New Hypocholesterolemic Abietamide Derivatives. II. Synthesis and Hypocholesterolemic Activity of *N*-Phenyl-Δ^8-dihydroabietamides

Yukio FUJITA, Yoshiaki YOSHIKUNI,* Tomoko SOTOMATSU, Tamiki MORI, Takayuki OZAKI, Kenji SEMPUKU, Akio OGINO, Masahiro KISE, and Hiroshi ENOMOTO

Research Laboratories, Nippon Shinyaku Co., Ltd., Nishioji-Hachijo, Manami-ku, Kyoto 601, Japan. *Received September 7, 1990*

A series of *N*-phenyl-Δ^8-dihydroabietamide analogs were prepared and tested for hypocholesterolemic activity. The effects of substituents of the phenyl moiety on the activities were quantitatively analyzed by using various substituent parameters. The activities were enhanced by the electron-donating effect of *ortho* and *para* substituents and the bulkiness of *ortho* substituents. A combination of 2,6-dimethylaniline with resin acids other than Δ^8-dihydroabietic acid produced lower activities than *N*-(2,6-dimethylphenyl)-Δ^8-dihydroabietamide, abietane-type carboxamides being somewhat stronger than pimarane-type carboxamides. The conversion of the carboxamide group to other groups resulted in more or less of a decrease in activity, giving evidence that the carboxamide group is important to hypocholesterolemic activity.

Keywords *N*-phenyl-Δ^8-dihydroabietamide; resin acid; secondary carboxamide; hypocholesterolemic activity; quantitative structure–activity relationship; regression analysis; cholesterol-fed rats

The etiological cause of atherosclerosis remains obscure although a considerable amount of research has been done on it. Therapeutic approaches to this disease have therefore focused on the minimization of epidemiologically defined risk factors, primarily on the reduction of serum cholesterol levels.

In a previous paper,[1] we reported that the coexistence of a secondary carboxamide group in resin acid arylmethylamides and a phenyl ring was a necessary constituent of the amine moiety in abietamide derivatives for hypocholesterolemic activity and that tetrahydroabietic (I) or Δ^8-dihydroabietic acid (II) was superior in terms of the activity to their less saturated analogs (*e.g.* abietic (III) or dehydroabietic acid (IV)) as an abietane-type acid moiety. The activity of *N*-benzyl-Δ^8-dihydroabietamide (V) was remarkably intensified by substitution in the phenyl ring or at the benzyl position in the amine moiety, as represented by *N*-(4-methoxybenzyl)-(VI) and *N*-(α-benzylbenzyl)-Δ^8-dihydroabietamide (VII).

Further investigation revealed that some Δ^8-dihydroabietanilide derivatives had potent hypocholesterolemic activity. We here report the synthesis of arylamides of Δ^8-dihydroabietic acid, some other abietane-type acids, and some pimarane-type acids. To elucidate the factors that affected the activities, quantitative structure–activity relationship (QSAR) analysis was done for Δ^8-dihydroabietic acid derivatives with various substituents of the phenyl moiety.

Structure–Activity Relationship Many of the Δ^8-dihydroabietanilide derivatives shown in Table I have hypocholesterolemic properties. Various modifications were made in the substitution pattern of the phenyl ring of the aniline moiety in order to obtain more potent cholesterol-lowering activity than that of the parent carboxamide (**1**). These data were analyzed quantitatively by using the substituent parameters listed in Table II.

Equation 1 is given for the unsubstituted and 17 mono-*ortho*-, mono-*meta*-, and mono-*para*-substituted compounds in Table I.

$$pID_{50} = -1.516(\pm 0.707)\sigma - 0.353(\pm 0.276)E_s(AMD) - 2.372(\pm 0.252) \quad (1)$$
$$n=18,\ s=0.394,\ r=0.790,\ F=12.5$$

In these and the following equations, n is the number of

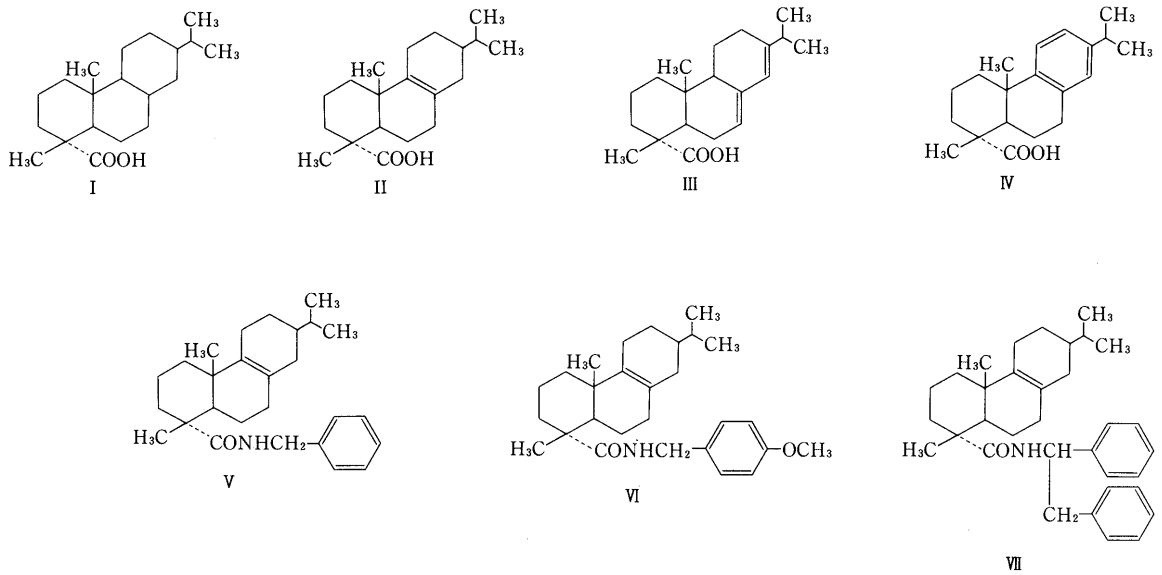
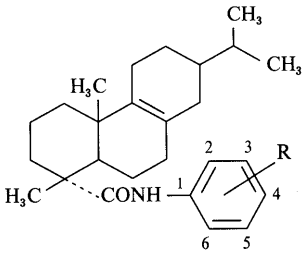


Chart 1

TABLE I. Hypocholesterolemic Activity of Δ^8-Dihydroabietanilide Derivatives



No.	R[a]	Formula	Yield (%)	mp (°C)	Crystn. solvent[b]	% inhibition							ID_{50} (ppm)
						3	10	30	100	300	1000	3000 ppm[c]	
1	H	$C_{26}H_{37}NO$	89	151—152	E	—	—	—	18	67	97	—	175
2	2-Me	$C_{27}H_{39}NO$	74	146—148	A	3	19	55	83	98	—	—	26
3	2-Et	$C_{28}H_{41}NO$	83	167—169	EA	13	43	78	98	—	—	—	12
4	2-Ph	$C_{32}H_{41}NO$	65	45—46	PE	5	11	41	103	—	—	—	37
5	2-CO_2Et	$C_{29}H_{41}NO_3$	58	Oil	—	—	—	—	—	23	—	—	—
6	2-Cl	$C_{26}H_{36}NOCl$	82	74—76	A	—	—	—	9	22	87	98	540
7	2-Br	$C_{26}H_{36}NOBr$	48	89—90	E	—	—	—	3	36	87	103	420
8	2-I	$C_{26}H_{36}NOI$	67	108—110	H	—	—	—	16	32	94	102	430
9	2-NO_2	$C_{26}H_{36}N_2O_3$	70	Oil	—	—	—	—	11	19	72	98	680
10	3-Me	$C_{27}H_{39}NO$	78	112—115	M	—	—	−36	8	85	—	—	195
11	3-CF_3	$C_{27}H_{36}NOF_3$	69	137—138	M	—	—	—	9	34	64	95	580
12	3-OMe	$C_{27}H_{39}NO_2$	76	151—152	M	—	−9	18	30	82	—	—	175
13	3-OPh	$C_{32}H_{41}NO_2$	63	92—94	H	−3	2	−10	12	—	—	—	—
14	3-Br	$C_{26}H_{36}NOBr$	85	98—101	E	—	—	4	10	61	94	—	250
15	4-Me	$C_{27}H_{39}NO$	71	84—86	H–B	—	—	—	—	22	66	91	480
16	4-OEt	$C_{28}H_{41}NO_2$	85	139—140	M	—	24	35	72	89	—	—	55
17	4-CO_2Me	$C_{28}H_{39}NO_3$	69	152—154	M	—	—	—	—	13	—	48	3000
18	4-Ph	$C_{32}H_{41}NO$	73	195—197	A–C	—	—	—	31	31	53	—	800
19	4-Cl	$C_{26}H_{36}NOCl$	61	90—92	H	—	—	—	15	43	87	88	360
20	4-OH	$C_{26}H_{37}NO_2$	72	180	E	—	—	10	61	76	110	—	70
21	2,3-Me_2	$C_{28}H_{41}NO$	70	182—184	A	9	53	67	91	114	—	—	9
22	2,4-Me_2	$C_{28}H_{41}NO$	68	148—150	A	—	42	58	88	95	—	—	20
23	2,5-Me_2	$C_{28}H_{41}NO$	62	85—87	B	2	41	57	88	111	—		17
24	2,6-Me_2	$C_{28}H_{41}NO$	76	195—197	MEK	31	53	79	97	103	—	—	8.8
25	3,4-Me_2	$C_{28}H_{41}NO$	74	113—115	A	—	—	—	−27	22	37	64	1700
26	3,5-Me_2	$C_{28}H_{41}NO$	70	151—154	A	9	−11	−8	46	98	—	—	108
27	2-Me-6-Et	$C_{29}H_{43}NO$	72	192—195	A	35	68	91	99	111	—	—	5.5
28	2,6-Et_2	$C_{30}H_{45}NO$	79	219—221	B–EA	25	47	82	89	—	—	—	11
29	2,6-iso-Pr_2	$C_{32}H_{49}NO$	69	255—258	C–M	−2	18	38	52	—	—	—	84
30	2-Me-5-Cl	$C_{27}H_{38}NOCl$	82	160—161	EA	—	6	59	72	84	—	—	22
31	2-Me-6-Cl	$C_{27}H_{38}NOCl$	86	187—189	EA	26	23	63	96	109	—	—	20
32	2,5-$(MeO)_2$	$C_{28}H_{41}NO_3$	65	120—123	A	—	−1	−4	39	76	—	—	140
33	2,4-Cl_2	$C_{26}H_{35}NOCl_2$	72	102—104	A	—	—	—	4	48	78	89	310
34	2,6-Cl_2	$C_{26}H_{35}NOCl_2$	63	190—192	A–M	−22	−22	52	84	100	—	—	28
35	3,4-Cl_2	$C_{26}H_{35}NOCl_2$	82	110—111	B	—	—	—	3	27	62	85	660
36	3-OH-4-CO_2H	$C_{27}H_{37}NO_4$	74	260	EA	—	—	—	—	7	19	66	1800
37	2,4,5-Me_3	$C_{29}H_{43}NO$	68	124—125	A	21	47	63	87	—	—	—	13
38	2,4,6-Me_3	$C_{29}H_{43}NO$	82	215—218	A	27	55	85	100	—	—	—	8
39	2,4,6-Me_3-3-Br	$C_{29}H_{42}NOBr$	72	231—232	MEK	38	55	74	98	—	—	—	7
40	2,3,5,6-F_4	$C_{26}H_{33}NOF_4$	53	215—217	H	0	0	25	45	92	—	—	115

a) Me: methyl, Et: ethyl, Ph: phenyl. *b*) A=acetone, B=benzene, C=chloroform, E=ethanol, EA=ethyl acetate, H=hexane, M=methanol, MEK=methylethylketone, PE=petroleum ether. *c*) Concentration of test compounds in the atherogenic diet containing 1% cholesterol and 0.25% cholate.

compounds, s is the standard deviation, r is the correlation coefficient, and F is the value of the F-ratio between variances of the observed and calculated data. The figures in parentheses are the 95% confidence interval of the regression coefficients and intercept.

In Eq. 1, σ is the Hammett electronic substituent constant.[2] The Hammett σ constant for *ortho*-substituents is unavailable, and we put $\sigma_{ortho}=\sigma_{para}$.[3] E_s(AMD) is a set of steric parameter for *ortho*-substituents defined by us.[4] The E_s (AMD) value for *meta*- and *para*-substituents is necessarily zero. Equation 1 means that the electron-donating substituents and bulky *ortho*-substituents favor the activity.

The variations in the activity of *meta* derivatives are small, showing relatively weak effects of *meta*-substituents. For this reason, we examined the significance of the electronic effect of *meta*-substituents by separating the σ paramater set into $\sigma(m)$ for *meta*-substituents and $\sigma(op)$ for *ortho*- and *para*-substituents. These modified electronic parameter sets are listed in Table II.

$$\begin{aligned} pID_{50} = &-0.288(\pm 1.393)\sigma(m) - 1.861(\pm 0.715)\sigma(op) \\ &-0.456(\pm 0.266)E_s(AMD) - 2.473(\pm 0.246) \\ &n=18,\ s=0.350,\ r=0.850,\ F=12.2 \end{aligned} \quad (2)$$

In Eq. 2, the 95% confidence interval for $\sigma(m)$ term was very large, and $\sigma(m)$ was significant only above 26%. Exclusion of the $\sigma(m)$ term gave Eq. 3.

$$pID_{50} = -1.862(\pm 0.689)\sigma(op) - 0.468(\pm 0.247)E_s(AMD) - 2.490(\pm 0.214) \quad (3)$$
$$n=18,\ s=0.340,\ r=0.849,\ F=19.3$$

The quality of Eq. 3 is comparable to that of Eq. 2. The effects of *para*- and *ortho*-substituents are large, whereas those of *meta*-substituents are actually negligible. The correlation coefficient of Eq. 3 is not excellent, but the standard deviation is small enough.

Mono-substituted and poly-substituted analogs were then analyzed together, to give Eq. 4.

$$pID_{50} = -1.488(\pm 0.413)\sigma(op) - 0.471(\pm 0.136)E_s(AMD) - 2.416(\pm 0.174) \quad (4)$$
$$n=36,\ s=0.350,\ r=0.899,\ F=69.0$$

The addition of the $\sigma(m)$ term did not improve the correlation, as for the case of Eq. 3. Equation 4 shows that the electron-donating effect of *ortho*- and *para*-substituents and the bulkiness of *ortho*-substituents enhanced the hypocholesterolemic activities of Δ^8-dihydroabietanilide derivatives. Although the structural variations are large for the 36 compounds of Eq. 4, only two substituent parameters are needed to explain their activity variations. The expected values according to Eq. 4 are summarized in Table II.

To get more active compounds, there are two ways. First is to increase the bulkiness of *ortho*-substituents. However, 2,6-diisopropyl derivative is less active than 2,6-dimethyl or 2-ethyl-6-methyl derivatives, as can be seen in Table II. This fact suggests that highly crowded substituents such as 2,6-di-*tert*-butyl are not favorable to the activities and that the 2,6-dimethyl or 2-ethyl-6-methyl are most desirable *ortho*-substituents. Second is to increase the electron-donating properties of *ortho*- and *para*-substituents. Alkyl groups at the *ortho* positions have electron-donating properties. Hence, substitution of electron-donating groups such as OH, OMe, NMe_2 at the *para* position of 2,6-dimethyl or 2-ethyl-6-methyl derivatives should increase the hypocholesterolemic activities.

In Eq. 4, the use of the Taft–Kutter–Hansch E_s steric parameter[5] instead of $E_s(AMD)$ gave statistically less significant equations (correlation coefficient $r=0.814$ for the 18 compounds, and $r=0.896$ for the 36 compounds). We also examined the hydrophobic effect on the activities, but hydrophobic substituent parameters such as 1-octanol/water partition coefficient (π)[2] were insignificant in this set of compounds. Among the compounds listed in Table I, 3,4-Me_2 and 2,6-(iso-Pr)$_2$ derivatives were excluded from the analysis, because the calculated values for these compounds largely deviated from the correlation line. The reasons for these deviations remain unfortunately unclear.

In Eq. 4, the simple sum of steric parameters for 2- and 6-position substituents was used for 2,6-disubstituted derivatives. For these compounds, the two *ortho*-substituents were classified according to their bulkiness; the one with the more negative $E_s(AMD)$ value was defined as being the larger. Using $E_s(AMD)^S$ for the smaller and $E_s(AMD)^L$ for the larger substituents, we derived Eq. 5 for 36 compounds used in Eq. 4. For mono-*ortho*-substituted derivatives, the smaller *ortho*-substituent was taken to be hydrogen, and the $E_s(AMD)^S$ value was put zero, because

TABLE II. Substituent Parameters Used for Correlation Analyses[a] and Hypocholesterolemic Activity of *N*-Phenyl-Δ^8-dihydroabietamides

No.	R	$E_s(AMD)$[b]	E_s[c]	σ[c]	$\sigma(m)$[d]	$\sigma(op)$[e]	pID_{50} Obsd.	pID_{50} Calcd[f]
1	H	0.00	0.00	0.00	0.00	0.00	−2.243	−2.416
2	2-Me	−1.16	−1.24	−0.17	0.00	−0.17	−1.415	−1.617
3	2-Et	−1.33	−1.31	−0.15	0.00	−0.15	−1.079	−1.566
4	2-Ph	−2.19	−1.01	−0.01	0.00	−0.01	−1.568	−1.369
5	2-COOEt	—[g]	—[g]	0.45	0.00	0.45		
6	2-Cl	−0.98	−0.97	0.23	0.00	0.23	−2.732	−2.296
7	2-Br	−1.12	−1.16	0.23	0.00	0.23	−2.623	−2.231
8	2-I	−1.44	−1.40	0.18	0.00	0.18	−2.633	−2.005
9	2-NO_2	−1.65	−1.01	0.78	0.00	0.78	−2.833	−2.799
10	3-Me	0.00	0.00	−0.07	−0.07	0.00	−2.290	−2.416
11	3-CF_3	0.00	0.00	0.43	0.43	0.00	−2.763	−2.416
12	3-OMe	0.00	0.00	0.12	0.12	0.00	−2.243	−2.416
13	3-OPh	0.00	0.00	0.25	0.25	0.00		−2.416
14	3-Br	0.00	0.00	0.39	0.39	0.00	−2.398	−2.416
15	4-Me	0.00	0.00	−0.17	0.00	−0.17	−2.681	−2.163
16	4-OEt	0.00	0.00	−0.24	0.00	−0.24	−1.740	−2.059
17	4-COOMe	0.00	0.00	0.45	0.00	0.45	−3.477	−3.086
18	4-Ph	0.00	0.00	−0.01	0.00	−0.01	−2.903	−2.401
19	4-Cl	0.00	0.00	0.23	0.00	0.23	−2.556	−2.758
20	4-OH	0.00	0.00	−0.37	0.00	−0.37	−1.845	−1.866
21	2,3-Me_2	−1.16	−1.24	−0.24	−0.07	−0.17	−0.954	−1.617
22	2,4-Me_2	−1.16	−1.24	−0.34	0.00	−0.34	−1.301	−1.364
23	2,5-Me_2	−1.16	−1.24	−0.24	−0.07	−0.17	−1.230	−1.617
24	2,6-Me_2	−2.32	−2.48	−0.34	0.00	−0.34	−0.944	−0.817
25	3,4-Me_2	0.00	0.00	−0.24	−0.07	−0.17	−3.230	−2.163
26	3,5-Me_2	0.00	0.00	−0.14	−0.14	0.00	−2.033	−2.416
27	2-Me-6-Et	−2.49	−2.55	−0.32	0.00	−0.32	−0.740	−0.767
28	2,6-Et_2	−2.66	−2.62	−0.30	0.00	−0.30	−1.041	−0.716
29	2,6-iso-Pr_2	−3.32	−3.42	−0.30	0.00	−0.30	−1.924	−0.405
30	2-Me-5-Cl	−1.16	−1.24	0.20	0.37	−0.17	−1.342	−1.617
31	2-Me-6-Cl	−2.14	−2.21	0.06	0.00	0.06	−1.301	−1.497
32	2,5-$(OMe)_2$	−0.40	−0.55	−0.15	0.12	−0.27	−2.146	−1.826
33	2,4-Cl_2	−0.98	−0.97	0.46	0.00	0.46	−2.491	−2.639
34	2,6-Cl_2	−1.96	−1.94	0.46	0.00	0.46	−1.447	−2.177
35	3,4-Cl_2	0.00	0.00	0.60	0.37	0.23	−2.820	−2.758
36	3-OH-4-COOH	0.00	0.00	0.57	0.12	0.45	−3.255	−3.086
37	2,4,5-Me_3	−1.16	−1.24	−0.41	−0.07	−0.34	−1.114	−1.364
38	2,4,6-Me_3	−2.32	−2.48	−0.51	0.00	−0.51	−0.903	−0.564
39	2,4,6-Me_3-3-Br	−2.32	−2.48	−0.12	0.39	−0.51	−0.845	−0.564
40	2,3,5,6-F_4	−0.64	−0.92	0.80	0.68	0.12	−2.061	−2.293

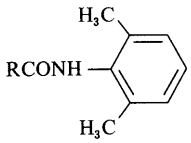
a) Compounds **5**, **13**, **25** and **29** were excluded from analysis. *b*) Taken from reference 4). *c*) Taken from reference 2). *d*) The values for *ortho* and *para* substituents were put at zero. *e*) The values for *meta* substituents were put at zero. *f*) Calculated according to Eq. 4. *g*) Unavailable parameter.

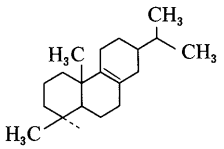
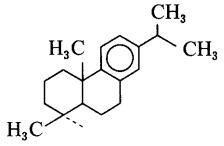
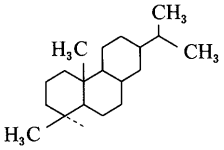
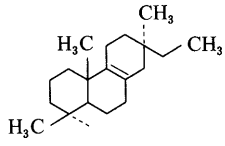
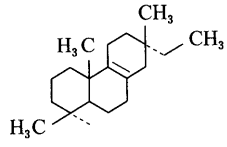
TABLE III. Relative Hypocholesterolemic Activity

No.	ID_{30} ppm	ID_{30} Ratio[a]	ID_{40} ppm	ID_{40} Ratio[a]	ID_{50} ppm	ID_{50} Ratio[a]	ID_{90} ppm	ID_{90} Ratio[a]
24	2.8	1.0	5.0	1.0	8.8	1.0	63	1.0
2	14	0.2	20	0.3	26	0.3	155	0.4
3	7	0.4	9	0.6	12	0.7	56	1.1
4	23	0.1	30	0.2	37	0.2	90	0.7
21	5	0.6	7	0.7	9	1.0	90	0.7
22	—	—	8	0.6	20	0.4	110	0.6
23	7	0.4	10	0.5	17	0.5	120	0.5
27	2.3	1.2	3.8	1.3	5.5	1.6	28	2.3
28	4	0.7	7	0.7	11	0.8	150	0.4
30	14	0.2	17	0.3	22	0.4	460	0.1
31	8	0.4	13	0.4	20	0.4	80	0.8
34	13	0.2	18	0.3	28	0.3	130	0.5
38	3.4	0.8	5.2	1.0	8	1.0	44	1.4
39	2.0	1.4	3.6	1.4	7	1.3	65	1.0

a) ID_x of test compound/ID_x of **24**.

TABLE IV. Variation in Hypocholesterolemic Activity with Change in the Acid Moiety



No.	R	Formula	Yield (%)	mp (°C)	Crystn. solvent[a]	% inhibition				ID_{50} (ppm)
						10	30	100	300 ppm[b]	
24		$C_{28}H_{41}NO$	76	195—197	MEK	53	79	97	103	8.8
41		$C_{28}H_{37}NO$	76	227—229	EA	8	24	66	92	68
42		$C_{28}H_{43}NO$	82	218—220	A	17	39	72	—	48
43		$C_{28}H_{41}NO$	54	187—189	MEK	−4	17	46	74	120
44		$C_{28}H_{41}NO$	58	173—176	MEK	7	6	36	60	180
45		$C_{16}H_{23}NO$	76	198	M	—	—	7	17	1100

a, b) See Table I.

the E_s(AMD) for hydrogen is zero.

$$pID_{50} = -1.511(\pm 0.431)\sigma(op) - 0.409(\pm 0.303)E_s(AMD)^S - 0.505(\pm 0.203)E_s(AMD)^L - 2.427(\pm 0.182) \quad (5)$$
$$n=36,\ s=0.354,\ r=0.899,\ F=45.0$$

The coefficients with the $E_s(AMD)^S$ and $E_s(AMD)^L$ terms were very close to each other, meaning that the susceptibility of the activity to steric effect is almost identical for the two *ortho*-substituents. Thus, the overall steric effect was expressible by the simple sum of the two E_s(AMD) constants in this series of compounds.

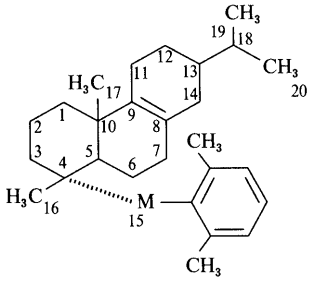
The relative hypocholesterolemic activities of those derivatives comparable to the activity of **24** are listed in Table III. The inhibitory doses at which serum cholesterol elevation was inhibited by 30, 40, 50 and 90% were calculated. Accurate relative activities for these derivatives could be estimated by comparing many inhibitory doses. When derivatives that had considerable hypocholesterolemic activity were compared in terms of activity at 30, 40, 50 and 90% inhibitory doses, four analogs (**24**, **27**, **38**, **39**) had about the same degree of activity.

Hypocholesterolemic Activity of *N*-(2,6-Dimethylphenyl)-Analogs of Several Resin Acids We compared the hypocholesterolemic activities of various amide derivatives of 2,6-dimethylaniline in order to assess the effect of the acid moiety.

Table IV shows that the abietane-type carboxamides (**41**, **42**) appear to be preferable to the pimarane-type analogs (**43**, **44**) in terms of activity. *N*-(2,6-Dimethylphenyl)-1-methylcyclohexanecarboxamide (**45**), having a structure that resembles ring A in the resin acid, was inactive.

Variation in Hypocholesterolemic Activity Due to Conversion of the Carboxamide Group in *N*-(2,6-Dimethylphenyl)-Δ^8-Dihydroabietamide Table V shows the effect of the conversion of the carboxamide group in **24** on hypocholesterolemic action. The reversed-type carboxamide (**46**) of **24** was decreased markedly, to about 1/205 the activity of the parent carboxamide (**24**). The thioamide (**47**) had only about 1/18 the parent activity, and the ester (**48**) no activity. These results indicate the importance of the carboxamide group for hypocholesterolemic activity. On the derivatives synthesized, *N*-(2,6-dimethylphenyl)-Δ^8-dihydroabietamide, **24**, was the most potent in the series. The structural

TABLE V. Variation in Hypocholesterolemic Activity Due to Conversion of the Carboxamide Group



No.	M	Formula	Yield (%)	mp (°C)	Crystn. solvent[a)]	% inhibition				ID_{50} (ppm)
						100	300	1000	3000 ppm[b)]	
46	NHOC	$C_{28}H_{41}NO$	67	104—106	C–M	16	22	24	68	1800
47	CSNH	$C_{28}H_{41}NS$	85	215—217	C–M	36	64	95	—	160
48	CO_2	$C_{28}H_{40}O_2$	58	(wax)	—	—	—	3	10	—

a, b) See Table I.

resemblance of Δ^8-dihydroabietic acid to cholesterol is considered to be a factor affecting cholesterol absorption.

Chemistry The carboxamides (**1**—**45**) were prepared by the Schotten–Baumann reaction. The reversed type of carboxamide (**46**) of **24** was prepared as follows: Δ^8-dihydroabietic acid was converted to 4-amino-15-nor-8-abietene by the Curtius reaction, after which the product was condensed with 2,6-dimethylbenzoyl chloride. The thioamide (**47**) was derived from **24** by treatment with phosphorous pentasulfide. The ester (**48**) was prepared by reacting Δ^8-dihydroabietoyl chloride with sodium 2,6-dimethylphenoxide.

The method for the preparation of these compounds is described in detail in Experimental.

Assay Method for Hypocholesterolemic Activity As described elsewhere,[1)] 4-week-old male Wistar rats were fed synthetic basal and cholesterol-containing diets *ad libitum* for 3 d. They then were killed after overnight starvation and their serum cholesterol concentrations measured. The test compounds were added to the cholesterol diet. Hypocholesterolemic activity was expressed as the % of inhibition of serum cholesterol elevation induced by cholesterol feeding and the ID_{50}. The % of inhibition of each test compound at concentrations from 3×10^{-4} to 3×10^{-1}% is shown in Table I. The ID_{50} is the concentration of test compounds in the diet which produces 50% inhibition of the serum cholesterol elevation.

Experimental

Melting points were measured in open capillary tubes with a Büchi melting point apparatus, and are uncorrected. The boiling points of oily compounds were not determined. Infrared (IR) absorption spectra were measured with a Hitachi 215 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded in deuterochloroform with a Varian A-60 or Varian XL-200 that had tetramethylsilane (TMS) as the internal standard. Chemical shifts are expressed in ppm downfield from TMS. Column chromatography was done on silica gel (Wakogel, C-200).

***N*-(2,6-Dimethylphenyl)-Δ^8-dihydroabietamide (24)** A mixture of Δ^8-dihydroabietic acid (6.10 g, 20 mmol), thionyl chloride (7.14 g, 60 mmol), and benzene (30 ml) was refluxed for 2 h. A pale brown resinous product was obtained by removal of the solvent and excess thionyl chloride under reduced pressure. The acid chloride (IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1783) was used without further purification. It was first dissolved in toluene (30 ml), then at an ambient temperature, added by drops with stirring to a solution of 2,6-xylidine (2.54 g, 21 mmol), triethylamine (2.23 g, 22 mmol) and toluene (20 ml). After additional stirring for 4 h, the reaction mixture was washed with 5% HCl (20 ml), water (20 ml × 3), 5% NaOH (20 ml), and water (20 ml × 3) in that order. The organic layer was dried with anhydr. magnesium sulfate, filtered, and evaporated. The residual mass was crystallized from acetone. Recrystallization from methyl ethyl ketone gave colorless needles (6.21 g, 76%), mp 195—197 °C. IR ν_{max}^{KBr} cm^{-1}: 1635. NMR δ: 0.88 (6H, d, J=5 Hz), 1.02 (3H, s), 1.28 (3H, s), 2.13 (6H, s), 7.02 (3H, s). *Anal.* Calcd for $C_{28}H_{41}NO$: C, 82.50; H, 10.14; N, 3.44. Found: C, 82.81; H, 10.27; N, 3.46.

***N*-(3-Bromo-2,4,6-trimethylphenyl)-Δ^8-dihydroabietamide (39)** The acid chloride prepared from Δ^8-dihydroabietic acid (6.10 g, 20 mmol) was dissolved in acetone (20 ml) then added by drops to a stirred and ice-cooled solution containing acetone (20 ml), triethylamine (2.23 g, 22 mmol) and 3-bromomesidine (4.71 g 22 mmol) as described by Adams and Dankert.[6)] After additional stirring for 3 h, the reaction mixture was poured into water (100 ml). The crystals that precipitated were collected, washed twice with 20 ml of water, then dried. Recrystallization from methyl ethyl ketone gave colorless needles (7.22 g, 72%), mp 231—232 °C. IR ν_{max}^{KBr} cm^{-1}: 1640. NMR δ: 0.88 (6H, d, J=5 Hz), 1.00 (3H, s), 1.28 (3H, s), 2.00 (3H, s), 2.20 (3H, s), 2.34 (3H, s), 6.90 (1H, br), 7.32 (1H, br). *Anal.* Calcd for $C_{29}H_{42}BrNO$: C, 69.58; H, 8.46; N, 2.80. Found: C, 69.57; H. 8.58; N, 2.56.

***N*-(2,6-Dimethylphenyl)-Δ^8-dihydropimaramide (43)** Δ^8-Dihydropimaric acid was prepared from pimaric acid by partial reduction followed by isomerization in the presence of an acid catalyst according to the method of Edwards and Howe.[7)] The acid chloride prepared from Δ^8-dihydropimaric acid (1.00 g, 3.3 mmol) and thionyl chloride (1.17 g, 99 mmol) was added to a solution of benzene (30 ml) containing 2,6-xylidine (0.49 g, 4.0 mmol) and triethylamine (0.46 g, 4.5 mmol). This reaction mixture was treated by the procedure described above. Recrystallization from methyl ethyl ketone gave colorless needles (0.72 g, 54%), mp 187—189 °C. IR ν_{max}^{KBr} cm^{-1}: 1638. NMR (200 MHz) δ: 0.760 (3H, s), 0.819 (3H, t, J=7.4 Hz), 1.053 (3H, s), 1.357 (3H, s), 2.186 (6H, s), 7.048 (3H, s). *Anal.* Calcd for $C_{28}H_{41}NO$: C, 82.50; H, 10.14; N, 3.44. Found: C, 82.42; H, 10.20; N, 3.44.

***N*-(2,6-Dimethylphenyl)-Δ^8-dihydroisopimaramide (44)** Isopimaric acid was purified from the resin of *Cryptomeria japonica* D. DON by silica gel column chromatography and recrystallized several times from methyl acetate as *n*-butanolamine salt.[8)] The amine salt was suspended in ethyl ether and decomposed with 10% sulfuric acid, the resulting solution was treated in the usual manner to give the acid. Δ^8-Dihydroisopimaric acid was prepared from isopimaric acid by the method of Edwards and Howe.[7)] A solution of (chloroform, 10 ml) the acid chloride prepared from Δ^8-dihydroisopimaric acid (2.0 g, 6.6 mmol) and thionyl chloride (2.34 g, 19.8 mmol) was added to a stirred solution of 2,6-xylidine (0.98 g, 8.0 mmol), triethylamine (0.92 g, 9.0 mmol) and chloroform (20 ml). After additional stirring for 4 h, this reaction mixture was worked up in the usual manner. Recrystallization from methyl ethyl ketone gave colorless needles (1.55 g, 58%), mp 173—176 °C. IR ν_{max}^{KBr} cm^{-1}: 1636. NMR (200 MHz) δ: 0.782 (3H, t, J=7.4 Hz), 0.807 (3H, s), 1.052 (3H, s), 1.363 (3H, s), 2.195 (6H, s), 7.054 (3H, s). *Anal.* Calcd for $C_{28}H_{41}NO$: C, 82.50; H, 10.14; N, 3.44. Found: C, 82.54; H, 10.09; N, 3.46.

***N*-(15-Nor-8-abieten-4-yl)-2,6-dimethylbenzamide (46)** 4-Amino-15-nor-8-abietene was prepared from Δ^8-dihydroabietic acid by the Curtius reaction.[9] A 20% aq. solution of sodium azide (38.8 g, 120 mmol) was added with vigorous stirring to a cooled (15 °C) solution in acetone (92 ml) of acid chloride prepared from Δ^8-dihydroabietic acid (30.45 g, 100 mmol) and thionyl chloride (35.70 g, 300 mmol). After stirring for 30 min, water (300 ml) was added and the mixture was then treated twice with benzene (100 ml) (IR ν_{max}^{film} cm^{-1}: 1780). After the benzene solution had been refluxed for 5 h, the solvent was removed *in vacuo*, giving a brown oily product (IR ν_{max}^{film} cm^{-1}: 2250). This product was purified by column chromatography on silica gel (50 g) eluting with *n*-hexane (500 ml). Removal of the solvent gave a colorless oil (28.3 g). A mixture of conc. sulfuric acid (30 ml) and water (5 ml) was added dropwise during 30 min to a stirred and cooled solution of the oil obtained above in diethyl ether (300 ml). After additional stirring for 30 min, ice and water were added. The colorless crystals formed were filtered and dissolved in chloroform (300 ml). The chloroform solution was washed with 5% sodium hydroxide (300 ml) and with water, and was dried over anhydr. magnesium sulfate. The solvent was removed *in vacuo* giving a clear oil (27.4 g, 85%). NMR δ: 0.88 (6H, d, J=6 Hz), 0.95 (3H, s), 1.02 (3H, s), 1.28 (2H, br). Hydrochloride monohydrate; mp 173—175 °C. *Anal.* Calcd for $C_{19}H_{33}N \cdot HCl \cdot H_2O$: C, 69.92; H, 11.60; N, 4.25. Found: C, 69.45; H, 11.52; N, 4.38. A solution of toluene (30 ml) and 2,6-dimethylbenzoyl chloride, prepared from the corresponding acid (3.00 g, 20 mmol) and thionyl chloride (7.14 g, 60 mmol), was treated with a mixture of 4-amino-15-nor-8-abietene (4.13 g, 15 mmol) and triethylamine (2.02 g, 20 mmol). After the reaction had continued for 4 h, the mixture was worked up as described above. The resulting product was crystallized from a small volume of acetone and then recrystallized from chloroform–methanol (1 : 1) to give colorless needles (4.09 g, 67%), mp 104—106 °C. IR ν_{max}^{KBr} cm^{-1}: 1625. NMR δ: 0.90 (6H, d, J=5 Hz), 1.00 (3H, s), 1.39 (3H, s), 2.36 (6H, s), 5.35 (1H br), 7.00 (3H, m). *Anal.* Calcd for $C_{28}H_{41}NO$: C, 82.50; H, 10.14; N, 3.44. Found: C, 82.71; H, 10.21; N, 3.48.

***N*-(2,6-Dimethylphenyl)-Δ^8-dihydroabietenecarbothioamide (47)** A mixture of the carboxamide **24** (10.00 g, 24.5 mmol), phosphorus pentasulfide (3.00 g, 13.5 mmol) and anhydr. benzene (100 ml) was refluxed for 1 h. After cooling, 5% sodium hydroxide (100 ml) was added and the reaction mixture was stirred for 1 h. The benzene layer was separated, filtered, and dried over anhydr. magnesium sulfate. After removal of the drying agent, the solvent was evaporated under reduced pressure. The resulting residue crystallized from chloroform–methanol (10 : 7) gave pale yellow needles (8.83 g, 85%), mp 215—217 °C. IR ν_{max}^{KBr} cm^{-1}: 1493, 1340, 1200. NMR δ: 0.87 (6H, d, J=5 Hz), 1.07 (3H, s), 1.50 (3H, s), 2.12 (3H, s), 2.20 (3H, s), 7.05 (3H, s), *Anal.* Calcd for $C_{28}H_{41}NS$: C, 79.38; H, 9.76; N, 3.31; S, 7.55. Found: C, 79.21; H, 9.42; N, 3.48; S, 7.44.

2,6-Dimethylphenyl Δ^8-Dihydroabietate (48) A mixture of Δ^8-dihydroabietoyl chloride (6.10 g, 20 mmol) and sodium 2,6-dimethylphenoxide, prepared from 2,6-xylenol (3.67 g, 30 mmol) and sodium hydride (1.44 g, 30 mmol, 50% in oily suspension), was stirred in anhydr. benzene (20 ml) for 3 h. This reaction mixture was then washed, dried and filtered. Removal of the solvent gave a brown oil which was purified by column chromatography on silica gel (200 g). Elution with *n*-hexane–benzene (1 : 1, 300 ml), followed by removal of the solvent, gave an almost colorless oil (4.75 g, 58%) which solidified into a waxy material on standing for several days. IR ν_{max}^{film} cm^{-1}: 1735. NMR δ: 0.86 (6H, d, J=5 Hz), 1.05 (3H, s), 1.35 (3H, s), 2.10 (6H, s), 6.95 (3H, s). *Anal.* Calcd for $C_{28}H_{37}O_2$: C, 82.92; H, 9.19. Found: C, 83.01; H, 9.23.

References and Notes

1) Y. Fujita, K. Sempuku, K. Kitaguchi, T. Mori, H. Murai, Y. Yoshikuni, H. Enomoto, and R. Löser, *Chem. Pharm. Bull.*, **28**, 453 (1980).
2) C. Hansch and A. J. Leo, "Substituent Constants for Correlation Analysis in Chemistry and Biology", John Wiley & Sons, New York, 1979, p 65.
3) T. Fujita and T. Nishioka, *Progr. Phys. Org. Chem.*, **12**, 49 (1976).
4) T. Sotomatsu and T. Fujita, *J. Org. Chem.*, **54**, 4443 (1989).
5) E. Kutter and C. Hansch, *J. Med. Chem.*, **12**, 647 (1969).
6) R. Adams and L. J. Dankert, *J. Am. Chem. Soc.*, **62**, 2191 (1940).
7) O. E. Edwards and R. Howe, *Can. J. Chem.*, **37**, 760 (1959).
8) M. Sogo and K. Hata, *Nippon Nogeikagaku Kaishi*, **35**, 724 (1961).
9) R. N. Seelye and W. B. Watkins, *Tetrahedron*, **25**, 447 (1969).