TABLE VIII

MOLAR CONCENTRATIONS FOR 50% INHIBITION OF DIHYDROFOLIC ACID REDUCTION BY THREE ISOLATED ENZYMES

Compd	50% inhibitory concn ×10⁸, M: Rat liver	*E. coli*	*Ps. aeruginosa*
1	20,000	14,000	
7	4,400	140	
12	280	14	
14			100
15	42	1.9	14
18	46	50	70
20			30
21			37
22			40
23			600
24			700
25	25	40	46
31	42		160
33	2,200	270	320
35	180	23	85
37	7.0	1.5	3.0
38	26	2.0	2.0
39		0.20	0.80
40	6.0	0.38	1.2
41			0.70
42			0.40
43	3.0	0.92	1.4
44	3.5	0.78	1.8
45	4.0	1.0	0.23
53	25		
54	6.0	120	
58	1.5		

derivatives (**14**, **18**, **21**, **22**, **23**) activity reaches a peak in **18** ($R_6 = C_4H_9$).

For antibacterial activity, the size of the 5 substituent is quite limited since only 5-methyl and 5-unsubstituted compounds show appreciable activity. This is illustrated in the series of 6-benzyl-7-unsubstituted compounds (**25**, **45**, **51**, **54**, **57**). As the group in the 5 position increases above methyl, activity is sharply decreased. The rat liver enzyme is not as sensitive to changes in the 5 substituent as are the bacterial enzymes. As is shown in Table VIII, **54** is nearly as inhibitory as **45** to the rat liver enzyme, whereas **54** is only $^1/_{100}$ as inhibitory as **45** toward the *E. coli* enzyme. There is a notable change in the spectra of activity between the 5-unsubstituted and 5-methyl series of derivatives which has been documented previously,[7] and which can be seen in Tables I and IV. Generally the 5-unsubstituted derivatives are more active against *S. aureus* than against *E. coli* or *P. vulgaris* and the 5-methyl derivatives are more active against *E. coli* and *P. vulgaris* than against *S. aureus* (compare **18** with **38**, and **25** with **45**).

An over-all picture has been developed of a 2,4-diaminopyrido[2,3-*d*]pyrimidine derivative having no substituent in the 7 position, no substituent or a methyl group in the 5 position, and a substituent of medium bulk, consisting of an alkyl group of four or five carbon atoms or a benzyl group, in the 6 position. Such derivatives are potent inhibitors of bacterial dihydrofolate reductases and thus have general antibacterial activity. The spectrum of this activity depends primarily on the substituent in the 5 position. The action of the derivative is potentiated by sulfonamides and combinations of the two drugs have useful chemotherapeutic indices for the treatment of bacterial infections in mammalian species.

Acknowledgments.—The authors wish to thank Messrs. A. Iannotti, N. Rigopoulos, and G. Tharrington for technical assistance. Our thanks are also due R. A. Neal, M. L. Clarke, and W. H. G. Richards for the tests against protozoal infections.

Synthesis and Biological Activity of Some N⁶-Alkyladenosines

M. H. FLEYSHER, M. T. HAKALA, A. BLOCH, AND R. H. HALL

Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, New York

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The synthesis of N⁶-isoamyl-, N⁶-*n*-propyl-, N⁶-isopropyl-, and N⁶-allyladenosine and N⁶-isoamyladenine was carried out by a general method involving the condensation of 6-chloropurine riboside or its base with an excess of the appropriate amine in an alcoholic medium in the presence of calcium carbonate. By this method essentially pure products were readily obtained. The biological effects of these compounds were examined with cell cultures of Sarcoma 180 and its subline AH/S and with cultures of *Streptococcus faecalis* and *Escherichia coli*. All the compounds synthesized showed growth inhibitory activity in one or the other of these test systems.

N⁶-(Δ^2-Isopentenyl)adenosine[1,2] (IPA) is a very potent cytokinin with activity equal to or better than kinetin and zeatin in the bud tests of Wickson and Thimann.[3] This compound was also shown to inhibit the growth of human and mouse tumor cells *in vitro*.[4] Because of this biological activity of IPA and because several N⁶-alkylpurine bases have shown kinetin activity in tobacco callus growth tests,[5] it was of interest to determine whether other N⁶-alkyl derivatives of adenosine would also show biological activity. For this reason the following adenosine derivatives were prepared and their biological activity was examined: N⁶-isoamyl- (I), N⁶-*n*-propyl- (II), N⁶-isopropyl- (III), N⁶-allyl- (IV), N⁶-isoamyl- (V), and N⁶-methyladenosine. Compounds I–IV have not been reported thus far, while V has been studied by Strong[5a] and has been shown to possess kinin activity; however, the method of

(1) R. H. Hall, M. J. Robins, L. Stasiuk, and R. Thedford, *J. Am. Chem. Soc.*, **88**, 2614 (1966).

(2) M. J. Robins, R. H. Hall, and R. Thedford, *Biochemistry*, **6**, 1837 (1967).

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TABLE I
PAPER CHROMATOGRAPHY, R_f VALUES, AND UV-ABSORPTION SPECTRA OF N^6-ALKYLPURINES

Compd	Solvent system[c] A	B	C	D	E	F	UV data pH 1.0 λ_{max}, mμ	ε × 10⁻³	pH 7.0 λ_{max}, mμ	ε × 10⁻³	pH 12.0 λ_{max}, mμ	ε × 10⁻³
N^6-Isoamyladenosine	0.79	0.91	0.94	0.83	0.80	0.89	264	18.5	267.5	17.5	267.5	17.5
N^6-*n*-Propyladenosine	0.62	0.80	0.90	0.65	0.64	0.82	263	18.6	267	17.5	267	17.6
N^6-Isopropyladenosine	0.66	0.83	0.93	0.65	0.69	0.83	263	18.7	267	18.0	267	17.9
N^6-Allyladenosine	0.62	0.75	0.88	0.63	0.56	0.81	264	19.0	267	18.8	267	18.8
N^1-Allyladenosine	0.03	0.72	0.70	0.46	0.30	0.37	259[a]	...	259.5[a]	...	259.5[a] (sh 266 and 300)	...
N^6-Isoamyladenine	0.86	0.92	0.96	0.86	0.91	0.89	272	16.0	268	17.1	274	17.0
N^6-(Δ^2-Isopentenyl)adenosine[b]	0.79	0.90	0.92	0.80	0.80	0.86	265	20.4	269	20.0	269	20.0
N^6-(Δ^2-Isopentenyl)adenine[b]	0.87	0.93	0.96	0.83	0.86	0.89	273	18.1	269.5	19.4	275	19.2

[a] From eluted chromatographic spots. Product later converted to the N^6 derivative. [b] Reference 2. [c] The solvent systems used for descending chromatography (Whatman no. 1 paper) (measured by volume): A, EtOAc–PrOH–H_2O (4:1:2) (upper phase); B, *i*-PrOH–H_2O–NH_4OH (7:2:1); C, *i*-PrOH–1% $(NH_4)_2SO_4$ (2:1); D, *i*-PrOH–concentrated HCl–H_2O (680:170:144); E, *n*-BuOH–H_2O–concentrated NH_4OH (86:14:5); F, *n*-BuOH–AcOH–H_2O (5:3:2).

TABLE II
BIOLOGICAL ACTIVITY OF N^6-ALKYLPURINES

Compd	Inhib of growth of Sarcoma 180 cells *in vitro*, concn required for 50% inhib, $M \times 10^{-6}$ Parent S180 cells	Subline AH/S cells	Inhib of growth of *E. coli* and *S. faecalis*, concn for 50% growth inhib, *M* *E. coli*	*S. faecalis*
Adenine	...	...	2×10^{-5}	$>10^{-3}$
Adenosine	>300	100	7×10^{-7}	$>10^{-3}$
N^6-Methyladenosine	>300	130	...	...
N^6-*n*-Propyladenosine	150	3.1	$>10^{-3}$	5×10^{-4}
N^6-Isopropyladenosine	30	2.6	$>10^{-3}$	$>10^{-3}$
N^6-Isoamyladenosine	>100	11.0	$>10^{-3}$	$>10^{-3}$
N^6-Allyladenosine	20	3.7	$>10^{-3}$	8×10^{-5}
N^6-(Δ^2-Isopentenyl)adenosine[1,2]	17	2.5	9×10^{-5}	$>10^{-3}$
N^6-Isoamyladenine	100	...	$>10^{-3}$	$>10^{-3}$
N^6-(Δ^2-Isopentenyl)adenine[1,2]	...	170	$>10^{-3}$	$>10^{-3}$

synthesis and a description of its physical properties were not reported. Compound VI was prepared by the method of Jones and Robins.[6]

Preparation of these compounds followed the same general method. The 6-chloropurine riboside or its base were refluxed together with an excess of alkylamine in an alcoholic medium, in the presence of $CaCO_3$ until condensation was complete. The products were then isolated from the calcium salts as described below. The presence of an excess of both the amine and $CaCO_3$ resulted in a complete nucleophilic exchange so that only minimal purification was required to completely eliminate the toxic 6-chloropurine riboside. The physical data are given in Table I.

Testing of the compounds in mammalian and microbial cell systems was carried out to compare the biological effects of the newly synthesized compounds. The results presented in Table II show that all of these compounds were inhibiting the growth of one or the other of the cell systems examined. Although the substituents at the N^6 position of propyl, isopropyl, isopentenyl, and allyladenosines differ in length, branching, and saturation, the compounds are equally good inhibitors of the growth of AH/S cells, a subline of Sarcoma 180 (Table II). N^6-Isoamyladenosine is one-third less active. The bases N^6-isoamyl- and N^6-isopentenyladenine are from 40 to 70 times less active than the corresponding nucleosides. Adenine itself is a more effective growth inhibitor than are the base analogs.

The N^6-nucleosides are more inhibitory than the corresponding free bases and the fact that N^6-isopentenyladenosine is 70 times more inhibitory than N^6-isopentenyladenine is paralleled by the fact that adenosine itself has been found to be more active pharmacologically (blood pressure, coronary blood flow, etc.) than adenine.[7] It is to be noted that of the six alkyladenosines tested only IPA has so far been shown to occur in nature as a component of s-RNA.[1,2]

The data in Table II further show that the parent S180 cells are considerably less sensitive to the action of the N^6-alkyladenosines than are the AH/S cells. Similar differences have been noted previously between different cell lines, even in their response to the inhibitory effects of natural purines. Thus it was found that HeLa cells were inhibited by 3×10^{-4} *M* adenine, while S180 cells were not.[8] The difference between parent S180 and AH/S is surprising in view of their common origin.

The differential response of various cell types to the N^6-substituted adenosines is also seen in the microbial systems (Table II). The growth of *Escherichia coli* is inhibited by IPA but not by any of the other N^6-alkyl derivatives; that of *Streptococcus faecalis* is affected only by the N^6-propyl- and N^6-allyladenosines. In the *E. coli* strain used, adenine and adenosine themselves

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(7) K. Boettge, K. H. Jaeger, and H. Mittenzwei, *Arzneimittel-Forsch.*, **7**, 24 (1957).

(8) M. T. Hakala and E. Taylor, *J. Biol. Chem.*, **234**, 126 (1959).

are inhibitory at 1×10^{-7} and 7×10^{-7} M, respectively, whereas *S. faecalis* is not affected by these nucleosides even at 1×10^{-3} M.

To gain some information concerning the mode of action of these compounds, the reversal of growth inhibition by N^6-isopentenyladenine and IPA was investigated in both the parent S180 and in the AH/S subline systems. Inhibition of growth was not prevented by adenine, adenosine, hypoxanthine, inosine, guanosine, deoxyguanosine, cytidine, deoxycytidine, or deoxyuridine. This would indicate that in these cells the *de novo* synthesis of purines or pyrimidines was not affected by the presence of the inhibitor. The fact that these two compounds were as inhibitory when AH/S cells were grown in an amethopterin medium (containing thymidine, hypoxanthine, and glycine)[9] as they were in Eagle's medium would also support this assumption. When in the amethopterin medium[9] hypoxanthine was replaced by isopentenyladenosine, and no growth of S180 cells was observed, indicating that the analog cannot support cellular multiplication.

Whereas the IPA inhibition of mammalian cells could not be reversed by pyrimidines, the inhibition of *E. coli* by isopentenyladenosine was preventable by cytosine and its nucleoside, and by uridine, deoxyuridine, and thymidine.[10] The purines, on the other hand, enhanced the inhibition.[10] This indicates that in this microbial system, interference with the pyrimidine metabolism may be responsible for interference with cell growth.

This differential response of various cell types *in vitro* to the action of the N^6-alkyladenosine derivatives also has its parallel in man and the selectivity of action of these compounds appears to be of value in chemotherapy.[11]

Experimental Section

The melting points were determined on a Mel-Temp melting point apparatus and are not corrected. Uv spectra were obtained on a Cary Model 14 recording spectrophotometer. The optical rotation was measured on a Jasco Model ORD-UV5 optical rotatory dispersion recorder. The solvent systems used for chromatography are given in Table I below. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

N^6-Isoamyladenosine (I).—6-Chloropurine 9β-D-ribofuranoside (2.00 g, 7 mmoles), isoamylamine (1.83 g, 21 mmoles), $CaCO_3$ (1.4 g, 14 mmoles), and 100 ml of EtOH were refluxed for 18 hr with stirring. Chromatographic examination of the reaction mixture showed one absorbing spot with an R_f different from that of 6-chloropurine or its ribonucleoside. The mixture was filtered, while still hot, to remove calcium salts. The product crystallized from the filtrate on cooling. It was filtered off, washed with chilled EtOH, and dried *in vacuo;* yield 2.02 g (86%), mp 158°. An additional yield of 0.34 g (14%), mp 156°, $[\alpha]^{25}D$ −86.5° (*c* 0.104, EtOH), was obtained from the filtrate. *Anal.* ($C_{15}H_{23}N_5O_4$) C, H, N.

Chromatographic data for this and other preparations and the uv-absorption spectra data are presented in Table I.

N^6-*n*-Propyladenosine (II).—6-Chloropurine 9β-D-riboside (2 g, 7 mmoles), 1.239 g (21 mmoles) of *n*-propylamine, and 1.40 g (14 mmoles) of $CaCO_3$ were refluxed in 100 ml of EtOH as in I for 20 hr. Chromatographic examination of the reaction mixture revealed one uv spot of product uncontaminated by 6-chloropurine riboside. The mixture was worked up as in I; yield 2.10 g (97%), mp 161°, $[\alpha]^{25}D$ −90.5° (*c* 0.116, EtOH). *Anal.* ($C_{13}H_{19}N_5O_4 \cdot 0.2H_2O$) C, H, N.

N^6-Isopropyladenosine (III) was prepared exactly as was II except that 1.239 g of isopropylamine was employed. The reaction mixture showed the absence of 6-chloropurine riboside after 8 hr of refluxing. After filtration from calcium salts, the filtrate was evaporated to dryness and the residue was crystallized from 3:1 (vol) MeCN–EtOH and dried (P_2O_5) *in vacuo* since the product was found to be very soluble in EtOH; yield 1.40 g (65%), mp 157°, $[\alpha]^{25}D$ −82.5° (*c* 0.164, EtOH). *Anal.* ($C_{13}H_{19}N_5O_4 \cdot 0.33H_2O$) C, H, N.

N^6-Allyladenosine (IV).—A mixture of 6-chloropurine riboside (2.00 g, 7 mmoles), allylamine (1.197 g, 21 mmoles), $CaCO_3$ (1.40 g, 14 mmoles), and 100 ml of EtOH was refluxed for 18 hr so that no residual 6-chloropurine riboside remained. The filtrates from the Ca salts were evaporated to dryness by several additions of anhydrous EtOH during evaporation. The residue was recrystallized from H_2O (charcoal) containing a trace of EtOH and dried (P_2O_5) *in vacuo* at 78°; yield 1.35 g (63%), mp 166–167°, $[\alpha]^{25}D$ −101° (*c* 0.094, EtOH). *Anal.* ($C_{13}H_{17}N_5O_4$) C, H, N.

This compound was also made by a modification of the method employed by Jones and Robins[6] and Leonard, *et al.*[12] Adenosine (7.5 mmoles) and allyl bromide (22.5 mmoles) in DMF (30 ml) were agitated at 33° for 24 hr to form N^1-allyladenosine (65%). After removal of the excess of allyl bromide and DMF by evaporation, the residue was heated to 80–90° in NH_4OH (pH 10–12) to convert the N^1-allyladenosine to N^6-allyladenosine. The product was obtained by chromatography on a Celite column using solvent system A. The product, N^6-allyladenosine, came off the column first leaving the residual adenosine adsorbed on the Celite. Evaporation of the eluate to dryness, followed by crystallization of the product from H_2O containing a trace of EtOH, gave a 55% yield of IV. The physical properties were the same as given above.

N^6-Isoamyladenine (V).—The biological properties of this compound have been previously reported by Strong;[4a] however, its synthesis and physical properties have not been described. It was synthesized and tested in connection with this work. A mixture of 6-chloropurine (1.082 g, 7 mmoles), isoamylamine (1.827 g, 21 mmoles), $CaCO_3$ carbonate (1.40 g, 14 mmoles), and 2-methoxyethanol (60 ml) was stirred and refluxed for 5 hr, after which time chromatographic examination revealed the absence of 6-chloropurine. The hot reaction mixture was filtered and the Ca salts were washed with hot methoxyethanol. The combined filtrates were evaporated *in vacuo* and the tan residue azeotroped five times with EtOH. The material was crystallized from H_2O containing a trace of EtOH (charcoal) and after evaporation of most of the EtOH the crystals were filtered, washed (H_2O), and dried (P_2O_5) *in vacuo* to yield 1.17 g (81.5%) of V, mp 201°. *Anal.* ($C_{10}H_{15}N_5$) C, H, N.

Effect on the Growth of Sarcoma 180 Cells *in Vitro*.—The compounds were added in aqueous solution to the cultures of S180 cells and to a subline AH/S[13] grown as monolayers in T-15 flasks in Eagle's[14] medium containing 5% horse serum. The cells were exposed to the compounds for 7 days involving four changes of the medium. During this time the control cultures increased by 15–20-fold, as estimated by protein determinations.[15] The results are given in Table II.

Microbial Assay Procedures.—The microbial assays were carried out according to previously published techniques.[16] *E. coli* K-12 was grown in the synthetic medium described by Gray and Tatum.[17] *S. faecalis* 8043 was grown in the medium of Flynn, *et al.*,[18] from which uracil and the purines had been omitted and to which 1 mμg/ml of folic acid was added. The compounds were added to the medium at 10^{-3} to 10^{-6} M concentrations. Results are given in Table II.

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Antiviral Agents. I. Analogs and Derivatives of 2-Diethylaminoethyl 4-Methylpiperazine-1-carboxylate

ROBERT B. ANGIER, K. C. MURDOCK, WILLIAM V. CURRAN, PAULA YURKANIS SOLLENBERGER,[1a] AND JEREMIAH P. CASEY[1b]

Organic Chemical Research Section, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York 10965

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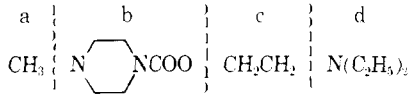
A variety of analogs and derivatives of 2-diethylaminoethyl 4-methylpiperazine-1-carboxylate (1) have been synthesized and examined for antiviral activity *vs.* influenza in mice. Nineteen compounds were accepted as active but none was superior to 1. A structure–activity relationship is discussed and methods of synthesis are described. At elevated temperatures some 2-dialkylaminoethylurethans were found to act as alkylating agents toward their corresponding 2-alkylamino ethoxide ions to form symmetrical bis-2-dialkylaminoethyl ethers (IV).

The discovery[2] that 2-diethylaminoethyl 4-methylpiperazine-1-carboxylate (**1**) exhibits significant antiviral activity against an Influenza A (PR8) infection in mice led us to synthesize various analogs and derivatives. This report describes the structure–activity relationships of these compounds as well as some of the chemistry involved in their syntheses.



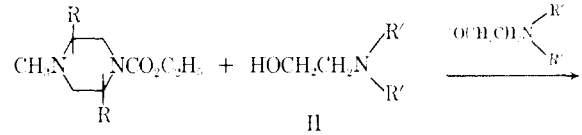
1

Chemistry.—For purposes of discussion **1** may be considered to consist of four parts, a, b, c, and d. The synthesis of analogs and derivatives of **1** will be considered under those four headings.

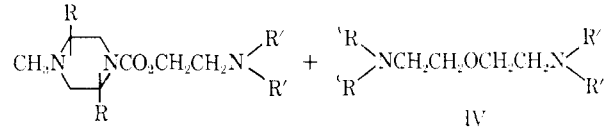
Variations in a (Table I).—Various alkyl groups were attached by the reaction of 2-diethylaminoethyl piperazine-1-carboxylate (**2**) with an alkyl halide, as in procedure A. Other variations in a are listed in Table I. Their syntheses were classical and uncomplicated and are described in the Experimental Section.

Variations in c, d, and c + d (Tables II and III).—Most of the compounds of this class were prepared by one of the following three methods: procedure B, a transesterification reaction using ethyl 4-methylpiperazine-1-carboxylate (**1**) as the starting material; procedure C, from phosgene *via* a chloroformate ester; or D, from 4-methylpiperazine-1-ylcarbonyl chloride.

The transesterification method described as procedure B is a normal base-catalyzed reaction. However, we should emphasize the fact that in order to obtain high yields and avoid the production of by-product the reaction must be carried out at a temperature not to exceed *ca.* 125°. In the early phases of the investigation the conditions used for this reaction were similar to those described by Turner[3a] in which ethyl 4-methylpiperazine-1-carboxylate (I), an amino alcohol (II), and its sodium salt were mixed and heated, first under reduced pressure for 6–8 hr and then at reflux temperature under atmospheric pressure for 7–9 hr. As the boiling point of the amino alcohol, and therefore of the reaction mixture, increased, the yield of the transesterified product III decreased. In two instances (**28**, Table II, and **68**, Table V) by-products were isolated and shown to be symmetrical ethers (IV) from the starting amino alcohol. (Under the conditions of procedure B little or none of the ethers was formed.)

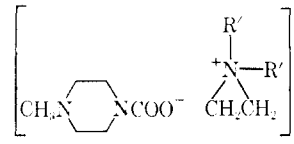


I II



III IV

The production of such ethers is apparently due to a nucleophilic attack of the dialkylaminoethoxide anion at the O-alkyl carbon of III, perhaps facilitated by an ion pair such as IIIA.[3b]



IIIA

A number of analogs (VII) of **1** were prepared by allowing an N-tertiary amino alcohol V to react first with phosgene to give a chloroformate intermediate VI (which was not isolated), and then with 4-methylpiperazine or other amines (procedure C). Although the yields ranged from moderately good to low, this approach was versatile and, in contrast to ester inter-

(1) (a) Summer employee, Career Training Program, 1964; (b) summer employee, Career Training Program, 1965.

(2) H. F. Lindh and M. Forbes, *Proc. Soc. Exp. Biol. Med.*, **121**, 65 (1966).

(3) (a) R. J. Turner, U. S. Patent 2,617,803 (1952). (b) A related reaction, an N-alkylation of hindered amines by dialkylaminoethyl carbonate esters, was recently described by L. Weintraub and R. Terrel, *J. Org. Chem.*, **30**, 2470 (1965).