Studies on Hypolipidemic Agents. II.[1] Synthesis and Pharmacological Properties of Alkylpyrazole Derivatives[2]

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A series of 5-alkylpyrazole derivatives was synthesized and evaluated for potent hypo-lipidemic activity in rats. Many pyrazole derivatives with an alkyl group at the 5 position of the pyrazole ring were found to possess high hypolipidemic activity. Homologation of the alkyl chain led to marked increase in activity, but introduction of other substituents at other sites on the pyrazole ring failed to enhance the activity. In addition, the replacement of the pyrazole ring with an isoxazole ring resulted in a marked decrease in activity. Among the compounds tested, 5-n-tridecylpyrazole-3-carboxylic acid (**5k**) exhibited the most favorable spectrum of activity and was as effective as clofibrate. This compound, **5k**, showed fairly low toxicity in an acute test ($LD_{50} = 10.0$ g/kg) and hence is now undergoing further pharmacological evaluation.

Many new classes of hypolipidemic agents have been investigated during the past decade. For example, some fatty acid-like compounds have recently been reported to have hypolipidemic activity and/or antiatherosclerotic effects.[3−9]

In the course of studies on hypolipidemic agents in our laboratories, it was found that some kinds of alkylpyrazole derivatives showed potent hypolipidemic activity in rats. This report deals with the synthesis of various alkylpyrazole derivatives and with their structure–hypolipidemic activity relationship.

Results and Discussion

Chemistry

The pyrazole derivatives treated in this study are represented by the following general formula (**1**):

$$R_3 \underset{\underset{R_1}{\overset{|}{N}}}{\overset{\overset{4\ 3}{\underset{5\ 1\ 2}{N}}}{\fbox{}}} R_2$$
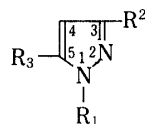
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Chart 1

where R_1 represents a hyrogen atom, of alkyl, hydroxycarbonyl alkyl or phenyl group, R_2 a carboxylic acid, carbinol, or amide group, and R_3 an alkyl group having from 1 to 17 carbon atoms. Although some of these derivatives are known already,[10] nothing has been reported concerning their pharmacological properties except for 5-methylpyrazole-3-carboxylic acid (**5a**).[11,12] The general synthetic routes for preparation of the present compounds are shown in Charts 2, 3 and 4. The starting higher-alkyl methyl ketones (chain lengths of more than 12

carbon atoms) (2) except for the commercially available ones were prepared by means of the Friedel–Crafts reaction[13] from the corresponding acid chloride and tetramethylsilane. Sodium enolates (3) were obtained by the Claisen condensation[14] of 2 with diethyloxalate. Treatment of 3 with hydrazine hydrate followed by hydrolysis with alcoholic NaOH gave the 5-alkylpyrazole-3-carboxylic acids (5a—n) in 56—90% yields. The esters (4) or free acids (5h, i, k) were converted to the corresponding carbinol or amide derivatives by the usual methods as detailed in the experimental section (Chart 2). The N-substituted pyrazole carboxylic acids (8a—n) were prepared by the usual methods from 3 and alkyl- or aryl-hydrazine, or from the esters (4) and ethyl bromoalkylcarboxylate (Chart 3). The structures of the compounds thus synthesized are shown in Table I and their physicochemical properties in Table III. The isoxazole analogs (9a, b) were synthesized by reacting the corresponding 3 with hydroxylamine in the presence of sodium hydroxide or acetic acid (Chart 4). The physicochemical properties of the compounds obtained by these methods are detailed in the experimental section.
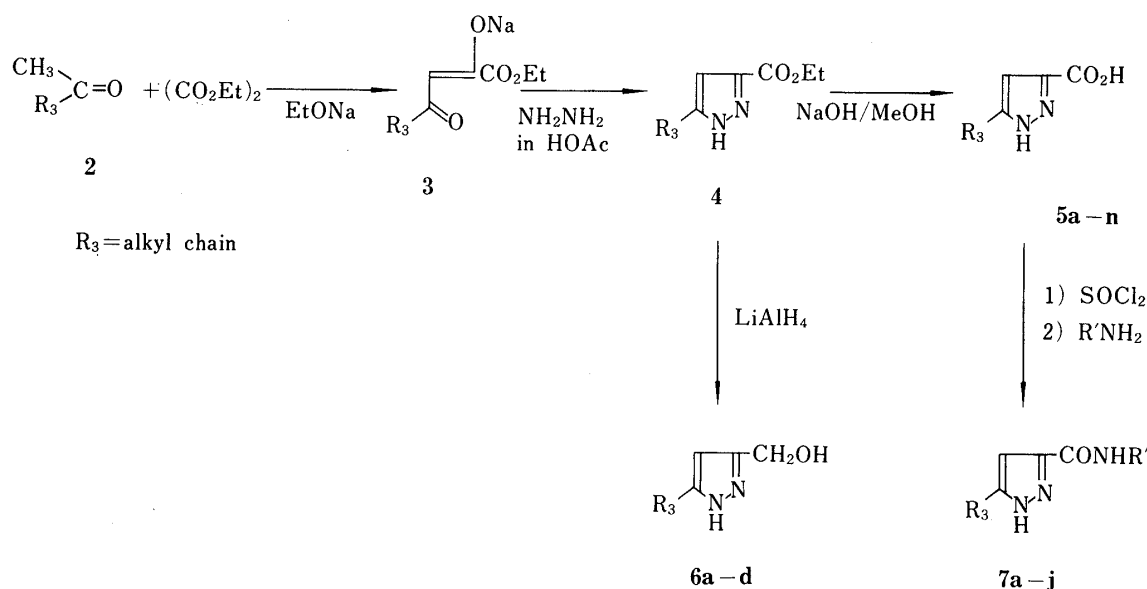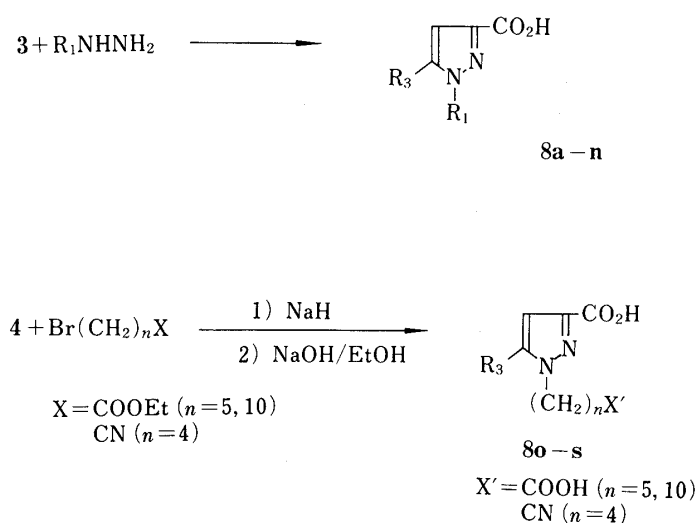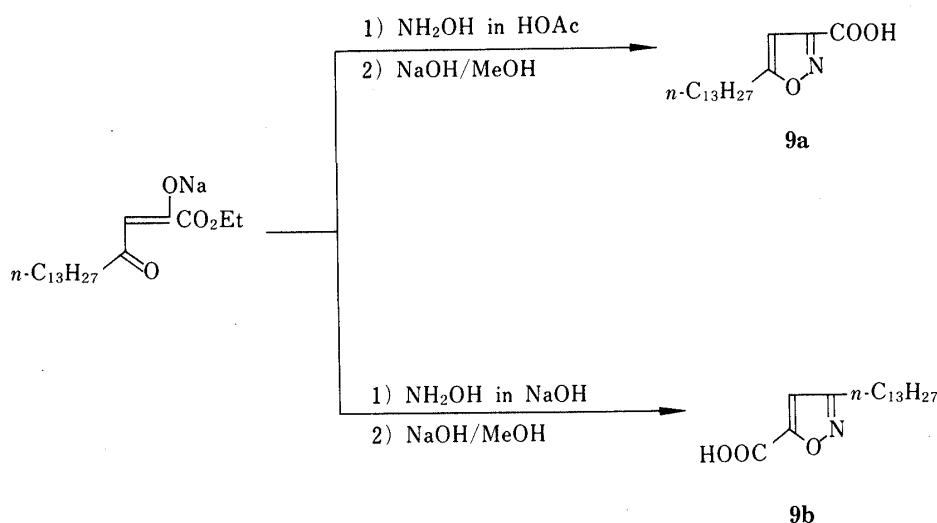
Chart 2

Chart 3

1) NH$_2$OH in HOAc
2) NaOH/MeOH

n-C$_{13}$H$_{27}$—COOH (isoxazole) **9a**

ONa
CO$_2$Et
n-C$_{13}$H$_{27}$—O

1) NH$_2$OH in NaOH
2) NaOH/MeOH

HOOC—n-C$_{13}$H$_{27}$ (isoxazole) **9b**

Chart 4

Pharmacology

The hypolipidemic activity was assayed in rats with hypertriglyceridemia induced by fructose, according to the method reported previously.[1] The results are shown in Tables I and II.

Structure–Activity Relationships

1. Alkyl Chain Homologation——The pharmacological effect of increasing the length of the alkyl side chain is shown in Table I. Variation of the alkyl chain length at the 5 position

TABLE I. Structure and Hypolipidemic Activity of Alkylpyrazole Derivatives

$$R_3-\underset{\underset{R_1}{\overset{|}{N}}-N}{\text{pyrazole}}-R_2$$
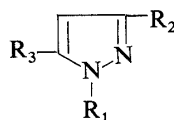
Compd. No.	Structure			Dose (mg/kg)	Hypolipidemic activity[a]	
	R_1	R_2	R_3		Triglyceride	Cholesterol
5a	H	COOH	CH$_3$	300	21.4[c]	8.6
5b	H	COOH	n-C$_3$H$_7$	300	31.5[c]	25.1[d]
5c	H	COOH	iso-C$_3$H$_7$	300	46.0[d]	10.4
5d	H	COOH	n-C$_4$H$_9$	300	29.1[c]	14.8[b]
5e	H	COOH	iso-C$_4$H$_9$	300	5.9	7.8
5f	H	COOH	n-C$_5$H$_{11}$	300	3.0	16.2[b]
5g	H	COOH	n-C$_7$H$_{15}$	300	40.9[d]	7.3
5h	H	COOH	n-C$_9$H$_{19}$	300	68.4[d]	24.9[d]
5i	H	COOH	n-C$_{11}$H$_{23}$	75	45.9[d]	12.3[b]
				150	56.8[d]	24.0[d]
				300	83.7[d]	53.1[d]
5j	H	COOH	n-C$_{12}$H$_{25}$	150	56.2[d]	34.8[d]
5k	H	COOH	n-C$_{13}$H$_{27}$	75	50.3[d]	24.0[d]
				150	66.7[d]	39.9[d]
				300	82.2[d]	61.1[d]
5l	H	COOH	n-C$_{14}$H$_{29}$	150	58.2[d]	19.8[c]
5m	H	COOH	n-C$_{15}$H$_{31}$	300	67.8[d]	34.1[d]
5n	H	COOH	n-C$_{17}$H$_{35}$	300	17.3[b]	18.8[c]
6a	H	CH$_2$OH	n-C$_7$H$_{15}$	150	28.0[c]	1.0
6b	H	CH$_2$OH	n-C$_9$H$_{19}$	150	44.5[d]	4.0

TABLE I. (continued)

Compd. No.	R$_1$	R$_2$	R$_3$	Dose (mg/kg)	Triglyceride	Cholesterol
6c	H	CH$_2$OH	n-C$_{11}$H$_{23}$	150	65.4$^{d)}$	11.1
6d	H	CH$_2$OH	n-C$_{13}$H$_{27}$	150	56.6$^{d)}$	20.6$^{b)}$
7a	H	CONHCH$_2$CH$_2$OH	n-C$_9$H$_{19}$	150	22.0$^{b)}$	18.6$^{c)}$
7b	H	CONHCH$_2$CO$_2$C$_2$H$_5$	n-C$_9$H$_{19}$	150	23.6	15.0$^{b)}$
7c	H	CONHCH$_2$CH$_2$OH	n-C$_{11}$H$_{23}$	150	17.8	6.9
7d	H	CONHCH$_2$CO$_2$C$_2$H$_5$	n-C$_{11}$H$_{23}$	150	18.9	5.5
7e	H	CONHCH$_2$CH$_2$OH	n-C$_{13}$H$_{27}$	150	57.4$^{d)}$	7.5
7f	H	CONHCH$_2$CO$_2$C$_2$H$_5$	n-C$_{13}$H$_{27}$	150	58.1$^{d)}$	24.9$^{d)}$
7g	H	CONHCH(sec-C$_4$H$_9$)–CO$_2$C$_2$H$_5$	n-C$_{13}$H$_{27}$	150	34.2$^{d)}$	13.3$^{b)}$
7h	H	CONH$_2$	n-C$_{13}$H$_{27}$	150	34.3$^{b)}$	13.0$^{b)}$
7i	H	CONHC$_4$H$_9$	n-C$_{13}$H$_{27}$	150	54.8$^{d)}$	11.7$^{b)}$
7j	H	CONHC$_{10}$H$_{21}$	n-C$_{13}$H$_{27}$	150	−8.0	−3.6
8a	CH$_3$	COOH	n-C$_7$H$_{15}$	150	2.3	−6.6
8b	CH$_3$	COOH	n-C$_9$H$_{19}$	150	28.0$^{b)}$	3.2
8c	CH$_3$	COOH	n-C$_{11}$H$_{23}$	150	17.3	9.3
8d	CH$_3$	COOH	n-C$_{13}$H$_{27}$	150	1.8	12.8$^{b)}$
8e	n-C$_8$H$_{17}$	COOH	CH$_3$	150	−7.8	−2.9
8f	n-C$_{10}$H$_{21}$	COOH	CH$_3$	150	−1.6	6.3
8g	n-C$_{12}$H$_{25}$	COOH	CH$_3$	150	−7.6	6.3
8h	Phenyl	COOH	n-C$_9$H$_{19}$	150	44.5$^{d)}$	4.0
8i	Phenyl	COOH	n-C$_{11}$H$_{23}$	150	4.9	1.6
8j	Phenyl	COOH	n-C$_{13}$H$_{27}$	150	−10.1	−2.5
8k	p-CH$_3$Phenyl	COOH	n-C$_{13}$H$_{27}$	150	30.6$^{b)}$	10.3
8l	p-Cl Phenyl	COOH	n-C$_{13}$H$_{27}$	150	38.3$^{b)}$	30.5$^{d)}$
8m	p-CH$_3$O Phenyl	COOH	n-C$_{13}$H$_{27}$	150	15.5	11.7$^{b)}$
8n	p-NH$_2$Phenyl	COOH	n-C$_{13}$H$_{27}$	150	12.2	7.9
8o	(CH$_2$)$_5$COOH	COOH	CH$_3$	150	−36.0$^{b)}$	−8.9
8p	(CH$_2$)$_5$COOH	COOH	n-C$_{13}$H$_{27}$	150	−7.7	4.4
8q	(CH$_2$)$_{10}$COOH	COOH	CH$_3$	150	−39.8$^{b)}$	−6.3
8r	(CH$_2$)$_{10}$COOH	COOH	n-C$_{13}$H$_{27}$	150	−7.7	4.4
8s	(CH$_2$)$_4$CN	COOH	n-C$_{13}$H$_{27}$	150	0.1	4.5
	Clofibrate			75	48.6$^{d)}$	31.3$^{d)}$
				150	55.7$^{d)}$	44.3$^{d)}$
				300	62.7$^{d)}$	48.3$^{d)}$

a) Each value is the percentage reduction from the control level. The serum triglyceride and cholesterol levels of control groups in three experiments with a total of 18 rats averaged 184 and 52 mg/dl, respectively.
b) $p < 0.05$, c) $p < 0.01$, d) $p < 0.001$ vs. control.

TABLE II. Structure and Hypolipidemic Activity of Alkylisoxazole Derivatives

Compd. No.	R$_1$	R$_2$	Dose (mg/kg)	Triglyceride	Cholesterol
9a	COOH	n-C$_{13}$H$_{27}$	150	34.9$^{b)}$	11.9$^{b)}$
9b	n-C$_{13}$H$_{27}$	COOH	150	0.7	4.5

See footnote to Table I.

TABLE III. Physicochemical Properties of Alkylpyrazole Drivatives

Compd. No.	Yield (%)	mp (°C)	Recryst. solvent	IR ν_{max}^{Nujol} cm^{-1}	MS (m/e) M$^+$	Formula	Analysis (%) Calcd (Found)		
							C	H	N
5a	70.0	241—242	H$_2$O	3240, 1700	126	C$_5$H$_6$N$_2$O$_2$	47.62 (47.33	4.80 4.75	22.22 22.02)
5b	72.2	189—190	Acetone	3240, 1700	154	C$_7$H$_{10}$N$_2$O$_2$	54.53 (54.32	6.54 6.30	18.17 17.93)
5c	76.7	153—154	H$_2$O	3260, 1715	154	C$_7$H$_{10}$N$_2$O$_2$	54.53 (54.64	6.54 6.53	18.17 17.93)
5d	70.2	167—169	Acetone	3100, 1680	168	C$_8$H$_{12}$N$_2$O$_2$	57.13 (57.22	7.19 7.45	16.66 16.81)
5e	65.3	186—188	Acetone	3240, 1710	168	C$_8$H$_{12}$N$_2$O$_2$	57.13 (57.20	7.19 7.43	16.66 16.75)
5f	61.2	163—164	Acetone	3240, 1700	182	C$_9$H$_{14}$N$_2$O$_2$	59.32 (59.40	7.74 7.89	15.37 15.21)
5g	75.2	169—171	H$_2$O–MeOH	3240, 1700	210	C$_{11}$H$_{18}$N$_2$O$_2$	62.83 (62.71	8.63 8.50	13.32 13.42)
5h	67.3	147—149	Acetone–EtOH	3260, 1680	238	C$_{13}$H$_{22}$N$_2$O$_2$	65.51 (65.60	9.31 9.23	11.76 11.82)
5i	86.3	151—153	EtOH	3260, 1700	266	C$_{15}$H$_{26}$N$_2$O$_2$	67.63 (67.36	9.84 9.85	10.52 10.79)
5j	89.3	155—156	EtOH	3250, 1710	280	C$_{16}$H$_{28}$N$_2$O$_2$	68.53 (68.20	10.07 10.21	9.99 10.20)
5k	79.2	148—149	EtOH	3230, 1680	294	C$_{17}$H$_{30}$N$_2$O$_2$	69.33 (69.21	10.30 10.31	9.51 9.62)
5l	73.1	150—151	EtOH–MeOH	3250, 1710	308	C$_{18}$H$_{32}$N$_2$O$_2$	70.09 (69.88	10.46 10.49	9.08 8.88)
5m	56.0	133—135	EtOH	3250, 1710	322	C$_{19}$H$_{34}$N$_2$O$_2$	70.76 (70.88	10.63 10.75	8.69 8.98)
5n	69.5	125—127	EtOH	3240, 1700	350	C$_{21}$H$_{38}$N$_2$O$_2$	71.95 (71.75	10.93 10.85	7.99 7.88)
6a	76.9	40—41	Ether	3160	196	C$_{11}$H$_{20}$N$_2$O	67.30 (67.03	10.27 10.18	14.27 13.99)
6b	85.2	52—53	Ether	3200	224	C$_{13}$H$_{24}$N$_2$O	69.60 (69.70	10.78 10.68	12.49 12.74)
6c	83.6	56—58	Ether	3200	252	C$_{15}$H$_{28}$N$_2$O	71.38 (71.30	11.18 11.46	11.10 11.95)
6d	81.7	64—66	Ether	3200	280	C$_{17}$H$_{32}$N$_2$O	72.80 (72.85	11.50 11.60	9.99 10.01)
7a	51.8	48—50	Acetone	3120, 1630	281	C$_{15}$H$_{27}$N$_3$O$_2$	64.20 (63.69	9.67 9.72	14.93 14.78)
7b	46.4	Oil	—	3200, 1720	323	C$_{17}$H$_{29}$N$_3$O$_3$	63.13 (62.79	9.04 9.35	12.99 12.73)
7c	38.3	63—65	Acetone	3120, 1630	309	C$_{17}$H$_{31}$N$_3$O$_2$	65.98 (66.09	10.10 10.19	13.58 13.28)
7d	43.8	48—49	Acetone	3240, 1750	351	C$_{19}$H$_{33}$N$_3$O$_3$	64.92 (64.37	9.46 9.38	11.96 11.45)
7e	45.1	78—79	Acetone	3120, 1630	337	C$_{19}$H$_{35}$N$_3$O$_2$	67.61 (67.51	10.45 10.16	12.45 12.20)
7f	47.4	54—55	Acetone	3180, 1730	379	C$_{21}$H$_{37}$N$_3$O$_3$	66.45 (66.30	9.83 10.03	11.07 10.81)
7g	49.7	46—48	Ether	3180, 1720	435	C$_{25}$H$_{45}$N$_3$O$_3$	68.92 (68.82	10.41 10.50	9.65 9.55)
7h	75.1	148—150	Acetone	3200, 1690	293	C$_{17}$H$_{31}$N$_3$O	69.58 (69.82	10.65 10.81	14.32 14.24)

TABLE III. (continued)

Compd. No.	Yield (%)	mp (°C)	Recryst. solvent	IR ν_{max}^{Nujol} cm^{-1}	MS (m/e) M$^+$	Formula	Analysis (%) Calcd (Found)		
							C	H	N
7i	71.1	65—67	Ether	3120, 1720	349	$C_{21}H_{39}N_3O$	72.15 (71.93	11.25 11.23	12.02 11.91)
7j	25.9	71—73	Acetone	3160, 1630	433	$C_{27}H_{51}N_3O$	74.77 (74.51	11.85 11.86	9.69 9.60)
8a	56.5	80	EtOH	1680	224	$C_{12}H_{20}N_2O_2$	64.25 (64.50	8.99 9.12	12.49 12.50)
8b	64.7	87	Acetone–isoPr$_2$O	1680	252	$C_{14}H_{24}N_2O_2$	66.63 (66.38	9.59 9.57	11.10 11.28)
8c	75.0	79	Acetone–isoPr$_2$O	1680	280	$C_{16}H_{28}N_2O_2$	68.53 (68.79	10.07 10.08	9.99 10.15)
8d	57.2	82—83	Acetone–isoPr$_2$O	1680	308	$C_{18}H_{32}N_2O_2$	70.09 (70.26	10.46 10.38	9.08 8.88)
8e	57.9	78—79	EtOH	1670	238	$C_{13}H_{22}N_2O_2$	65.51 (65.39	9.31 9.45	11.76 11.70)
8f	60.3	105—106	CHCl$_3$	1680	266	$C_{15}H_{26}N_2O_2$	67.63 (67.30	9.84 9.86	10.52 10.41)
8g	54.6	76—77	EtOH	1670	294	$C_{17}H_{30}N_2O_2$	69.34 (69.43	10.27 10.44	9.52 9.53)
8h	61.7	87—88	EtOH	1630	314	$C_{19}H_{26}N_2O_2$	72.58 (72.47	8.34 8.05	8.91 8.84)
8i	91.1	53—55	EtOH	1690	342	$C_{21}H_{30}N_2O_2$	73.64 (73.70	8.83 8.91	8.18 8.40)
8j	59.8	89—90	EtOH	1610	370	$C_{23}H_{34}N_2O_2$	74.55 (74.70	9.25 9.38	7.56 7.76)
8k	46.3	85—86	Ether	1700	384	$C_{24}H_{36}N_2O_2$	74.96 (74.94	9.44 9.41	7.28 7.48)
8l	49.9	78—80	Ether	1680	404	$C_{23}H_{38}ClN_2O_2$	68.21 (67.97	8.21 8.05	6.92 7.06)
8m	63.0	88—89	Ether	1740	400	$C_{24}H_{36}N_2O_3$	71.96 (71.95	9.06 9.16	6.99 6.94)
8n	91.2	162—163	Ether	1700	385	$C_{23}H_{35}N_3O_2$	71.65 (71.38	9.15 9.17	10.90 10.80)
8o	86.4	Oil	—	1720	240	$C_{11}H_{16}N_2O_4$	54.99 (54.76	6.71 6.77	11.66 11.48)
8p	55.5	170—172	MeOH	1650	408	$C_{23}H_{40}N_2O_4$	67.61 (67.32	9.87 9.98	6.86 6.71)
8q	53.2	137—139	MeOH	1710	310	$C_{16}H_{26}N_2O_4$	61.91 (61.70	8.44 8.51	9.03 8.95)
8r	41.8	Oil	—	1700	478	$C_{28}H_{60}N_2O_4$	70.25 (70.35	10.53 10.59	5.85 6.00)
8s	73.0	74—75	EtOH	3460, 1690	375	$C_{22}H_{37}N_3O_2$	70.36 (68.93	9.93 9.79	11.19 10.86)

of pyrazole-3-carboxylic acids drastically affected the hypolipidemic activity. Thus, higher-alkyl compounds were more effective than lower-alkyl ones in terms of both triglyceride- and cholesterol-lowering activities. In particular, the activities increased remarkably with elongation of the alkyl chain from 5 to 14 carbon atoms. However, an abrupt drop in activity was observed in compounds (5m, n) with an alkyl chain of more than 15 carbon atoms. The above results suggest that the optimal length of alkyl side chain at the 5 position is 11 to 14 carbon atoms. Of these compounds, 5k showed the highest activity, almost identical with that of

clofibrate [ethyl 2-(p-chlorophenoxy)-2-methylpropionate].

2. **Replacement of Free Carboxylic Acid Moiety by Other Functional Groups**——In one group of compounds (6a—d), the free carboxylic acid moiety was converted into a carbinol, while in another group (7a—j), amides were formed with various amines (amino acid, ethanolamine and alkylamine). The alcohols (6a—d) retained significant triglyceride-lowering activity while the cholesterol-lowering activity was approximately 1/2 that of the corresponding parent acid (5i vs. 6c, 5k vs. 6d at a dose of 150 mg/kg). On the other hand, a number of amide derivatives exhibited moderate activity, but they were not as active as the corresponding free acids. The above results suggest that the conversion of the free carboxylic acid moiety into other functional groups does not enhance the activity.

3. **Introduction of Aryl or Alkyl Groups into the N-1 Site of the Pyrazole Ring**—— Several kinds of substituents were introduced into the N-1 site of 5-alkylpyrazole-3-carboxylic acids as shown in Table I: lower-alkyl (8a—d), higher-alkyl (8e—g), ω-hydroxycarbonyl or ω-cyanoalkyl (8o—s), phenyl (8h—j) and p-substituted phenyl (8k—n) groups. These derivatives were weakly active or ineffective. It is especially noteworthy that the compounds (8e—g) with chain lengths of 8, 10 and 12 carbon atoms in the N-alkyl series were inactive. In other words, a higher-alkyl substituent at the 5 position of the pyrazole ring is considered to be an essential structural requisite for hypolipidemic activity.

The derivative substituted with a phenyl group (8j) at the N-1 site of the pyrazole ring of 5k was inactive, while the p-chloro- and p-methylphenyl derivatives (8k, l) showed moderate activity. The above results suggest that electronic effects of the substituent on the phenyl ring play a slight role in the activity. In any case, it can be said that the introduction of a substituent at N-1 of the pyrazole ring, in general, reduces the activity.

Judging from these results, the hydrogen atom at N-1 and a higher-alkyl group at the 5 position of the pyrazole ring seem to be essential for the hypolipidemic activity.

4. **Replacement of Pyrazole Ring by an Isoxazole Ring**——In order to ascertain whether or not the pyrazole ring was essential for biological activity, 5-n-tridecylisoxazole-3-carboxylic acid (9a) and its isomer (9b) were examined. Interestingly, the hypolipidemic activity of 9a was approximately 1/2 that of the corresponding pyrazole compound (5k), while the isomeric isoxazole analog, 3-n-tridecylisoxazole-5-carboxylic acid (9b) was completely inactive. Thus, hypolipidemic activity was essentially diminished by this change, indicating that the pyrazole ring is desirable for activity.

Acute Toxicity

Since compound 5k was the most potent hypolipidemic compound among the compounds tested, the LD_{50} values of 5k and clofibrate were examined in mice (Table IV). The LD_{50} value in per os administration of 5k was about 10.0 g/kg, which is very different from that of clofibrate (1.22 g/kg). Thus, acute toxicological studies showed that the safety range of 5k is much wider than that of clofibrate.

TABLE IV. Acute Toxicity of 5k in Mice

Compd.	LD_{50} (g/kg)
5k[a)]	=10.0
Clofibrate	1.22
	(1.07—1.39)

a) This compound was given orally at doses of 2.5, 5.0 and 10.0 g/kg to 6 male mice per dose level.

Conclusion

Various substituted pyrazole derivatives and related analogs were prepared and subjected to hypolipidemic activity testing in rats. It is apparent from the data presented that several requirements can be defined for optimal activity. An n-tridecyl side chain at the 5 position and a carboxylic moiety at the 3 position in the pyrazole ring seem to be the most desirable for hypolipidemic activity; **5k**, 5-n-tridecylpyrazole-3-carboxylic acid was the most promising candidate in this series. Although the activity of **5k** was almost equivalent to that of clofibrate, it was about 8 times less toxic than clofibrate in mice.

This compound is now undergoing further pharmacological evaluation. Details of the hypolipidemic profiles of the compound, including the results in other experimental models will be reported elsewhere.

Experimental

Chemistry

Melting points were determined with a Yanagimoto micro-melting point apparatus and are uncorrected. Infrared (IR) spectra were determined with a Hitachi model 215 spectrometer. Mass spectra were measured with a JEOL JMS 01SG mass spectrometer.

Preparation of n-Tridecyl Methyl Ketone——n-Tridecyl methyl ketone was prepared by a modified Friedel-Crafts reaction.[13] Tetradecanoyl chloride (24.7 g, 0.1 mol) and tetramethylsilane (9.1 g, 0.1 mol) were added to a solution of $AlCl_3$ (14.3 g, 0.1 mol) in CH_2Cl_2 (140 ml). The mixture was stirred at room temperature for 4 h, then 5% aq. HCl was added and the deposited precipitate was removed by filtration. The filtrate was concentrated *in vacuo* and extracted with $CHCl_3$. The $CHCl_3$ extract was washed successively with sat. $NaHCO_3$ solution and water, then dried (Na_2SO_4), and concentrated. The residue was distilled *in vacuo* to give 21 g (95%) of n-tridecyl methyl ketone as a colorless oil, bp 110—112 °C (0.16 mmHg).

The higher-alkyl methyl ketones of more than 12 carbon atoms were prepared in the same manner as described above for n-tridecyl methyl ketone.

Preparation of 5-n-Tridecylpyrazole-3-carboxylic Acid (5k)——A liquid mixture of n-tridecyl methyl ketone (100 g, 0.44 mol) and diethyloxalate (64 g, 0.44 mol) was slowly dropped into a solution of metallic sodium (10.4 g, 0.45 mol) in anhyd. EtOH (500 ml). After being stirred at 60 °C for 5 h, the mixture was treated with ice-H_2O. The deposited yellow precipitate was collected and recrystallized from EtOH to give 103.3 g (68%) of sodium 1-ethoxycarbonyl-3-oxo hexadecenolate as pale yellow crystals, mp 68—70 °C. Hydrazine hydrate (5.5 g, 0.11 mol) was slowly added to a solution of the above compound (34.8 g, 0.1 mol) in acetic acid (23 ml) under ice-cooling. The mixture was heated for 8 h under reflux, then cooled, poured into ice-H_2O, neutralized with sat. $NaHCO_3$ solution, and extracted with benzene. The benzene extract was washed with sat. $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to dryness. The residue was recrystallized from EtOH to give 22.6 g (70%) of ethyl 5-n-tridecylpyrazole-3-carboxylate as colorless needles, mp 45—46 °C.

A solution of the above compound (10 g, 0.031 mol) in 5% methanolic NaOH was refluxed for 5 h. After removal of the solvent, the residue was made acidic (pH 2.0) with conc. HCl. The deposited precipitate was collected and recrystallized from EtOH to give 7.2 g (79%) of 5-n-tridecylpyrazole-3-carboxylic acid (**5k**) as needles, mp 148—149 °C.

The compounds (**5a**—**n**) other than **5k** in this group were prepared in the same manner as described for **5k**.

Preparation of 3-Hydroxymethyl-5-n-tridecylpyrazole (6d)——A suspension of $LiAlH_4$ (1.6 g, 0.042 mol) in anhyd. tetrahydrofuran (THF, 150 ml) was added to a solution of ethyl 5-n-tridecylpyrazole-3-carboxylate (11.0 g, 0.034 mol) in anhyd. THF (100 ml) under ice-cooling. The mixture was stirred at room temperature for 12 h, then H_2O-containing THF was added. The deposited colorless precipitate was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was recrystallized from Et_2O to give 7.8 g (82%) of 3-hydroxymethyl-5-n-tridecylpyrazole (**6d**) as colorless needles, mp 64—66 °C.

The compounds (**6a**—**c**) other than **6d** in this group were prepared in the same manner as described for **6d**.

Preparation of 3-(N-(2-Hydroxyethyl)-carbamoyl)-5-n-tridecylpyrazole (7e)——An excess of $SOCl_2$ (8.4 ml, 0.11 mol) was added to **5k** (4.0 g, 0.014 mol) and the mixture was stirred at 42 °C for 2 h. The reaction mixture was then concentrated to dryness *in vacuo* to give 5-n-tridecylpyrazole-3-carboxylic acid chloride as yellow crystals. Next, a solution of ethanolamine (1.1 g, 0.018 mol) and triethylamine (10 ml, 0.072 mol) in CH_2Cl_2 (70 ml) was slowly dropped onto the acid chloride under ice-cooling. The mixture was stirred at room temperature for 8 h, then the deposited triethylamine hydrochloride was filtered off and ice water was added to the filtrate. The organic phase was separated, dried (Na_2SO_4), and concentrated. The residue was recrystallized from Me_2CO to give 2.1 g (45%) of 3-(N-(2-hydroxyethyl)-carbamoyl)-5-n-tridecylpyrazole (**7e**) as colorless needles, mp 78—79 °C.

The compounds (7a—j) other than 7e in this group were prepared in the same manner as described for 7e.

Preparation of 1-Methyl-5-*n*-tridecylpyrazole-3-carboxylic Acid (8d)——A mixture of sodium 1-ethoxycarbonyl-3-oxohexadecenolate (20 g, 0.058 mol) and methylhydrazine (10.1 g, 0.053 mol) was dissolved in H_2O (45 ml). The solution was stirred at 80 °C for 1 h, then made acidic with 6 N aq. H_2SO_4 and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with sat. brine, dried (Na_2SO_4), and concentrated. The residue was recrystallized from Me_2CO–isoPr₂O to give 10.1 g (57%) of 1-methyl-5-*n*-tridecylpyrazole-3-carboxylic acid (8d) as colorless needles, mp 82—83 °C.

The compounds (8a—g) other than 8d in this group were prepared in the same manner as described for 8d.

Preparation of 1-Phenyl-5-*n*-tridecylpyrazole-3-carboxylic Acid (8j)——In the same manner as described for the preparation of the 1-alkyl derivatives (8a—g), sodium 1-ethoxycarbonyl-3-oxo-1-hexadecenolate (9.0 g, 0.026 mol) was reacted with phenylhydrazine sulfate (6.3 g, 0.02 mol) to give the corresponding 1-phenylpyrazole derivative. The crude product was recrystallized from EtOH to give 4.4 g (60%) of 1-phenyl-5-*n*-tridecylpyrazole-3-carboxylic acid (8j) as colorless needles, mp 89—90 °C.

The compounds (8h—n) other than 8j in this group were prepared in the same manner as described for 8j.

Preparation of 1-(5-Carboxypentyl)-5-*n*-tridecylpyrazole-3-carboxylic Acid (8p)——A solution of NaH (50% in oil) (1.9 g, 0.04 mol) in toluene (150 ml) was added dropwise to a stirred suspension of ethyl 5-*n*-tridecylpyrazole-3-carboxylate (10.3 g, 0.03 mol) in toluene (40 ml) at room temperature. The mixture was stirred at 60 °C for 1 h, then ethyl 6-bromohexanate (7.4 g, 0.03 mol) was added and the whole was heated at 120 °C for 5 h, then treated with H_2O and extracted with benzene. The benzene extract was washed with H_2O, dried (Na_2SO_4), and concentrated to give 13 g (93%) of ethyl 1-(5-ethoxycarbonylpentyl)-5-*n*-tridecylpyrazole-3-carboxylate as a colorless oil. Then, the ester (13 g, 0.03 mol) was dissolved in 5% ethanolic NaOH, and refluxed for 3 h. After removal of the solvent, the residue was made acidic with 10% aq. HCl. The solid was filtered off and the crude solid was washed with H_2O, then recrystallized from CH_3OH to give 6.3 g (56%) of 1-(5-carboxypentyl)-5-*n*-tridecylpyrazole-3-carboxylic acid (8p) as colorless needles, mp 170—172 °C.

The compounds (8o—s) other than 8p in this group were prepared in the same manner as described for 8p.

Preparation of 5-*n*-Tridecylisoxazole-3-carboxylic Acid (9a)——A solution of sodium 1-ethoxycarbonyl-3-oxohexadecenolate (5.2 g, 0.015 mol) in acetic acid (40 ml) was stirred at 50 °C for 30 min and then a solution of hydroxylamine hydrochloride (2.1 g, 0.03 mol) in H_2O (10 ml) was added dropwise at 50 °C. The mixture was heated at 60 °C for 8 h and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with sat. brine, then dried (Na_2SO_4), and concentrated. The residue was recrystallized from EtOH to give 3.6 g (75%) of ethyl 5-*n*-tridecylisoxazole-3-carboxylate. A solution of ethyl 5-*n*-tridecylisoxazole-3-carboxylate (2.0 g, 0.006 mol) in 5% methanolic NaOH (12 ml) was refluxed for 2 h. After removal of the solvent, the residue was made acidic (pH 5.0) with 5% aq. HCl. The deposited precipitate was collected by filtration, washed with cold water, and recrystallized from MeOH to give 1.5 g (80%) of 5-*n*-tridecylisoxazole-3-carboxylic acid (9a) as colorless needles, mp 105—106 °C. IR v_{max}^{Nujol} cm⁻¹: 1690 (C=O). MS *m/e*: 295 (M⁺). *Anal.* Calcd for $C_{17}H_{29}NO_3$: C, 69.11; H, 9.90; N, 4.74. Found: C, 69.42; H, 10.05; N, 4.67.

Preparation of 3-*n*-Tridecylisoxazole-5-carboxylic Acid (9b)——A solution of sodium 1-ethoxycarbonyl-3-oxohexadecenolate (15.3 g, 0.044 mol) and hydroxylamine hydrochloride (3.1 g, 0.044 mol) in 1.8 N aq. NaOH (24 ml) was heated at 70 °C for 3.5 h under stirring, followed by treatment in the same manner as described for the preparation of 9a. The crude solid was recrystallized from MeOH to give 1.1 g (78%) of 3-*n*-tridecylisoxazole-5-carboxylic acid (9b) as colorless needles, mp 118—119 °C. IR v_{max}^{Nujol} cm⁻¹: 1720 (C=O). MS *m/e*: 295 (M⁺). *Anal.* Calcd for $C_{17}H_{29}NO_3$: C, 69.11; H, 9.90; N, 4.74. Found: C, 68.82; H, 9.85; N, 4.84.

Pharmacological Evaluation

Hypolipidemic Activity——Male Sprague-Dawley rats (Charles River Japan, Inc.) weighing 220—230 g were employed in this study. The hypolipidemic activities of synthetic analogs were assayed by the method reported previously.[1] Serum triglyceride and cholesterol were determined by enzymatic methods, using commercially available reagent sets (cholesterol·CHOD·PAP, Boehringer Mannheim; triglyceride G-test Wako, Wako Pure Chemicals). The data are presented in Tables I and II as the decrease from the control levels. The significance level (P) was determined by using Student's *t*-test.

Acute Toxicity——The test compounds were administered orally to ICR male mice (21—25 g), which had been fasted for 18 h prior to the experiment. At 7 d after treatment, mortality ratios were obtained and LD_{50} values were calculated according to Litchfield and Wilcoxon.[15]

References and Notes

1) K. Seki, T. Yamashita, J. Isegawa, M. Fukuda, H. Shimamura and M. Ohki, *Chem. Pharm. Bull.*, **31**, 4116

(1983).

2) This work was presented at the 102nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April 1982.

3) V. G. DeVries, D. B. Moran, G. A. Allen and S. J. Riggi, *J. Med. Chem.*, **19**, 946 (1976).

4) W. Hollander, S. Prusty, S. Nagraj, B. Kirkpatrick, J. Paddock and M. Colombo, *Atherosclerosis*, **31**, 307 (1978).

5) J. D. Albright, S. A. Schaffer and R. G. Shepherd, *J. Pharm. Sci.*, **68**, 936 (1979).

6) T. Watanabe, K. Hayashi, S. Yoshimatsu and K. Sakai, *J. Med. Chem.*, **23**, 50 (1980).

7) K. Takashima, T. Mori, K. Ohyama, S. Nitta and S. Takeyama, *Chem. Pharm. Bull.*, **26**, 2454 (1978).

8) K. Takashima, K. Ohyama, T. Mori and S. Takeyama, *Biochem. Pharmacol.*, **27**, 2631 (1978).

9) K. Takashima and S. Takeyama, *Biochem. Pharmacol.*, **27**, 2637 (1978).

10) H. Keshin and Y. Onural, Istanbul Univ. Fen Fak, Mecum, Seri C, **34**, 95 (1969) [*Chem. Abstr.*, **77**, 163991c (1972)].

11) G. C. Gerritson and W. E. Dulin, *J. Pharmacol. Exp. Ther.*, **150**, 491 (1965).

12) J. N. Pereira and G. F. Holland, *J. Pharmacol. Exp. Ther.*, **157**, 381 (1967).

13) T. Ho, B. G. B. Gupta and G. A. Olah, *Synthesis*, **1977**, 677.

14) L. Claisen, *Berichte*, **42**, 59 (1909).

15) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).