(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 051 828**
B1

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **14.03.84**

(21) Application number: **81109293.1**

(22) Date of filing: **29.10.81**

(51) Int. Cl.³: **C 07 C 103/84,**
C 07 C 102/00,
A 61 K 31/165

(54) **N-benzoyl-alpha-anilino alkane carboxylic acids, salts and esters thereof, process for producing the same and pharmaceutical preparations containing the same.**

(30) Priority: **11.11.80 DE 3042482**

(43) Date of publication of application:
19.05.82 Bulletin 82/20

(45) Publication of the grant of the patent:
14.03.84 Bulletin 84/11

(84) Designated Contracting States:
AT BE CH FR GB IT LI LU NL SE

(56) References cited:
EP - A - 0 000 494
EP - A - 0 006 218
GB - A - 2 016 448

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EP 0 051 828 B1

Courier Press, Leamington Spa, England.

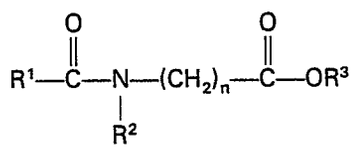
N-benzoyl-alpha-anilino alkane carboxylic acids, salts and esters thereof, process for producing the same and pharmaceutical preparations containing the same

The present invention refers to new N-Benzoyl-ω-anilino-C_{7-10}-alkano carboxylic acids, their pharmaceutically compatible salts and C_{1-7}-alkylesters, process for producing these compounds and pharmaceutical preparations containing the same.

N-Benzoyl-ω-anilino-C_1—C_6-alkano carboxylic acids already have been tested several times for their pharmacological activity (D. Evans et al., M. Med. Chem. *12* (1969) pgs. 1006 to 1010; German Offenlegungsschrift 19 17 036). The compounds partly showed choleretic activity. However, the tests further showed that such compounds do not have an antiinflammatory activity.

Surprisingly, the new N-benzoyl-ω-anilino-C_{7-10}-alkano carboxylic acids, their alkali salts and esters show pharmacological properties which have not been expected namely antiallergic, thrombocyte aggregation inhibitory, antiinflammatory and lipide lowering activity. Since the new compounds furthermore show a low toxicity and a good compatibility, they are in particular useful for the treatment of allergic, asthmatic, thromboembolic, inflammatory and arteriosclerotic diseases. The new compounds may also be preferably combined with other active agents such as anticoagulantia, in particular heparine, heparinates and coumarine derivatives. In particular, in the prophylaxis of thromboembolic complications it is desirable to influence the thrombocyte aggregation and the coagulation of the blood. In this respect, the compounds of the present application show particular activity in combination with anticoagulantia, in particular with heparine and heparinates.

Thus, object of the present invention are the new N-benzoyl-ω-anilino alkane carboxylic acids and their derivatives of the general formula I



I

wherein

n is a positive integer ranging from 7 to 10,

R^1 and R^2, which may be identical or different from each other, represent the unsubstituted phenyl group or the phenyl groups substituted by 1 to 4 equal or different radicals selected from the group of halogen, in particular chlorine or fluorine; C_{1-4}-alkyl, in particular methyl; C_{1-4}-alkoxy, in particular methoxy or ethoxy; C_{1-4}-alkylthio, in particular methylmercapto or ethylmercapto; acyloxy, in particular C_{1-4}-alkanacyl, most preferably, acetoxy, propionyloxy or benzoyloxy; halo-C_{1-4}-alkyl, in particular trifluoromethyl; hydroxy; phenoxy; benzyloxy; di-C_{1-4}-alkylamino, in particular dimethylamino;

R^3 is hydrogen, an alkali metal ion, in particular the sodium metal ion, or a straight or branched saturated hydrocarbon group having from 1 to 7 carbon atoms such as and in particular ethyl, isopropyl or heptyl; or the benzyl group.

Preferred substituted phenyl groups R^1 are: 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-(trifluoromethyl)-phenyl, 3-(trifluoromethyl)-phenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-acetoxyphenyl, 3-acetoxyphenyl, 4-acetoxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-benzyloxyphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 2-phenoxyphenyl, 3-phenoxyphenyl, 2-methylmercaptophenyl, 4-methylmercaptophenyl, 3-(dimethylamino)-phenyl, 4-(dimethylamino)-phenyl, 2.6-difluorophenyl, 2.4-dichlorophenyl, 2.5-dichlorophenyl, 2.6-dichlorophenyl, 3.4-dichlorophenyl, 3.5-dichlorophenyl, 2.3-dimethylphenyl, 2.4-dimethylphenyl, 2.5-dimethylphenyl, 2.6-dimethylphenyl, 3.4-dimethylphenyl, 3.5-dimethylphenyl, 2.3-dihydroxyphenyl, 2.4-dihydroxyphenyl, 2.5-dihydroxyphenyl, 2.6-dihydroxyphenyl, 3.4-dihydroxyphenyl, 3.5-dihydroxyphenyl, 2.3-dimethoxyphenyl, 2.4-dimethoxyphenyl 2.6-dimethoxyphenyl, 3.4-dimethoxyphenyl, 3.5-dimethoxyphenyl, 3.4-methylendioxyphenyl, 2.4.6-trimethylphenyl, 2.3.4-trimethoxyphenyl, 2.4.5-trimethoxyphenyl, 3.4.5-trimethoxyphenyl, 3-fluoro-4-methylphenyl, 5-fluoro-2-hydroxyphenyl, 2-chloro-6-fluorophenyl, 3-chloro-4-hydroxyphenyl, 4-chloro-2-hydroxyphenyl, 5-chloro-2-hydroxyphenyl, 4-chloro-2-methoxyphenyl, 5-chloro-2-methoxyphenyl, 4-dimethylamino-2-hydroxyphenyl, 2-hydroxy-4-methoxyphenyl, 2-hydroxy-3-methoxyphenyl, 2-hydroxy-5-methoxyphenyl, 4-hydroxy-3-methoxyphenyl, 2-hydroxy-3-methylphenyl, 3-hydroxy-4-methylphenyl, 3-methoxy-4-methylphenyl, 3.5-dichloro-4-hydroxyphenyl, 3.5-dimethoxy-4-hydroxyphenyl.

Preferred substituted phenyl groups R^2 are: 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-(trifluoromethyl)-phenyl, 3-(trifluoromethyl)-phenyl, 4-(trifluoromethyl)-phenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 4-phenoxyphenyl, 2-methylmercaptophenyl, 3-methylmercaptophenyl, 4-(dimethylamino)-phenyl, 2.4-difluorophenyl, 2.6-difluorophenyl, 2.3-dichlorophenyl, 2.4-dichlorophenyl, 2.5-dichlorophenyl, 2.6-dichlorophenyl, 3.4-dichlorophenyl, 3.5-dichlorophenyl, 2.3-dimethyl-

phenyl, 2.4-dimethylphenyl, 2.5-dimethylphenyl, 2.6-dimethylphenyl, 3.4-dimethylphenyl, 3.5-dimethylphenyl, 2.4-dimethoxyphenyl, 2.5-dimethoxyphenyl, 3.4-dimethoxyphenyl, 3.5-dimethoxyphenyl, 3.4-methylendioxyphenyl, 2.4.6-trimethylphenyl, 3.4.5-trimethoxyphenyl, 5-fluoro-2-methylphenyl, 5-chloro-2-hydroxyphenyl, 2-chloro-4-methylphenyl, 2-chloro-6-methylphenyl, 3-chloro-2-methylphenyl, 3-chloro-4-methylphenyl, 4-chloro-2-methylphenyl, 5-chloro-2-methylphenyl, 2-chloro-5-methoxyphenyl, 2-chloro5-(trifluoromethyl)-phenyl, 4-chloro-3-(trifluoromethyl)-phenyl, 2-hydroxy-4-methylphenyl, 2-hydroxy-5-methylphenyl, 4-hydroxy-2-methylphenyl, 2-methoxy-5-methylphenyl, ,4-methoxy-2-methylphenyl, 5-methoxy-3-(trifluoromethyl)-phenyl, 5-chloro-2.4-dimethoxyphenyl, 3.5-dichloro-4-hydroxyphenyl.

Subject matter of the present invention is furthermore a process for producing the compounds of the general formula I which is characterized in that a benzanilide of formula II

$$R^1—\overset{\overset{\displaystyle O}{\|}}{C}—NH—R^2 \qquad \text{II}$$

wherein R^1 and R^2 have the same meaning as in formula I is subjected to reaction with an alkylating agent of formula III

$$X(CH_2)_n—\overset{\overset{\displaystyle O}{\|}}{C}—OR^3 \qquad \text{III}$$

wherein n has the same meaning as in formula I, R^3 is a C_{1-7}-alkyl group and X is a halogen atom such as a chlorine, bromine or iodine atom, in an organic solvent such as acetone, methylethylketone, dimethylformamide, with the addition of a basic compound such as sodium hydride and possibly in the presence of an alkali metal iodide as catalyst.

The benzanilide of formula II may readily be obtainable in known manners by acylation of an aniline derivative of the formula IV

$$R^2—NH_2 \qquad \text{IV}$$

with a reactive benzoic acid derivative of formula V

$$R^1—\overset{\overset{\displaystyle O}{\|}}{C}—Y \qquad \text{V}$$

such as an acid halogenide, acid anhydride, acid imidazolide or a reactive ester.

The esters of formula I are optionally hydrolysed at room temperature in usual manners by reaction with an alkali hydroxide in aqueous, alcoholic or alcoholic-etheric solvents to yield an alkali salt of formula I (R^3=alkali metal) with subsequent addition of a mineral acid to yield an acid of formula I (R^3=H).

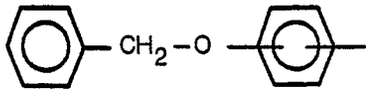
The esters of formula I may also be produced in that an aniline derivative of formula IV is subjected to reaction with an alkylating agent of formula III in a suitable organic solvent such as benzene, toluene, cyclohexane, dimethylformamide, possibly with the addition of a tertiary amine such as triethylamine, ethyldiisopropylamine, optionally in the presence of an alkali metal iodide as catalyst, and subjecting the resulting ω-anilinoalkane carboxylic acid esters of formula VI

$$R^2—NH—(CH_2)_n—\overset{\overset{\displaystyle O}{\|}}{C}—OR^3 \qquad \text{VI}$$

wherein R^2, R^3 and n have the same meaning as in formula I, in a suitable organic solvent such as benzene, toluene, diethylether, tetrahydrofurane, dioxane, possibly in the presence of a tertiary amine such as triethylamine, ethyldiisopropylamine, pyridine, to reaction with a reactive benzoic acid derivative of formula V.

The acides of formula (R^3 = H) may also be produced in that an ω-anilinoalkane carboxylic acid ester of formula VI (R^3=alkyl) is saponified in usual manner to yield an ω-anilinoalkane carboxylic acid of formula VI (R^3=H) and acylating the same in an aqueous ethereal solvent in the presence of an alkali metal hydroxide with a benzoic acid halogenide.

Finally, the esters of formula I (R^3=alkyl) having at least one free phenolic hydroxy group may be produced in that a compound of formula I (R^3=H, alkyl) wherein at least one R^1 and R^2 represents a benzyloxy substituted phenyl group of formula VII



VII

is subjected to reaction with hydrogen in the presence of a suitable catalyst such as Raney-nickel, platinumoxide, palladium, in a suitable solvent such as anhydrous methanol or ethanol.

If desired, the acids of formula I (R^3=H) may be reacted with an alkali metal hydroxide or carbonate in usual manner to yield the alkali metal salts of formula I (R^3=alkali metal) or, respectively, with an acid or alkali salt of the formula I (R^3=H, alkali metal) may be reacted in a suitable solvent such as dimethylformamide, optionally in the presence of an alkali metal carbonate, with an alkylating agent of formula VIII

$$Z—R^3 \qquad \text{VIII}$$

wherein Z is a halogen such as chlorine, bromine, iodine or another suitable group to be split off and R^3 is a straight or branched C_{1-7}-alkyl group or an aralkyl group to yield the corresponding esters.

Starting materials of formula II are for instance the benzanilides, R^1 and R^2 having the same meaning as in formula I. Starting materials of formula III are for instance the esters of the following ω-halogenoalkane carboxylic acids: 8-chlorocaprylic acid, 8-bromocaprylic acid, 8-iodocaprylic acid, 9-chloropelargonic acid, 9-bromopelargonic acid, 9-iodopelargonic acid, 10-chlorocaprinic acid, 10-bromocarinic acid, 10-iodocaprinic acid, 11-chloroundecanic acid, 11-bromoundecanic acid, 11-iodo-undecanic acid.

Starting materials of formula IV are for instance the aniline derivatives, R^2 having the same meaning as in formula I. Starting materials of formula V are for instance suitable derivatives such as acid halogenides, acid anhydrides, acid imidazolides, reactive esters of benzoic acid, R^1 having the same meaning as in formula I.

Alkylating agents of formula VIII are for instance: Iodomethane, bromoethane, iodoethane, 1-chloropropane, 1-iodopropane, 2-chloropropane, 2-bromopropane, 1-chlorobutane, 1-bromobutane, 2-bromo-2-methylpropane, 2-chlorobutane, 2-bromobutane, 1-chloropentane, 2-bromopentane, 1-bromo-2-methylbutane, 1-chlorohexane, 1-bromohexane, 1-chloroheptane, 1-bromoheptane, benzylchloride, benzylbromide, 2-chlorobenzylchloride, 4-chlorobenzylchloride, 4-fluorobenzyl-chloride, 4-(trifluoromethyl)-benzylchloride, 4-methoxybenzylchloride, 3.4.5-trimethoxybenzylchloride, 1-chloro-2-phenylethane, 1-chloro-1-phenylethane, 3-chloro-1-phenylpropane, 2-chloro-1-phenyl-propane, 4-chloro-1-phenylbutane, dimethylsulfate, p-toluene sulfonic acid ether ester.

Subject matter of the present invention are pharmaceutical preparations containing one or several of the new compounds of formula I besides non-toxic, inert pharmaceutical suitable carrier materials and processes for producing the same.

Subject matter of the present invention are furthermore suitable preparations in dosage form such as tablets, dragees, capsules, pills, suppositories and ampoules containing the active agent in fraction or in a multitude of a single dose. The dosage unit forms may contain 1, 2, 3 or 4 single dosages of 1/2, 1/3 or 1/4 of a single dosage.

The single dosage preferably contains such amount of the active agent which is administered during application and in general corresponding to a daily dose, half a daily dose, or one third or one quarter of a daily dose.

Non-toxic inert, pharmaceutically useful carrier materials are solid, semi-solid or liquid diluents, fillers and additives of any known kind. Preferred pharmaceutical preparations are tablets, dragees, capsules, pills, granulates, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, lotions, powders and sprays.

Tablets, dragees, capsules, pills and granulates may contain one or several active agents according to the present invention besides usual carrier material such as fillers and diluents (for instance starch products, lactose, sucrose, glucose, mannitol and silicic acid), binders (for instance carboxymethyl cellulose, alginates, gelatine, polyvinylpyrrolidone), humidifiers (for instance glycerol), desintergrants (for instance agar-agar, calcium carbonate and sodium carbonate), anti-soluents (for instance paraffine) and resorption increasing agents (for instance quaternary ammonium compounds), adsorbents (for instance kaoline and bentonite) and lubricants (for instance talcum, calcium stearate and magnesium stearate and solid polyethylene glycoles) or mixtures of the above compounds.

The tablets, dragees, capsules, pills and granulates may comprise the usual covers which may contain agents for rendering them opaque and may be so constructed in usual manner that they deliberate the active agent or agents only or only partly or retarded the embedding materials, for instance being polymeric products and waxes.

The active agent or agents may possibly also be present in microcapsules in order to obtain a retarding effect.

Suppositories may contain in addition to the active agent or agents usual carrier materials soluble or insoluble in water such as polyethylene glycoles, fats such as cacao butter fat or higher esters such

as C_{14}-alcohol with C_{16}-fatty acid; or mixtures of the above.

Ointments, pastes, cremes and gels may beside the active agent or agents contain usual carrier materials for instance fats of animal or plant origin, waxes, paraffines, starches, tragant or mixtures of the above products.

Powders and sprays besides the active agent or agents may contain usual carrier materials such as lactose, talcum, silicic acid, aluminum hydroxide or mixtures of the above compounds. Sprays furthermore may contain usual propellants.

Solutions or emulsions beside the active agent or agents may contain usual carrier materials such as solvents, solubilizers and emulgators, for instance water, ethylalcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, oils, in particular cotton seed oil, peanut oil, corn seedling oil, olive oil and sesame oil, glycerol, polyethylene glycol or mixtures of the above compounds.

For parenteral application, the solutions and emulsions may be sterilized and may be in blood isotonic form.

Suspensions beside the active agent or agents may contain usual carrier materials such as liquid diluents for instance water, ethyl alcohol, propylene glycol, emulgators such as ethoxylated isostearyl alcohol, polyoxyethylene sorbitol and polyoxyethylene sorbitolesters, microcrystalline cellulose or mixtures of the above compounds.

The above products may also contain coloring agents, as well as additives improving the smell and taste thereof such as peppermint oil and eucalyptus oil as well as sweeteners for instance saccharine.

The therapeutic active agents are present in the above pharmaceutical preparations in amounts ranging from about 0.1 to about 99.5, preferably from about 0.5 to about 95% of the weight of the total mix.

Besides the active agent or agents according to the present invention, the above pharmaceutical preparations may futher contain other pharmaceutical active agents such as heparine, heparinates or coumarine derivatives.

The production of the above pharmaceutical preparations occurs in usual manner by usual methods for instance by mixing of the active agent or agents with the carrier material or materials.

A further part of the present invention is the use of the above new active agents of formula I as well as the pharmaceutical preparations containing one or several active agents according to the present invention in the human and veterinary medicine in the treatment of thromboembolic, inflammatory and arteriosclerotic processes in the human and in animal organisms.

The active agents or the pharmaceutical preparations may be administered locally, orally, parenterally, intraperitoneally and/or rectally, preferably orally and/or parenterally.

In general it is preferred in human medicine to use the active agent or agents in a total amount of about 10 to 2,000, preferably 30 to 500 mg per each 24 hours, possibly in the form of several single dosages in order to obtain best results. Each single dosage contains the active agent, preferably in amounts of about 10 to about 300, in particular 50 to 200 mg per dosage.

However, if necessary the above dosages may be increased and this depending upon the kind and the body weight of the being to be treated, the kind and severeness of the illness, the kind of preparation and application of the active agent and the interval at which single dosages are applied. For instance it may be sufficient in some cases to use less amounts of the active agent as above indicated while in other cases the above amounts may have to be increased. The single dose to be applied for obtaining optimal results may be determined by the doctor according to his general knowledge.

The preparation of the compounds according to the present invention is further illustrated in the following examples.

The reactive benzoic acid derivatives according to formula V and the benzanilides according to formula II are known compounds and may be produced according to known processes (L. GATTERMANN and H. WIELAND, Die Praxis des organischen Chemikers, 35. Auflage, p. 112; W. DE GRUYTER ET AL., Berlin 1953; H. FRANZEN, Ber. Dtsch. Chem. Ges. *42*, (1909) p. 2465).

The recited melting points have been determined in Büchi 510 apparatus and are not corrected. The IR spectra have been determined on a Perkin-Elmer 257 and the mass spectra on a Varian MAT-311A (70eV).

Example 1

8-(N-Phenyl-benzamido)-caprylic acid

R^1=phenyl, R^2=phenyl, n=7, R^3=H

a) 8-(N-Phenyl-benzamido)-caprylic acid methyl ester

2.4 g (0.1 mol) of sodium hydride are added to a solution of 19.7 g (0.1 mol) of benzanilide in 200 cc. of dimethylformamide. The mixture is stirred at about 40°C until termination of hydrogen formation.

Thereafter, 23.7 g (0.1 mol) of 8-bromocaprylic acid methyl ester and 3 g (0.02 mol) of sodium iodide are added and the mixture is stirred at 90°C for 6 hours. After cooling, the majority of the solvent is distilled off in a vacuum and the residue is poured into about 300 cc. of water. The separated crude

product is dissolved in chloroform, the chloroform layer is washed with 5% sulfuric acid, with water, with 5% bicarbonate solution and finally again with water. The organic layer is dried over Na_2SO_4 and the solvent is distilled off in a vacuum. The crude product is used in the next step without any further purification.

Yield: 28.2 g (80%) of a read oil
IR (film): 1740 and 1646 cm^{-1}

b) 8-(N-Phenyl-benzamido)-caprylic acid

21.7 g (0.06 mol) of 8-(N-phenyl-benzamido)-caprylic acid methylester are dissolved in 80 cc. of methanol. 3.9 g (0.07 mol) of potassium hydroxide are added thereto. The mixture is stirred at 25°C for 48 hours, the solvent is distilled off and the residue is dissolved in water. The aqueous phase is several times shaken with ether, the ethereal layers are discarded. The aqueous phase is acidified with dilute hydrochloric acid and is extracted with ether. The ethereal layer is washed with water and dried over $MgSO_4$. The solvent is distilled off and the residue is purified chromatographically on silicic acid using a mixture of chloroform and methanol as eluant.

Yield: 4.7 g (23% of the theoretical), Fp. 58—60°C
IR (in KBr): 1710 and 1645 cm^{-1}
MS (m/e): 339 (17%), 197 (39%), 105 (100%), 77 (20%).

Example 2

8-[4-Chloro-N-(4-chlorophenyl)-benzamido]-caprylic acid
R^1=4-Chlorophenyl, R^2=4-Chlorophenyl, n=7, R^3=H

a) 8-[4-Chloro-N-(4-chlorophenyl)-benzamido]-caprylic acid methyl ester

As described in example 1a), 2.4 g (0.1 mol) of sodium hydride, 25.2 g (0.1 mol) of 4-chloro-N-(4-chlorophenyl)-benzamid, 200 ml dimethylformamide, 23.7 g (0.1 mol) of 8-bromocaprylic acid methyl ester and 3 g (0.02 mol) of sodium iodide are reacted. Reaction time 5.5 hours; reaction temperature: 110°C. The crude product is used in the next step without any further purification.

Yield: 40 g (95% of the theoretical) of a read oil.

b) 8-[4-Chloro-N-(4-chlorophenyl)-benzamido]-caprylic acid

As described in example 1b), the reaction is carried out with 40 g of 8-[4-chloro-N-(4-chlorophenyl)benzamido]-caprylic acid methyl ester, 150 ml of methanol and 4 g (0.1 mol) of sodium hydroxide. Reaction time: 4 hours; reaction temperature: 25°C. The purification of the resulting crude product occurs chromatographically on silicic acid using a mixture of chloroform and methanol as eluant.

Yield: 8.9 g (23% of the theoretical) Fp. 94—95°C (from ethyl acetate)
IR (in KBr): 1720 and 1640 cm^{-1}
MS (m/e): 407 (15%), 265 (23%), 139 (100%), 111 (14%)

Example 3

8-[4-Methoxy-N-(4-methoxyphenyl)-benzamido]-caprylic acid
R^1=4-Methoxyphenyl, R^2=Methoxyphenyl, n=7, R^3=H

a) 8-(4-Methoxyphenylamino)-caprylic acid methyl ester

A mixture of 19.7 g (0.16 mol) of p-anisidine, 37.9 g (0.16 mol) of 8-bromocaprylic acid methyl ester, 16.2 g (0.16 mol) of triethylamine and 120 ml of cyclohexane are stirred with boiling for 3 hours. The precipitated triethylamine-hydrobromide is filtered off from the hot mixture, the solvent is distilled off from the filtrate, and residue is recrystallized from cyclohexane.

Yield: 21.3 g (48% of the theoretical) Fp. 72—73°C (from cyclohexane)
IR (in KBr): 3400 and 1735 cm^{-1}
MS (m/e): 279 (51%), 248 (7%), 136 (100%), 108 (3%).

b) 8-[4-Methoxy-N-(4-methoxyphenyl)-benzamido]-caprylic acid methyl ester

12 g (43 mmol) of 8-(4-methoxyphenylamino)-caprylic acid methyl ester are dissolved in 400 cc. of ether. 5.1 g (50 mmol) of triethylamine are added thereto. 7.3 g (43 mmol) of 4-methoxybenzoic acid chloride are added dropwise to the mixture with stirring and cooling with ice. After the addition, stirring is continued at 25°C for 5 hours. The separated triethylamine-hydrochloride is filtered off with suction and the ethereal phase is washed in sequence with water, 5% bicarbonate solution, water, 2n hydrochloric acid and water is dried over Na_2SO_4, and the solvent is distilled off. The crude product is

used in the next step without any further purification.

Yield: 15.8 g (89% of the theoretical) of a colourless oil.

c) 8-[4-Methoxy-N-(4-methoxyphenyl)-benzamido]-caprylic acid
As described in example 1b), 10 g (24 mmol) of 8-[4-methoxy-N-(4-methoxyphenyl)-benzamido]-caprylic acid methyl ester is reacted with 2 g (50 mmol) of sodium hydroxide and 200 cc. of methanol. Reaction time: 6 hours, reaction temperature: 25°C.

Yield: 8.8 g (92% of the theoretical) of a colourless oil.
IR (film): 1735, 1710, 1640, 1615 cm^{-1}
MS (m/e): 399 (35%), 257 (5%), 135 (100%), 107 (3%).

Example 4

8-[4-Chloro-N-(4-methoxyphenyl)-benzamido]-caprylic acid
R^1=4-Chlorophenyl, R^2=4-Methoxyphenyl, n=7, R^3=H

a) 8-[4-Chloro-N-(4-methoxyphenyl)-benzamido]-caprylic acid methyl ester
As described in example 1a), the reaction is carried out with 130.7 g (0.5 mol) of 4-chloro-N-(4-methoxyphenyl)-benzamide, 24.5 g (1 mol) sodium hydride, 700 cc. of dimethylformamide and 118.5 g (0.5 mol) of bromo-caprylic acid methyl ester. Reaction time and reaction temperature: 5 hours at 80°C, thereafter 12 hours at 110°C. The reaction mixtures are further processed as described in example 1a). The crude product is dissolved in 300 cc. of ether. After standing for a prolonged period, the unreacted 4-chloro-N-(4-methoxyphenyl)-benzamide separates by crystallisation and is filtered off. The solvent is partly distilled off and the resulting oily crude product (181 g) is separated. 125 g are used in the next step without further purification, the remainder (56 g) is purified chromatographically on silicic acid using chloroform as eluant.

Yield: 19 g (30% of the theoretical) of a colourless oil.
IR (film): 1742 and 1647 cm^{-1}
MS (m/e): 417 (40%), 261 (29%), 139 (100%), 136 (10%), 125 (9%).

b) 8-[4-Chloro-N-(4-methoxyphenyl)-benzamido]-caprylic acid
As described in example 1b), the reaction is carried out with 125 g (0.3 mol) of 8-[4-chloro-N-(4-methoxyphenyl)-benzamido]-caprylic acid methyl ester, 500 cc. of methanol and 12 g (0.3 mol) of sodium hydroxide. Reaction time: 2 days, reaction temperature: 25°C. 40 g of the crude product (96.3 g) are purified chromatographically on silicic acid using a mixture of chloroform and methanol (99:1) as eluant.

Yield: 32.8 g (67% of the theoretical) of a colorless oil.
IR (film): 1735, 1715, 1645, 1625 cm^{-1}
Ms (m/e): 403 (65%), 261 (17%), 139 (100%), 136 (17%), 111 (11%).

Example 5

9-[4-Chloro-N-(4-methoxyphenyl)-benzamido]-pelargonic acid
R^1=4-Chlorophenyl, R^2=4-Methoxyphenyl, n=8, R^3=H

a) 9-(4-Methoxyphenylamino)-pelargonic acid methyl ester
As described in example 3a), the reaction is carried out with 6.2 g (0.05 mol) of p-anisidine, 5.1 g (0.05 mol) of triethylamine, 12.6 g (0.05 mol) of 9-bromoperlargonic acid methyl ester and 40 cc. of cyclohexane.

Yield: 2.3 g (15% of the theoretical) Fp. 50—52°C (from ethanol).
R (in KBr): 3400 and 1735 cm^{-1}
MS (m/e): 293 (29%), 262 (4%), 136 (100%).

b) 9-[4-Chloro-N-(4-methoxyphenyl)-benzamido]-pelargonic acid methyl ester
As described in example 3b) the reaction is carried out with 2 g (6.8 mmol) of 9-(4-methoxyphenylamino)-pelargonic acid methyl ester, 0.75 g (7.5 mmol) of triethylamine, 1.2 g (6.8 mmol) of 4-chlorobenzoic acid chloride and 80 cc. of ether. The crude product is used in the next reaction step without further purification.

Yield: 2.8 g (95% of the theoretical) of a colourless oil.

c) 9-[4-Chloro-N-(4-methoxyphenyl)-benzamido]-pelargonic acid

As described in example 1b), the reaction is carried out with 2.8 g (6.5 mmol) of 9-[4-chloro-N-(4-methoxyphenyl)-benzamido]-pelargonic acid methyl ester, 0.3 g (7.8 mmol) of sodium hydroxide and 50 cc. of methanol. Reaction time: 42 hours, reaction temperature; 25°C.

Yield: 2 g (74% of the theoretical) of a colourless oil.
IR (film): 1732, 1710, 1640 and 1618 cm^{-1}
MS (m/e): 417 (45%), 261 (31%), 139 (100%), 136 (17%), 111 (10%).

Example 6

11-[4-Chloro-N-(4-methoxyphenyl)-benzamido]-undecanoic acid
R^1=4-Chlorophenyl, R^2=4-Methoxyphenyl, n=10, R^3=H

a) 11-[4-Chloro-N-(4-methoxyphenyl)-benzamido]-undecanoic acid methyl ester

As described in example 1a), the reaction is carried out with 28.7 g (0.11 mol) of 4-chloro-N-(4-methoxyphenyl)-benzamide, 4.5 g (0.18 mol) of sodium hydride, 36.7 g (0.13 mol) of 11-bromo-undecanoic acid methyl ester, 100 cc. of dimethylformamide and 3 g (0.02 mol) of sodium iodide. Reaction time: 5 hours, reaction temperature: 80°C. The crude product is used in the next step without further purification.

Yield: 31.2 g (62% of the theoretical) of a brownish oil.

b) 11-[4-Chloro-N-(4-methoxyphenyl)-benzamido]-undecanoic acid

As described in example 1b), the reaction is carried out with 31.2 g (68 mmol) of 11-[4-chloro-N-(4-methoxyphenyl)-benzamido]-undecanoic acid methyl ester, 4.4 g (0.11 mol) of sodium hydroxide and 200 cc. of methanol. Reaction time: 15 hours, reaction temperature: 25°C. The crude product is further purified chromatographically on silicic acid gel using chloroform as eluant.

Yield 3.2 g (11% of the theoretical) of a colourless oil.
IR (film): 1730, 1711, 1642, 1620 cm^{-1}
MS (m/e): 445 (79%), 261 (20%), 139 (100%), 136 (19%), 111 (6%).

Example 7

8-[4-Fluoro-N-(4-methoxyphenyl)-benzamido]-caprylic acid
R^1=4-Fluorophenyl, R^2=4-Methoxyphenyl, n=7, R^3=H

a) 8-[4-Fluoro-N-(4-methoxyphenyl)-benzamido]-caprylic acid methyl ester

As described in example 3b), the reaction is carried out with 5.6 g (20 mmol) of 8-(4-methoxy-phenylamino)-capyrlic acid methyl ester, 5 g (50 mmol) of triethylamine, 150 cc. of toluene and 4 g (25 mmol) of 4-fluorobenzoic acid chloride. Reaction time: 5 hours, reaction temperature: 25°C. The crude product is used in the next reaction step without further purification.

Yield: 7.4 g (92% of the theoretical) of a colourles oil.

b) 8-[4-Fluoro-N-(4-methoxyphenyl)-benzamido]-caprylic acid

As described in example 1b), the reaction is carried out with 7.4 g (18 mmol) of 8-[4-fluoro-N-(4-methoxyphenyl)-benzamido]-caprylic acid methyl ester, 1.4 g (35 mmol) of sodium hydroxide and 70 cc. of methanol. Reaction time: 10 hours, reaction temperature: 25°C. The crude product is further purified chromatographically on silicic acid gel using chloroform as eluant.

Yield: 5.2 g (73% of the theoretical) of a colourless oil.
IR (film): 1730, 1710, 1645, 1630 cm^{-1}
MS (m/e): 387 (52%), 264 (14%), 245 (29%), 136 (13%), 123 (100%).

Example 8

8-[3-Trifluoromethyl-N-(4-methoxyphenyl)-benzamido]-caprylic acid
R^1=3-(Trifluoromethyl)-phenyl, R^2=4-Methoxyphenyl, n=7, R^3=H

a) 8-(4-Methoxyphenylamino)-caprylic acid

As described in example 1b), the reaction is carried out with 10 g (36 mmol) of 8-(4-methoxyphenylamino)-caprylic acid methyl ester, 1.43 g (36 mmol) of sodium hydride and 200 cc. of methanol. Reaction time: 24 hours, reaction temperature: 25°C.

Yield: 8.3 g (87% of the theoretical) Fp. 94—95°C (from ether).
IR (in KBr): 3370 and 1713 cm^{-1}

MS (m/e): 265 (29%), 136 (100%), 108 (4%).

b) 8-[3-Trifluoromethyl-N-(4-methoxyphenyl)-benzamido]-caprylic acid

6.1 g (23 mmol) of 8-(4-Methoxyphenylamino)-caprylic acid are dissolved in 40 cc. of 0.2 n soda lye. A solution of 4.4 g (23 mmol) of 3-(trifluoromethyl)-benzoic acid fluoride in 50 cc. of ether are added thereto within 20 minutes with vivid stirring dropwise at 25°C, holding the pH at between 7.2 and 8 by the dropwise addition of 0.2 n soda lye. After the addition, vivid stirring is continued for 30 minutes. The mixture is then acidified to pH 3 by the addition of 2 n hydrochloric acid. The aqueous and ethereal layers are separated. The aqueous phase is extracted several times with ether and then is rendered alkaline by the addition of calcium hydroxide. The separated calcium fluoride is filtered off with suction and is discarded. The purified ethereal phase is shaken with water, dried over $MgSO_4$ and the solvent is distilled off. The residue is purified chromatographically on silicic acid gel using chloroform as eluant.

Yield: 0.65 g (6.5% of the theoretical) of a colourless oil.
IR (film): 1738, 1715, 1648, 1625 cm^{-1}
MS (m/e): 437 (45%), 295 (36%), 173 (100%), 145 (19%), 136 (18%), 125 (19%).

Example 9

8-[2.4-Dichloro-N-(4-methoxyphenyl)-benzamido]-caprylic acid
R^1=2.4-Dichlorophenyl, R^2=4-Methoxyphenyl, n=7, R^3=H

a) 8-[2.4-Dichloro-N-(4-methoxyphenyl)-benzamido]-caprylic acid methyl ester

As described in example 1a), the reaction is carried out with 32.8 g (0.1 mol) of 2.4-dichloro-N-(4-methoxyphenyl)-benzamide [produced by acylation of p-anisidine with 2.4-dichlorobenzoic acid chloride in toluene in the presence of triethylamine, Fp. 164°C (from ethanol) 7, 2.4 g (0.1 mol) of sodium hydride, 200 cc. of dimethylformamide, 23.7 g (0.1 mol) of 8-bromocaprylic acid methyl ester and 6 g (0.04 mol) of sodium iodide. Reaction time: 2.5 hours, reaction temperature: 110—120°C. The crude product is used in the next reaction step without further purification.

Yield: about 35 g (77% of the theoretical) of a brownish oil.

b) 8-[2.4-Dichloro-N-(4-methoxyphenyl)-benzamido]-caprylic acid

As described in example 1b), the reaction is carried out with 35 g (77 mmol) of 8-[2.4-dichloro-N-(4-methoxyphenyl)-benzamido]-caprylic acid methyl ester, 4 g (0.1 mol) of sodium hydroxide, 15 cc. of methanol and 5 cc. of water. Reaction time: 24 hours, reaction temperature: 25°C. The crude product is further purified chromatographically on silicic acid gel using a mixture of n-hexane and ethyl acetate (2:1) as eluant.

Yield: 20.5 g (61% of the theoretical). Fp. 67°C.
IR (in KBr): 1735, 1712, 1652, 1625 cm^{-1}.
MS (m/e): 437 (55%), 314 (9%), 295 (51%), 173 (100%), 136 (21%), 125 (19%).

Example 10

8-[4-Chloro-N-(2.6-dimethylphenyl)-benzamido]-caprylic acid
R^1=4-Chlorophenyl, R^2=2.6-Dimethylphenyl, n=7, R^3=H

a) 8-[4-Chloro-N-(2.6-dimethylphenyl)-benzamido]-caprylic acid methyl ester

As described in example 1a), the reaction is carried out with 11 g (42 mmol) of 4-chloro-N-(2.6-dimethylphenyl)-benzamide, 1.8 g (75 mmol) of sodium hydroxide, 12 g (50 mmol) of 8-bromocaprylic acid methyl ester, 100 cc. of dimethylformamide and 1.2 g (8 mmol) of sodium iodide. Reaction time: 4 hours, reaction temperature; 110—120°C. The crude product is used in the next reaction step without further purification.

Yield: 15.8 g (90% of the theoretical) of a read oil.
IR (film): 1745 and 1645 cm^{-1}

b) 8-[4-Chloro-N-(2.6-dimethylphenyl)-benzamido]-caprylic acid

As described in example 1b), the reaction is carried out with 15.8 g (38 mmol) of 8-[4-Chloro-N-(2.6-dimethylphenyl)-benzamido]-caprylic acid methyl ester, 2.2 g (55 mmol) of sodium hydroxide, 100 cc. of methanol and 5 cc. of water. Reaction time: 20 hours, reaction temperature: 25°C. The crude product is further purified chromatographically on silicic acid gel using chloroform as eluant.

Yield: 2.2 g (14% of the theoretical) of a colourless oil.
IR (film): 1735, 1714, 1645, 1618 cm^{-1}

MS (m/e): 401 (15%), 280 (18%), 259 (100%), 139 (99%), 125 (30%), 120 (17%).

Example 11

8-[2-Chloro-N-(3-chlorophenyl)-benzamido]-caprylic acid

R^1=2-Chlorophenyl, R^2=3-Chlorophenyl, n=7, R^3=H

a) 8-(3-Chlorophenylamino)-caprylic acid methyl ester

As described in example 3a), the reaction is carried out with 6.4 g (50 mmol) of 3-chloroaniline, 5 g (50 mmol) of triethylamine, 13 g (55 mmol) of 8-bromocaprylic acid methyl ester and 40 cc. of cyclohexane. Reaction time: 6 hours, reaction temperature: 80°C.

Yield: 3.7 g (26% of the theoretical). Fp. 47—49°C (from ethanol.
IR (inKBr): 3400 and 1732 cm^{-1}
MS (m/e): 283 (19%), 252 (5%), 140 (100%), 127 (8%).

b) 8-[2-Chloro-N-(3-chlorophenyl)-benzamido]-caprylic acid methyl ester

As described in example 3b), the reaction is carried out with 10 g (35 mmol) of 8-(3-chlorophenylamino)-caprylic acid methyl ester, 6.2 g (35 mmol) of 2-chlorobenzoic acid chloride, 3.9 g (39 mmol) of triethylamine and 100 cc. of ether. Reaction time: 24 hours, reaction temperature: 25°C. The crude product is further purified chromatographically on silicic acid gel using chloroform as eluant.

Yield: 11.4 g (77% of the theoretical) of a colourless oil.
IR (film): 1740 and 1660 cm^{-1}
MS (m/e): 421 (5%), 390 (3%), 348 (2%), 265 (31%), 230 (5%), 139 (100%), 111 (13%).

c) 8-[2-Chloro-N-(3-chlorophenyl)-benzamido]-caprylic acid

As described in example 1b), the reaction is carried out with 3.8 g (9 mmol) of 8-[2-chloro-N-(3-chlorophenyl)-benzamido]-caprylic acid methyl ester, 0.48 g (12 mmol) of sodium hydroxide and 50 cc. of methanol. Reaction time: 24 hours, reaction temperature: 25°C. The crude product is purified chromatographically on silicic acid gel using chloroform as eluant.

Yield: 1 g (27% of the theoretical) of a colorless oil.
IR (film): 1710 and 1655 cm^{-1}
MS (m/e): 407 (10%), 265 (31%), 193 (100%), 111 (10%).

Example 12

8-{3.4.5-Trimethoxy-N-[3-(trifluoromethyl)-phenyl]-benzamido}-caprylic acid

R^1=3.4.5-Trimethoxyphenyl, R^2=3-(Trifluoromethyl)-phenyl, n=7, R^3=H

a) 8-[3-(Trifluoromethyl)-phenylamino]-caprylic acid methyl ester

As described in example 3a), the reaction is carried out with 16.1 g (0.1 mol) of 3-(trifluoromethyl)-aniline, 10.1 g (0.1 mol) of triethylamine, 23.7 g (0.1 mol) of 8-bromocaprylic acid methyl ester and 80 cc. of cyclohexane. Reaction time: 6 hours, reaction temperature: 80°C.

Yield: 8 g (25% of the theoretical). Fp. 47—48°C (from ethanol).
IR (in KBr): 3400 and 1740 cm^{-1}
MS (m/e): 317 (18%), 286 (5%), 174 (100%), 161 (10%), 145 (2%).

b) 8-{3.4.5-Trimethoxy-N-[3-(trifluoromethyl)-phenyl]-benzamido}-caprylic acid methyl ester

As described in example 3b), the reaction is carried out with 6.3 g (20 mmol) of 8-[3-(trifluoromethyl)-phenylamino]-caprylic acid methyl ester, 6.9 g (30 mmol) of 3.4.5-trimethoxybenzoic acid chloride, 2.5 g (25 mmol) of triethylamine and 150 cc. of ether. Reaction time: 24 hours, reaction temperature: 25°C. The crude product is used in the next reaction step without further purification.

Yield: 8.6 g (84% of the theoretical) of a colourless oil.

c) 8-{3.4.5-Trimethoxy-N-[3-(trifluoromethyl)-phenyl]-benzamido]-caprylic acid

As described in example 1b), the reaction is carried out with 8.6 g (16.8 mmol) of 8-{3.4.5-trimethoxy-N-[3-(trifluoromethyl)-phenyl]-benzamido}-caprylic acid methyl ester, 0.96 g (24 mmol) of sodium hydroxide and 100 cc. of methanol. Reaction time: 24 hours, reaction temperature: 25°C. The crude product is further purified chromatographically on silicic acid gel using chloroform as eluant.

Yield: 0.9 g (11% of the theoretical) of a colourless oil.
IR(film): 1715 and 1650 cm^{-1}
MS (m/e): 497 (12%), 355 (6%), 195 (100%), 167 (3%).

Example 13

8-[4-Chloro-N-(4-hydroxyphenyl)-benzamido]-caprylic acid

R^1=4-Chlorophenyl, R^2=4-Hydroxyphenyl, n=7, R^3=H

a) 8-(4-Benzyloxyphenylamino)-caprylic acid methyl ester

As described in example 3a), the reaction is carried out with 22 g (0.11 mol) of 4-benzyloxy-aniline, 12.1 g (0.12 mol) of triethylamine, 26.1 g (0.11 mol) of 8-bromocaprylic acid methyl ester and 80 cc. of cyclohexane. Reaction time: 6 hours, reaction temperature: 80°C. The reaction product is further purified chromatographically on silicic acid gel using chloroform as eluant.

Yield: 8.3 g (21% of the theoretical). Fp. 61—62°C (from ethanol).
IR (in KBr): 3400 and 1736 cm^{-1}
MS (m/e): 355 (22%), 324 (5%), 264 (100%), 122 (11%), 108 (7%), 91 (14%), 55 (8%).

b) 8-[4-Chloro-N-(4-benzyloxyphenyl)-benzamido]-caprylic acid methyl ether

As described in example 3b), the reaction is carried out with 5.5 g (15.5 mmol) of 8-(4-benzyloxy-phenylamino)-caprylic acid methyl ester, 2.7 g (15.5 mmol) of 4-chlorobenzoic acid chloride, 1.8 g (18 mmol) of triethylamine and 150 cc. ether. Reaction time: 24 hours, reaction temperature: 25°C. The crude product is used in the next reaction step without further purification.

Yield: 7.4 g (95% of the theoretical) of a colourless oil.

c) 8-[4-Chloro-N-(4-benzyloxyphenyl)-benzamido]-caprylic acid

As described in example 1b), the reaction is carried out with 7.4 g (15 mmol) of 8-[4-chloro-N-(4-benzyloxyphenyl)-benzamido]-caprylic acid methyl ester, 1 g (23 mmol) of sodium hydroxide and 200 cc. of methanol. Reaction time: 48 hours, reaction temperature: 25°C. The crude product is used in the next reaction step without further purification.

Yield: 6 g (83% of the theoretical) of a yellow oil.

d) 8-[4-Chloro-N-(4-hydroxyphenyl)-benzamido]-caprylic acid ethyl ester

Hydrogen is bubbled into a mixture of 6 g (12.5 mmol) of 8-[4-chloro-N-(4-benzyloxyphenyl)-benzamido]-caprylic acid, 250 cc of ethanol and 1.2 g of palladium-activated carbon-hydrogenation catalyst (containing 10 weight% of Pd) at 25°C and normal pressure with vivid stirring. After 2 hours and the uptake of 280 cc. (12.2 mmol) of hydrogen, the reaction is stopped. The catalyst is filtered off and the ethanol is distilled off under reduced pressure. The residue is dissolved in 150 cc. of ether, the ethereal solution is mixed with dilute sodium carbonate solution, dried over sodium sulphate and the solvent is distilled off. The residue is recrystallized from a mixture of ether and n-hexane.

Yield: 3.5 g (67% of the theoretical). Fp. 89—90°C (from ether/n-hexane).
IR (in KBr): 3200, 1735 and 1610 cm^{-1}
MS (m/e): 417 (31%), 372 (8%), 247 (32%), 139 (100%), 125 (9%), 122 (8%), 111 (9%), 105 (19%).

e) 8-[4-Chloro-N-(4-hydroxyphenyl)-benzamido]-caprylic acid

As described in example 1b), the reaction is carried out with 3.5 g (8.4 mmol) of 8-[4-chloro-N-(4-hydroxyphenyl)-benzamido]-caprylic acid ethyl ester, 0.7 g (17.5 mmol) of sodium hydroxide and 100 cc. of ethanol. Reaction time: 24 hours, reaction temperature: 25°C.

Yield: 1.8 g (55% of the theoretical). Fp. 138—139°C (from ethanol)
IR (in KBr): 3400, 1715 and 1620 cm^{-1}
MS (m/e): 389 (28%), 355 (10%), 247 (27%), 139 (100%), 122 (25%), 111 (12%), 105 (35%).

Example 14

8-[3-Hydroxy-N-(4-hydroxyphenyl)-benzamido]-caprylic acid

R^1=3-Hydroxyphenyl, R^2=4-Hydroxyphenyl, n=7, R^3=H

a) 8-[3-Benzyloxy-N-(4-benzyloxyphenyl)-benzamido]-caprylic acid methyl ester

As described in example 3b), the reaction is carried out with 4.7 g (13 mmol) of 8-(4-benzyloxy-phenyl-amino)-caprylic acid methyl ester, 3.3 (13 mmol) of 3-benzyloxy-benzoic acid chloride, 1.5 g (5 mmol) of triethylamine and 100 cc. of ether. Reaction time: 24 hours, reaction temperature: 25°C. The crude product is used in the next reaction step without further purification.

Yield: 7 g (93% of the theoretical) of a yellow oil.

b) 8-[3-Hydroxy-N-(4-hydroxyphenyl)-benzamido]-caprylic acid methyl ester

Hydrogen is bubbled into a mixture of 7 g (12 mmol) of 8-[3-benzyloxy-N-(4-benzyloxyphenyl)-benzamido]-caprylic acid methyl ester, 200 cc. of methanol and 0.7 g of a palladium-activated carbon-hydrogenation catalyst (containing 10 weight% of Pd) at 25°C and normal pressure with vivid stirring. After 1 hour and the uptake of 560 cc. (24 mmol) of hydrogen, the reaction is stopped. The catalyst is filtered off. Methanol is distilled off under reduced pressure and the residue is purified chromatographically on silicic acid gel using a mixture of ethyl acetate and n-hexane as eluant.

Yield: 2.6 g (57% of the theoretical). Fp. 132—133°C (from ethyl acetate/n-hexane).
IR (in KBr): 3410, 1745 and 1580 cm^{-1}
MS (m/e): 385 (35%), 354 (5%), 264 (8%), 242 (13%), 229 (26%), 135 (5%), 121 (100%), 93 (14%).

c) 8-[3-Hydroxy-N-(4-hydroxyphenyl)-benzamido]-caprylic acid

As described in example 1b), the reaction is carried out with 1.3 g (3.4 mmol) of 8-[3-hydroxy-N-(4-hydroxyphenyl)-benzamido]-caprylic acid methyl ester, 0.2 g (5 mmol) of sodium hydroxide and 50 cc. of methanol. Reaction time: 4 days, reaction temperature: 25°C.

Yield: 0.92 g (74% of the theoretical). Fp. 133°C (from ethanol)
IR (in KBr): 3400, 1700, 1605 and 1570 cm^{-1}
MS (m/e): 371 (30%), 250 (8%), 242 (12%), 229 (23%), 135 (4%), 121 (100%), 93 (16%).

Example 15

8-[4-Chloro-N-(4-chlorophenyl)-benzamido]-caprylic acid sodium salt

R^1=4-Chlorophenyl, R^2=4-Chlorophenyl, n=7, R^3=Na

2.6 g (4.9 mmol) of 8-[4-chloro-N-(4-chlorophenyl)-benzamido]-caprylic acid are dissolved in 50 cc. of methanol. A solution of 0.25 g (4.6 mmol) of sodium methylate in 50 cc. of methanol are added thereto and the mixture is stirred for 15 minutes at 25°C. The sodium salt is precipitated by the addition of ether, is filtered off with suction, is dried and powdered.

Yield: 1.3 g (62% of the theoretical).
IR (in KBr): 1655 cm^{-1}.

Example 16

8-(N-Phenyl-benzamido)-caprylic acid sodium salt

R^1=Phenyl, R^2=Phenyl, n=7, R^3=Na

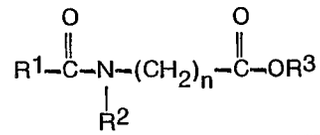
8-(N-phenyl-benzamido)-caprylic acid is dissolved in ethanol and neutralized with an ethanolic soda lye. The solution is evaporated in a vacuum and the solid residue is powdered.

IR (in KBr): 1648 and 1568 cm^{-1}.

Examples 17 to 28

The examples have been carried out as described in example 16. The corresponding IR-dates are given in the following table I.

N-Benzoyl-ω-anilino-alkanoic carboxylic acid sodium salts of formula I (R^3 = Na) from the corresponding acids of formula I (R^3 = H)



I

Example No.	R^1	R^2	n	R^3	IR–dates (in KBr) cm^{-1}	Example No.	R^1	R^2	n	R^3	IR–dates (in KBr) cm^{-1}
17	CH_3–O–	CH_3O–	7	Na	1645, 1568	23	Cl, Cl	CH_3O–	7	Na	1655, 1565
18	Cl–	CH_3O–	7	Na	1642, 1568	24	Cl–	CH_3, CH_3	7	Na	1645, 1570
19	Cl–	CH_3O–	8	Na	1645, 1568	25	Cl	Cl	7	Na	1660, 1570
20	Cl–	CH_3O–	10	Na	1650, 1570	26	CH_3O, CH_3O, CH_3O	CF_3	7	Na	1655, 1570
21	F–	CH_3O–	7	Na	1645, 1568	27	Cl–	HO–	7	Na	3400, 1625, 1565
22	CF_3	CH_3O–	7	Na	1645, 1570	28	HO	HO–	7	Na	3400, 1620, 1580

Example 29

8-(N-Phenyl-benzamido)-caprylic acid ether ester

R^1=Phenyl, R^2=Phenyl, n=7, R^3=—CH_2—CH_3

0.33 g (2.9 mmol) of ethyl bromide are added to a mixture of 1 g (2.9 mmol) of 8-(N-phenyl-benzamido)-caprylic acid, 20 cc. of dimethylformamide and 0.48 g (5.8 mmol) $NaHCO_3$. The mixture is stirred for 3 days and 25°C. Thereafter 100 cc. of water are added and the mixture is extracted with ethyl acetate. The organic layer is washed with water, dried over Na_2SO_4 and the solvent is distilled off in a vacuum. The residue is purified chromatographically on silicic acid gel using chloroform as eluant.

Yield: 0.33 g (31% of the theoretical) of a yellow oil.
IR (film): 1738 and 1645 cm^{-1}
MS (m/e): 367 (25%), 322 (11%), 197 (42%), 105 (100%), 77 (16%).

Example 30

8-[4-Chloro-N-(4-methoxyphenyl)-benzamido]-caprylic acid isopropyl ester

R^1=4-Chlorophenyl, R^2=4-Methoxyphenyl, n=7, R^3=—$CH(CH_3)_2$

As described in example 29, the reaction is carried out with 3 g (7.5 mmol) of 8-[4-Chloro-N-(4-methoxyphenyl)-benzamido]-caprylic acid, 50 cc. of dimethylformamide, 1.26 g (15 mmol) $NaHCO_3$ and 9.2 g (75 mmol) of 2-bromopropane.

Yield: 0.4 g (12% of the theoretical) of a colourless oil.
IR (film): 1730 and 1645 cm^{-1}.
MS (m/e): 445 (47%), 386 (15%), 261 (40%), 139 (100%), 125 (13%).

Example 31

8-[4-Chloro-N-(4-methoxyphenyl)-benzamido]-caprylic acid heptyl ester

R^1=4-Chlorophenyl, R^2=4-Methoxyphenyl, n=7, R^3=—$(CH_2)_6CH_3$

As described in example 29, the reaction is carried out with 3 g (7.5 mmol) of 8-[4-chloro-N-(4-methoxyphenyl)-benzamido]-caprylic acid, 50 cc. of dimethylformamide, 1.26 g (15 mmol) of $NaHCO_3$ and 13.4 g (75 mmol) of 1-bromoheptane.

Yield: 0.8 g (22% of the theoretical) of a colourless oil.
IR (film): 1737 and 1647 cm^{-1}.
MS (m/e): 501 (83%), 386 (11%), 261 (43%), 139 (100%), 125 (12%).

Example 32

8-[2.4-Dichloro-N-(4-methoxyphenyl)-benzamido]-caprylic acid benzyl ester

R^1=2.4-Dichlorophenyl, R^2=4-Methoxyphenyl, n=7, R^3=Benzyl

As described in example 29 the reaction is carried out with 2 g (4.6 mmol) of 8-[2.4-dichloro-N-(4-methoxyphenyl)-benzamido]-caprylic acid, 40 cc. of dimethylformamide, 0.77 g (9 mmol) of $NaHCO_3$ and 7.8 g (46 mmol) of benzylbromide.

Yield: 0.9 g (37% of the theoretical) of a colourless oil.
IR (film): 1740 and 1655 cm^{-1}
MS (m/e): 527 (63%), 420 (9%), 295 (54%), 173 (100%), 136 (15%), 91 (72%).

The following examples refer to mixtures of compounds of formula I with carrier and auxiliary agents usual in pharmacy which mixtures can be used as drugs.

Example 33

Tablets

A mixture consisting of 50 g of the sodium salt of 8-[4-chloro-N-(4-chlorophenyl)-benzamido]-caprylic acid, 50 g of lactose, 15 g of corn starch, 2 g of cellulose powder and 2 g of magnesium stearate, pressed in usual manner to tablets such that each tablet contains 250 mg of active agent.

Example 34

Dragees

As described in example 33, tablets are pressed and then are coated with a coating consisting of sugar, corn starch, talcum and tragent.

Example 35

Ampoules

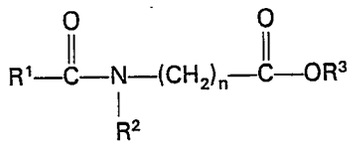
100 g of the sodium salt of 8-[4-chloro-N-(4-chlorophenyl)-benzamido]-caprylic acid are dissolved in a mixture of 9.5 litre of distilled water and 0.5 litre of ethylene glycol, filtered and filled into

ampoules each containing 10 cc. of the solution under sterile conditions. The ampoules thereafter are closed by fusion.

In analogous manner there are produced tablets, dragees, and ampoules containing one or several active agents of formula I with the addition of an anticoagulating agent.

Claims

1. N-Benzoyl-ω-anilinoalkane carboxylic acid of the general formula I



I

wherein

n is a positive integer ranging from 7 to 10;

R^1 and R^2, which may be different from each other or identical, represent the unsubstituted phenyl group or the phenyl group substituted by 1 to 4 identical or different groups selected from the group of halogen, C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylthio, halogeno-C_{1-4}-alkyl, hydroxy, phenoxy, benzyloxy, acyloxy or di-C_{1-4}-alkylamino,

R^3 is hydrogen, an alkali metal ion or a straight or branched saturated hydrocarbon group having 1 to 7 carbon atoms or the benzyl group.

2. N-Benzoyl-ω-anilino alkane carboxylic acids according to claim 1 and formula I wherein

n is 7 or 8;

R^1 and R^2, which may be identical or different from each other, represent the unsubstituted phenyl or phenyl substituted by 1 to 3 Cl—, F—, CF_3—, CH_3—, HO— and/or CH_3O— groups;

R^3 is hydrogen, an alkali metal ion, preferably the sodium metal ion or a straight or branched saturated hydrocarbon group having from 1 to 7 carbon atoms.

3. 8-(N-Phenyl-benzamido)-caprylic acid and the pharmaceutically compatible salts and esters thereof according to claim 1.

4. 8-[4-Chloro-N-(4-chlorophenyl)-benzamido]-caprylic acid and the pharmaceutically compatible salts and esters thereof according to claim 1.

5. 8-[4-Methoxy-N-(4-methoxyphenyl)-benzamido]-caprylic acid and the pharmaceutically compatible salts and esters thereof according to claim 1.

6. 8-[4-Chloro-N-(4-methoxyphenyl)-benzamido]-caprylic acid and the pharmaceutically compatible salts and esters thereof according to claim 1.

7. 9-[4-Chloro-N-(4-methoxyphenyl)-benzamido]-pelargonic acid and the pharmaceutically compatible salts and esters thereof according to claim 1.

8. 11-[4-Chloro-N-(4-methoxyphenyl)-benzamido]-undecanoic acid and the pharmaceutically compatible salts and esters thereof according to claim 1.

9. 8-[4-Fluoro-N-(4-methoxyphenyl)-benzamido]-caprylic acid and the pharmaceutically compatible salts and esters thereof according to claim 1.

10. 8-[3-Trifluoromethyl-N-(4-methoxyphenyl)-benzamido]-caprylic acid and the pharmaceutically compatible salts and esters thereof according to claim 1.

11. 8-[2.4-Dichloro-N-(4-methoxyphenyl)-benzamido]-caprylic acid and the pharmaceutically compatible salts and esters thereof according to claim 1.

12. 8-[4-Chloro-N-(2.6-dimethylphenyl)-benzamido]-caprylic acid and the pharmaceutically compatible salts and esters thereof according to claim 1.

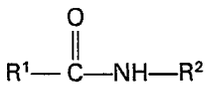
13. 8-[2-Chloro-N-(3-chlorophenyl)-benzamido]-caprylic acid and the pharmaceutically compatible salts and esters thereof according to claim 1.

14. 8-[3.4.5-Trimethoxy-N-]3-(trifluoromethyl)-phenyl[-benzamido)-caprylic acid and the pharmaceutically compatible salts and esters thereof according to claim 1.

15. 8-[4-Chloro-N-(4-hydroxyphenyl)-benzamido)-caprylic acid and the pharmaceutically compatible salts and esters thereof according to claim 1.

16. 8-[3-Hydroxy-N-(4-hydroxyphenyl)-benzamido)-caprylic acid and the pharmaceutically compatible salts and esters thereof according to claim 1.

17. Process for the production of the compounds according to formula I characterized in that a benzanilide of formula II



II

wherein R^1 and R^2 have the same meaning as in formula I, is subjected to reaction with an ω-halogeno alkane carboxylic acid of formula III

$$X—(CH_2)_n—\overset{\overset{\displaystyle O}{\|}}{C}—OR^3 \qquad \text{III}$$

wherein n has the same meaning as in formula I and R^3 is a straight or branched hydrocarbon group having from 1 to 7 carbon atoms and X is an halogen atom and the resulting N-benzoyl-ω-anilino-alkane carboxylic acid ester of formula II is optionally saponified in usual manner to the carboxylic acids according to formula I and optionally converted into one of its alkali metal salts.

18. Process for the production of the compounds according to formula I characterized in that

a) an anilino compound of formula IV

$$R^2—NH_2 \qquad \text{IV}$$

wherein R^2 has the same meaning as in formula I, is subjected to alkylation with an ω-halogenoalkane carboxylic acid ester of formula III and the resulting ω-anilinoalkane carboxylic acid ester of formula V

$$R^2—NH—(CH_2)_n—\overset{\overset{\displaystyle O}{\|}}{C}—OR^3 \qquad \text{V}$$

wherein R^2 and n have the same meaning as in formula I and R^3 has the same meaning as in formula III, is subjected to reaction with a reactive benzoic acid derivative of formula VI

$$R^1—\overset{\overset{\displaystyle O}{\|}}{C}—Y \qquad \text{VI}$$

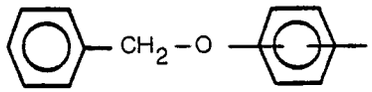
wherein R^1 has the same meaning as in formula I and Y is a group to split off or is a

$$R^1—\overset{\overset{\displaystyle O}{\|}}{C}—O—$$

group and the resulting N-benzoyl-ω-anilinoalkane carboxylic acid ester of formula I is optionally saponified in usual manner to the carboxylic acids of formula III and optionally converted into one of its alkali metal salts or

b) an ω-anilinoalkane carboxylic acid ester of formula V (R^3 = alkyl) is saponified and the resulting ω-anilinoalkane carboxylic acid of formula V (R^3 = H) is subjected to reaction with a reactive benzoic acid derivative of formula VI and the resulting N-benzoyl-ω-anilinoalkane carboxylic acid of formula I is optionally converted in usual manner into an alkali metal salt or a C_{1-7}-alkylester of formula I or

c) a N-benzoyl-ω-anilinoalkane carboxylic acid or a C_{1-7}-alkylester thereof of formula I (R^3 = H or alkyl) at least one of R^1 or R^2 is a benzyloxy substituted phenyl of formula VII



VII

is subjected to hydrogenolysis to yield a N-benzoyl-ω-anilinoalkane carboxylic acid ester of formula I having at least one free phenolic OH-group and this ester is optionally converted in usual manner into a carboxylic acid ester of formula I and optionally into an alkali metal salt or formula I.

19. Pharmaceutical preparations characterized in that they contain at least one compound or a pharmaceutically compatible salt thereof according to claims 1 to 16 with a pharmaceutically usual diluent or carrier material.

Revendications

1. Acide N-benzoyl-oméga-anilinoalcanecarboxylique de la formule générale I

$$R^1—\overset{\overset{\displaystyle O}{\|}}{C}—\underset{\underset{\displaystyle R^2}{|}}{N}—(CH_2)_n—\overset{\overset{\displaystyle O}{\|}}{C}—OR^3 \qquad \text{I}$$

dans laquelle

n est un nombre entier positif de 7 à 10;

R^1 et R^2, qui peuvent être identiques ou différents, représentent chacun un groupe phényle non-substitué ou substitué par 1 à 4 groupes identiques ou différents choisis parmi les halogènes et les groupes alcoyle en C_{1-4}, alcoxy en C_{1-4}, alcoylthio en C_{1-4}, halogénoalcoyle en C_{1-4}, hydroxy, phénoxy, benzyloxy, acyloxy ou di(alcoyl en C_{1-4})-amino,

R^3 est de l'hydrogène, un ion de métal alcalin ou un groupe d'hydrocarbure saturé à chaîne droite ou ramifiée ayant de 1 à 7 atomes de carbone ou le groupe benzyle.

2. Acides N-benzoyl-oméga-anilino-alcanecarboxyliques selon la revendication 1 et de formule I dans lesquels

n est 7 ou 8;

R^1 et R^2, qui peuvent être identiques ou différents, représentent chacun un groupe phényle non-substitué ou substitué par un à trois substituants Cl—, F—, CF_3—, CH_3— HO— et/ou CH_3O—;

R^3 est de l'hydrogène, un ion de métal alcalin, de préférence l'ion de sodium ou un groupe d'hydrocarbure saturé à chaîne droite ou ramifiée ayant de 1 à 7 atomes de carbone.

3. Acide 8-(N-phényl-benzamido)-caprylique et ses sels et esters pharmaceutiquement compatibles selon la revendication 1.

4. Acide 8-[4-chloro-N-(4-chlorophényl)-benzamido]-caprylique et ses sels et esters pharmaceutiquement compatibles selon la revendication 1.

5. Acide 8-[4-méthoxy-N-(4-méthoxyphényl)-benzamido]-caprylique et ses sels et esters pharmaceutiquement compatibles selon la revendication 1.

6. Acide 8-[4-chloro-N-(4-méthoxyphényl)-benzamido]-caprylique et ses sels et esters pharmaceutiquement compatibles selon la revendication 1.

7. Acide 9-[4-chloro-N-(4-méthoxyphényl)-benzamido]-pélargonique et ses sels et esters pharmaceutiquement compatibles selon la revendication 1.

8. Acide 11-[4-chloro-N-(4-méthoxyphényl)-benzamido]-undécanoïque et ses sels et esters pharmaceutiquement compatibles selon la revendication 1.

9. Acide 8-[4-fluoro-N-(4-méthoxyphényl)-benzamido]-caprylique et ses sels et esters pharmaceutiquement compatibles selon la revendication 1.

10. Acide 8-[3-trifluorométhyl-N-(4-méthoxyphényl)-benzamido]-caprylique et ses sels et esters pharmaceutiquement compatibles selon la revendication 1.

11. Acide 8-[2,4-dichloro-N-(4-méthoxyphényl)-benzamido]-caprylique et ses sels et esters pharmaceutiquement compatibles selon la revendication 1.

12. Acide 8-[4-chloro-N-(2,6-diméthylphényl)-benzamido]-caprylique et ses sels et esters pharmaceutiquement compatibles selon la revendication 1.

13. Acide 8-[2-chloro-N-(3-chlorophényl)-benzamido]-caprylique et ses sels et esters pharmaceutiquement compatibles selon la revendication 1.

14. Acide 8-[3,4,5-triméthoxy-N-]3-(trifluorométhyl)-phényl[benzamido]-caprylique et ses sels et esters pharmaceutiquement compatibles selon la revendication 1.

15. Acide 8-[4-chloro-N-(4-hydroxyphényl)-benzamido]-caprylique et ses sels et esters pharmaceutiquement compatibles selon la revendication 1.

16. Acide 8-[3-hydroxy-N-(4-hydroxyphényl)-benzamido]-caprylique et ses sels et esters pharmaceutiquement compatibles selon la revendication 1.

17. Procédé pour la production des composés de formule I caractérisé en ce qu'un benzanilide de formule II

$$R^1—\overset{\overset{\displaystyle O}{\|}}{C}—NH—R^2 \qquad \text{II}$$

où R^1 et R^2 ont la même signification que dans la formule I est soumis à une réaction avec un acide oméga-halogéno-alcanecarboxylique de formule III

$$X—(CH_2)_n—\overset{\overset{\displaystyle O}{\|}}{C}—OR^3 \qquad \text{III}$$

où n a la même signification que dans la formule I et R^3 est un groupe d'hydrocarbure à chaîne droite ou ramifiée ayant de 1 à 7 atomes de carbone et X est un atome d'halogène et l'ester d'acide N-benzoyl-oméga-anilino-alcanecarboxylique de formule II résultant est éventuellement saponifié de manière usuelle pour donner les acides carboxyliques de formule I et éventuellement transformé en un de ses sels de métaux alcalins.

18. Procédé pour la production des composés de formule I caractérisé en ce que

(a) un composé anilino de formule IV

$$R^2—NH_2 \qquad IV$$

où R^2 a la même signification que dans la formule I est soumis à une alcoylation avec un ester d'acide oméga-halogéno-alcanecarboxylique de formule III et l'ester d'acide oméga-anilino-alcanecarboxylique résultant de formule V

$$R^2—NH—(CH_2)_n—\overset{\overset{\displaystyle O}{\|}}{C}—OR^3 \qquad V$$

où R^2 et n ont la même signification que dans la formule I et R^3 a la même signification que dans la formule III est soumis à une réaction avec un dérivé réactif d'acide benzoïque de formule VI

$$R^1—\overset{\overset{\displaystyle O}{\|}}{C}—Y \qquad VI$$

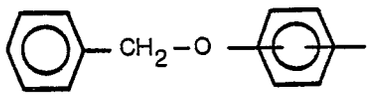
où R^1 la la même signification que dans la formule I et Y est un groupe à éliminer ou est un groupe

$$R^1—\overset{\overset{\displaystyle O}{\|}}{C}—O— $$

et l'ester d'acide N-benzoyl-oméga-anilino-alcanecarboxylique de formule I résultant est éventuellement saponifié de manière usuelle pour donner l'acide carboxylique de formule III et éventuellement transformé en un de ses sels de métaux alcalins ou

(b) un ester d'acide oméga-anilino-alcanecarboxylique de formule V (R^3 = alcoyle) est saponifié et l'acide oméga-anilino-alcanecarboxylique résultant de formule V (R^3 = H) est soumis à une réaction avec un dérivé d'acide benzoïque de formule VI et l'acide N-benzoyl-oméga-anilino-alcanecarboxylique de formule I résultant est éventuellement transformé de manière usuelle en un sel de métal alcalin ou en un ester d'alcoyle en C_{1-7} de formule I ou

(c) un acide N-benzoyl-oméga-anilino-alcanecarboxylique ou ester d'alcoyle en C_{1-7} de formule I (R^3 = H ou un groupe alcoyle) où au moins un des substituants R^1 et R^2 est un groupe benzyloxyphényle de formule VII



VII

est soumis à une hydrogénolyse pour donner un ester d'acide N-benzoyl-oméga-anilino-alcane carboxylique de formule I ayant au moins un hydroxyle phénolique libre et cet ester est éventuellement transformé de manière usuelle et un ester d'acide carboxylique de formule I et éventuellement en un sel de métal alcalin de formule I.

19. Préparations pharmaceutiques caractérisées en ce qu'elles contiennent au moins un composé, ou un sel pharmaceutiquement compatible de ce composé, selon l'une des revendications 1 à 16 avec un diluant ou une matière de support pharmaceutiquement usuels.

Patentansprüche

1. N-benzoyl-ω-anilinoalkan-carboxylsäure der allgemeinen Formel I

$$R^1—\overset{\overset{\displaystyle O}{\|}}{C}—\underset{\underset{\displaystyle R^2}{|}}{N}—(CH_2)_n—\overset{\overset{\displaystyle O}{\|}}{C}—OR^3 \qquad I$$

worin bedeuten:

n eine positive ganze Zahl innerhalb des Bereiches von 7 bis 10;

R^1 und R^2, die voneinander verschieden oder identisch sein können, eine unsubstituierte Phenylgruppe oder eine Phenylgruppe, die substituiert ist durch 1 bis 4 identische oder verschiedene Gruppen, ausgewählt aus der Gruppe Halogen, C_{1-4}-Alkyl, C_{1-4}-Alkoxy, C_{1-4}-Alkylthio, Halogeno-C_{1-4}-alkyl, Hydroxy, Phenoxy, Benzyloxy, Acyloxy oder Di-C_{1-4}-alkylamino,

R^3 Wasserstoff, ein Alkalimetallion oder eine unverzweigte oder verzweigte gesättigte Kohlenwasserstoffgruppe mit 1 bis 7 Kohlenstoffatomen oder die Benzylgruppe.

2. N-Benzoyl-ω-anilino-alkan-carboxylsäuren nach Anspruch 1 und der Formel I, worin bedeuten:
n 7 oder 8;
R^1 und R^2 die identisch oder voneinander verschieden sein können, unsubstituiertes Phenyl oder Phenyl, substituiert durch 1 bis 3 Cl—, F—, CF_3—, CH_3—, HO— und/oder CH_3O-Gruppen;
R^3 Wasserstoff, ein Alkalimetallion, vorzugsweise das Natriummetallion, oder eine unverzweigte oder verzweigte gesättigte Kohlenwasserstoffgruppe mit 1 bis 7 Kohlenstoffatomen.

3. 8-(N-Phenyl-benzamido)-caprylsäure und die pharmazeutisch verträglichen Salze und Ester davon nach Anspruch 1.

4. 8-[4-Chloro-N-(4-chlorophenyl)-benzamido]-caprylsäure und die pharmazeutisch verträglichen Salze und Ester davon nach Anspruch 1.

5. 8-[4-Methoxy-N-(4-methoxyphenyl)-benzamido]-caprylsäure und die pharmazeutisch verträglichen Salze und Ester davon nach Anspruch 1.

6. 8-[4-Chloro-N-(4-methoxyphenyl)-benzamido]-caprylsäure und die pharmazeutisch verträglichen Salze und Ester davon nach Anspruch 1.

7. 9-[4-Chloro-N-(4-methoxyphenyl)-benzamido]-pelargonsäure und die pharmazeutisch verträglichen Salze und Ester davon nach Anspruch 1.

8. 11-[4-Chloro-N-(4-methoxyphenyl)-benzamido]-undecansäure und die pharmazeutisch verträglichen Salze und Ester davon nach Anspruch 1.

9. 8-[4-Fluoro-N-(4-methoxyphenyl)-benzamido]-caprylsäure und die pharmazeutisch verträglichen Salze und Ester davon nach Anspruch 1.

10. 8-[3-Trifluoromethyl-N-(4-methoxyphenyl)-benzamido]-caprylsäure und die pharmazeutisch verträglichen Salze und Ester davon nach Anspruch 1.

11. 8-[2,4-Dichloro-N-(4-methoxyphenyl)-benzamido]-caprylsäure und die pharmazeutisch verträglichen Salze und Ester davon nach Anspruch 1.

12. 8-[4-Chloro-N-(2,6-dimethylphenyl)-benzamido]-caprylsäure und die pharmazeutisch verträglichen Salze und Ester davon nach Anspruch 1.

13. 8-[2-Chloro-N-(3-chlorophenyl)-benzamido]-caprylsäure und die pharmazeutisch verträglichen Salze und Ester davon nach Anspruch 1.

14. 8-[3,4,5-Trimethoxy-N-]3-(trifluoromethyl)-phenyl[-benzamido]-caprylsäure und die pharmazeutisch verträglichen Salze und Ester davon nach Anspruch 1.

15. 8-[4-Chloro-N-(4-hydroxyphenyl)-benzamido]-caprylsäure und die pharmazeutisch verträglichen Salze und Ester davon nach Anspruch 1.

16. 8-[3-Hydroxy-N-(4-hydroxyphenyl)-benzamido]-caprylsäure und die pharmazeutisch verträglichen Salze und Ester davon nach Anspruch 1.

17. Verfahren zur Herstellung von Verbindungen der Formel I, dadurch gekennzeichnet, daß ein Benzanilid der Formel II

$$R^1—\overset{\overset{\displaystyle O}{\|}}{C}—NH—R^2 \qquad \text{II}$$

worin R^1 und R^2 die gleiche Bedeutung wie in der Formel I haben, mit einer ω-Halogeno-alkan-carboxylsäure der Formel III

$$X—(CH_2)_n—\overset{\overset{\displaystyle O}{\|}}{C}—OR^3 \qquad \text{III}$$

worin n die gleiche Bedeutung wie in der Formel I hat und R^3 eine unverzweigte oder verzweigte Kohlenwasserstoffgruppe mit 1 bis 7 Kohlenstoffatomen und X ein Wasserstoffatom bedeuten, umgesetzt wird und der resultierende N-Benzoyl-ω-anilinoalkan-carboxylsäureester der Formel II ebenfalls auf übliche Weise zu den Carboxylsäuren der Formel I verseift und gegebenenfalls in eines ihrer Alkalisalze umgewandelt wird.

18. Verfahren zur Herstellung der Verbindungen der Formel I, dadurch gekennzeichnet, daß
a) eine Anilinoverbindung der Formel IV

$$R^2—NH_2 \qquad \text{IV}$$

worin R^2 die gleiche Bedeutung wie in der Formel I hat, mit einem ω-Halogenoalkan-carboxylsäureester der Formel III alkyliert wird und der resultierende ω-Anilinoalkan-carboxylsäureester der Formel V

$$R^2—NH—(CH_2)_n—\overset{\overset{\displaystyle O}{\|}}{C}—OR^3 \qquad \text{V}$$

worin R^2 und n die gleiche Bedeutung wie in der Formel I haben und R^3 die gleiche Bedeutung wie in der Formel III hat, mit einem reaktionsfähigen Benzoesäurederivat der Formel VI umgesetzt wird

$$R^1-\overset{\overset{\displaystyle O}{\|}}{C}-Y \qquad \text{VI}$$

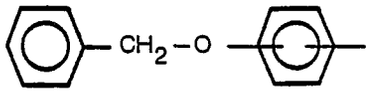
worin R^1 die gleiche Bedeutung wie in der Formel I hat und Y eine abspaltbare Gruppe oder eine

$$R^1-\overset{\overset{\displaystyle O}{\|}}{C}-O- $$

Gruppe bedeutet, und der resultierende N-Benzoyl-ω-anilinoalkan-carboxylsäureester der Formel I gegebenenfalls auf übliche Weise zu den Carboxylsäuren der Formel III verseift und gegebenenfalls in eines ihrer Alkalimetallsalze umgewandelt wird, oder

b) ein ω-Anilinoalkan-carboxylsäureester der Formel V (R^3 = Alkyl) verseift wird und die resultierende ω-Anilinoalkan-carboxylsäure der Formel V (R^3 = H) mit einem reaktionsfähigen Benzoesäurederivat der Formel VI umgesetzt wird und die resultierende N-Benzoyl-ω-anilinoalkan-carboxylsäure der Formel I gegebenenfalls auf übliche Weise in ein Alkalimetallsalz oder einen C_{1-7}-Alkylester der Formel I umgewandelt wird, oder

c) eine N-Benzoyl-ω-anilinoalkan-carboxylsäure oder ein C_{1-7}-Alkylester davon der Formel I (R^3 = H oder Alkyl), wobei mindestens einer der Reste R^1 und R^2 ein benzoyloxy-substituiertes Phenyl der Formel VII ist



VII

einer Hydrogenolyse unterworfen wird unter Bildung eines N-Benzoyl-ω-anilinoalkan-carboxylsäureesters der Formel I mit mindestens einer freien phenolischen OH-Gruppe und dieser Ester gegebenenfalls auf übliche Weise in einen Carboxylsäureester der Formel I und gegebenenfalls in ein Alkalimetallsalz der Formel I ungewandelt wird.

19. Pharmazeutische Präparate, dadurch gekennzeichnet, daß sie mindestens eine Verbindung oder ein pharmazeutische verträgliches Salz davon nach den Ansprüchen 1 bis 16 zusammen mit einem pharmazeutisch üblichen Verdünnungsmittel oder Trägermaterial enthalten.