosphate and the yields were determined spectrophotometrically. The solution was evaporated to dryness in vacuo below 30 °C using ethanol until a solid residue was obtained. This residue was dissolved in anhydrous methanol (2 ml), filtered and treated with 1 M NaI in acetone (0.5 ml): Excess of acetone was then added and the white precipitate was collected, washed with acetone, and dried over P₂O₅ in vacuo at 25 °C.

Result and Discussion

The method for synthesizing AMP and ATP derivatives containing N⁶-aminoalkyl (C₅-C₆) group for enzymatic studies as anticancer agents was reported by Hampton's research group.^{2,5,8} N⁶-aminoalkyl (C₁-C₃) derivatives, however, have not been reported.

The purpose of introduction of methyl or other alkyl groups on N⁶-nitrogen atom in the ribonucleotide molecule which the author synthesized is to restrict the free rotation of the N⁶-nitrogen atom with the alkyl side chain, and amide group in the N⁶-alkyl side chain is to prevent its free rotation by introducing a partially double bond character through the interaction of the lone paired electron on the nitrogen atom with on sp² orbit of the carbonyl group.⁸ The ribonucleotides, in which the alkyl and the amine groups were introduced, were also the aim at the evaluation to determine their selectivity to the substrate specificity of enzyme.^{5,8}

The yields and other back-up data for structural identification of the compounds of 17 new N⁶-aminoalkyl derivatives of AMP and ATP are given in the Table 1, and the results of the elemental analyses for the each compound are given in the Table 2.

The infrared spectra of the compounds were confirmed the presence of amine, amide and carbonyl bonds by the characteristic bond at 3500–3450 cm^{-1} regions and 1640 cm^{-1} for each step. In the case of each compound, spot tests such as spraying of ninhydrin after elution on descending paper chromatography were helpful for identification. The ultraviolet spectra and elemental analyses were very convenient for the calculation of yield, purity and characterization for each step in this synthetic approach (see Table 1 and 2).

The synthetic method of producing mono and triphosphate from 6-CPR derivatives was the general one used by Hampton's research group and others.⁵⁻⁸ In step II, which is a nucleophilic substitution of primary or secondary amine with 6-CPR, the control of pH 7 of the reaction medium with HCl was very critical in order for the reaction to occur, and the separation of product was achieved through the elution of Dowex-1 (acetate) anion column with a linear gradient of water:1*N* acetic acid = 1:1. A diagram of fractional collections in the synthesis of Compound II was shown in the Figure 1. The application of EEDQ to the introduction of the amide bond formation was very successful to get even more yield

than the use of *N*-succinimidyl ester. Compound VI was converted to its triethylammonium salt by passing it through the DEAE cellulose (triethylammonium bicarbonate form) column at 4 °C. *N*⁶-aminoacyl derivatives of AMP protected with CBZ-group were easily hydrogenated with Pd-C in acetic acid medium to give a quantitative yield greater than that of any other procedure. The addition of *N*-hydroxysuccinimidyl

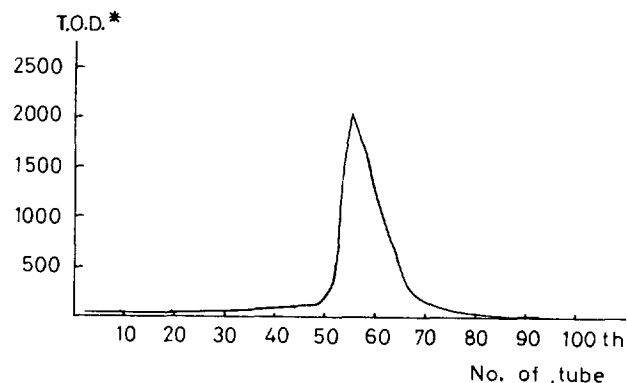


Figure 1. Fractional collections in the synthesis of Compound II.

* Total optical density.

TABLE 1: Result Data of *N*⁶-Aminoalkyl AMP and ATP Derivatives

Com- pound	Yield ^a (%)	PC, $R_f(\times 10^{-2})^b$ Solvent system ^c				HVE, ^d $R_f(\times 10^{-2})$		H_2O^e λ_{max} (nm)	Ninthy- drain Test	Ext. coef. (ϵ)	Remarks
		A	B	C	D	pH	pH				
						7.5	3.5				
AMP		10	26		56	100	100	250			
ATP		3	9		42		234	259			
I	86							268	-	16000	
II	66	62	27			77		274	-	18439	
III	55					96		267	-	15900	2Na ⁺
IV	30				45		203	274	-	15900	4Na ⁺
V	40					96		274	-	18750	2TEA ⁺ *
VI	55	60				96		274	-	18750	2TEA ⁺ *
VII	25				65		200	274	-	18423	4Na ⁺
VIII	75	74	64			86		274	-	18750	2NH ₄ ⁺
IX	64	78	65			85		274	-	18634	2NH ₄ ⁺
X	85	80	72			84		274	-	18640	2NH ₄ ⁺
XI	75	49				55		274	+	18750	2NH ₄ ⁺
XII	82	57	31			52		274	+	18750	2NH ₄ ⁺
XIII	83	58	38			59		274	+	18750	2NH ₄ ⁺
XIV	68		54	38		80		274	-	18700	2Na ⁺
XV	48		54	37		82		274	-	18750	2Na ⁺
XVI	34				80		210	274	-	18750	4Na ⁺
XVII	55				82		220	274	-	18653	4Na ⁺

^aYields were determined spectrophotometrically based upon a value of 18750 as the ϵ for *N*⁶-dialkyl-adenosines, J. Johnson, J. Thomas, H. Schaeffer, *J. Amer. Chem. Soc.*, **80**, 699–702 (1958). ^bPaper chromatography (descending) was employed on Whatman No. 3,3MM paper. ^cEach solvent system was; A: 2-propanol:conc. NH_4OH :water = 7:1:2, B: 1-butanol:acetic acid:water = 5:2:3, C: 1-butanol:acetic acid:water = 4:1:5 (upper layer), D: 2-methylpropionic acid:1*M* NH_4OH = 5:3. ^dHigh voltage electrophoresis (Flat form electrophoresis, Savant Instrument Inc.) was performed on Whatman no. 1 paper at 40 kV/cm for 30 minutes at pH 7.5, 0.05*M* diethylammonium bicarbonate or pH 3.5, 0.015*M* sodium citrate buffer. Mobility values (R_f) are relative to that of AMP. Spots on chromatogram were detected by their ultraviolet absorption of specificity.

^eUltraviolet spectra were determined with a Cary Model 17 spectrophotometer. * TEA: Triethylammonium

TABLE 2: Elemental Analyses (%)

Com- pound	Calculated				Found				Mole wt.	Remarks
	C	H	N	P	C	H	N	P		
I	36.97	5.49	19.90		36.88	5.60	19.75		422.35	1H ₂ O
II	38.46	6.24	17.94	6.61	38.61	6.25	17.85	6.31	468.42	2H ₂ O
III	27.92	3.01	13.96	5.14	27.80	3.05	14.00	5.24	602.21	2Na ⁺
IV	19.55	2.81	9.77		19.34	2.92	9.76		860.20	4Na ⁺ 3H ₂ O
V	41.53	7.21	13.36		41.47	7.09	13.20		838.72	2TEA ⁺ 2H ₂ O
VI	50.25	8.84	15.13		49.98	8.91	15.20		740.87	2TEA ⁺ 2H ₂ O
VII	28.37	4.39	10.45	11.55	28.40	4.40	10.50	11.60	804.44	4Na ⁺ 3H ₂ O
VIII	41.15	6.63	17.28		41.08	6.57	17.37		729.68	2NH ₄ ⁺ 4H ₂ O
IX	43.03	6.67	17.37		43.27	6.78	17.32		725.69	2NH ₄ ⁺ 3H ₂ O
X	42.79	6.92	16.64		42.59	6.95	16.78		757.73	2NH ₄ ⁺ 4H ₂ O
XI	36.49	6.85	22.53		36.41	6.83	22.37		559.52	2NH ₄ ⁺ 2H ₂ O
XII	37.69	7.03	21.98		37.47	7.12	21.86		573.55	2NH ₄ ⁺ 2H ₂ O
XIII	38.84	7.21	21.46		38.69	7.18	21.40		587.58	2NH ₄ ⁺ 2H ₂ O
XIV	28.54	5.39	11.65	3.68	28.46	5.44	10.50	3.29	841.48	2Na ⁺ 8H ₂ O
XV	31.47	4.90	12.23		31.23	4.88	12.21		801.44	2Na ⁺ 4H ₂ O
XVI	24.68	3.62	10.07		24.53	3.58	9.99		973.35	4Na ⁺ 3H ₂ O
XVII	27.02	3.35	10.51	9.96	27.05	3.38	10.54	9.93	933.34	4Na ⁺

iodoacetate to N⁶-aminoacyl derivatives of AMP was carried out without difficulty, and the paper chromatogram was developed in solvent system C (see Table 1) and the band at R_B 0.37-0.38 was further eluted with water at 4 °C.

Elemental analyses for the Compound II, III, VII, XIV, and XVII were performed by Galbraith Labs, Inc., Organic Microanalyses, Knoxville, TN, U.S.A., and others were determined with C, H & N Analyzer, Hewlett Packard, Model 185B.

The fractional collections were used with Fractomette Alpha 200 Fraction collector (Buchler) 115V 60HZ, 3 ml/ per min., and collected 12 ml/ per each tube.

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- (8) Partial work for this paper was done while the author was a research fellow of the Institute for Cancer Research, Philadelphia, U.S.A. in 1975. However, for this paper, the author repeated the procedure for perfection.

The Vacancies-in-Solid Model Applied to Molar Volumes and Isothermal Compressibilities of Solid Krypton and Xenon

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