substance P also significantly contributes to its function at a site.

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Synthesis and Hypocholesterolemic Activities of Eritadenine Derivatives

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More than 100 derivatives of eritadenine were synthesized and their hypocholesterolemic activities were evaluated. The most active derivatives were carboxylic acid esters with short-chain monohydroxy alcohols, which were 50 times more active than eritadenine and effective in lowering serum cholesterol of rats at the dose of 0.0001% in the diet. The carboxyl function and at least one hydroxy group appear to be essential for activity. The intact adenine structure seems to be required for activity except for the N^1 position where an oxygen or an alkoxy group could be attached without loss of activity.

Eritadenine is a hypolipidemic substance isolated from the Japanese mushroom shiitake (*Lentinus edodes*) and its chemical structure has been identified as 2(*R*),3(*R*)-dihydroxy-4-(9-adenyl)butyric acid by two independent groups of workers.[1,2] Eritadenine lowers all the lipid components of plasma lipoproteins (cholesterol, triglyceride, and phospholipid) and is active in several animal species including man.[3] Its hypocholesterolemic property has been studied in detail in the rat.[4-6]

In order to study the structure–activity relationship of this naturally occurring hypolipidemic agent, and also in the hope of finding a derivative with the best possible therapeutic index, numerous derivatives and analogs of eritadenine were synthesized in these laboratories and their hypocholesterolemic activities were evaluated in normal rats.

Chemical Procedures. Preparation of the eritadenine esters and amides (compounds **1–50**) was carried out by the common methods, which are described in the Experimental Section.

Syntheses of the stereoisomers of eritadenine (compounds **51–56**), noreritadenine (compound **70**), homoeritadenine (compounds **73–77**), α-*O*-alkyleritadenine (compound **68b**) and the reversed nucleosides (compounds **78–82**) have been reported by Kawazu, *et al.*[7,8]

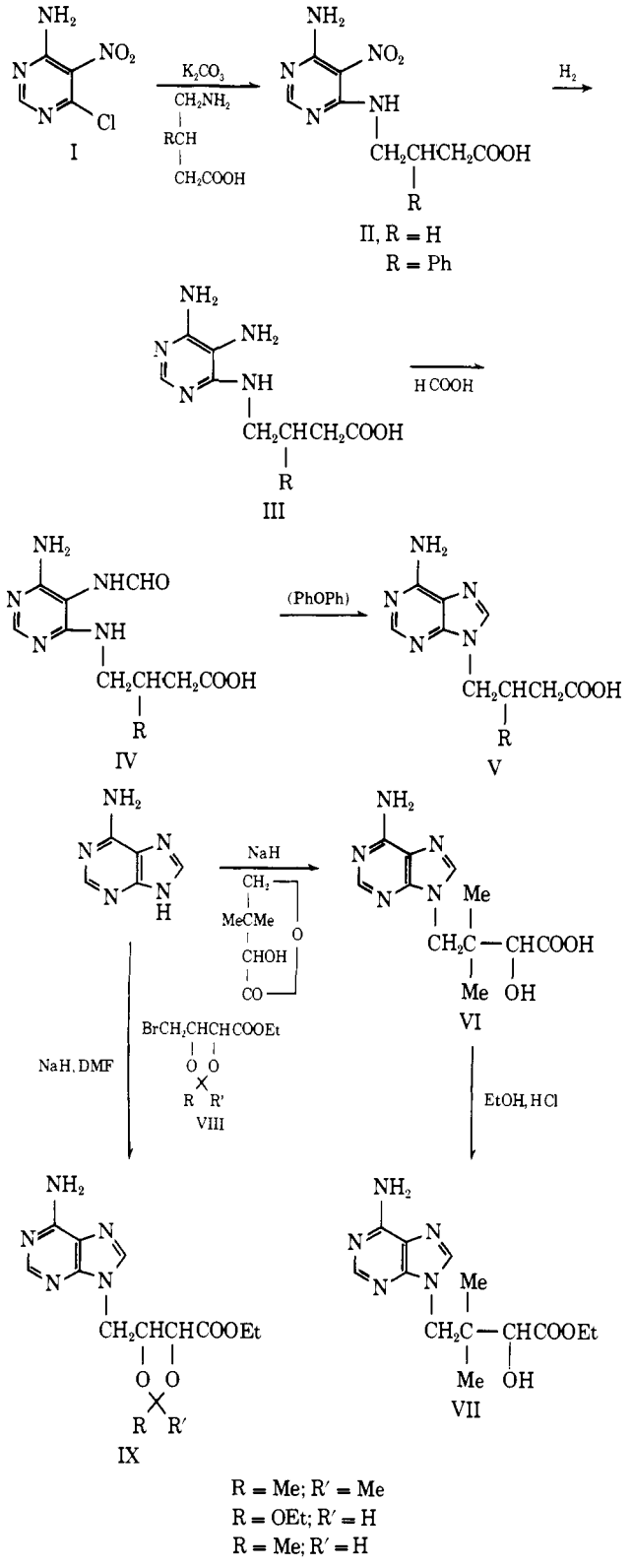
Compounds **57** and **58** were synthesized by direct alkylation of adenine with an O-protected ethyl 4-bromo-2,3-dioxybutyrate. The latter was obtained by warming D-erythronolactone in ethanol saturated with hydrogen bromide and, after removal of the ethanol, by treating the residue with a protecting agent such as ethyl orthoformate, acetone, or acetaldehyde. Compounds **59**, **60**, and **61** were prepared by condensation of the eritadenine ester with the cyclic ketones in the presence of an acid.

Compound **63** was prepared by reaction of the sodium salt of adenine with pantolactone.

Compounds **64** and **65** were synthesized from the pyrimidine derivatives employing the usual synthetic method for the purine skeleton as reported for the synthesis of eritadenine.[1,9]

The amino acids (compounds **66–68**) were synthesized from the reversed nucleoside of adenine, 5-(adenine-9*H*-9-yl)-3-acylamino-D-ribose, by oxidation with oxygen under conditions similar to those for synthesis of homoerit-

Scheme I



adenine series.[8,10] The hypoxanthine analog **83** was synthesized from eritadenine by diazotization. The 6-methylmercaptopurine derivative **84** was prepared from 4-(6-methylmercapto-9*H*-purin-9-yl)-2(*R*),3(*R*)-(cyclohexylidenedioxy)butyric acid.[11] Compounds **85–99** (except **96** and **97**) were prepared by the usual methods shown in the Experimental Section.

The N^6-formyl derivatives **90–94** were obtained by treating eritadenine with dimethylformamide dialkylacetal and purified by silica gel chromatography. These compounds were probably produced *via* an intermediate, N^6-dimethylaminomethylene eritadeninate, which could be hydrolyzed owing to the acidity of silica to the formyl derivatives during the purification process.

Preparation of compounds **96, 121,** and **123** was carried out by oxidation of corresponding reversed nucleosides according to the method by Kanno, *et al.*[12]

N^1-Oxyeritadenine (compound **100**) was prepared from eritadenine by oxidation with hydrogen peroxide in acetic acid, and N^1-alkoxyeritadenine derivatives (compounds **112–116**) were obtained by alkylation of the N^1-oxyeritadenine derivatives with alkyl halides (Scheme I).

The structures of these compounds were confirmed by means of elemental analysis and uv spectroscopy. Absorption maxima in water at 261 (pH 2), 235, 264 (pH 6.8), 232, and 268 nm (pH 13) for compound **114** were compared with those for N^1-oxyadenine-9*H*-9-yl derivatives reported by Stevens, *et al.*,[13] and with those for N^1-alkoxyadenine-9*H*-9-yl derivatives reported by Fujii, *et al.*[14]

The N^7 isomers (compounds **119** and **120**) were obtained *via* the synthetic route shown in Scheme II. After removing the protective groups of XII, oxidation with oxygen in dilute alkali solution was successfully carried out.

Synthesis of the N^3 isomers (compounds **117** and **118**) has been reported by Okumura, *et al.*[11]

Biological Results. The hypocholesterolemic rates of eritadenine at the doses of 5 and 10 mg % in the diet were 18 (mean of seven experiments) and 25% (mean of 23 experiments), respectively, under the present conditions.

Scheme II

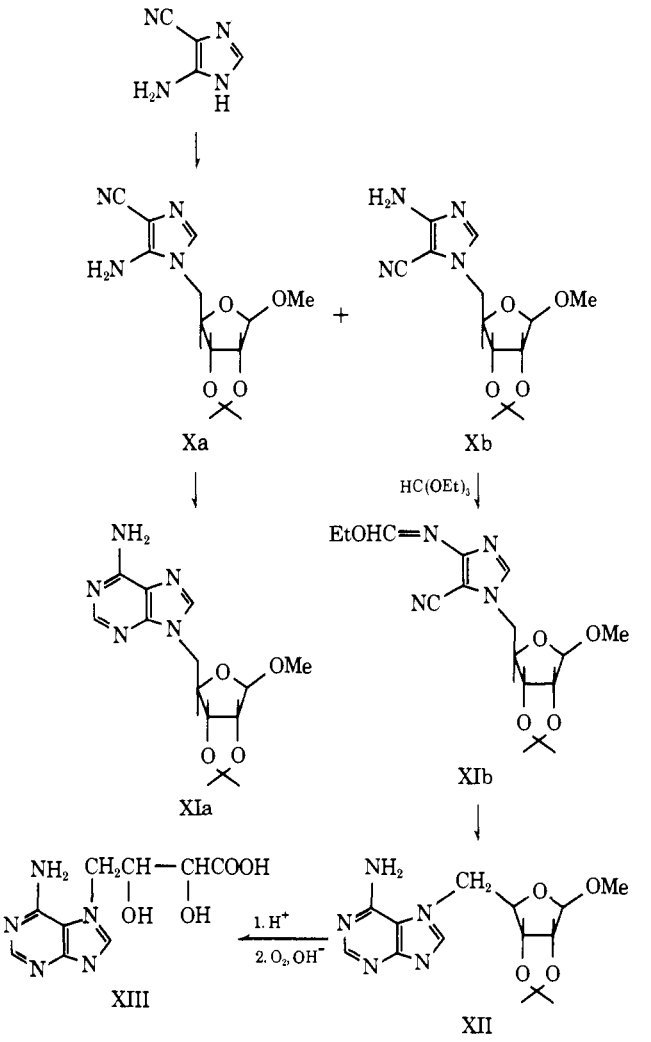


Table I

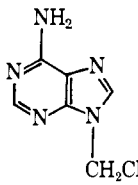
$ACH_2CHCHCOY^m$ (RO, OR)

No.	Y	R	Method	Yield, %	Recrystn solvent[a]	Mp, °C	MED, mg %	Formula
Eritadenine							5	
1	OCH_3	H	A[d]	85.6	A	228–230	0.2, >0.05	$C_{10}H_{15}N_5O_4$
2	OC_2H_5	H	A	93.5	B	191–193	0.1, >0.05	$C_{11}H_{17}N_5O_4$
3	O-*n*-C_3H_7	H	A	85.5	C	176–178	0.1–0.05	$C_{12}H_{17}N_5O_4$
4	$OCH_2CH{=}CH_2$	H	A	68.5	B	140–142	0.3, >0.1	$C_{12}H_{15}N_5O_4$[e]
5	$OCH_2C{\equiv}CH$[b]	H	A	25.8	A	190–192	0.3, >0.05	$C_{12}H_{13}N_5O_4$[f]
6	O-*i*-C_3H_7	H	A	42.9	D	182–185	0.2, >0.05	$C_{12}H_{17}N_5O_4$[g]
7	O-*n*-C_4H_9	H	A	88.9	E	156–158	0.2, >0.05	$C_{15}H_{19}N_5O_4$
8	O-*i*-C_4H_9	H	A	80.5	F	183–185	0.1–0.05	$C_{13}H_{19}N_5O_4$
9	O-*n*-C_5H_{11}	H	A	77.6	G	153–155	0.15	$C_{14}H_{21}N_5O_4$
10	O-*i*-C_5H_{11}	H	A	53.2	G	161–163	0.1	$C_{14}H_{21}N_5O_4$
11	O-*sec*-C_5H_{11}	H	A	39.0	B–G	146–151	0.1	$C_{14}H_{21}N_5O_4$
12	O-*n*-C_6H_{13}	H	A	66.0	F	151–153	0.3, >0.2	$C_{15}H_{23}N_5O_4$
13	O-*n*-C_8H_{17}	H	A	61.6	A	159–161	0.2–0.3	$C_{17}H_{27}N_5O_4$
14	O-*n*-$C_{12}H_{25}$	H	A	14.3	A	165–166	2, >0.3	$C_{21}H_{35}N_5O_4$
15	O-*n*-$C_{18}H_{37}$	H	A	9.6	A	165–167	1, >0.25	$C_{27}H_{47}N_5O_4$
16	$OCH_2C_6H_5$	H	A	65.5	H–I	195–197	1, >0.5	$C_{16}H_{17}N_5O_4$
17	OCH_2-α-furyl	H	B	3.6	B	168–170	1, >0.2	$C_{14}H_{15}N_5O_5$
18	$O(CH_2)_3Cl$	H	A	65.5	B	148–150	>0.2	$C_{12}H_{16}N_5O_4Cl$
19	$O(CH_2)_5Cl$	H	B	16.0	D	131–133	0.1	$C_{14}H_{20}N_5O_4Br$
20	$O(CH_2)_2OH$	H	A	80.0	A–H	214–215	5, >0.5	$C_{11}H_{15}N_5O_5$
21	$O(CH_2)_3OH$	H	A	68.0	B–H	161–165	>1	$C_{12}H_{17}N_5O_5$[h]
22	$OCH_2C(OH)HCH_2OH$	H	A	27.5	A–B	154–156 dec	>5	$C_{12}H_{17}N_5O_6$
23	OCH_2CH_2O-Erit[c]	H	A	40.6	A	219–221 dec	0.1	$C_{20}H_{24}N_{10}O_8$
24	$O(CH_2)_2OCH_3$	H	A	57.0	D	112–115	5, >1	$C_{12}H_{17}N_5O_5$
25	$O(CH_2)_2OC_2H_5$	H	A	69.0	D	126–128	>0.2	$C_{13}H_{19}N_5O_5$
26	$O(CH_2)_2OC_5H_6$	H	A	43.0	B	162–164	>0.2	$C_{17}H_{19}N_5O_5$
27	$OCH_2CO_2C_2H_5$	H	B	55.5	D	173–175	1, >0.5	$C_{13}H_{17}N_5O_6$
28	$OCH_2COC_6H_5$	H	B	56.0	H–L	177 dec	<0.5	$C_{17}H_{17}N_5O_5 \cdot 0.25H_2O$
29	$OCH_2COC_6H_4NO_2$	H	B	65.0	H–L	169–170	>1	$C_{17}H_{16}N_6O_7$[i]
30	$OCH_2OC(=O)(CH_2)_4CH_3$	H	B	7.0	H–L	153	>2	$C_{16}H_{23}N_5O_6$
31	4-*N*-Methylpiperidyl	H	C	21.2	H	222–223	>1	$C_{15}H_{22}N_6O_4$
32	*O*-Cholesteryl	H	B	4.7	B–H	234–235	10, >2	$C_{38}H_{59}N_5O_4$
33	*O*-β-Sitosteryl	H	B	3.5	H–L	233–235	>2	$C_{40}H_{63}N_5O_4$
34	2,3,4-Tri-*O*-acetyl-D-xylose	H	B	20.0	H–I	200 dec	>2	$C_{20}H_{25}N_5O_{11}$
35	2,3,4,6-Tetra-*O*-acetyl-D-glucose	H	B	38.0	H–I	209	>10	$C_{23}H_{29}N_5O_{13}$
36	OCH_3	$COCH_3$	E	84.4	D	215–217	<5	$C_{14}H_{17}N_5O_6$

37	OC_2H_5	$COCH_3$	81.0	B	198–201	0.2	$C_{15}H_{19}N_5O_6$
38	O-*n*-C_3H_7	$COCH_3$	69.4	B	180–182	0.1	$C_{16}H_{21}N_5O_6$
39	O-*i*-C_4H_9	$COCH_3$	82.4	B	182–184	0.2	$C_{17}H_{26}N_5O_6$
40	O-*n*-C_6H_{17}	$COCH_3$	64.5	B	162–164	>0.25	$C_{21}H_{31}N_5O_6$[f]
41	OC_2H_5	COC_2H_5	70.0	B–J	130–132	0.1, >0.05	$C_{17}H_{23}N_5O_6$
42	O-*n*-C_3H_7	COC_2H_5	53.3	B–K	118–121	0.1	$C_{18}H_{25}N_5O_6$
43	O-*i*-C_4H_9	COC_2H_5 E	55.0	B–K	128–130	0.2	$C_{19}H_{27}N_4O_6$
44	O-*n*-C_6H_{17}	COC_2H_5 E	36.8	A–K	105–106	>0.25	$C_{22}H_{35}N_5O_6$
45	OH	*n*-COC_3H_7 E	50.0	B	202–204	5	$C_{17}H_{23}N_5O_6$
46	OC_2H_5	*n*-COC_3H_7 E	65.0	B–J	110–112	0.2	$C_{19}H_{27}N_5O_6$
47	NH_2	H F	73.5	L	253–255	>5	$C_9H_{12}N_6O_3$
48	$NHCH_2C_6H_5$	H F	81.8	B	193–195	>5	$C_{16}H_{18}N_6O_3$[k]
49	S-*i*-C_5H_{11}	H D	43.0	G	166–168	0.1	$C_{14}H_{21}N_5O_3S$
50	SCH_2CH_2Cl	H D	10.0	D	162–164	0.2, >0.1	$C_{11}H_{14}N_5O_3SCl$[l]

[a] A, MeOH; B, EtOH; C, *n*-C_3H_7OH; D, *i*-C_3H_7OH; E, dioxane; G, CH_3CN; H, DMF; I, Et_2O; J, petroleum ether; K, isopropyl ether; L, H_2O. [b] Esterified in benzene using TsOH as a catalyst. [c] Erit = $-COC(OH)HC(OH)HCH_2A$. [d] See Experimental Section. [e] N: calcd, 23.88; found, 23.37. [f] N: calcd, 24.05; found, 23.62. [g] N: calcd, 23.72; found, 23.28. [h] C: calcd, 46.30; found, 45.88. N: calcd, 22.50; found, 22.09. [i] N: calcd, 19.77; found, 20.19. [j] C: calcd, 56.11; found, 56.60. [k] N: calcd, 24.55; found, 23.68. [l] N: calcd, 21.11; found, 20.52. [m] A = aden-9-yl.

Table II



$CH_2CH(OH)CH(OH)COOR$

No.	R	Stereoisomerism	MED, mg %
51	H	D-Threo	20
52	C_2H_5	D-Threo	5, >0.2
53	Na	L-Erythro	>20
54	C_2H_5	L-Erythro	5, >0.2
55	Na	L-Threo	>20
56	C_2H_5	L-Threo	>5

This activity is about ten times as active as clofibrate, the most widely used synthetic hypocholesterolemic agent. The hypocholesterolemic activity of eritadenine was immensely augmented by esterifying the carboxyl group with lower (C_1–C_5) monohydroxy alcohols (**1–3, 6–11**). These compounds were 25 to 50 times as active as the parent compound and their minimal effective doses in the diet were as low as 0.1–0.2 mg/kg of body weight/day when calculated from the amount of food consumption.

Esters with alcohols possessing an aliphatic chain of six or more carbon atoms (**12–15**) or aromatic rings (**16** and **17**) were less active than the lower esters, but they were more active than eritadenine. The effect of substitution of a halogen atom at the ω carbon of lower linear alcohols in the eritadenine esters was inconsistent (**18** and **19**).

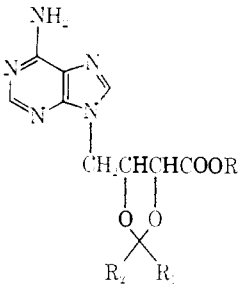
Introduction of a double bond (**4**) or a triple bond (**5**) in the aliphatic chain seems to be somewhat detrimental. Substitution of OH (**20–22**) or OR (**24–26**) on the aliphatic chain appears to diminish markedly the activity of the parent ester, sometimes to levels lower than that of eritadenine. The ethylene glycol bisester **23** of eritadenine showed an activity comparable to those of unsubstituted lower alkyl esters. Carbonyl- or carbonyloxy-substituted methyl esters (**27–30**) were less active than the unsubstituted methyl ester, although some of them (*e.g.*, **27** and **28**) may be more active than eritadenine.

Esterification with a hydroxyl function which is directly attached to a bulky ring structure seems to give no advantage over unesterified eritadenine (**31–35**). Amide derivatives are probably less active than eritadenine (**47** and **48**). Esters with mercaptans are probably as active as those with ordinary alcohols (**49** and **50**). Acylation of the two hydroxyl groups of the eritadenine side chain with short-chain aliphatic carboxylic acids does not seem to affect the activities of eritadenine and its esters (**36–46**) (Table I).

Eritadenine is the D-erthro isomer of four possible optical isomers resulting from the two asymmetric centers of the side chain. Among the three other isomers of eritadenine, the D-threo isomer (**51, 52**) was the most active, but it was less active than eritadenine. The L-threo isomer (**55, 56**) was the least active (probably totally inactive), and the L-erythro isomer (**53, 54**) was intermediate between the above two isomers (Table II).

Ether bond formation at one (**68b**) or both (**58–60**) of the hydroxyl groups abolished the activity except for the ethoxymethylene derivative **57**, which is chemically unstable. Displacement of the hydroxyl groups by hydrogen (**64**), or by a phenyl group at 3-C and by hydrogen at 2-C (**65**), or substitution of two methyl groups at 3-C (**62**) led to loss of activity. Substitution of an amino or acetylamino group for the hydroxyl group at 2-C (**66, 68**) weakened

Table III



No.	R	R_1	R_2	Yield, %	Recrystn solvent[a]	Mp, °C	MED, mg %	Formula
57	Et	OEt	H	26.7	M-N	140.5–142	10, >0.2	$C_{14}H_{15}C_9O_5$
58	Et	CH_3	H	20.0	A	210.5–212	>10	$C_{13}H_{17}N_3O_4$
59	Et	$-(CH_2)_4-$		65.5	P	129–131	>10	$C_{16}H_{21}N_3O_5$
60	Me	$-(CH_2)_5-$		55.8	O	143–146	>10	$C_{16}H_{21}N_3O_5$[b]
61	Et	$-(CH_2)_6-$		27.7	I	129–133		$C_{18}H_{25}N_3O_4$

[a] A, MeOH; I, Et_2O; N, CCl_4; O, AcOEt; P, benzene; M, $CHCl_3$. [b] C: calcd, 55.32; found, 55.74.

the activity considerably but apparently not to zero as judged by the activity of the ethyl ester of **66** (**67**) (Tables III and IV).

Substitution of a formylmethyl group (**69**), 5-deoxypentoses (**78–80**) and 6-deoxyhexoses (**81**, **82**) for the entire side chain, and reduction of the carboxyl function (**71**, **72**) gave compounds without activity. Deletion of one hydroxymethylene group (**70**), or insertion of one with either configuration between 2-C and COOH (**73**, **76**), did not nullify the activity as judged by the activities of their lower alkyl esters (**74**, **75**, **77**), although the activity was reduced substantially in comparison with eritadenine (Table V).

Substitution of OH at C^6 (**83**), SCH_3 at C^2 (**85**, **86**), C^6 (**84**), or C^8 (**89**), or Br at C^8 (**87**, **88**) on the purine ring gave inactive compounds. Formylation of the amino group at C^6 did not affect the activity (**90–94**). Gastric acidity is expected to liberate the formyl group after ingestion. Substitution of an alkyl (**95**, **96**), phenylalkyl (**97**), or N-substituted carbamoyl (**98**, **99**) group on the C^6 amino nitrogen seems to impair the activity (Table VI).

The N^1-oxide of eritadenine (**100**) and its lower alkyl esters (**101–107**) were nearly as active as eritadenine and its corresponding esters. The benzyl (**108**) and 2,3-dihydroxypropyl (**111**) esters of eritadenine N^1-oxide were much less active than the lower alkyl esters. The 2-chloroethyl ester of the N^1-oxide (**110**) was less active than the unsubstituted ethyl ester. The cyclohexyl ester (**109**) showed an activity equal to or higher than that of eritadenine (Table VII).

Lower alkyl esters of N^1-alkoxy- (C_1–C_5) eritadenine (**112–116**) appear to be as active as the corresponding esters of eritadenine (Table VIII).

A position isomer of eritadenine with the side chain at N^3 (**117**) seems to retain some activity while the other N^7 isomer (**119**) was inactive as judged by the activities of their respective lower alkyl esters (**118**, **120**) (Table IX).

Substitution of benzimidazole (**121**), uracil (**123**), or ammonia (**124**) for the adenine moiety of eritadenine resulted in an entire loss of activity. The isoamyl ester of a 4,5-substituted imidazole analog of eritadenine (**122**) was unexpectedly active, although less active than eritadenine (Table X).

In conclusion, the minimum structural requirements for the hypocholesterolemic activity of eritadenine include the carboxy function, at least one hydroxy group on the side chain, and the intact adenine nucleus where an oxygen or alkoxy group could be attached at N^1 without loss of activity. Esterification of the carboxy group with lower monohydroxy alcohols invariably amplifies the activities of parent compounds.

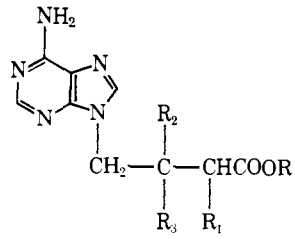
Discussion

The most noteworthy of the above results is the marked augmentation of the hypocholesterolemic property observed upon esterification of eritadenine with lower alcohols. One of the factors that determine the activities of these esters is absorbability from the intestinal tract, since Meshi, *et al.*,† in these laboratories found that only about 10% of an oral dose of eritadenine was absorbed in the rat, whereas the bulk of an oral dose of lower alkyl esters of eritadenine was absorbed. They also showed that the longer the alkyl chain of the alcohol the more susceptible to hydrolysis in the intestine and, hence, the less permeable through the intestinal barrier. This explains the relatively diminished activities of the esters with higher alcohols. Whether these esters act *per se* at the receptor site or only after hydrolysis to unesterfied eritadenine is unknown. In this respect it is of interest that Iwai, *et al.*,[15] in these laboratories have observed that some of the eritadenine esters are more potent inhibitors than eritadenine in cell-free cyclic AMP-dependent protein kinase systems from rat liver and fat tissue. In view of the extremely low minimal effective doses of the eritadenine esters and structural similarity with cyclic AMP that functions in minute concentrations in the cells, an effect on some cyclic AMP-mediated system would be an attractive hypothesis as the mechanism of action of eritadenine derivatives.

Determination of Hypocholesterolemic Activity. Male Sprague-Dawley rats were purchased from Nihon CLEA Co., Ltd., Tokyo, and maintained on commercial laboratory chow (Nihon CLEA CE-2 pellets) for at least 1 week before the experiments. At the start of each experiment rats weighing 120–140 g were anesthetized with ether, blood samples of about 0.5 ml were taken from the tail tip, and serum cholesterol levels were determined by the method of Zak, *et al.*[16] After the rats showing extremely low or high serum cholesterol levels had been eliminated, the rest were divided into groups of five rats in such a way that the average serum cholesterol levels and the average body weights of all the groups were as close to each other as possible. In this way experimental errors arising from

† T. Meshi, *et al.*, unpublished results.

Table IV



No.	R	R_1	R_2	R_3	Yield, %	Recrystn solvent[a]	Mp, °C	MED, mg %	Formula
62	Et	OH	CH_3	CH_3	61	M-O	161–163	>20	$C_{13}H_{19}N_5O_3$
63	H	OH	CH_3	CH_3	6	A	196–197.5		$C_{11}H_{15}N_5O_2 \cdot CH_3OH$
64	H	H	H	H	84.3[b]	H	297–298[c]	>20	$C_9H_{11}N_5O_2$
65	H	H	H	Ph	51[b]	H-L	281–285	>20	$C_{15}H_{15}N_5O_2$
66	H	NH_2	OH	H				>20	
67	C_2H_5	NH_2	OH	H				5	
68	Na	$NHCOCH_3$	OH	H				>10	
68b	*i*-Bu	OMe	OH	H				>20	

[a]A, MeOH; H, DMF; L, H_2O; M, $CHCl_3$; O, AcOEt. [b]Compounds **64** and **65** were obtained by thermal cyclization of 4-(4-amino-5-formylaminopyrimidine-6-yl)aminobutyric acid derivatives in diphenyl ether. [c]This compound was independently synthesized by N. J. Leonard and K. Ito, *J. Amer. Chem. Soc.*, **95**, 4010 (1973).

the variation of the natural serum cholesterol level of individual rats were minimized.

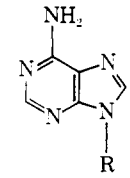
Each test compound was mixed with the powder chow of Nihon CLEA CE-2 in a mortar and fed *ad libitum* from a powder-feeding dish (Natsume Seisakusho Co., Ltd., Tokyo) for 7 days. Control rats were fed the CE-2 powder. Calculation from the consumed amount of the diet showed that the concentration of the test compound expressed in mg % (mg per 100 g powder chow) could be taken in approximation as the dose expressed in mg/kg of body weight/day.

After the feeding period of 7 days serum cholesterol levels of all the rats were determined as described above. A test compound in a given dosage was judged to be effective when the hypocholesterolemic rate calculated by the following formula was 15% or more.

$$\text{hypocholesterolemic rate} = 1 - \frac{\text{mean serum cholesterol of treated rats}}{\text{mean serum cholesterol of control rats}} \times 100\%$$

The hypocholesterolemic activities of the test compounds are listed in the tables as minimal effective doses (MED) which represent the lowest effective concentration (mg %) examined of each compound in the diet.

Table V



No.	R	MED, mg %
69	CH_2CHO	>5
70	$CH_2CHOHCOOC_2H_5$, *R*	5, >0.5
71	$CH_2CHOHCHOHCH_2OH$, 1,2*S*,3*R*	>5
72	$CH_2CHOHCHOHCH_2OH$, 1,2*R*,3*S*	>5
73	$CH_2(CHOH)_3COONa$, 2*S*,3*R*,4*R*	>10
74	$CH_2(CHOH)_3COOC_2H_5$, 2*S*,3*R*,4*R*	10, >1
75	$CH_2(CHOH)_3COOiC_4H_9$, 2*S*,3*R*,4*R*	1, >0.5
76	$CH_2(CHOH)_3COOH$, 2*R*,3*R*,4*R*	>10
77	$CH_2(CHOH)_3COOiC_4H_9$, 2*R*,3*R*,4*R*	10, >1
78	5-Deoxy-D-arabinose (5)	>10
79	5-Deoxy-L-arabinose (5)	>10
80	5-Deoxy-D-ribose (5)	>10
81	6-Deoxy-D-glucose (6)	>20
82	6-Deoxy-D-fructose (6)	>10

Experimental Section

General Procedures for the Preparation of the Eritadenine Ester and Amide Derivatives (Compounds 1–50). Method A. By the Reaction with Alcohols in the Presence of Acid Catalyst. A mixture of eritadenine, an equal amount of concentrated H_2SO_4, and an alcohol (50 times) was heated at 70–100°. After cooling at 60°, the mixture was neutralized with Amberlite IR-45 and the resin was removed by filtration. The filtrate was concentrated to dryness *in vacuo*, and the residue was crystallized from an appropriate solvent to afford the product.

Method B. By Alkylation of the Metal Salt of Eritadenine. A suspension of the metal (sodium or silver) salt of eritadenine and a small excess of an alkyl halide (or *O*-tosylate in some cases) in DMF (20 times) was heated at 100° for 10–20 hr. After cooling, the reaction mixture was filtered to remove the inorganic precipitate and the unchanged material, and the filtrate was concentrated to dryness *in vacuo*. Purification by recrystallization or, if necessary, by column chromatography on silica gel gave the product.

Method C. By the Ester-Exchange Reaction. Sodium (46 mg) was dissolved in anhydrous *N*-methyl-4-piperidinol (46 g). To this solution was added eritadenine ethyl ester (8 g), and the mixture was heated at 130 ± 5° for 24 hr. After cooling, the reaction mixture was diluted with ether and the precipitate was collected by filtration. Recrystallization from DMF gave compound **31** (2.1 g).

Method D. By the DCCD Method (Example). To a cooled solution of 2,3-(*O*-cyclohexylidene)eritadenine (1.0 g) in DMF (10 ml) were added isoamyl mercaptan (830 mg) and DCCD (825 mg), and the mixture was stirred at 25° for 5 hr. The reaction mixture was diluted with ether (10 ml). The precipitate was removed by filtration and the filtrate was concentrated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel (20 g) to give 2,3-(*O*-cyclohexylidene)eritadenine isoamyl thioester (640 mg, 51%): mp 123–125°; nmr ($CDCl_3$) δ 0.93 (d, 6 H), 2.9 (t, 2 H), 4.0–4.75 (m, 4 H), 6.09 (s, 2 H), 7.95 (s, 1 H), 8.37 (s, 1 H). A portion (420 mg) of this sample was treated with 70% HCO_2H (10 ml) at 25° for 4 days. The solution was concentrated to dryness *in vacuo*, and the residual solid was recrystallized from MeCN to afford compound **49** (290 mg, 85%).

Method E. By Acylation of Eritadenine Esters. A mixture of an eritadenine ester, pyridine (30–40 times), and an acid anhydride (4 molar equiv) was warmed at 40–45° for 3 hr. The pyridine was removed by evaporation *in vacuo* and the residue was crystallized by trituration with isopropyl ether. The crystals were collected by filtration and recrystallized from an appropriate solvent to give the pure product.

Method F. By Aminolysis of Eritadenine Ethyl Ester. A mix-

Table VI

No.	R_1	R_2	R_3	R	Yield, %	Recrystn solvent[a]	Mp, °C	MED, mg %	Formula
83	H	OH	H	NH_4	82.0	B–L	222–224	>20	$C_9H_{13}N_5O_5$
84	H	SCH_2	H	H	83.5	F	156–159	>10	$C_{10}H_{12}N_4O_4S \cdot C_4H_8O_2$
85	SCH_3	NH_2	H	H		L	242	>20	$C_{10}H_{13}N_5O_4S$
86	SCH_3	NH_2	H	C_2H_5	70.0	B	169–170	>10	$C_{12}H_{17}N_5O_4S$
87	H	NH_2	Br	Na	34.0	B–L	217 219	>10	$C_9H_9N_5O_4BrNa \cdot 0.5H_2O$
88	H	NH_2	Br	C_2H_5	70.0	B	182–183	>1	$C_{11}H_{14}N_5O_4Br$
89	H	NH_2	SCH_3	C_2H_5	38.4	B	143–145	>10	$C_{12}H_{17}N_5O_4S \cdot H_2O$
90	H	NHCHO	H	CH_3	20.4	A	169–171	<10	$C_{11}H_{13}N_5O_5$
91	H	NHCHO	H	C_2H_5	22.6	B	160–161	0.2	$C_{12}H_{15}N_5O_5$
92	H	NHCHO	H	*n*-C_5H_{11}	11.4	B	132–134	0.2	$C_{15}H_{21}N_5O_5$
93	H	NHCHO	H	*i*-C_5H_{11}	21.4	B	167–168	0.2	$C_{15}H_{21}N_5O_5$
94	H	NHCHO	H	CH_2Ph	27.0	B	109–111	>0.2	$C_{17}H_{17}N_5O_5 \cdot 0.25H_2O$
95	H	NHEt	H	H	6.0	B–I	190–192	>2	$C_{11}H_{15}N_5O_4 \cdot 1.5H_2O$
96	H	NH-*n*-Bu	H	*i*-Bu				>0.2	
97	H	$NHCH_2Ph$	H	H				>10	
98	H	NHCONHEt	H	C_2H_5	12.4	B	177–180	>1	$C_{14}H_{20}N_6O_5$
99	H	NHCONHPh	H	C_2H_5	13.6	B	186–188	>1	$C_{18}H_{20}N_6O_5$

ture of eritadenine ethyl ester and a large excess of an amine was heated at 80–85° for 24 hr. After cooling, the reaction mixture was diluted with isopropyl ether and the precipitate was collected by filtration. Recrystallization from an appropriate solvent afforded the pure product. The reaction with an amine which has a low boiling point was run in ethanolic solution in a sealed tube.

Ethyl 4-Bromo-2,3-dihydroxybutyrate. A solution of 12 g of D-erythronolactone in 20 ml of EtOH was saturated with hydrogen bromide below 40° and allowed to stand overnight at room temperature.

The reaction mixture was evaporated *in vacuo*, then poured into ice-water, neutralized with 10% Na_2CO_3 solution, and extracted with ether. The extract was washed with NaCl-saturated water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was distilled *in vacuo* to give a colorless oil (10 g): bp 124–125° (4 mm); ν_{max} (neat) 3380 (OH), 1725 (–C=O), 1210, 1090 cm^{-1} (–CO–).

General Procedure for Preparation of the Masked Ethyl 4-Bromo-2,3-dihydroxybutyrate VIII. Ethyl 4-bromo-2,3-dihydroxybutyrate (0.1 mol) was dissolved in 200 ml of the masking reagent; then 5 ml of concentrated H_2SO_4 was added dropwise to this solution at 5°. The mixture was allowed to stand overnight at room temperature and poured into a saturated caustic baryta solution at 0° with stirring. The inorganic substance was removed by filtration, and the mother liquor was spin evaporated *in vacuo*. The residue was extracted with benzene. The extract was dried and evaporated. Distillation of the residue under reduced pressure gave a respective masked compound. For compound VIII with R = R′ = CH_3, bp 80–81° (4 mm), ν_{max} (neat) 1740 cm^{-1} (CO), yield 88%; R = H, R′ = CH_3, bp 103–106° (4 mm), ν_{max} (neat) 1740 cm^{-1} (CO), yield 75%; R = H, R′ = OEt, bp 129–133° (4 mm), ν_{max} (neat) 1740 cm^{-1} (CO), yield 78%.

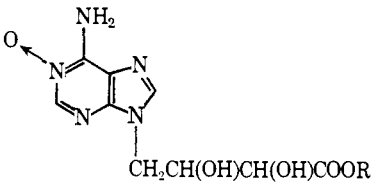
General Procedure for Preparation of 4-(4-Amino-5-formylaminopyrimidin-6-yl)aminobutyric Acid Derivatives IV. A mixture of 4-amino-5-nitro-6-chloropyrimidine (0.02 mol), amino acid (0.022 mol), K_2CO_3 (0.035 mol), Me_2CO (50 ml), and H_2O (25 ml) was stirred for 3 hr at 40°, and then the acetone was removed by distillation. The residual solution was acidified with HCl to give a crystalline product II. The crude product was dissolved in a 5% KOH solution and reduced with H_2 in the presence of Raney nickel at room temperature. After removal of the catalyst by filtration, the filtrate was acidified with HCOOH to give a crystalline 4-(4,5-diaminopyrimidin-6-yl)aminobutyric acid derivative III. The crude amino acid was dissolved in formic acid (*ca.* 15 times volume) and refluxed for 4 hr. The formic acid was evaporated *in vacuo* to give the formyl derivative. Recrystallization from water gave pure IV: λ_{max} (MeOH) 270 (H^+), 278 nm (OH^-). For compound IV with R = H, mp 237–239°, total yield 51.5%, ν_{max} (Nujol) 3360, 3160 (NH), 1670 (CO), 1630 cm^{-1} (NHCO); R = Ph, mp 228–230°, total yield 70.5%, ν_{max} (Nujol) 3410, 3270 (NH), 1680 (CO), 1635 cm^{-1} (NHCO).

D-4-(Aden-9-yl)pantoic Acid VI. To a mixture of adenine (5.4 g) and DMF (140 ml) was added sodium hydride (960 mg) at 10° with stirring. After heating at 55–60° for 1.5 hr, 8.6 g of pantolactone was added to the solution and the temperature was maintained for 18 hr. Then the solvent was removed by distillation under reduced pressure. To the residue was added 20 ml of H_2O and the mixture was adjusted at pH 3 with 0.1 *N* HCl and allowed to stand overnight in a refrigerator. The crystals which separated were collected on a funnel and washed with H_2O, then triturated in a $NaHCO_3$ solution. After removal of the undissolved adenine by filtration, the filtrate was again adjusted to pH 3 with 0.1 *N* HCl and allowed to stand 2 days in a cold room to give the crude product as lightly brown precipitate. Recrystallization of the precipitate from MeOH gave 570 mg (5.4%) of pure D-4-(aden-9-yl)-pantoic acid: mp 196–197.5°; ν_{max} (Nujol) 3280 (OH), 3120 (NH), 1690 cm^{-1} (CO).

Ethyl D-4-(Aden-9-yl)pantoate VII. A suspension of D-4-(aden-9-yl)pantoic acid (450 mg) in 50 ml of EtOH was saturated with HCl. After refluxing for 7 hr, EtOH was removed *in vacuo*. The residue was triturated with a $NaHCO_3$ solution and extracted with EtOAc. The extract was washed with H_2O and dried over anhydrous Na_2SO_4. The solvent was removed by distillation; then the residue was recrystallized from $CHCl_3$–EtOAc to give 270 mg (60.8%) of pure **62**: mp 160.5–162°; ν_{max} (Nujol) 3280 (OH), 3100 (NH), 1732 cm^{-1} (–CO).

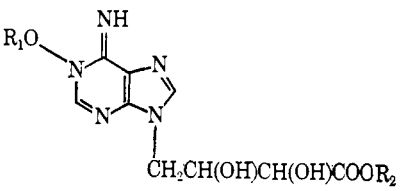
Reaction of the Masked Ethyl 4-Bromo-2,3-dihydroxybutyrate with the Sodium Salt of Adenine IX. Sodium hydride (1 g, 60% oil suspension) was added to 60 ml of DMSO with stirring at 10°. After 1 hr, 4 g of adenine was added and the solution was

Table VII



No.	R	Yield, %	Recrystn solvent[a]	Mp, °C	MED, mg %	Formula
100	H	61.0	L	260–264	10	$C_9H_{11}N_5O_5$
101	C_2H_5	69.4	B	215–216	0.2	$C_{11}H_{15}N_5O_5 \cdot 0.5H_2O$
102	*n*-C_3H_7	35.0	B	171–172	0.2	$C_{12}H_{17}N_5O_5 \cdot 0.5H_2O$
103	*n*-C_4H_9	50.0	H	198–199	0.2	$C_{13}H_{19}N_5O_5$
104	*i*-C_4H_9	65.0	H	216–217	0.2	$C_{13}H_{19}N_5O_5$
105	*sec*-C_4H_9	28.4	H	218–220	0.2	$C_{13}H_{19}N_5O_5 \cdot 0.5H_2O$
106	*i*-C_5H_{11}	87.0	H	204–205	0.2	$C_{14}H_{21}N_5O_5$
107	*n*-C_8H_{17}	12.4	H	176–179	0.2	$C_{17}H_{27}N_5O_5$
108	$CH_2C_6H_5$	56.0	H	192–194	>0.5	$C_{16}H_{17}N_5O_5$
109	Cyclohexyl	59.0	H	230–232	2	$C_{15}H_{21}N_5O_5$
110	CH_2CH_2Cl	53.7	B–H	175–177	>0.2	$C_{11}H_{14}N_5O_5Cl \cdot 0.5H_2O$
111	$CH_2CH(OH)CH_2OH$	55.0	B–L	195–197	>1	$C_{12}H_{19}N_5O_7 \cdot H_2O$

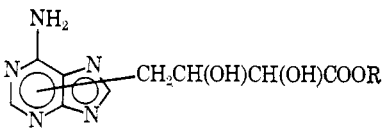
Table VIII



No.	R_1	R_2	Yield, %	Recrystn solvent[a]	Mp, °C	MED, mg %	Formula
112	CH_3	C_2H_5	15	M	80–82	10	$C_{12}H_{17}N_5O_5 \cdot 0.75C_4H_8O$[b]
113	CH_3	*i*-C_5H_{11}	32.8	N	113–116	0.1	$C_{15}H_{23}N_5O_5$
114	C_2H_5	C_2H_5	33.7	F	140	5	$C_{13}H_{19}N_5O_5$
115	*i*-C_5H_{11}	C_2H_5	81.0	D	131–134	0.5	$C_{16}H_{25}N_5O_5$
116	*i*-C_5H_{11}	*i*-C_5H_{11}	16.6	N	110–112	0.1	$C_{19}H_{31}N_5O_5$

[a]B, EtOH; D, *i*-C_3H_7OH; F, dioxane; H, DMF; I, Et_2O; L, H_2O; M, $CHCl_3$; N, CCl_4; A, MeOH. [b]The sample contained dioxane as crystalline solvent.

Table IX



No.	Substn at	R		Yield, %	Recrystn solvent[a]	Mp, °C	MED, mg %	Formula
117	3	Na	*b*		B–I	281–282	>10	$C_9H_{10}N_5O_4Na \cdot 1.5H_2O$
118	3	*i*-C_4H_9	*c*	70.0	F–H	217–219	10	$C_{13}H_{19}N_5O_4$
119	7	H		*d*	H–L	278–279	>20	$C_9H_{11}N_5O_4$
120	7	C_2H_5			B	183–185	>10	$C_{11}H_{15}N_5O_4$

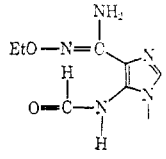
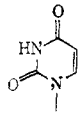
[a]See footnote *a*, Table VIII. [b]K. Okumura, *et al.*, *J. Org. Chem.*, **36,** 1573 (1971). [c]Esterified with isobutyl alcohol in the presence of concentrated H_2SO_4. [d]See Experimental Section.

stirred for 1 hr at 50°. To this mixture was added 3 mmol of the masked ethyl 4-bromo-2,3-dihydroxybutyrate, and the reaction mixture was heated at 85–95° for 12 hr and then spin evaporated *in vacuo*. The residue was triturated with 100 ml of EtOH and the unchanged adenine precipitate was removed by filtration. The filtrate was spin evaporated *in vacuo*, and the residue was dissolved in $CHCl_3$, washed with water, and then dried over anhydrous Na_2SO_4. The solvent was removed, and the residue was recrystallized from a respective solvent to give a pure sample of the eritadenine derivative.

General Procedure for Protection of the Hydroxy Groups of Eritadenine Esters (59–61). A mixture of eritadenine ester (0.01 mol), cyclic ketone (0.3 mol), $TsOH \cdot H_2O$ (0.015 mol), and $CHCl_3$ (200 ml) was heated under reflux until separation of H_2O was no longer observed (10–20 hr). The reaction mixture was concentrated *in vacuo* and the residue was dissolved in AcOEt. The solution was washed first with aqueous $NaHCO_3$ and then with H_2O and dried. Evaporation of the solvent gave the crude product, which was recrystallized from the respective solvent to give the pure product.

4-(Aden-9-yl)-1,2(*S*),3(*R*)-butanetriol (71). To a suspension of eritadenine ethyl ester (3.0 g, 0.011 mol) in EtOH (100 ml) was added portionwise $NaBH_4$ (1.75 g, 0.046 mol) with stirring at 25°, and stirring was continued for 5 hr. The reaction mixture was concentrated *in vacuo* to give the crude product. The crude product was dissolved in H_2O and the solution was passed through a column of Amberlite IR-120 (H^+ form). The column was washed with H_2O and then eluted with 5% NH_4OH. The eluate was

Table X

No.	$XCH_2CH(OH)CH(OH)COOR$ X	R	MED, mg %
121		Et	>10
122[a]		*i*-C_5H_{11}	10, >0.5
123		Et	>5
124	$-NH_2$	H	>50

[a]This compound was obtained as a by-product in the preparation of isopentyl N^1-ethoxyeritadenate, mp 151° (AcOEt). *Anal.* Calcd for $C_{15}H_{27}O_6N_5$: C, 49.86; H, 7.06; N, 18.17. Found: C, 50.02; H, 7.01; N, 18.13.

evaporated to dryness *in vacuo*. The residue was recrystallized from H_2O to give 4-(6-amino-9*H*-purin-9-yl)-1,2(*S*),3(*R*)-butanetriol‡ (2.05 g, 80.4 %) as colorless prisms: mp 222–224° dec. *Anal.* Calcd for $C_9H_{13}N_5O_3$: C, 45.17; H, 5.47; N, 29.27. Found: C, 45.03; H, 5.45; N, 29.30.

Preparation of the Compounds Listed in Table VI. Compound 83. Diazotization of Eritadenine. To a solution of eritadenine (0.5 g, 2 mmol) in 50% HNO_3 (14 ml) was added $NaNO_2$ (0.69 g, 0.01 mol) in small portions with stirring at 25°. After stirring for 5 hr, the reaction mixture was concentrated to dryness *in vacuo* and the residue was dissolved in H_2O. The aqueous solution was passed through a column of Diaion SKI-B resin (H^- form of a sulfonic acid-type ion-exchange resin). The column was thoroughly washed with H_2O and then eluted with 5% NH_4OH. The eluate was evaporated *in vacuo* to afford the crude product, which was recrystallized from aqueous MeOH to give 4-(6-hydroxy-9*H*-purin-9-yl)-2(*R*),3(*R*)-dihydroxybutyric acid (0.44 g, 82%): mp 218–220° dec.

Compound 84. Hydrolysis of the Protecting Group. A solution of 4-(6-methylmercapto-9*H*-purin-9-yl)-2(*R*),3(*R*)-(*O*-cyclohexylidenedioxy)butyric acid (1.0 g) in 50% aqueous HCO_2H (15 ml) was allowed to stand at 25° for 4 days. The solution was concentrated to dryness *in vacuo*, and the residue was recrystallized from dioxane to give 4-(6-methylmercapto-9*H*-purin-9-yl)-2(*R*),3(*R*)-dihydroxybutyric acid (0.65 g, 83.5%) as colorless needles.

Compound 88. Esterification with the Alcohol in the Presence of Acid Catalyst. A mixture of the sodium salt of 8-bromoeritadenine (hemihydrate, 1.09 g, 3 mmol), absolute EtOH (80 ml), and concentrated H_2SO_4 (1.1 g) was refluxed for 3 hr. After cooling, the reaction mixture was neutralized with Amberlite IR-45 (9 g). The resin was removed by filtration and the filtrate was concentrated *in vacuo*. The resulting crystals were recrystallized from EtOH to give 8-bromoeritadenine ethyl ester (755 mg, 70%) as colorless needles: mp 182–183°.

Compound 87. Bromination of Eritadenine. To a solution of bromine (2.4 g, 0.015 mol) in H_2O (150 ml) was added the sodium salt of eritadenine (hemihydrate, 2.84 g, 0.01 mol). The mixture was allowed to stand at 25° for 6 hr. The precipitate formed was collected by filtration, washed with H_2O, and dissolved in 1 *N* NaOH (20 ml). The solution was diluted with EtOH to precipitate the sodium salt of 8-bromoeritadenine. Recrystallization from 70% aqueous EtOH afforded the pure sample (1.24 g, 34%) as colorless plates: mp 217–219° dec.

Compounds 90–94. N^6-Formyleritadenine Esters. To a suspension of eritadenine (2.53 g, 0.01 mol) in DMF (25 ml) was added a dimethylformamide dialkylacetal (0.04 mol) and the mixture was stirred at 25° for 10 hr. The reaction mixture was concentrated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$ and the $CHCl_3$ layer was passed through a column of silica gel (1.2 × 50 cm). The product was eluted with $CHCl_3$–EtOH (4:1 v/v). The fractions were monitored by tlc [silica gel GF 254 (Merck), with the same solvent system] and the fractions which had the respective R_f values listed in Table XI were collected. Evaporation of the solvent and recrystallization of the residue gave the N^6-formyleritadenine alkyl ester.

Table XI

Compd	R_f	λ_{max} (MeOH), nm (log ϵ)
90	0.42	274 (4.29), 282 (4.14)
91	0.53	274.5 (4.29), 282 (4.14)
92	0.74	274.5 (4.28), 283 (4.13)
93	0.74	274.5 (4.28), 283 (4.14)
94	0.76	274 (4.26), 282 (4.11)

Compound 95. N^6-Ethyleritadenine. A solution of eritadenine ethyl ester (4.0 g, 0.015 mol) and ethyl iodide (8.0 g) in DMF (50 ml) was heated at 60° for 2 days. After cooling, ether was added to the reaction mixture to separate an oil, which was treated with 3% aqueous NaOH at 90° for 1 hr. The solution was passed through a column of Amberlite IR-120 (H^- form) and the column was thoroughly washed with H_2O. The product was eluted with dilute ammonium hydroxide. Concentration of the eluate afforded the crude product, which was recrystallized from EtOH-Et_2O to give N^6-ethyleritadenine (0.3 g, 6.0 %): mp 190–192°.

Compounds 98 and 99. N^6-Carbamoyl Derivatives (Example). A mixture of the sodium salt of 4-(6-amino-9*H*-purin-9-yl)-2(*R*),3(*R*)-(*O*-cyclohexylidenedioxy)butyric acid (12.5 g, 0.035 mol), ethyl tosylate (14 g, 0.07 mol), and DMF (50 ml) was stirred at 70° for 2 hr. The mixture was concentrated to dryness *in vacuo*, and the residue was extracted with $CHCl_3$. The extract was concentrated and the residue was purified by column chromatography with silica gel to afford ethyl 4-(6-amino-9*H*-purin-9-yl)-2(*R*),3(*R*)-(*O*-cyclohexylidenedioxy)butyrate (5.0 g, 37%): mp 80–82°. One gram (2.77 mmol) of this sample was treated with ethyl isocyanate (0.485 g, 6.85 mmol) in benzene (20 ml) at the reflux temperature for 24 hr. The mixture was concentrated to dryness *in vacuo* and the residue was recrystallized from isopropyl alcohol to give ethyl 4-[6-(ethylcarbamoyl)amino-9*H*-purin-9-yl]-2(*R*),3(*R*)-(cyclohexylidenedioxy)butyrate (0.61 g, 51.5%): mp 113–115°. *Anal.* Calcd for $C_{20}H_{28}N_6O_5$: C, 55.54; H, 6.53; N, 19.43. Found: C, 55.47; H, 6.64; N, 19.14. Removal of the protecting group by treatment with 70% HCO_2H at 40° for 3 days gave ethyl 4-[6-(ethylcarbamoyl)amino-9*H*-purin-9-yl]-2(*R*),3(*R*)-dihydroxybutyrate in 64% yield.

In the case of compound **99**, the intermediate, ethyl 4-[6-(phenylcarbamoyl)amino-9*H*-purin-9-yl]-2(*R*),3(*R*)-(*O*-cyclohexylidenedioxy)butyrate, was obtained in 50% yield: mp 182°. *Anal.* Calcd for $C_{24}H_{28}N_6O_5$: C, 59.99; H, 5.87; N, 17.49. Found: C, 59.89; H, 5.68; N, 17.10.

General Procedures for Preparation of the N^1-Oxyeritadenine Ester Derivatives (Compounds 100–111). (I) By Oxidation with H_2O_2 in AcOH. To a solution of an eritadenine ester (0.01 mol) in AcOH (30 ml) was added dropwise 30% H_2O_2 (9 ml) at 25°. The mixture was heated at 40–50° for 26 hr and then concentrated to dryness below 40° *in vacuo*. The residue was crystallized with Et_2O. The crystals were purified by recrystallization from an appropriate solvent to afford the product.

(II) By Esterification of N^1-Oxyeritadenine with Alcohols in the Presence of Acid Catalyst. A mixture of N^1-oxyeritadenine (1.34 g, 5 mmol), concentrated H_2SO_4 (1.34 g), and an alcohol (70 ml) was heated at 60–70° for 4 hr. The reaction mixture was neutralized with Amberlite IR-45 (OH^- form) while hot, and the resin was removed by filtration. The filtrate was allowed to stand in a refrigerator. The crystals formed were collected by filtration to give the crude product, which was recrystallized from an appropriate solvent.

General Procedure for Preparation of N^1-Alkoxyeritadenine Esters. A solution of a N^1-oxyeritadenine alkyl ester and an alkyl iodide (2 molar equiv) in DMF (ten times) was stirred at 25° for 24 hr. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in MeOH. The methanolic solution was neutralized with Amberlite IR-45 (OH^- form) and concentrated to dryness *in vacuo*. The residue was extracted with $CHCl_3$ and

‡4-(Aden-9-yl)-1,2(*S*),3(*R*)-butanetriol was independently prepared by Kamiya, *et al.*,[17] by reduction of eritadenine methyl ester with $NaBH_4$ in 2-propanol: mp 219–220°; $[\alpha]_D$ +30° (1 *N* HCl), 4-(6-Amino-9*H*-purin-9-yl)-1,2(*R*),3(*S*)-butanetriol (72) was prepared from D-glucose and adenine according to the method of Ikehara, *et al.*:[18] mp 218–219°; $[\alpha]^{17}D$ −32.4° (*c* 1.05, 1 *N* HCl).

the $CHCl_3$ layer was concentrated *in vacuo* to afford the crude product. Recrystallization from an appropriate solvent gave the pure product.

Synthesis of N^7-Isoeritadenine Xa and Xb. Reaction of 4-Amino-5-cyanoimidazole with Methyl 2,3-*O*-Isopropylidene-5-*O*-tosyl-D-ribonucleoside. To a solution of 4-amino-5-cyanoimidazole (6.0 g, 0.055 mol) in DMF (150 ml) was added NaH (52% oil dispersion, 2.7 g, 0.055 mol) and the mixture was warmed at 50° for 30 min. A solution of methyl 2,3-*O*-isopropylidene-5-*O*-tosyl-D-ribonucleoside (18.0 g, 0.55 mol) in DMF (50 ml) was added to the mixture at 30°. The whole mixture was heated at 90–100° for 2 hr and concentrated to dryness *in vacuo*. The residue was extracted with EtOAc. Evaporation of the solvent from the dried EtOAc layer gave a mixture of the crude products (11.0 g). This crude mixture was extracted with $CHCl_3$ and the $CHCl_3$-insoluble crystals were recrystallized from EtOH to afford methyl 5-(4′-amino-5′-cyanoimidazol-3′-yl)-2,3-*O*-isopropylidene-D-ribonucleoside (II): 4.5 g (31%); mp 208–209°; uv max (2×10^3) 247 nm (13.0) at pH 6.9; uv max 238 (11.2), 254 (8.2) at pH 1.4; uv max 247 (14.6) at pH 12.3. *Anal.* Calcd for $C_{13}H_{18}N_4O_4$: C, 53.05; H, 6.16; N, 19.04. Found: C, 52.98; H, 6.16; N, 19.19. The $CHCl_3$ extract was concentrated to dryness *in vacuo*, and the residue was recrystallized from EtOH to give methyl 5-(4′-amino-5′-cyanoimidazol-1′-yl)-2,3-*O*-isopropylidene-D-ribonucleoside (II′, 4.3 g, 29%) as colorless leaflets: mp 190–191.5°; uv max ($\epsilon \times 10^3$) 258 nm (9.3) at pH 6.9; uv max 237 (8.2), 260 (7.6) at pH 1.4; uv max 258 (10.0) at pH 12.3. *Anal.* Calcd for $C_{13}H_{18}N_4O_4$: C, 53.05; H, 6.16; N, 19.04. Found: C, 52.90; H, 6.15; N, 19.30.

Methyl 5-(6′-Amino-9′*H*-purin-9′-yl)-2,3-*O*-isopropylidene-D-ribonucleoside XIa. A solution of Xa (0.43 g) and $HC(OEt)_3$ (10 ml) in DMF (20 ml) was refluxed for 10 hr. The reaction mixture was concentrated *in vacuo* to give an oily product. The oil was dissolved in 20% methanolic ammonia and the solution was stirred at 25° for 2 hr. The precipitate which formed was collected by filtration to give almost pure IV (0.2 g): mp 251.5°. This was identified with an authentic sample by the mixed fusion test and comparison of the ir spectra.

Methyl 5-(6′-Amino-7′*H*-purin-7′-yl)-2,3-*O*-isopropylidene-D-ribonucleoside XII. A solution of Xb (4.2 g) and $HC(OEt)_3$ (5 ml) in DMF (80 ml) was refluxed for 4 hr. The reaction mixture was concentrated *in vacuo*. The residue was recrystallized from isopropyl ether to afford methyl 5-(5′-cyano-4′-ethoxymethyleneiminoimidazol-1′-yl)-2,3-*O*-isopropylidene-D-ribonucleoside (XIb, 4.5 g, 92%): mp 89–91°. *Anal.* Calcd for $C_{10}H_{22}N_4O_5$: C, 54.84; H, 6.33; N, 15.99. Found: C, 54.82; H, 6.32; N, 16.21. This sample was treated with 20% methanolic ammonia (50 ml) at 25° for 2 hr. The solution was concentrated to dryness *in vacuo*, and the residue was recrystallized from MeOH to give XII (4.0 g, 89.7%) as colorless needles: mp 157–159°. *Anal.* Calcd for $C_{14}H_{19}N_5O_4 \cdot 0.5H_2O$: C, 50.90; H, 6.06; N, 21.2. Found: C, 50.72; H, 5.76; N, 21.05.

7-Isoeritadenine. A solution of XII (4.0 g) in 0.1 *N* HCl (100 ml) was heated at 80–90° for 3 hr. After cooling, the solution was made alkaline with NaOH (1.7 g), and oxygen was bubbled into the solution for 10 hr. The solution was neutralized with HCO_2H and concentrated to a volume of 30 ml and acidified to pH 3.0 with HCO_2H. The precipitate was collected by filtration to give 7-isoeritadenine XIII (1.6 g, 45.4%) as colorless prisms: mp 278–279°. *Anal.* Calcd for $C_9H_{11}N_5O_4$: C, 42.69; H, 4.38; N, 27.67. Found: C, 42.57; H, 4.39; N, 27.27.

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