Modification of the 5′ Position of Purine Nucleosides. 2. Synthesis and Some Cardiovascular Properties of Adenosine-5′-(*N*-substituted)carboxamides[1,2]

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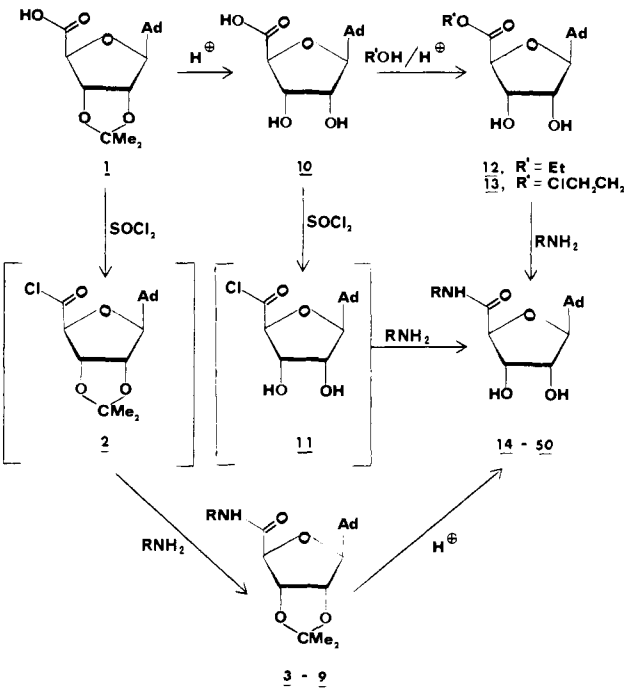
We have shown previously that the esters of adenosine-5′-carboxylic acid (**10**) represent a new class of potent nontoxic coronary vasodilators. For example, the ethyl ester (**12**), which is active by an intraduodenal or intravenous route in dogs, causes a large increase in coronary sinus PO_2 and coronary blood flow. Because of the pronounced vasoactive properties of the esters of adenosine-5′-carboxylic acid, a systematic study of the corresponding amides (**14–50**) was undertaken. In addition, several other analogues containing the N^1-oxide function (**51–52**) or 2′,3′ substituents (**3–9**, **53–54**) were studied.

The synthetic steps leading to the formation of the amides (**14–50**) of adenosine-5′-carboxylic acid are outlined in Scheme I.

The known 2′,3′-*O*-isopropylideneadenosine-5′-carboxylic acid (**1**)[4] was converted to the corresponding acid chloride (**2**) by reacting it with thionyl chloride.[2,5] Reaction of **2** with appropriate amines gave the amides (**3–9**; Table III) of 2′,3′-*O*-isopropylideneadenosine-5′-carboxylic acid. Mild acid hydrolysis of the latter gave the desired adenosine amides (Table I).

Another route for the preparation of the amides was by esterification of adenosine-5′-carboxylic acid (**10**) and subsequent treatment of the esters (**12** and **13**) with the appropriate amines. It was noted that adenosine-5′-(β-chloroethyl)carboxylate[2] (**13**) was better than other esters for its facile conversion to the desired amide. Details of the methods are described under Experimental Section.

Scheme I



Results and Discussion

All compounds reported herein were evaluated for PO_2 activity in open-chest anesthetized dogs, as described earlier.[2] The results are reproduced in Table II. The first point to be noted is the potency of the compounds. The ethyl amide **16**, for example, at 0.01 mg/kg caused an increase in coronary sinus PO_2 of 250%; the effect was initiated almost instantaneously after injection, it peaked within 1–2 min, and lasted for more than 5 h. Adenosine, on the other hand, at 2 mg/kg in a similar preparation caused an increase of 200% in coronary sinus PO_2 which lasted only 2 min. The active amides, in general, were more potent and the effect was considerably longer lasting when compared to adenosine.

Keeping R_2 constant as H, the compounds in which R_1 = H, Me, Et, etc. showed maximal activity with the monoethyl derivative **16**. As R^1 was increased further, the activity dropped sharply. Thus, the *n*-butyl derivative **28**, at 10 times the dose, caused only approximately 10% of the PO_2 increase of the ethyl derivative. In the cycloalkyl series, the activity peaked with the cyclopropyl derivative **25**. Replacement of the alkyl groups by aryl groups (as in **36** and **37**) caused a sharp decrease in activity in the PO_2 test.

When both protons of the amide nitrogen atom were substituted by alkyl groups, further loss in potency was noted. Thus, the dimethyl and diallyl amides (**44** and **48**), similar to the piperidine (**45**) or the morpholine (**46**) analogues, caused no change in PO_2 at 1 mg/kg. This suggests that a hydrogen atom on the amide nitrogen is essential for maximal activity in the series.

The N^1-oxides (**51–52**; prepared by the oxidation of the corresponding amides) were less potent than the parent amides, **16** and **25**. When the 2′,3′-OH groups in the amides **16** and **25** were converted into the corresponding diacetates **53** and **54**, again there was some drop in activity, probably due to a slow in vivo conversion of **53** and **54** into **16** and **25**. The 2′,3′-*O*-isopropylidene derivatives **5** and **6**, however, were almost completely devoid of PO_2 activity,

(1) (a) Presented in part at the 59th Conference, Chemical Institute of Canada, London, Ontario, June 8, 1978, ME-6; (b) Stein, H. H.; Somani, P.; Prasad, R. N. *Ann. N.Y. Acad. Sci.* **1975**, *255*, 380; (c) Stein, H. H.; Brondyk, H.; Prasad, R. N.; Bariana, D. S.; Savic, M.; Tietje, K.; Fung, A. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1974**, *33*, 489.
(2) For part 1 of this series, see Prasad, R. N.; Fung, A.; Tietje, K.; Stein, H. H.; Brondyk, H. *J. Med. Chem.* **1976**, *19*, 1180.
(3) Deceased.
(4) Harmon, R. E.; Zenarosa, C. V.; Gupta, S. K. *Chem. Ind. (London)* **1969**, 1141.
(5) Schmidt, R. R.; Fritz, H.-J. *Chem. Ber.* **1970**, *103*, 1867.

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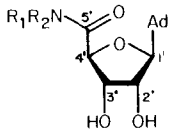
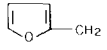
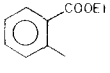
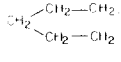
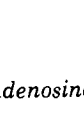
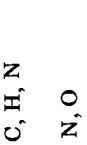
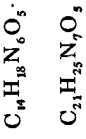
Table I



no.	R_1	R_2	mp, °C	recrystn solvent[a]	method (time, h) and % yield[b]	$[\alpha]_D$, deg	opt rotation	concn	solvent[c]	R_f[d]	formula	anal.
15	CH_3	H	240-241		A (0.75), 25 B, 37	−23 ± 0.6	27	3.2	HCl	0.50 (X)	$C_{11}H_{14}N_6O_4 \cdot 0.5H_2O$	C, H, N, O
16	CH_3CH_2	H	249-250	W or E[d] or E[e]	A (0.75), 32 E, 91	−16.3 ± 0.54	26	0.92	HCl	0.55 (X)	$C_{12}H_{16}N_6O_4 \cdot 0.5H_2O$	C, H, O
17	$HOCH_2CH_2$	H	196-198	E	E, 50	−28.8 ± 1	22	1.6	HCl	0.32 (Y) 0.52 (X)	$C_{12}H_{16}N_6O_5$ $C_{14}H_{18}N_6O_6 \cdot H_2O$	C, H, N, O C, H, N
18	$EtOC(=O)CH_2$	H	113-118[o]	E + W	D (1.0), 50							
19	$EtOCH_2CH_2$	H	107-110	E	C (*f*), 25	−7.4 ± 0.9	26	0.54	HCl	0.44 (Y)	$C_{14}H_{20}N_6O_5$	C, H, N, O
20	$PhOCH_2CH_2$	H	125-129	E	C (1.6), 33 E, 71	+50 ± 3	26	0.74	HCl	0.62 (Y)	$C_{18}H_{20}N_6O_5 \cdot 0.5H_2O$	N
21	$Me_2NCH_2CH_2$	H	165-167	E	E, 70	−44 ± 2	26	0.80	H_2O		$C_{14}H_{21}N_7O_4$	C, H, N
22	$Et_2NCH_2CH_2$	H	194-197	W	E, 73	−20 ± 2	26	0.97	EtOH		$C_{16}H_{25}N_7O_4$	C, H, N
23	*n*-C_3H_7	H	220-222	M + A + Et	C (0.5),[g] 25						$C_{13}H_{18}N_6O_4 \cdot CH_3OH$	C, H, O
24	*i*-C_3H_7	H	137-141	E	C (1.0), 23	−9 ± 2.2	26	0.223	HCl	0.53 (Y)	$C_{13}H_{18}N_6O_4$	C, H, N, O
25	c-C_3H_5	H	249-250	E	C (3.0), 20 E, 82	−6.8 ± 0.8	26	0.584	HCl	0.54 (X)	$C_{13}H_{16}N_6O_4$	C, H, N, O
26	$CH_2=CHCH_2$	H	224-225	E	C (0.8), 29 E, 80	−13.5 ± 1.4	26	0.369	HCl	0.50 (Y)	$C_{13}H_{16}N_6O_4 \cdot H_2O$	C, H, N, O
27	$CH{\equiv}CCH_2$	H	135-137	E	C (2),[h] 20	−27.5 ± 0.5	26	0.44	HCl	0.44 (Y)	$C_{13}H_{14}N_6O_4$	C, H, N, O
28	*n*-C_4H_9	H	125	M + A	C (*g*, *i*), 20						$C_{14}H_{20}N_6O_4$	C, H, N, O
29	c-C_4H_7	H	234-235	E	E, 86						$C_{14}H_{18}N_6O_4$	C, H, N
30	c-C_3H_5-CH_2	H	216-218	E	E, 51	−17.7 ± 2	26	0.56	HCl		$C_{14}H_{18}N_6O_4 \cdot EtOH$	C, H, O
31	$CH_2=C(CH_3)CH_2$	H	198-200	W	C, 41	−10 ± 1	26	1.0	HCl	0.59 (Y)	$C_{14}H_{18}N_6O_4$	C, H, N, O
32	c-C_5H_9	H	165-170	A + Et	C (1.0), 15	−3.7 ± 0.23	26	2.16			$C_{15}H_{20}N_6O_4$	C, H, N, O
33	Et_2CH	H	*j*	M + Et	C (1),[g] 10	−1.61 ± 0.8	26	0.63			$C_{15}H_{22}N_6O_4$	N
34		H	145	M + A	A (0.5),[g] 30						$C_{15}H_{20}N_6O_5$	C, H, N, O
35	*n*-C_6H_{13}	H	104-106	K	C (0.75), 19	−8.9 ± 1.5	26	0.334	HCl	0.56 (Y)	$C_{16}H_{24}N_6O_4 \cdot 0.5H_2O$	C, H, N, O
36	C_6H_5	H	252-254	E	D (3.0), 18						$C_{16}H_{16}N_6O_4$	C, H, N
37	*p*-FC_6H_4	H	243-245	M	D (5.0), 44						$C_{16}H_{15}FN_6O_4$	C, H, N
38	$C_6H_5CH_2$	H	130-133	W	C (2.0), 19	−6.3 ± 1.5	26	0.315	HCl	0.55 (Y)	$C_{12}H_{18}N_6O_4$	C, H, N, O
39	2,6-$(CH_3)_2C_6H_3$	H	203	M + D	B, 52	14.8 ± 2	26	1.7	HCl	0.62 (Y)	$C_{18}H_{20}N_6O_4 \cdot 3H_2O$	N
40	adamantyl	H	175-179	M	C (1.0), 22	−3.3 ± 1	26	1.5	CH_3COOH	0.61 (Y)	$C_{20}H_{27}N_6O_4$	C, H, N, O
41		H	229-235	E	D (4.0), 34						$C_{19}H_{20}N_6O_6 \cdot 0.5H_2O$	C, H, N
43	$CH_3CH_2CH_2O$	H	177-179	E	D (1.0), 17						$C_{13}H_{18}N_6O_5 \cdot 0.5H_2O$	C, H, N
45			228	M + A	C (1.0), 30	−5.5 ± 1.3	26	0.36	HCl		$C_{15}H_{20}N_6O_4$	C, H, N, O

46			256–258	M + W	C (1.0), 17	−4.7 ± 1.2	26	0.422	HCl	0.23 (Y)	$C_{14}H_{18}N_6O_5 \cdot 2H_2O$	C, H, N
47			224–225	M	C (1.0), 40						$C_{21}H_{25}N_7O_5$	N, O
48	$CH_2{=}CHCH_2$		224–227	E	C (1.5), 25	−50 ± 3	26	0.80	HCl	0.62 (Y)	$C_{16}H_{20}N_6O_4$	C, H, N
49		H	82–90°	E	m					0.62 (X)	$C_{20}H_{24}N_6O_6$	N, O
50		H	126–130°	E + Ea	n						$C_{23}H_{24}N_6O_6 \cdot H_2O$	N

[a] A, $(CH_3)_2CO$; B, C_6H_6; D, DMF; E, EtOH; Ea, Ethyl acetate; Et, Et_2O; Ed, compound dissolved in EtOH, filtered and evaporated to dryness under reduced pressure, and dried in vacuo over P_2O_5; M, MeOH; W, H_2O. [b] Unless otherwise specified, percent yields given are those of crude solids under each method and are overall yields from the carboxylic acids 1 or 10 for compounds obtained by methods A, C, and D. Time (in hours) required for hydrolysis of the isopropylideneadenosine amides to the corresponding adenosine amides are indicated in parentheses. [c] Unless otherwise specified, 1 N HCl was used for solution at 26 °C. [d] Solvent systems used for TLC are indicated in parentheses and described under Experimental Section. [e] After recrystallization from EtOH, the compound melts at 120 °C, solidifies, and melts again at 213–216 °C dec. Drying for several days in vacuo raises the melting point to 245–246 °C. [f] Twenty days at room temperature for hydrolysis. [g] $CHCl_3$ was used as solvent for the initial reaction. [h] Et_2O was used as solvent for the initial reaction. [i] Five days at room temperature for hydrolysis. [j] No sharp melting point. [k] The compound was analyzed without any recrystallization. [l] Heated for 4 h in DMF. [m] Obtained by heating (100 °C) the ethyl ester (12, R = Et) with a fivefold excess of the amine for 2 h. [n] Obtained in 14% yield from the β-chloroethyl ester (13) and 6 equiv of the amine (2 h at 140 °C). [o] Decomposition.

suggesting that the 2′,3′-OH groups were essential for potency.

In general, the cardiovascular activity and acute toxicity, as estimated by the LD_{50} in mice, were correlated. The lower alkyl and cycloalkyl derivatives were extremely toxic; the oral and ip LD_{50} values in some cases were 10 mg/kg and less. The dimethyl amide for example, was inactive at 1.0 mg/kg compared to the methyl amide, which showed marked activity at 0.01 and 0.1 mg/kg; the ip and oral LD_{50} values were correspondingly 10 and 50 times larger. The mechanism of toxicity was not investigated.

The ^1H NMR spectra of several simple adenosine amide derivatives possessing significantly different activity were examined in an attempt to observe a correlation between an NMR parameter representing a structural or conformational factor and biological activity. The unsubstituted (**14**), *N*-methyl (**15**), *N*-ethyl (**16**), and *N*,*N*-dimethyl (**44**) amides were chosen for this study. Aromatic and furanose ring proton chemical shifts and coupling constants are collected in Table IV.

The data clearly show the *N*,*N*-dimethyl derivative (**44**) to be unique, as there are substantial differences in both the chemical shifts and coupling constants. The most significant difference is the change in the chemical shift of H-4′. This chemical-shift difference likely arises from changes in the orientation of H-4′ in relation to the carboxamido group and not from differences in the sugar torsion angle with the heterocyclic base. However, the chemical-shift change does, nevertheless, give evidence for the syn/anti conformation.

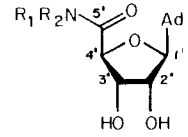
Dreiding molecular model constructions show that compounds in the syn conformation can be stabilized by favorable hydrogen bonding between the carboxamido proton and the adenine ring nitrogen as shown in Figure 1. In this conformation, H-4′ is eclipsed by the amide carbonyl. Karabatsos and others[6] have shown that this arrangement results in a shielding of the proton (upfield shift). In compounds that are not conformationally constrained, we would expect the chemical shift of H-4′ to be further downfield; examination of Table IV shows that the observed chemical shifts are in agreement with the proposed explanation.

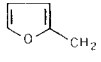
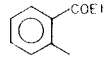
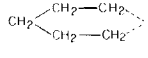
It should be stressed that the observed differences in the spectra arise from changes in the orientation of the carboxamido group. This means that the *N*,*N*-dimethyl compound (**44**) can have either syn or anti conformations as long as the orientation of the carboxamido group is such that H-4′ is deshielded (Figure 2 or 3).

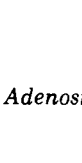
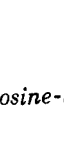
Nuclear Overhauser enhancement (NOE) experiments were employed to determine the predominant conformation of **44** and to confirm the syn assignment of **14–16**. An extensive literature exists on the use of NOE experiments for determination of nucleoside conformation.[7] The experimental conditions were first established and the method was standardized by repeating published NOE experiments,[8] using 2′,3′-isopropylideneadenosine and 2′,3′-isopropylideneguanosine and obtaining comparable results as summarized in Table V. When the experiments were performed using **14–16** and **44**, the results collected in Table VI were obtained. Also included are results for the related ethyl ester (**12**) and the parent adenosine.

(6) Karabatsos, G. J.; Ferroglio, D. J. "Topics in Stereochemistry", Eliel, E. L.; Allinger, N. L., Eds.; Wiley-Interscience: New York, 1970; Vol. V, p 167.
(7) (a) Schirmer, R. E.; Noggle, J. H.; Davis, J. P.; Hart, P. A. *J. Am. Chem. Soc.* **1970**, *92*, 3266; (b) Hart, P. A.; Davis, J. P. *Ibid.* **1971**, *93*, 753.
(8) Hart, P. A.; Davis, J. P. *J. Am. Chem. Soc.* **1969**, *91*, 512.

Table II



no.	R_1	R_2	dose,[a] mg/kg	PO_2[b] %	PO_2[b] duration[c]	BP[d] mmHg	BP[d] duration[c]	HR[e] %	HR[e] duration[c]	LD_{50}, mg/kg[f] ip	LD_{50}, mg/kg[f] po
14	H	H	0.01	79	25	−8	20	38	25	5	50
			0.10	41	240	22	240	72	240		
15	CH_3	H	0.01	105	14	−18	60	21	240	5	20
			0.10	215	240	−44	240				
16	CH_3CH_2	H	0.01	250	345	−15	120	73	345	0.5	5
17	$HOCH_2CH_2$	H	0.01	75	90	−21	90	−13	42	2	5
			0.10	163	240	−42	240	−29	15		
18	$EtOC(=O)CH_2$	H	10.00	9	30	−6	30	−10	11	>300	>300
19	$EtOCH_2CH_2$	H	0.10	25	6	−8	1	0	0	50	>1000
			1.00	135	120	−15	120	39	120		
20	$C_6H_5CH_2CH_2$	H	1.00	9	25	11	1	−4	18	500	>1000
			5.00	44	60	−10	60	7	6		
21	$Me_2NCH_2CH_2$	H	10.00	13	2	−5	15	−9	15	20	500
22	$Et_2NCH_2CH_2$	H	1.00	57	6	0	0	0	0	50	>1000
			10.00	25	60	−7	22	11	60		
23	n-C_3H_7	H	0.10	61	120	−14	37	47	120	5	200
			1.00	122	120	−62	120	−51	120		
24	i-C_3H_7	H	0.01	43	240	−5	70	29	240	5	5
25	c-C_3H_5	H	0.01	136	150	−39	150	66	150	2	5
26	$CH_2=CHCH_2$	H	0.01	129	20	0	0	0	0	200	>1000
27	$CH\equiv C\text{-}CH_2$	H	0.10	50	70	−5	70	13	60	200	>1000
			1.00	133	180	−40	180	−51	82		
28	n-C_4H_9	H	0.10	30	40	−5	40	16	40		
29	c-C_4H_7	H	0.01	79	90	−45	90	−24	48	2	5
30	c-C_3H_5-CH_2	H	0.05	47	120	−3	120	0	0	20	200
31	$CH_2=C(CH_3)CH_2$	H	0.10	38	60	−1	15	19	60	500	>1000
32	c-C_5H_9	H	0.10	83	120	−12	120	25	120	200	200
33	$(Et)_2CH$	H	0.10	28	110	−9	110	11	110	50	>300
34		H	1.00	22	20	−1	20	66	20		
35	n-C_6H_{13}	H	1.00	100	40	0	0	25	6	200	500
36	C_6H_5	H	1.00	127	120	0	0	8	7	>1000	>1000
37	p-FC_6H_4	H	10.00	30	120	0	0	0	0	500	>1000
38	$C_6H_5CH_2$	H	1.00	48	60	−5	60	−13	24	200	>1000
39	2,6-$(Me)_2C_6H_3$	H	10.00	−15	30	−13	30	25	5	>1000	>1000
40	adamantyl	H	1.00	56	30	−22	1	55	2	>300	>300
			5.00	209	60	−5	8	29	60		
41		H	10.00	39	16	−5	40	14	40	>1000	>1000
42	CH_3O	H	0.01	157	60	−9	41	20	60	20	50
			0.10	143	90	−39	90	−2	10		
43	$CH_3CH_2CH_2O$	H	0.10	52	60	−1	13	−6	3	200	>1000
44	CH_3	CH_3	1.00	0	0	0	0	0	0	50	1000
45			10.00	52	8	−7	20	3	30	>1000	>1000

46			10.00	0	0	0	0	0	0	>300	>300	
47			10.00	107	15	−7	60	12	60	>300	>300	
48	CH_2=$CHCH_2$		1.00	66	40	0	0	0	0	>300	>300	
49		H	1.00	42	7	3	30	8	1	>300	>300	
50		H	9.00	152	18	−8	7	−3	12	>300	>300	
51	CH_3CH_2	H	0.001	37	120	−27	120	65	120	2	20	
52	c-C_3H_5	H	0.01	66	75	−15	60	13	60	5	5	
53	CH_3CH_2	H	0.01	52	120	−12	70	39	120	2	2	
54	c-C_3H_5	H	0.01	67	270	−31	270	13	270	5	20	
5	CH_3CH_2	H	10.00	27	30	0	0	−5	16			
6	c-C_3H_5	H	10.00	9	60	−26	1	6	1	>300	>300	
7	CH_2=$CHCH_2$	H	1.00	0	0	14	30	16	5	>1000	>1000	
	adenosine		2.00	200	2	−60	2	−52	4			

[a] Compounds were administered by the intravenous route. [b] PO_2 = partial pressure of oxygen, change from control; initial values ranged from 15 to 25 mmHg. [c] Duration is the total time (in minutes) elapsed from the initiation of the change until return to the pretest value. [d] BP means aortic blood pressure, change from control. [e] HR = heart rate, beats/minute change from control. [f] Approximate values in mice, three animals per dose. [g] N'-Oxide. [h] 2',3'-O-Diacetyl derivative. [i] 2',3'-O-Isopropylidene derivative.

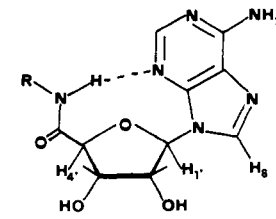


Figure 1. Syn conformation.

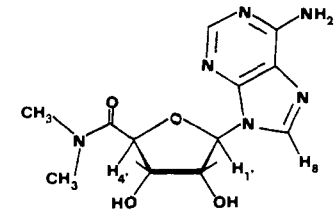


Figure 2. Syn conformation.

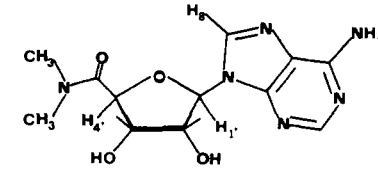


Figure 3. Anti conformation.

The marked enhancement of H-8 in **12** and **14–16** when H-1′ was irradiated confirms the close proximity of these protons as required in the syn conformation (Figure 1). In contrast, the complete lack of H-8 enhancement in the *N,N*-dimethyl amide (**44**) supports a totally different spacial arrangement where H-8 and H-1′ are not proximate, as would be the case in the anti conformer (Figure 3). While adenosine and 2′,3′-isopropylideneadenosine show substantial H-8 enhancement when H-2′ is irradiated (Tables V and VI), the amide **16** and ester **12** show no measurable interaction. This is taken to indicate that the syn conformation predominates in the case of **12** and **16** compared to the parent adenosine, where both conformations are thought to be present.[8] It is interesting to note that there is an increase in H-8 enhancement among **12** and **14–16** which parallels their relative activity. Thus, these data indicate that the syn conformation favors increased biological activity.

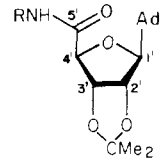
Experimental Section

Chemical Methods and Materials. Unless otherwise specified, thin-layer chromatography (TLC) was performed using Eastman 6060 silica gel chromagram sheets with fluorescent indicator utilizing the following solvent systems: X, *n*-BuOH–H_2O (47:3); Y, *n*-BuOH–NH_4OH–H_2O (86:5:14). The instruments used to determine the physical properties of these compounds were: Thomas-Hoover apparatus (melting point, uncorrected); Unicam SP-800A UV spectrometer (UV spectra); Beckman IR-8 spectrometer (IR spectra, KBr); Hilger and Watts Standard (MK-III) polarimeter (optical rotation); Varian HA-100 spectrometer (NMR spectra); and AEI MS-902 spectrometer (mass spectra). The NMR spectra were measured on approximately 10% (w/v) solutions in Me_2SO-d_6 with Me_4Si an an internal standard.

Elemental analyses were performed by the Microanalytical Services of Abbott Laboratories, North Chicago, Ill. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

General procedures followed for the preparation of the amides (**14–50**; listed in Table I) are illustrated by the following examples. In most of the cases, the intermediate 2′,3′-*O*-isopropylidene-

Table III



no.	R	mp, °C	recrystn solvent[a]	method and % yield[b]	optical rotation $[\alpha]_D$, deg	optical rotation concn (c)	optical rotation solvent[c]	R_f[d]	formula	anal.
3	C_6H_5	195-196.5	E	D, 42					$C_{19}H_{20}N_6O_4$	N, O
4	CH_3O	229-230	E	D, 66					$C_{14}H_{18}N_6O_5$	C, H, N
5	CH_3CH_2	225-229	E	A, 44.5	−22 ± 2	0.89	HCl	0.66 (X)	$C_{15}H_{20}N_6O_4$	C, H, N
6	c-C_3H_5	185-187	E	A, 38	−5 ± 1	1.0	EtOH		$C_{16}H_{20}N_6O_4$	C, H, N
7	CH_2=$CHCH_2$	214-216	E	A, 47	−36 ± 0.8	1.4	HCl		$C_{16}H_{20}N_6O_4$	C, H, N
8	$EtOC(=O)CH_2$	210	A + M	D, 33[e]				0.73 (X)	$C_{17}H_{22}N_6O_6$	C, H, N, O
9		234-236	E	D, 15[f]					$C_{22}H_{24}N_6O_4$	C, H, N, O

[a] A, $(CH_3)_2CO$; E, EtOH, Ea, ethyl acetate; M, MeOH; W, H_2O. [b] Unless otherwise specified, yields given are those of crude solids under each method, starting from the acid 1. Syntheses of these intermediates are described under the particular methods used for the syntheses of the adenosine amides (14–50). [c] The acid used for solution was 1 N HCl. Optical rotations were determined at 26 °C. [d] Solvent systems used for TLC are indicated in parentheses and are described under Experimental Section. [e] Ether was used as the solvent for the initial reaction. [f] $CHCl_3$ was used as the solvent for initial reaction.

adenosine amides were not characterized, but those which were (3–9) are listed in Table III.

Method A. Adenosine-5′-carboxamide (14). Freshly prepared 2′,3′-*O*-isopropylideneadenosine-5′-carbonyl chloride[2] (**2**; from 6.4 g of **1**) was stirred (2 h) in 50 mL of anhydrous liquid NH_3 (where excess amine could not be used as a solvent, Et_2O or $CHCl_3$ was used at −60 to −40 °C). At the end of this period, the cooling bath was removed and the reaction mixture was stirred overnight at room temperature. The residue was triturated with cold aqueous $NaHCO_3$ solution, filtered, washed with cold water, and recrystallized from absolute ethanol to give 3.5 g (55%) of crude 2′,3′-*O*-isopropylideneadenosine-5′-carboxamide, melting at 220–222 °C.

The crude amide was mixed with 1 N HCl (100 mL), and, after 45 min (different time periods required for hydrolysis of the individual compounds are indicated in the tables) at 60–70 °C, the solution was cooled (10–15 °C), basified ($NaHCO_3$), and evaporated to dryness under reduced pressure. The residue was recrystallized three times from absolute ethanol to give 1.0 g of analytically pure **14**: mp 245–247 °C; $[\alpha]^{25}_D$ −29 ± 0.9° (*c* 1.08, 1 N HCl); TLC R_f 0.40 (solvent system X). Anal. ($C_{10}H_{12}N_6O_4$) C, H, N.

Method B. Adenosine-5′-(*N*-methyl)carboxamide (15). Crude adenosine-5′-carbonyl chloride (**11**), prepared as described previously[2] from 2.81 g (0.01 mol) of the acid (**10**), was slowly added to liquid methylamine (20 mL) at −40 to −20 °C. (In the case of 2,6-dimethylaniline or higher boiling amines, a suspension of **11** in Et_2O or $CHCl_3$ was stirred with an excess of the amine at room temperature.) After standing for 2 h at room temperature, the light blue reaction mixture was evaporated under reduced pressure. The gummy residue was washed several times with ether, dissolved in warm methanol (100 mL), and filtered, and the filtrate was stirred with approximately 45 mL of a weakly basic organic anion exchanger (Rexyn-203, OH^- form) for 15 min. The chloride-free supernatant layer was filtered, and the filtrate was evaporated (30–40 °C) to dryness under reduced pressure. The residue was stirred with ether and filtered to give 0.85 g (37%) of the desired product, identical with **15**, made by method A.

Method C. Adenosine-5′-(*N*-allyl)carboxamide (26). Crude 2′,3′-*O*-isopropylideneadenosine-5′-(*N*-allyl)carboxamide (**7**), prepared by method A, was dissolved in aqueous HCOOH (20 mL of 50% aqueous HCOOH/g of **7**) and kept at 60–70 °C for 50 min. (The isopropylidene group of most of the compounds could be cleaved within 40–45 min at 60–70 °C; exceptions are noted in Table I.) After completion of hydrolysis, the reaction mixture was filtered and the filtrate evaporated to dryness under reduced pressure. The residue was repeatedly washed with ether and recrystallized from ethanol to give the desired amide **26**.

Method D. Adenosine-5′-(*N*-methoxy)carboxamide (42, R_1 = CH_3O; R_2 = H). A clear solution of methoxyamine hydrochloride (14.0 g, 0.167 mol) in $CHCl_3$ (150 mL) containing triethylamine (40 mL) was mixed with 2′,3′-*O*-isopropylideneadenosine-5′-carbonyl chloride (**2**), prepared from 5.0 g (0.0156 mol) of the acid **1** at 5 °C. The mixture was stirred (15 h) at room temperature, filtered, and evaporated under reduced pressure. The residue (23.0 g) was triturated with an aqueous $NaHCO_3$ solution at 10 °C. The insoluble material was washed with ice-water and ether and recrystallized from absolute ethanol to give 1.6 g (29%) of 2′,3′-*O*-isopropylideneadenosine-5′-(*N*-methoxy)-carboxamide (**4**; Table III), melting at 229–230 °C dec.

A solution of **4** (1.2 g) in 50% HCOOH (20 mL) was kept at 70 °C for 2.5 h (time period required for hydrolysis of other compounds are indicated in Table I). The solution was evaporated under reduced pressure, and the residue was diluted with water and evaporated again. This process of dilution with water and evaporation under reduced pressure was repeated until most of the HCOOH was driven off. Finally, the residue was washed with a cold $NaHCO_3$ solution and recrystallized twice from warm water; the product (0.87 g, 79%) was dried in vacuo over P_2O_5 at room temperature to yield adenosine-5′-(*N*-methoxy)carboxamide as a monohydrate, softening above 95 °C and melting at 113 °C dec. Anal. ($C_{11}H_{14}N_6O_5 \cdot H_2O$) C, H, N.

Method E. Adenosine-5′-(*N*-cyclopropyl)carboxamide (25). Adenosine-5′-(β-chloroethyl)carboxylate[2] (**13**; 8.5 g, 0.0248 mol) in cyclopropylamine (30 mL) was refluxed under N_2. (If the amine had a high boiling point, the mixture was kept at 60–80 °C for 30–60 min.) After 1 h, the solvent was evaporated under reduced pressure, and the residue was recrystallized from ethanol to give 6.5 g (82%) of **25**, mp 245–248 °C dec. Another recrystallization from ethanol raised the melting point.

Method F. Adenosine-5′-(*N*,*N*-dimethyl)carboxamide Monohydrate (44). Crude 2′,3′-*O*-isopropylideneadenosine-5′-carbonyl chloride (13.5 g) was stirred with excess dry dimethylamine at −10 to 0 °C. When the initial reaction was over, the mixture was allowed to warm up to room temperature. After about 3 h, the unreacted dimethylamine had evaporated. The residue was washed with ether, taken up in cold aqueous $NaHCO_3$, and extracted with $CHCl_3$ (5 × 50 mL). The $CHCl_3$ extract was dried (Na_2SO_4), filtered, and evaporated. The residue was dissolved in dilute acetic acid and filtered, and the filtrate was again extracted with $CHCl_3$ (4 × 50 mL). The $CHCl_3$ extract as before was dried (Na_2SO_4), filtered, and evaporated to give 6.0 g (43%)

Table IV. NMR Parameters of 5′-(N-Substituted or unsubstituted)adenosinecarboxamides

			chemical shifts[a]						coupling constants[b]		
no.	R_1	R_2	H-2	H-8	H-1′	H-2′	H-3′	H-4′	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$
14	H	H	8.16	8.44	6.00	4.66	4.22	4.32	7.3	4.6	1.6
15	H	CH_3	8.25	8.40	5.98	4.61	4.17	4.34	7.4	4.4	1.5
16	H	Et	8.21	8.40	5.99	4.62	4.16	4.34	7.5	4.6	1.5
44	CH_3	CH_3	8.20	8.67	6.12	4.51	4.36	4.92	5.7	~4	2.5

[a] Chemical shifts are reported in parts per million (δ) downfield from internal Me_4Si. [b] Coupling constants are reported in hertz.

of the crude 2′,3′-O-isopropylideneadenosine-5′-(N,N-dimethyl)carboxamide, mp 106–110 °C. Hydrolysis by 1 N HCl (100 mL at 60–70 °C for 45 min), isolation and purification as described in method A, gave 3.0 g (23%) of **44** as a monohydrate: mp 190–191 °C; $[\alpha]^{27}_D$ −27 ± 0.3° (c 3.0, 1 N HCl). Anal. ($C_{12}H_{16}N_6O_4 \cdot H_2O$) C, H, N.

Adenosine-5′-(N-ethyl)carboxamide N^1-Oxide (51). Hydrogen peroxide (11 mL of 30% aqueous solution) was added to a suspension of adenosine-5′-(N-ethyl)carboxamide (16; 3.0 g, 0.01 mol) in acetic acid (100 mL). After the mixture was stirred for 4 days at room temperature, 1.0 g of 5% Pd/C was added and stirred (1.5 h) at 10 °C. The mixture was filtered and washed with methanol, and the filtrate was concentrated under reduced pressure. The residue was triturated with acetone–ether and recrystallized three times from ethanol to give 2.2 g (70%) of pure adenosine-5′-(N-ethyl)carboxamide N^1-oxide, melting slowly between 185 and 200 °C: TLC R_f 0.23 (solvent system Y); $[\alpha]^{26}_D$ −20 ± 2° (c, 1, H_2O). Anal. ($C_{12}H_{16}N_6O_5$) C, H, O.

Adenosine-5′-(N-cyclopropyl)carboxamide N^1-Oxide (52). This compound was prepared in a manner similar to that for **51**, from **25** and H_2O_2 in 73% yield, melting at 195–197 °C (ethanol): TLC R_f 0.26 (solvent system X); $[\alpha]^{26}_D$ −10 ± 14° (c 0.95, 1 N HCl). Anal. ($C_{13}H_{16}N_6O_5$) C, H.

2′,3′-Di-O-acetyladenosine-5′-(N-ethyl)carboxamide (53). A mixture of adenosine-5′-(N-ethyl)carboxamide (2 g, 0.0065 mol) and acetic anhydride (15 mL) in dry pyridine (25 mL) was stirred at 40 °C. After 2 h, the reaction mixture was cooled, diluted with absolute EtOH, and allowed to stand at room temperature. The reaction mixture was then evaporated under reduced pressure; the residue was diluted again with absolute EtOH and the solution evaporated under reduced pressure. This process was repeated several times. Finally, the residue (2 g, 80%; mp 60–80 °C dec) was washed with ether and taken up in methanol, and the solution was stirred with Rexyn-203 (OH^- form). After 10 min at room temperature, the mixture was filtered and the filtrate evaporated to dryness. The amorphous residue was washed with ether to give 1.4 g of 2′,3′-di-O-acetyladenosine-5′-(N-ethyl)carboxamide (**53**), melting at 96–102 °C: $[\alpha]^{26}_D$ −19 ± 2° (c 1.8, H_2O). Anal. ($C_{16}H_{20}N_6O_6$) O.

2′,3′-Di-O-acetyladenosine-5′-(N-cyclopropyl)carboxamide (54). This compound was prepared in a manner similar to **53** in 48% yield; it was purified by silica gel chromatography (eluted with ethyl acetate); mp 99–105 °C; $[\alpha]^{26}_D$ −17.3 ± 2° (c 0.58, EtOH); R_f 0.51 (solvent system X). Anal. ($C_{17}H_{20}N_6O_6$) C, H.

Table V. Nuclear Overhauser Enhancement

compd		% enhancement[a,b] this study	ref 8
2′,3′-isopropylideneadenosine	{1′}	23	23
	{2′}	13	9
2′,3′-isopropylideneguanosine	{1′}	18	12
	{2′}	10	12

[a] Enhancement of H-8 resonance when indicated proton is saturated. [b] Enhancements are averages of multi-determinations in which high and low are discarded and are generally ± 2–3%.

Table VI. Nuclear Overhauser Enhancement

no.		% enhancement[a,b] {1′}	{2′}
12	ethyl ester	11	nil
14	unsubstituted	16	na[c]
15	N-methyl	17	na
16	N-ethyl	22	nil
44	N,N-dimethyl	nil	na

[a] Enhancement of H-8 resonance when indicated proton is saturated. [b] Enhancements are averages of multi-determinations in which high and low are discarded and are generally ± 2–3%. [c] na = not available.

Pharmacological Studies. The cardiovascular tests were performed as described previously.[2] LD_{50} values were estimated in male and female mice; groups of three animals were each administered test compounds in increments of 0.5 log doses and observed for 3 days.

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