United States Patent [19]

Seki et al.

[11] **3,741,999**

[45] **June 26, 1973**

[54] **N-SUBSTITUTED AMIDES OF NATURAL FATTY ACIDS**

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[22] Filed: **Sept. 10, 1970**

[21] Appl. No.: **71,205**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 450,534, April 23, 1965, Pat. No. 3,551,462.

[30] **Foreign Application Priority Data**

Apr. 28, 1964	Japan	39/24061
May 20, 1964	Japan	39/28284
June 8, 1964	Japan	39/32324
Aug. 28, 1964	Japan	39/49073
Sept. 1, 1964	Japan	39/49812
Sept. 5, 1964	Japan	39/50947

[52] **U.S. Cl.** **260/404**, 424/324

[51] **Int. Cl.** **C09f 7/00**

[58] **Field of Search** 260/404; 424/320, 424/324

[56] **References Cited**

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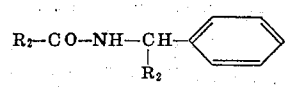
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[57] **ABSTRACT**

Novel N-α-(C_1-C_4)alkyl-benzyl natural fatty acid amides of the formula



wherein R_1 is a fatty acid residue of a naturally occurring oil such as safflower oil etc., and R_2 is alkyl of 1–4 carbon atoms having excellent blood cholesterol lowering effects are provided.

5 Claims, No Drawings

N-SUBSTITUTED AMIDES OF NATURAL FATTY ACIDS

This application is a continuation-in-part of Ser. No. 450,534, filed Apr. 23, 1965, now U.S. Pat. No. 3,551,462.

This invention relates to novel anti-atherosclerosis agents. More particularly, the invention pertains to novel N-substituted natural fatty acid amide derivatives which are useful for lowering the elevated levels of cholesterol or lipids.

Atherosclerosis is an adult disease for which there is no known satisfactory cure. Although the cause for atherosclerosis is not yet known in spite of discussions in the academic circles, it has broadly been recognized that one of the most significant histo-pathological manifestations of atherosclerosis is the deposition of cholesterol or lipids in the blood.

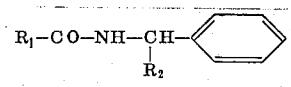
A number of experimental and clinical facts have been reported, which indicate that the reduction of the elevated blood cholesterol or lipid level is considered extremely important for the prevention of atherosclerosis.

The present inventors have found a group of novel compounds which are effective as cholesterol-lowering agents and which are substantially non-toxic.

An object of the present invention is to provide N-substituted natural fatty acid amide derivatives usable as anti-atherosclerosis agents having prominent effects and extremely high admissibility.

Other objects and merits of the invention will be apparent from the following description.

In order to accomplish these objects, the present invention provides novel N-α-alkyl-benzyl natural fatty acid amides of the formula

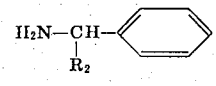


wherein R_1 is a fatty acid residue of a naturally occurring oil, said fatty acid having an iodine value of at least 50, and R_2 is C_1-C_4 alkyl, provided that in case the oil is sesame oil, safflower oil, soybean oil or cuttlefish oil, R_2 is C_2-C_4 alkyl.

The phrase "fatty acid residue of a naturally occurring oil" refers to fatty acid residues of fatty acids which are present in naturally occurring oils. Examples of the naturally occurring oils include vegetable oils, animal oils, etc., such as sesame oil, safflower oil, cuttlefish oil, linseed oil, soybean oil, sunflower oil, corn oil, cottonseed oil, olive oil, peanut oil, flatfish oil, sardine oil, cod oil, menhaden oil, whale oil, residual oil (liver oil from which vitamin A has been removed), perilla oil and menuke oil, the preferred examples being safflower oil, linseed oil, soybean oil, corn oil, cottonseed oil, sunflower oil, cuttlefish and sardine oil.

The processes for the production of the N-substituted natural fatty acid amides of the present inventon naturally vary, for example, depending upon the nature of R_1 and R_2 and the origin of the acid moiety of the amides. Owing to their great number it is not possible to describe all of them in detail, which is in any case unnecessary since they are all based on conventional organic chemistry processes. However, details of typical and suitable processes are given below.

A natural oil is hydrolyzed and the resultant natural fatty acid is reacted directly with an amine of the formula



(R_2 is as defined before) in the presence of a dehydrating agent such as a disubstituted carbodiimide compound, in an aqueous or organic solvent.

Typical examples of disubstituted carbodiimide compounds are as follows: dialkylcarbodiimides such as diisopropylcarbodiimide and the like: dicycloalkyl carbodiimides such as dicyclohexylcarbodiimides and the like; and diaryl carbodiimides such as diphenylcarbodiimides, dibenzylcarbodiimides and the like. Of course, carbodiimides other than those specifically mentioned can be employed without any trouble.

The condensation reaction between a hydrolyzed natural oil and an amine using a carbodiimide proceeds smoothly at room temperature, but when the reaction is vigorously exothermic, if necessary, it may be allowed to cool.

Water and substantially all organic solvents can be employed as solvent. Examples of organic solvents are as follows: ethers such as diethyl ether, tetrahydrofuran and dioxane; esters such as methyl acetate, ethyl acetate, and butyl acetate; ketones such as acetone, methyl ethyl ketone and methyl isobutyl ketone; halogeno alkanes such as chloroform, carbon tetrachloride and ethylene dichloride; and hydrocarbon solvents such as cyclohexane, n-hexane, petroleum ether, gasoline, benzene and toluene. They are employed alone or in the form of a mixture thereof in optional proportions.

The reaction procedure is as follows:

The natural fatty acid, the amine and the disubstituted carbodiimide compound, at least one of which is dissolved in a solvent, are mixed at room temperature or under cooling, if required, and the mixture is allowed to stand for 3 to 24 hours while being stirred as necessary. To the reaction mixture is added a small portion of acetic acid to decompose the excess carbodiimide and the urea derivative formed is filtered off to yield the fatty acid amide in the filtrate.

Alternatively, a natural oil is reacted with an amine of the aforesaid formula. That is, about 1 mol. of the oil and 1 to 100 equivalent mols of the amine are mixed in the absence or presence of solvents, e.g. alcohols such as methanol, ethanol or the like, aromatic hydrocarbones such as benzene, toluene, xylene or the like, halogenoalkanes such as methylenechloride, chloroform, carbon tetrachloride or the like, alkenes or alkanes such as petroleum ether, benzine, gasoline, ligroin or cyclohexane, and ethers such as tetrahydrofuran, dioxane and the like, or a mixture thereof, and the mixture is subjected to reaction in the absence or presence of a catalytic amount, or equimolar amount to the amine, or an auxiliary condensation agent, such as an alcoholate or an alkali metal, i.e. lithium methylate, lithium ethylate, sodium methylate, sodium ethylate, potassium-t-butylate and the like, or acidic auxiliary agents, i.e. p-toluenesulfonic acid and the like, to yield the amide derivatives. In this reaction, the alcohol formed may be removed from the reaction system.

It is a matter of course that the reaction will proceed even in the absence of solvents and auxiliary agents.

In case of using amines having a lower boiling point, if necessary, an autoclave may be employed, but in case of other amines the reaction mixture is stirred under atmospheric pressure while being heated as necessary, thereby easily yielding the objective amide.

In carrying out the reaction, the mixture of reactants is stirred at a suitable temperature of between room temperature and 400°C for about 3 hours to a month.

If necessary, the reaction is carried on in an atmosphere of an inactive gas such as nitrogen, helium and the like to prevent production of undesirable by-products and coloring, to yield the objective product, which can be subjected to a fractional distillation and recrystallization method using a petroleum hydrocarbon, acetone or the like, or the urea method, to remove saturated fatty acid amides. If alkali alcoholate is used as an auxiliary agent, conjugated double bond isomers are partially obtained. However, the present inventors confirmed that saturated and isomerized fatty acid amides cause no undesirable effect on the human body.

The process for the production of the amides of the invention is described in more detail with reference to the following examples, which are however to be construed for the purpose of illustration only and not as limiting the invention.

EXAMPLES 1–122

General procedure:

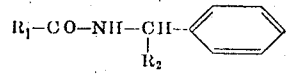
a. A natural oil is hydrolyzed in 1N solution of sodium hydroxide in methanol and the resulting natural fatty acid is treated with urea and methanol to remove the saturated fatty acid.

Ten grams of the thus obtained natural fatty acid, an α-alkylbenzylamine and dicyclohexylcarbodiimide are dissolved in benzene and the mixture is allowed to stand overnight at room temperature. Acetic acid is added thereto to decompose the excess amount of dicyclohexylcarbodiimide and the mixture is filtered to separate off the decomposed product. Then the filtrate is washed successively with 5 percent hydrochloric acid, 5 percent sodium carbonate aqueous solution and water, and dried over anhydrous sodium sulfate. Upon evaporation of the solvent, the residue is distilled in vacuo to yield N-α-alkylbenzyl natural oil fatty acid amide.

b. A natural oil and an α-alkylbenzylamine are mixed and stirred in an atmosphere of nitrogen at a temperature of 135°C to 140°C for 40 hours. Then the reaction mixture is distilled in vacuo to yield N-α-alkylbenzyl natural oil fatty acid amide.

According to one of the procedures mentioned above, the following N-α-alkylbenzyl natural oil fatty acid amides are obtained as shown in the following Table 1.

TABLE 1



Example No.	R_1-CO- (natural oil)	R_2	Procedure	Boiling Point (°C/mmHg)
1	sesame oil	C_2H_5	a	200–210/0.05
2	"	n-C_3H_7	a	198–206/0.06
3	"	i-C_3H_7	a	192–205/0.05
4	"	n-C_4H_9	a	199–213/0.05
5	"	i-C_4H_9	a	200–215/0.04
6	"	t-C_4H_9	a	203–218/0.04
7	safflower oil	C_2H_5	b	201–212/0.04
8	"	n-C_3H_7	b	199–214/0.05
9	"	i-C_3H_7	b	193–210/0.04
10	"	n-C_4H_9	b	198–213/0.04
11	"	i-C_4H_9	b	199–212/0.04
12	"	t-C_4H_9	b	205–220/0.05
13	Cuttlefish oil	C_2H_5	a	200–209/0.05
14	"	n-C_3H_7	a	200–208/0.05
15	"	i-C_3H_7	a	195–211/0.05
16	"	n-C_4H_9	a	199–211/0.05
17	"	i-C_4H_9	a	200–215/0.04
18	"	t-C_4H_9	a	200–222/0.05
19	linseed oil	CH_3	a	202–216/0.05
20	"	C_2H_5	a	203–208/0.01
21	"	n-C_3H_7	a	200–210/0.04
22	"	i-C_3H_7	a	194–211/0.05
23	"	n-C_4H_9	a	195–215/0.04
24	"	i-C_4H_9	a	195–214/0.04
25	"	t-C_4H_9	a	201–224/0.03
26	soybean oil	C_2H_5	b	203–218/0.05
27	"	n-C_3H_7	b	200–218/0.03
28	"	i-C_3H_7	b	198–219/0.02
29	"	n-C_4H_9	b	202–221/0.03
30	"	i-C_4H_9	b	203–222/0.04
31	"	t-C_4H_9	b	205–225/0.05
32	sunflower oil	CH_3	b	198–208/0.04
33	"	C_2H_5	b	200–211/0.05
34	"	n-C_3H_7	b	200–209/0.05
35	"	i-C_3H_7	b	198–210/0.05
36	"	n-C_4H_9	b	200–218/0.05
37	"	i-C_4H_9	b	200–219/0.05
38	"	t-C_4H_9	b	200–221/0.05
39	corn oil	CH_3	b	200–211/0.03
40	"	C_2H_5	b	203–218/0.05
41	"	n-C_3H_7	b	202–215/0.03
42	"	i-C_3H_7	b	200–213/0.05
43	"	n-C_4H_9	b	200–214/0.06
44	"	i-C_4H_9	b	201–214/0.05
45	"	t-C_4H_9	b	203–220/0.05
46	cottonseed oil	CH_3	b	203–218/0.05
47	"	C_2H_5	b	183–215/0.05
48	"	n-C_3H_7	b	192–209/0.03
49	"	i-C_3H_7	b	190–208/0.02
50	"	n-C_4H_9	b	194–210/0.05
51	"	i-C_4H_9	b	196–212/0.06
52	"	t-C_4H_9	b	201–224/0.04
53	olive oil	CH_3	a	198–209/0.08
54	"	C_2H_5	a	195–207/0.04
55	"	n-C_3H_7	a	195–204/0.03
56	"	i-C_3H_7	a	198–209/0.04
57	"	n-C_4H_9	a	203–214/0.03
58	"	i-C_4H_9	a	204–214/0.03
59	"	t-C_4H_9	a	208–223/0.03
60	peanut oil	CH_3	a	189–206/0.02
61	"	C_2H_5	a	188–205/0.05
62	"	n-C_3H_7	a	189–206/0.06
63	"	i-C_3H_7	a	188–203/0.03
64	"	n-C_4H_9	a	193–208/0.05
65	"	i-C_4H_9	a	192–209/0.06
66	"	t-C_4H_9	a	199–219/0.05
67	flatfish oil	CH_3	b	190–218/0.02
68	"	C_2H_5	b	185–208/0.03
69	"	n-C_3H_7	b	188–211/0.04
70	"	i-C_3H_7	b	186–213/0.03
71	"	n-C_4H_9	b	188–215/0.03
72	"	i-C_4H_9	b	189–216/0.03
73	"	t-C_4H_9	b	195–226/0.06
74	sardine oil	CH_3	b	188–216/0.02
75	"	C_2H_5	b	184–215/0.03
76	"	n-C_3H_7	b	185–216/0.05
77	"	i-C_3H_7	b	182–219/0.04
78	"	n-C_4H_9	b	185–220/0.04
79	"	i-C_4H_9	b	188–220/0.03
80	"	t-C_4H_9	b	194–225/0.06
81	cod oil	CH_3	b	189–220/0.04
82	"	C_2H_5	b	188–218/0.03
83	"	n-C_3H_7	b	190–210/0.03
84	"	i-C_3H_7	b	188–212/0.05
85	"	n-C_4H_9	b	192–214/0.05
86	"	i-C_4H_9	b	195–216/0.06
87	"	t-C_4H_9	b	203–226/0.05
88	menhaden oil	CH_3	a	189–219/0.06
89	"	C_2H_5	a	188–220/0.05
90	"	n-C_3H_7	a	189–221/0.05
91	"	i-C_3H_7	a	189–221/0.05
92	"	n-C_4H_9	a	192–222/0.04
93	"	i-C_4H_9	a	192–220/0.04
94	"	t-C_4H_9	a	198–224/0.04
95	whale oil	CH_3	a	193–218/0.05
96	"	C_2H_5	a	190–221/0.06
97	"	n-C_3H_7	a	192–218/0.05

98	"	i-C_3H_7	a	194–215/0.04
99	"	n-C_4H_9	a	199–218/0.04
100	"	i-C_4H_9	a	200–210/0.03
101	"	t-C_4H_9	a	202–226/0.06
102	residual oil	CH_3	b	194–217/0.04
103	"	C_2H_5	b	192–220/0.03
104	"	n-C_3H_7	b	194–217/0.04
105	"	i-C_3H_7	b	193–220/0.05
106	"	n-C_4H_9	b	197–222/0.05
107	"	i-C_4H_9	b	199–223/0.06
108	"	t-C_4H_9	b	200–226/0.05
109	perilla oil	CH_3	a	192–208/0.05
110	"	C_2H_5	a	190–210/0.05
111	"	n-C_3H_7	a	190–211/0.05
112	"	i-C_3H_7	a	190–213/0.06
113	"	n-C_4H_9	a	195–215/0.05
114	"	i-C_4H_9	a	196–216/0.06
115	"	t-C_4H_9	a	200–218/0.02
116	menuke oil	CH_3	a	184–215/0.06
117	"	C_2H_5	a	185–217/0.07
118	"	n-C_3H_7	a	188–218/0.05
119	"	i-C_3H_7	a	183–205/0.06
120	"	n-C_4H_9	a	190–211/0.05
121	"	i-C_4H_9	a	191–212/0.06
122	"	t-C_4H_9	a	200–222/0.03

As mentioned above, the N-α-alkylbenzyl natural fatty acid amides of the present invention have excellent cholesterol lowering effects. The effectiveness of the present amides are set forth as shown in the following test examples.

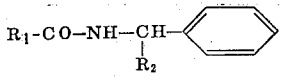
TEST EXAMPLES 1–122

Cholesterol Lowering Effects on Mice

Mice were fed on a special diet which was supplemented with cholesterol and bile acids. Blood cholesterol level of the mice had been elevated to 3 to 6 times the normal level. Each amide compound was well mixed to the specifical diet in 1 percent administration and fed orally to the mice for 10 days. At each dose level, 10 or 20 mice were used and serum total cholesterol levels of the blood serum were measured at the end of the experimental period. One group of mice, in each set of experiment, was given the specifical diet without the test compound and served as control. Mean level of serum total cholesterol of the treated group was expressed as a per cent of that of the control group (blood cholesterol index).

Results are shown in the following Table 2.

TABLE 2



Test Example No.	R_1-CO- (natural oil)	R_2	Blood Cholesterol Index (%)
Control (no drug)			100
linoleic acid			75–80
1	sesame oil	C_2H_5	40
2	"	n-C_3H_7	38
3	"	i-C_3H_7	34
4	"	n-C_4H_9	33
5	"	i-C_4H_9	37
6	"	t-C_4H_9	33
7	safflower oil	C_2H_5	38
8	"	n-C_3H_7	34
9	"	i-C_3H_7	35
10	"	n-C_4H_9	36
11	"	i-C_4H_9	35
12	"	t-C_4H_9	34
13	cuttlefish oil	C_2H_5	41
14	"	n-C_3H_7	33
15	"	i-C_3H_7	34
16	"	n-C_4H_9	38
17	"	i-C_4H_9	39
18	"	t-C_4H_9	40
19	linseed oil	CH_3	35
20	"	C_2H_5	32
21	"	n-C_3H_7	40
22	"	i-C_3H_7	34
23	"	n-C_4H_9	37
24	"	i-C_4H_9	38
25	"	t-C_4H_9	37
26	soybean oil	C_2H_5	40
27	"	n-C_3H_7	32
28	"	i-C_3H_7	43
29	"	n-C_4H_7	38
30	"	i-C_4H_9	34
31	"	t-C_4H_9	33
32	sunflower oil	CH_3	38
33	"	C_2H_5	39
34	"	n-C_3H_7	33
35	"	i-C_3H_7	30
36	"	n-C_4H_9	35
37	"	i-C_4H_9	42
38	"	t-C_4H_9	36
39	corn oil	CH_3	34
40	"	C_2H_5	35
41	"	n-C_3H_7	34
42	"	i-C_3H_7	39
43	"	n-C_4H_9	40
44	"	i-C_4H_9	39
45	"	t-C_4H_9	40
46	cottonseed oil	CH_3	35
47	"	C_2H_5	37
48	"	n-C_3H_7	40
49	"	i-C_3H_7	40
50	"	n-C_4H_9	38
51	"	i-C_4H_9	42
52	"	t-C_4H_9	38
53	olive oil	CH_3	34
54	"	C_2H_5	33
55	"	n-C_3H_7	37
56	"	i-C_3H_7	41
57	"	n-C_4H_9	37
58	"	i-C_4H_9	41
59	"	t-C_4H_9	43
60	peanut oil	CH_3	42
61	"	C_2H_5	42
62	"	n-C_3H_7	45
63	"	i-C_3H_7	37
64	"	n-C_4H_9	33
65	"	i-C_4H_9	34
66	"	t-C_4H_9	37
67	flatfish oil	CH_3	40
68	"	C_2H_5	39
69	"	n-C_3H_7	34
70	"	i-C_3H_7	36
71	"	n-C_4H_9	40
72	"	i-C_4H_9	44
73	"	t-C_4H_9	43
74	sardine oil	CH_3	43
75	"	C_2H_5	34
76	"	n-C_3H_7	34
77	"	i-C_3H_7	32
78	"	n-C_4H_9	38
79	"	i-C_4H_9	44
80	"	t-C_4H_9	35
81	Cod oil	CH_3	40
82	"	C_2H_5	40
83	"	n-C_3H_7	32
84	"	i-C_3H_7	33
85	"	n-C_4H_9	34
86	"	i-C_4H_5	35
87	"	t-C_4H_9	44
88	menhaden oil	CH_3	32
89	"	C_2H_5	37
90	"	n-C_3H_7	40
91	"	i-C_3H_7	42
92	"	n-C_4H_9	40
93	"	i-C_4H_9	37
94	"	t-C_4H_9	35
95	whale oil	CH_3	41
96	"	C_2H_5	38
97	"	n-C_3H_7	36
98	"	i-C_3H_7	36
99	"	n-C_4H_9	44
100	"	i-C_4H_9	33
101	"	t-C_4H_9	37
102	residual oil	CH_3	39
103	"	C_2H_5	40
104	"	n-C_3H_7	33
105	"	i-C_3H_7	41
106	"	n-C_4H_9	42
107	"	i-C_4H_9	42
108	"	t-C_4H_9	40
109	perilla oil	CH_3	33
110	"	C_2H_5	35
111	"	n-C_3H_7	35
112	"	i-C_3H_7	38
113	"	n-C_4H_9	43
114	"	i-C_4H_9	38

115	"	t-C_4H_9	38
116	menuke oil	CH_3	38
117	"	C_2H_5	40
118	"	n-C_3H_7	32
119	"	i-C_3H_7	39
120	"	n-C_4H_9	38
121	"	i-C_4H_9	39
122	"	t-C_4H_9	36

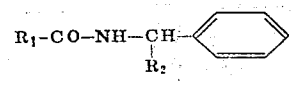
The extremely low toxicities of the instant amides are also an aspect of the present invention.

The cholesterol-lowering agent in this invention may be orally administered. Usually the amount orally administered is 0.1 g. – 20 g. per day for a human adult, preferably 0.5 g. – 5 g. per day, and the administration may be continued for 1–5 months, usually for about 3 months. For example, the amide can be orally administered to a human adult in an amount of 2.0 g. per day for about 3 months. The cholesterol-lowering agent may be employed in any suitable form which is conventional for oral administration. Thus, it may be encased in a capsule, in liquid form, in tablet form, or in powder form. In preparing the agents in these various forms, the active compound may be used as such, without being mixed with a carrier, or mixed with or impregnated in a suitable solid carrier, or it may be mixed with a liquid carrier such as an edible oil, preferably those containing linoleic acid. It is also possible to use a mixture of two or more of the acid amides of the invention. It may also be used as mixed with linoleic acid.

The content of the acid amide of the composition varies depending upon the kind of carrier used, and the content is adjusted so that the amide is administered to a patient within the indicated dosage range.

What is claimed is:

1. A compound of the formula



wherein R_1 is a fatty acid residue of a naturally occurring oil selected from the group consisting of sesame oil, safflower oil, cuttlefish oil, linseed oil, soybean oil, sunflower oil, corn oil, cottonseed oil, olive oil, peanut oil, flatfish oil, sardine oil, cod oil, menhaden oil, whale oil, residual oil, perilla oil and menuke oil, and

R_2 is an alkyl group containing 1–4 carbon atoms, with the proviso that when R_1 is a fatty acid residue of sesame oil, safflower oil, soybean oil or cuttlefish oil, R_2 is an alkyl group containing 2–4 carbon atoms.

2. A compound according to claim **1**, wherein R_1 is a fatty acid residue of safflower oil, linseed oil, soybean oil, cuttlefish oil or sardine oil.

3. A compound according to claim **1**, wherein R_1 is a fatty acid residue of linseed oil, sunflower oil, corn oil, cottonseed oil, olive oil, peanut oil, flatfish oil, sardine oil, cod oil, menhaden oil, whale oil, residual oil, perilla oil or menuke oil, and R_2 is methyl.

4. A compound according to claim **1**, wherein R_1 is a fatty acid residue of sesame oil, safflower oil, soybean oil or cuttlefish oil and R_2 is alkyl of 2–4 carbon atoms.

5. A compound according to claim **1**, wherein R_1 is a fatty acid residue of safflower oil and R_2 is alkyl of 2–4 carbon atoms.

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