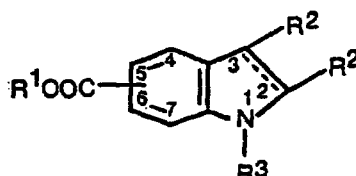


Description

This invention relates to new therapeutically useful indole and indoline derivatives, to processes for preparing them, and to pharmaceutical compositions containing them.

The indole and indoline derivatives of the present invention are those compounds of the general formula:—



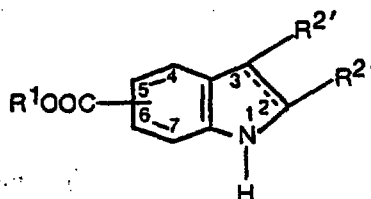
wherein — indicates a double bond or a single bond between carbon atoms, R¹ represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms (which may be substituted by one or more than one of the same type of substituents selected from the hydroxy group, alkenyl groups containing from 2 to 5 carbon atoms, e.g. vinyl, and alkanoyloxy groups containing from 2 to 7 carbon atoms, e.g. pivaloyloxy) or, more particularly, a hydrogen atom, and one of the symbols R² represents a straight- or branched-chain alkyl group containing from 7 to 24, preferably from 7 to 20, carbon atoms and the other symbol R² represents a straight- or branched-chain alkyl group containing from 1 to 24 carbon atoms (preferably a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms) or preferably a hydrogen atom, and R³ represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms or preferably a hydrogen atom, and pharmaceutically acceptable salts thereof.

When R¹ is an alkyl or substituted alkyl group it may be, for example, a methyl, ethyl, butyl, 2,3-dihydroxyprop-1-yl, allyl or pivaloyloxymethyl group.

The group R¹OOC is attached to the 4 or 7 or, preferably, the 5 or 6 position of the indole or indoline ring system.

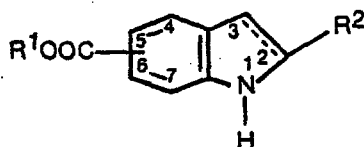
When one of the symbols R² represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms (preferably the methyl group) it is preferably attached to the 3 position of the indole or indoline ring system.

Preferred indole or indoline derivatives of the present invention are those compounds of the general formula:—



wherein — indicates a double bond or a single bond between carbon atoms, R¹ represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms (e.g. methyl, ethyl or butyl) or, more particularly, a hydrogen atom, and one of the symbols R²' represents a straight- or branched-chain alkyl group containing from 7 to 24, preferably 7 to 20, carbon atoms and the other symbol R²' represents a straight- or branched-chain alkyl group containing from 1 to 24 carbon atoms (preferably, when it represents an alkyl group containing from 1 to 6 carbon atoms it is attached to the 3 position of the indole or indoline ring system) and pharmaceutically acceptable salts thereof.

Other preferred indole or indoline derivatives of the present invention are those compounds of the general formula:—



wherein — indicates a double bond or a single bond between carbon atoms, R¹ represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms (e.g. methyl, ethyl or butyl) or, more particularly, a hydrogen atom, and R² represents a straight- or branched-chain alkyl group, containing from 7 to 24, preferably from 7 to 20, carbon atoms, and pharmaceutically acceptable salts thereof.

The group R¹OOC- depicted in general formulae II and III is attached to the 5 or 6 position of the indole or indoline ring system.

It will be understood by those skilled in the art that when — represents a single bond between carbon atoms and one of the symbols R² represents a hydrogen atom the compounds of general formula I may exist in optically isomeric forms. It will be further understood by those skilled in the art

that when the symbol --- represents a single bond between carbon atoms and both of the symbols R^2 represent alkyl groups the compounds of general formula I may exist in optically isomeric forms and also as diastereoisomers. Furthermore, in certain cases the substituents R^1 , R^2 and R^3 contribute to optical isomerism. All such forms are embraced by the present invention.

5 By the term "pharmaceutically acceptable salt" in relation to compounds of general formula I is meant a salt formed by reaction with an acid when --- indicates a single bond between carbon atoms or, when R^1 represents a hydrogen atom, by reaction with a base, so that the anion (in the case of an acid addition salt) or the cation (in the case of a salt formed by a compound of general formula I wherein R^1 represents a hydrogen atom) is relatively innocuous to the animal organism when used in
10 therapeutic doses so that the beneficial pharmacological properties of the parent compound of general formula I are not vitiated by side-effects ascribable to the said anion or cation.

Suitable acid addition salts include salts derived from inorganic acids, for example hydrochlorides, hydrobromides, phosphates, sulphates and nitrates, and organic salts, for example
15 methanesulphonates, 2-hydroxyethanesulphonates, oxalates, lactates, tartrates, acetates, salicylates, citrates, propionates, succinates, fumarates, maleates, methylene-bis- β -hydroxynaphthoates, gentisates and di-*p*-toluoyltartrates.

Suitable salts formed by compounds of general formula I wherein R^1 represents a hydrogen atom include the alkali metal (e.g. sodium and potassium), alkaline earth metal (e.g. calcium and magnesium), and ammonium salts, and salts of amines known in the art to be pharmaceutically
20 acceptable, e.g. ethylene diamine, choline, diethanolamine, triethanolamine, octadecylamine, diethylamine, triethylamine, 2-amino-2-(hydroxymethyl)propane-1,3-diol and 1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol.

It is to be understood that, where in this specification reference is made to compounds of general formula I, it is intended to refer also to their pharmaceutically acceptable salts as indicated above,
25 where the context so permits.

The compounds of general formula I possess useful pharmacological properties, in particular hypolipidaemic activity, and some are intermediates for the preparation of the other therapeutically useful derivatives. For example, they lower the concentrations of cholesterol and of triglycerides in the blood. Furthermore, they reduce the proliferation of arterial smooth muscle cells which is a major
30 feature of atheromatous plaques. The compounds of general formula I also lower blood glucose levels in mice suffering from diabetes mellitus. Thus, they are of utility in the prevention or treatment of diabetes mellitus, hyperlipoproteinaemic states, of atherosclerosis, and of associated conditions such as angina, myocardial infarction, cerebral vascular occlusion, arterial aneurism, peripheral vascular disease, recurrent pancreatitis and xanthomas.

35 Compounds of general formula I which are of particular interest include the following compounds, their isomeric forms and their salts:—

	2-(n-tridecyl)indole-6-carboxylic acid	A
	2-(n-heptadecyl)indole-6-carboxylic acid	B
40	2-(n-undecyl)indole-6-carboxylic acid	C
	2-(n-pentadecyl)indole-6-carboxylic acid	D
	2-(n-heptadecyl)indole-5-carboxylic acid	E
	2-(n-undecyl)indole-5-carboxylic acid	F
	2-(n-pentadecyl)indole-5-carboxylic acid	G
45	2-(n-tridecyl)indole-5-carboxylic acid	H
	2-(n-pentadecyl)indole-7-carboxylic acid	I
	2-(n-pentadecyl)indole-4-carboxylic acid	J
	(RS)-2-(n-pentadecyl)indoline-6-carboxylic acid	K
	2-(n-nonyl)indole-6-carboxylic acid	L
50	2-(n-decyl)indole-5-carboxylic acid	M
	2-(n-decyl)indole-6-carboxylic acid	N
	2-(n-nonyl)indole-5-carboxylic acid	O
	2-(n-octyl)indole-6-carboxylic acid	P
	2-(n-heptyl)indole-5-carboxylic acid	Q
55	2-(n-heptyl)indole-6-carboxylic acid	R
	2-(n-dodecyl)indole-6-carboxylic acid	S
	2-(n-octadecyl)indole-5-carboxylic acid	T
	ethyl 2-(n-undecyl)-indole-5-carboxylate	U
	2-(n-octadecyl)indole-6-carboxylic acid	V
60	2-(n-undecyl)indole-4-carboxylic acid	W
	2-(n-octyl)indole-5-carboxylic acid	X
	2-(n-dodecyl)indole-5-carboxylic acid	Y
	2-(n-nonyl)indole-4-carboxylic acid	Z
	2-(n-eicosyl)indole-5-carboxylic acid	AA
65	ethyl 2-(n-pentadecyl)indole-5-carboxylate	BB

	ethyl 2-(n-dodecyl)indole-6-carboxylate	CC
	ethyl 2-(n-heptyl)indole-5-carboxylate	DD
	ethyl 2-(n-pentadecyl)indole-4-carboxylate	EE
	ethyl 2-(n-undecyl)indole-6-carboxylate	FF
5	n-butyl 2-(n-undecyl)indole-6-carboxylate	GG
	n-butyl 2-(n-pentadecyl)indole-5-carboxylate	HH
	ethyl 2-(n-dodecyl)indole-5-carboxylate	II
	methyl 2-(n-undecyl)indole-6-carboxylate	JJ
	n-butyl 2-(n-dodecyl)indole-5-carboxylate	KK
10	methyl 2-(n-pentadecyl)indole-5-carboxylate	LL
	n-butyl 2-(n-pentadecyl)indole-4-carboxylate	MM
	2-(n-tetradecyl)indole-5-carboxylic acid	NN
	2-(n-hexadecyl)indole-5-carboxylic acid	OO
	2-(n-nonadecyl)indole-5-carboxylic acid	PP
15	2-(n-tricosyl)indole-5-carboxylic acid	QQ
	(RS)-2-(1-methyldecyl)indole-5-carboxylic acid	RR
	2-(n-tetradecyl)indole-6-carboxylic acid	SS
	2-(n-hexadecyl)indole-6-carboxylic acid	TT
	2-(n-eicosyl)indole-6-carboxylic acid	UU
20	(RS)-2-(1-methyldecyl)indole-6-carboxylic acid	VV
	2-(n-nonyl)indole-7-carboxylic acid	WW
	2-(n-undecyl)indole-7-carboxylic acid	XX
	(RS)-2-(n-undecyl)indoline-5-carboxylic acid	YY
	(RS)-2-(n-decyl)indoline-6-carboxylic acid	ZZ
25	(RS)-2-(n-pentadecyl)indoline-5-carboxylic acid	AAA
	(RS)-2-(n-heptyl)indoline-5-carboxylic acid	ABB
	(RS)-2-(n-decyl)indoline-5-carboxylic acid	ACC
	(RS)-2-(n-heptadecyl)indoline-5-carboxylic acid	ADD
	(RS)-2-(n-heptyl)indoline-6-carboxylic acid	AEE
30	(RS)-2-(n-undecyl)indoline-6-carboxylic acid	AFF
	(RS)-2-(n-tetradecyl)indoline-6-carboxylic acid	AGG
	(RS)-ethyl 2-(n-undecyl)indoline-6-carboxylate	AHH
	methyl 2-(n-heptyl)indole-6-carboxylate	AIJ
	ethyl 2-(n-heptyl)indole-6-carboxylate	AJJ
35	n-butyl-(n-heptyl)indole-6-carboxylate	AKK
	n-butyl 2-(n-dodecyl)indole-6-carboxylate	ALL
	ethyl 2-(n-tridecyl)indole-6-carboxylate	AMM
	methyl 2-(n-pentadecyl)indole-6-carboxylate	ANN
	ethyl 2-(n-pentadecyl)indole-6-carboxylate	AOO
40	n-butyl 2-(n-pentadecyl)indole-6-carboxylate	APP
	n-butyl 2-(n-eicosyl)indole-6-carboxylate	AQQ
	n-butyl 2-(n-heptyl)indole-5-carboxylate	ARR
	methyl 2-(n-heptyl)indole-5-carboxylate	ASS
	methyl 2-(n-undecyl)indole-5-carboxylate	ATT
45	n-butyl 2-(n-undecyl)indole-5-carboxylate	AUU
	methyl 2-(n-dodecyl)indole-5-carboxylate	AVV
	methyl 2-(n-heptadecyl)indole-5-carboxylate	AWW
	(RS)(RS)-2,3-dihydroxyprop-1-yl 2-(n-decyl)-indoline-6-carboxylate	AXX
	methyl 3-(n-dodecyl)indole-6-carboxylate	AYY
50	methyl 3-(n-octyl)indole-6-carboxylate	AZZ
	methyl 3-(n-hexadecyl)indole-6-carboxylate	BAA
	methyl 3-(n-octadecyl)indole-6-carboxylate	BBB
	methyl 3-(n-hexadecyl)indole-5-carboxylate	BCC
	3-(n-dodecyl)indole-6-carboxylic acid	BDD
55	3-(n-octyl)indole-6-carboxylic acid	BEE
	3-(n-hexadecyl)indole-6-carboxylic acid	BFF
	3-(n-octadecyl)indole-6-carboxylic acid	BGG
	3-(n-hexadecyl)indole-5-carboxylic acid	BHH
	(RS)-1-methyl-2-(n-undecyl)indoline-6-carboxylic acid	BII
60	(RS)-1-methyl-2-(n-undecyl)indoline-5-carboxylic acid	BJJ
	(RS)-methyl 3-(n-octadecyl)indoline-5-carboxylate	BKK
	(RS)-methyl 3-(n-decyl)indoline-5-carboxylate	BLL
	(RS)-methyl 3-(n-octyl)indoline-5-carboxylate	BMM
	(RS)-methyl 3-(n-hexadecyl)indoline-5-carboxylate	BNN
65	(RS)-3-(n-octadecyl)indoline-5-carboxylic acid	BOO

	(RS)-3-(n-decyl)indoline-5-carboxylic acid	BPP
	(RS)-3-(n-octyl)indoline-5-carboxylic acid	BQQ
	(RS)-3-(n-hexadecyl)indoline-5-carboxylic acid	BRR
5	3-(n-octadecyl)indole-5-carboxylic acid	BSS
	3-(n-octyl)indole-5-carboxylic acid	BTT
	(RS)-methyl 3-(n-undecyl)indoline-6-carboxylate	BUU
	(RS)-methyl 3-(n-decyl)indoline-6-carboxylate	BVV
	(RS)-methyl 3-(n-pentadecyl)indoline-6-carboxylate	BWW
10	(RS)-3-(n-undecyl)indoline-6-carboxylic acid	BXX
	(RS)-3-(n-decyl)indoline-6-carboxylic acid	BYY
	(RS)-3-(n-pentadecyl)indoline-6-carboxylic acid	BZZ
	(RS)-3-(n-dodecyl)indoline-6-carboxylic acid	CAA
	(RS)-3-(n-octadecyl)indoline-6-carboxylic acid	CBB
15	(RS)-3-(n-octyl)indoline-6-carboxylic acid	CCC
	(RS)-3-(n-hexadecyl)indoline-6-carboxylic acid	CDD
	(RS)-methyl (n-octyl)indoline-6-carboxylate	CEE
	(RS)-methyl 3-(n-hexadecyl)indoline-6-carboxylate	CFF
	(RS)-1-methyl-2-(n-tetradecyl)indoline-6-carboxylic acid	CGG
20	1-methyl-2-(n-undecyl)indole-6-carboxylic acid	CHH
	1-methyl-2-(n-pentadecyl)indole-5-carboxylic acid	CII
	(RS)-2-(1-methylheptadecyl)indole-6-carboxylic acid	CJJ
	(RS)-2-(1-methylheptadecyl)indole-5-carboxylic acid	CKK
	(RS)(RS)-2-(1-methylheptadecyl)indoline-6-carboxylic acid	CLL
	(RS)(RS)-2-(1-methylheptadecyl)indoline-5-carboxylic acid	CMM
25	2(RS),3(RS)-2-(n-undecyl)-3-methylindoline-6-carboxylic acid	CNN
	2(RS),3(RS)-2-(n-undecyl)-3-methylindoline-5-carboxylic acid	COO
	2-(n-undecyl)-3-methylindole-6-carboxylic acid	CPP
	2-(n-undecyl)-3-methylindole-5-carboxylic acid	CQQ
30	(RS)-2-(n-undecyl)indoline-4-carboxylic acid	CRR
	(RS)-2-(n-eicosyl)indoline-5-carboxylic acid	CSS
	2(RS),3(RS)-2-(n-heptyl)-3-methylindoline-6-carboxylic acid	CTT
	(RS)-2-(1-ethyldecyl)indole-6-carboxylic acid	CUU
	(RS)-2,3-dihydroxyprop-1-yl 2-(n-undecyl)-indole-6-carboxylate	CVV

35 The letters A to CVV are assigned to the compounds for easy reference later in the specification, for example in the following Tables.

The pharmacological properties of the compounds of general formula I or salts thereof were demonstrated in the following tests:—

40 *Hypolipidaemic Activity in Rats*

Male Wistar rats each weighing between 120 and 150 g were caged in groups of eight and fed a powdered diet for 10 days. For the last 7 days of that period the test compound was administered orally by mixing the compound in the diet and allowing the animals to feed normally. Food consumption was measured on day 9 for each group.

45 At noon on day 10 the animals were killed by inhalation of carbon dioxide from solid carbon dioxide. A sample of blood was removed by cardiac puncture and the serum cholesterol and serum triglycerides were analysed by means of an auto-analyser.

Control groups (receiving only the normal, unmedicated diet) were included with each test.

50 The percentage reductions in the concentrations of serum cholesterol and serum triglycerides were calculated by comparison with the simultaneous controls, for each concentration of the test compound used.

The results obtained are shown in Table I hereafter.

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TABLE I

Compound	Form	% w/w dose in diet	% change in serum compared with control	
			cholesterol	triglycerides
A	parent compound	0.2	-26	-33
B	parent compound	0.2	+5	-4
C	parent compound	0.2	-18	-31
		0.2	-48	-63
		0.1	-28	-39
C	sodium salt	0.2	-41	-46
D	parent compound	0.2	-26	-40
		0.2	-16	-30
D	sodium salt	0.2	-39	-63
		0.2	-41	-54
		0.1	-10	-18
E	parent compound	0.2	-54	-65
		0.1	-42	-55
F	parent compound	0.2	-37	-73
		0.1	-18	-43
G	parent compound	0.2	-50	-87
		0.2	-69	-89
		0.1	-43	-71
		0.1	-47	-79
		0.03	-7	-41
H	parent compound	0.2	-48	-68
		0.1	-15	-26
I	parent compound	0.2	-26	-33
J	parent compound	0.2	-9	-2
K	parent compound	0.2	+5	-43
		0.2	-17	-26
K	sodium salt	0.2	-17	-60
		0.2	-22	-42

TABLE I (Continued)

Compound	Form	% w/w dose in diet	% change in serum compared with control	
			cholesterol	triglycerides
K	HCl salt	0.2	-25	-52
L	parent compound	0.2	-21	-25
L	sodium salt	0.2	-32	-42
U	parent compound	0.2	-13	-39
O	parent compound	0.2	-13	-44
P	parent compound	0.2	-32	-37
M	parent compound	0.2	-26	-65
R	parent compound	0.2	-12	-18
Q	parent compound	0.2	-10	-14
V	parent compound	0.2	+3	-1
W	parent compound	0.2	-3	+22
X	parent compound	0.2	-18	-25
Y	parent compound	0.1 0.2	-20 -30	-51 -80
Z	parent compound	0.2	-14	-14
S	parent compound	0.2	-26	-52

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TABLE I (Continued)

Compound	Form	% w/w dose in diet	% change in serum compared with control	
			cholesterol	triglycerides
T	parent compound	0.2 0.1	-43 -45	-57 -78
AA	parent compound	0.2	-36	-57
NN	parent compound	0.2	-39	-73
G	sodium salt	0.2	-50	-77
OO	parent compound	0.2	-52	-75
PP	parent compound	0.2	-13	-41
QQ	parent compound	0.2	-16	-36
RR	parent compound	0.2	-7	-88
N	parent compound	0.2	-20	-45
S	sodium salt	0.2	-30	-31
SS	parent compound	0.2	-14	+3
TT	parent compound	0.2	-8	-6
UU	parent compound	0.2	-15	-29
VV	parent compound	0.2	-40	-73
BEE	parent compound	0.2	-19	-18
BDD	parent compound	0.2	-2	-5
BFF	parent compound	0.2	+7	-17

TABLE 1 (Continued)

Compound	Form	% w/w dose in diet	% change in serum compared with control	
			cholesterol	triglycerides
BGG	parent compound	0.2	-7	-7
AZZ	parent compound	0.2	-18	+24
Z	parent compound	0.2	-14	-14
W	parent compound	0.2	-3	+22
J	parent compound	0.2	-9	-2
EE	parent compound	0.2	-5	-2
MM	parent compound	0.2	+25	-41
WW	parent compound	0.2	-3	+45
XX	parent compound	0.2	-2	+8
BHH	parent compound	0.2	-6	-10
BCC	parent compound	0.2	+2	+16
All	parent compound	0.2	+7	+20
AJJ	parent compound	0.2	-8	+6
AKK	parent compound	0.2	-3	-10
FF	parent compound	0.2	-13	-40
GG	parent compound	0.2	-11	-35

TABLE I (Continued)

Compound	Form	% w/w dose in diet	% change in serum compared with control	
			cholesterol	triglycerides
CC	parent compound	0.2	-17	-57
AMM	parent compound	0.2	-4	-12
ANN	parent compound	0.2	+1	-25
APP	parent compound	0.2	-2	-20
AQQ	parent compound	0.2	+6	-12
DD	parent compound	0.2	-6	-25
ARR	parent compound	0.2	+8	+20
ASS	parent compound	0.2	-2	-20
ATT	parent compound	0.2	-16	-70
U	parent compound	0.2	-13	-39
AUU	parent compound	0.2	-14	-57
EE	parent compound	0.2 0.1	-28 -22	-46 -39
KK	parent compound	0.2	-18	-34
AVV	parent compound	0.2 0.1	-21 -16	-80 -65
LL	parent compound	0.2 0.1	-16 -13	-22 -32
BB	parent compound	0.2	-19	-39

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TABLE I (Continued)

Compound	Form	% w/w dose in diet	% change in serum compared with control	
			cholesterol	triglycerides
HH	parent compound	0.2 0.1	-24 -25	-50 -38
AWW	parent compound	0.2	-24	-16
ABB	parent compound	0.2	-18	-34
ABB	HCl salt	0.2	-14	-25
ACC	parent compound	0.2	-26	-71
YY	parent compound	0.2 0.1	-32 -21	-64 -65
YY	parent compound	0.03	-25	-51
YY	HCl salt	0.2	-20	-49
YY	sodium salt	0.2	-17	-66
AAA	parent compound	0.2	-12	-55
AAA	HCl salt	0.2	-20	-61
ADD	parent compound	0.2	-6	-40
AEE	parent compound	0.2	-22	-37
AEE	HCl salt	0.2	+4	-27
ZZ	parent compound	0.2	-32	-77
ZZ	HCl salt	0.2	-38	-60
AFF	parent compound	0.2	-38	-58

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TABLE I (Continued)

Compound	Form	% w/w dose in diet	% change in serum compared with control	
			cholesterol	triglycerides
AFF	HCl salt	0.2	-54	-93
AFF	sodium salt	0.2	-39	-84
AGG	parent compound	0.2	-8	-23
AGG	HCl salt	0.2	-11	-51
K	parent compound	0.2	+5	-43
K	HCl salt	0.2	-22	-42
		0.2	-17	-60
K	sodium salt	0.2	-25	-52
BSS	parent compound	0.2	-9	-11
BTT	parent compound	0.2	0	+15
BJJ	parent compound	0.2	-15	-41
BII	parent compound	0.2	0	-30
CFF	parent compound	0.2	+6	+10
CEE	parent compound	0.2	-16	-16
BNN	parent compound	0.2	+7	-20
CCC	parent compound	0.2	-11	-28
BYY	parent compound	0.2	-23	-50
CAA	parent compound	0.2	-28	-46

TABLE I (Continued)

Compound	Form	% w/w dose in diet	% change in serum compared with control	
			cholesterol	triglycerides
BZZ	parent compound	0.2	-1	-29
CDD	parent compound	0.2	-19	-41
CBB	parent compound	0.2	+2	-7
BXX	parent compound	0.2	-10	-39
BQQ	parent compound	0.2	+11	+31
BRR	HCl salt	0.2	+12	0
BOO	parent compound	0.2	+3	+9
BPP	parent compound	0.2	-3	0
CNN	parent compound	0.2	-31	-72
CVV	parent compound	0.1	-16	-56

Aortic smooth muscle cell proliferation inhibiting activity

Smooth muscle cells were grown in culture from explants of pig thoracic aorta, using Dulbecco's Modified Eagles (DME) Medium containing 20% foetal calf serum (FCS) and antibiotics. The cells were incubated at 37°C in an atmosphere of 95% air and 5% carbon dioxide. At confluency the cells were routinely subcultured by trypsinising and replating at approximately one third of their confluent density in DME Medium containing 10% FCS and antibiotics.

The smooth muscle cells were plated out at densities of 100,000—200,000 cells per 35 x 10 mm Falcon dish in 2 ml DME Medium containing 10% FCS and antibiotics. After 24 hours, when the cells had attached to the dishes, the medium was replaced with 2 ml DME Medium containing 1% FCS and antibiotics. The cultures were incubated for a further three days to allow the cells to become quiescent (i.e. no longer undergoing cell division). The medium was then replaced by 2 ml control or test medium. The test medium consisted of DME Medium (containing 10% FCS and antibiotics) and the compound to be tested at a concentration of 5 µg/ml medium. The compounds were pre-dissolved in acetone such that the final concentration of acetone in the medium was 0.2% (v/v). The control medium consisted of DME Medium (containing 10% FCS and antibiotics) and acetone at 0.2% (v/v) concentration. After three days incubation in test or control medium, the medium was replaced with fresh test or control medium and the cells incubated for a further three or four days. At the end of the six or seven day incubation period cell numbers were determined by trypsinising the cells and counting the cell suspension in a Coulter counter.

All results in Table II hereafter represent the mean value for four dishes of cells. Percentage inhibition of proliferation was calculated using the following formula:—

$$\text{Percentage inhibition of proliferation} = 100 - \left(\frac{T-S}{C-S} \times 100 \right)$$

- 5 Where S = Mean cell number per dish at start of experiment (upon addition of control or test medium).
 T = Mean cell number per dish in test cultures at completion of experiment.
 C = Mean cell number per dish in control cultures at completion of experiment.

TABLE II

Compound	% Inhibition
G	51, 36
AJJ	45, 30
YY	78, 76, 46
T	30, 35
C	69, 45
TT	61, 64
NN	76, 78
ASS	36

30 Hypoglycaemic Activity in Diabetic Mice

Diabetic mice (strain C 57, black, MRI derived Obese/Obese) of either sex each weighing between 45 and 70 g were given the test compound orally at a dose of 200 mg/kg body weight per day for 3 days. Three hours after the last dose the animals were weighed, anaesthetised with carbon dioxide and bled by cardiac puncture.

- 35 The serum glucose levels were assessed by the glucose-oxidase method of God-Perid. Control groups (given doses of unmedicated tragacanth mucilage) were included with each test. The percentage reduction in the concentration of serum glucose was calculated by comparison with the simultaneous controls, for each of the test compounds used. The results obtained are shown in following Table III.

TABLE III

Compound	% change in serum glucose compared with control
CQQ	-40
BXX	-9

- 55 The utility of the compounds is enhanced by the fact that they are of only very low toxicity, as demonstrated in the following test:—

Oral Toxicity in Mice

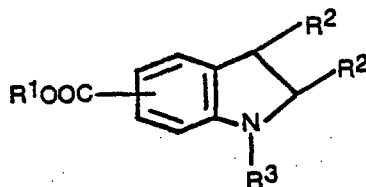
- 60 Groups of mice were dosed orally with graded doses of the test compound (in a 0.5% w/v aqueous suspension of tragacanth mucilage) and observed for 3 days thereafter. The percentages of animals which died during that period at each dose level were used to construct a graph, from which the LD 50, that is to say the dose in mg/kg animal body weight necessary to kill 50% of the mice, was calculated.

- 65 Compounds of the present invention were tested and the LD 50 of each compound was greater than 1000 mg/kg animal body weight.

Preferred compounds of the invention are those hereinbefore identified by the letters T, C, G, F, D, VV, YY, ACC, AFF, CNN, E, P, S and OO.

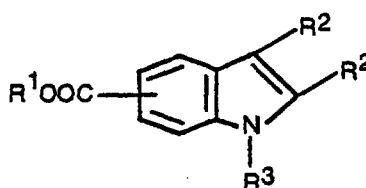
The compounds of general formula I may be prepared by the application or adaptation of known methods for the preparation of indole and indoline derivatives, for example by the following methods which are features of the present invention.

1. The compounds of general formula I wherein --- represents a single bond between carbon atoms, i.e. indoline compounds of the general formula:—



IV

(wherein R¹, R² and R³ are as hereinbefore defined), are prepared from compounds of general formula I wherein = represents a double bond between carbon atoms, i.e. indole compounds of the general formula:—



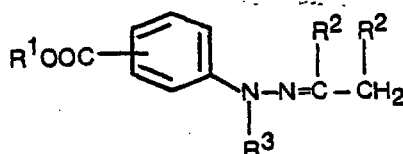
V

(wherein R¹, R² and R³ are as hereinbefore defined), by reduction, for example by catalytic hydrogenation using, for example, platinum oxide or palladium on charcoal.

The reaction may be effected in the presence of a strong acid, for example fluoroboric acid or a mixture of glacial acetic acid and perchloric acid, optionally in an organic solvent, for example ethanol or tetrahydrofuran.

2. The indole compounds of general formula I represented by general formula V are prepared from indoline compounds of general formula I represented by general formula IV by catalytic dehydrogenation using, for example, palladium on charcoal in an organic solvent, for example mesitylene.

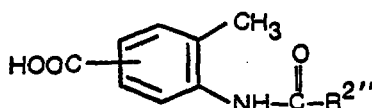
3. The indole compounds of general formula I wherein = represents a double bond between carbon atoms are prepared by the cyclisation of a compound of the general formula:—



VI

(wherein R¹, R² and R³ are as hereinbefore defined) by reaction with an inorganic acid, for example hydrochloric acid, sulphuric acid or polyphosphoric acid, or some other Lewis acid, for example boron trifluoride etherate or anhydrous zinc chloride, at an elevated temperature, for example between 70 and 150°C, optionally in the presence of an inert organic solvent for example ethanol.

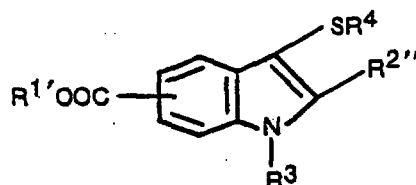
4. The indole compounds of general formula I wherein = represents a double bond between carbon atoms, the symbol R² attached to the 2-position of the indole ring system represents a straight- or branched-chain alkyl group containing from 7 to 24 carbon atoms, the symbol R² attached to the 3-position represents a hydrogen atom, and R¹ and R³ represent hydrogen atoms, are prepared by the cyclisation of a compound of the general formula:—



VII

(wherein R²'' represents a straight- or branched-chain alkyl group containing 7 to 24 carbon atoms) in the presence of a base, e.g. an alkali metal alkoxide containing from 1 to 6 carbon atoms, for example potassium *tert*-butoxide or sodium methoxide, or sodamide (a) at an elevated temperature, for example between 240 and 350°C (e.g. between 290 and 305°C) without solvent or preferably (b) at an elevated temperature, for example at from 180 to 240°C (e.g. at the reflux temperature of the reaction mixture) in the presence of an inert organic solvent, e.g. diethylaniline.

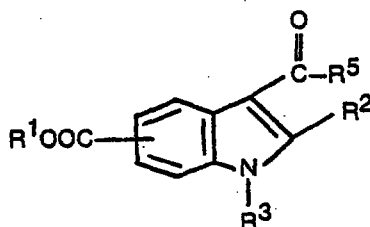
5. The indole compounds of general formula I wherein $\equiv$ represents a double bond between carbon atoms, R^1 represents an optionally substituted alkyl group as hereinbefore defined, the symbol R^2 attached to the 2-position of the indole ring system represents a straight- or branched-chain alkyl group containing from 7 to 24 carbon atoms, the symbol R^2 attached to the 3-position represents a hydrogen atom, and R^3 is as hereinbefore defined, are prepared by the reaction of a 3-alkylthio derivative of the general formula:—



VIII

- 15 (wherein $R^{2''}$ and R^3 are as hereinbefore defined, R^1 represents an optionally substituted alkyl group as hereinbefore defined for R^1 , and R^4 represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms) with Raney nickel in the presence of an inert organic solvent, for example dioxan.

6. The indole or indoline compounds of general formula I wherein the symbol R^2 in the 3-position of the indole ring system represents a straight- or branched-chain alkyl group containing from 1 to 24 carbon atoms, the symbol R^2 attached to the 2-position represents a straight- or branched-chain alkyl group containing 7 to 24 carbon atoms, or a hydrogen atom or a straight- or branched-chain alkyl group containing 1 to 6 carbon atoms when R^2 in the 3-position is an alkyl group containing from 7 to 24 carbon atoms, and R^1 and R^3 are as hereinbefore defined, are prepared from compounds of the general formula:—

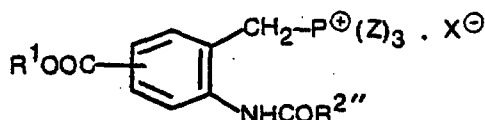


IX

- 25 (wherein R^1 and R^3 are as hereinbefore defined, R^5 represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 23 carbon atoms, and depicted R^2 represents a hydrogen atom or an alkyl group as appropriate to fit general formula I) by reduction of the carbonyl radical to methylene using, for example, borane when it is desired to obtain a product of general formula I wherein $\equiv$ represents a double bond between carbon atoms, or catalytic hydrogenation using, for example, palladium on charcoal, when it is desired to obtain a product of general formula I wherein $\equiv$ represents a single bond between carbon atoms.

The reaction with borane may be effected in an anhydrous organic solvent, for example tetrahydrofuran or ethyl acetate, at an elevated temperature, e.g. at a temperature between 50°C and the reflux temperature of the reaction mixture.

7. The indole compounds of general formula I wherein $\equiv$ represents a double bond between carbon atoms, R^1 is as hereinbefore defined, the symbol R^2 attached to the 2-position of the indole ring system represents a straight- or branched-chain alkyl group containing from 7 to 24 carbon atoms, the symbol R^2 attached to the 3-position represents a hydrogen atom, and R^3 represents a hydrogen atom, are prepared by cyclisation of a compound of the general formula:—

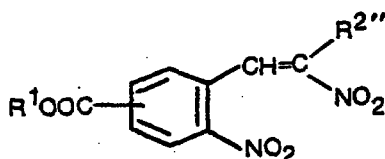


X

- 50 (wherein $X^\ominus$ represents an anion, preferably chloride, bromide or iodide, Z represents an optionally substituted phenyl group, and R^1 and $R^{2''}$ are as hereinbefore defined) in an inert organic solvent, e.g. toluene, in the presence of a base, e.g. an alkali metal alkoxide, preferably at an elevated temperature, e.g. between 80° and 150°C.

8. The indole compounds of general formula I wherein $\equiv$ represents a double bond between carbon atoms, R^1 is as hereinbefore defined, symbol R^2 attached to the 2-position of the indole ring system represents a straight- or branched-chain alkyl group containing from 7 to 24 carbon atoms, the

symbol R^2 attached to the 3-position represents a hydrogen atom, and R^3 represents a hydrogen atom, are prepared from compounds of the general formula:—

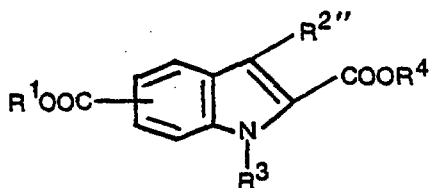


XI

(wherein R^1 and $R^{2''}$ are as hereinbefore defined) by catalytic hydrogenation, followed by cyclisation of the amine intermediate obtained.

Catalytic hydrogenation may be effected using, for example, palladium on charcoal as catalyst, optionally in the presence of glacial acetic acid, in an organic solvent or mixtures of organic solvents.

9. The indole compounds of general formula I wherein — represents a double bond between carbon atoms, R^1 is as hereinbefore defined, the symbol R^2 attached to the 3-position of the indole ring system represents a straight- or branched-chain alkyl group containing from 7 to 24 carbon atoms, the symbol R^2 attached to the 2-position represents a hydrogen atom and R^3 is as hereinbefore defined, are prepared from 2-alkoxycarbonyl derivatives of the general formula:—



XII

(wherein R^1 , $R^{2''}$, R^3 and R^4 are as hereinbefore defined) by decarboxylation with heating.

10. The carboxylic acids of general formula I (wherein R^1 represents a hydrogen atom, and R^2 and R^3 are as hereinbefore defined) are prepared by hydrolysis of the corresponding esters of formula I wherein R^2 and R^3 are as hereinbefore defined and R^1 represents an optionally substituted straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms. Preferably the hydrolysis is carried out in alkaline conditions, for example in the presence of an alkali metal hydroxide in an aqueous organic solvent system, and at an elevated temperature, e.g. in the presence of sodium hydroxide, in aqueous methanol or ethanol and at the reflux temperature.

11. The esters of general formula I (wherein R^1 represents an optionally substituted straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms, and R^2 and R^3 are as hereinbefore defined) are prepared by esterification of the corresponding carboxylic acids of general formula I wherein R^1 represents a hydrogen atom, and R^2 and R^3 are as hereinbefore defined. The esterification may be carried out by the application or adaptation of known methods, for example by reaction with an excess of the appropriate alcohol of the general formula:—



XIII

(wherein R^1 represents an optionally substituted — as hereinbefore specified — straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms) optionally as the solvent medium, and in the presence of an inorganic acid, e.g. hydrochloric acid, preferably at an elevated temperature, e.g. between 60° and 100°C or by reaction of a corresponding alkyl halide and salt of the acid.

12. The tertiary amine compounds of general formula I wherein the depicted nitrogen atom is alkylated are prepared by N-alkylation of the corresponding secondary amine compounds of general formula I (wherein R^3 represents a hydrogen atom) by the application or adaptation of known methods.

By the term "known methods" as used in this specification is meant methods heretofore used or described in the literature.

13. The compounds of general formula I may be converted, when applicable, to pharmaceutically acceptable salts, and *vice versa*, by the application or adaptation of known methods.

As well as being useful in itself, this procedure is useful for the purification of compounds of general formula I and their salts by taking advantage of differences in solubility in water and various organic solvents of the compounds and their salts and of any impurities present by means of known methods, such as crystallisation.

(i) Compounds of general formula I wherein — represents a single bond between carbon atoms may be converted to their pharmaceutically acceptable acid addition salts, for example, by reaction with the appropriate acid in solution or suspension in a suitable solvent, e.g. acetone, methanol or ethanol, followed if necessary by evaporation of part or all of the solvent, and collection of the solid salt.

(ii) On the other hand, the acid addition salts may be converted to the parent compounds of general

formula I, for example by reaction with aqueous ammonia in the presence of a suitable solvent, e.g. ethanol, followed by treatment with a weak acid, for example glacial acetic acid.

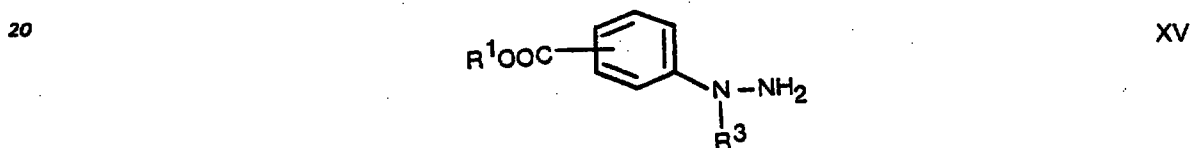
(iii) Compounds of general formula I wherein R¹ represents a hydrogen atom (R² and R³ being as hereinbefore defined) may be converted to their salts of pharmaceutically acceptable bases, for example by reaction with the appropriate base, for example the appropriate amine or a compound of the general formula:—



(wherein M¹ represents an alkali metal, e.g. sodium or potassium, and R⁶ represents an alkyl group containing from 1 to 6 carbon atoms, e.g. methyl or ethyl, or a hydrogen atom) in a suitable solvent, e.g. methanol or ethanol, or water followed if necessary by evaporation of part or all of the solvent, and collection of the solid salt.

(iv) Salts obtained as described in (iii) above may be converted to the parent acids of general formula I (wherein R¹ represents a hydrogen atom), for example by reaction with a suitable acid, e.g. glacial acetic acid, in solution in suitable solvent, e.g. water or ethanol, followed if necessary by evaporation of part or all of the solvent, and collection of the solid acid.

Compounds of general formula VI may be prepared by the reaction of a compound of the general formula:—

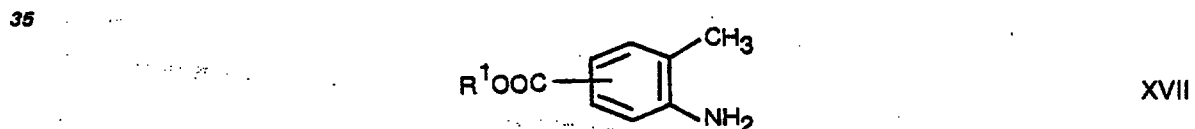


(wherein R¹ and R³ are as hereinbefore defined) with a compound of the general formula:—



(wherein the symbols R² are as hereinbefore defined) at an elevated temperature, e.g. at the reflux temperature of the reaction mixture, in an inert organic solvent, e.g. ethanol, in the presence of glacial acetic acid as catalyst, preferably under an inert atmosphere, e.g. nitrogen.

Compounds of general formula VII may be prepared by the reaction of a compound of the general formula:—

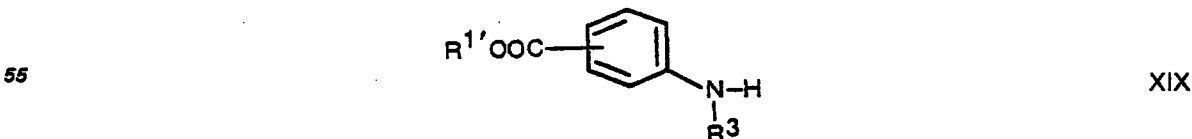


(wherein R¹ is as hereinbefore defined) with an acylating agent of the general formula:—

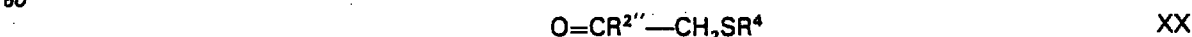


(wherein R² is as hereinbefore defined and X¹ represents a halogen, preferably chlorine, atom or a hydroxy group) optionally in an inert organic solvent, for example dimethylformamide or chloroform, at a temperature between 0°C and the reflux temperature of the reaction mixture, preferably under anhydrous conditions and optionally in the presence of an acid-binding agent, for example a trialkylamine, e.g. triethylamine or tributylamine, followed by hydrolysis of the ester to the corresponding acid.

Compounds of general formula VIII may be prepared by the reaction of a compound of the general formula:—



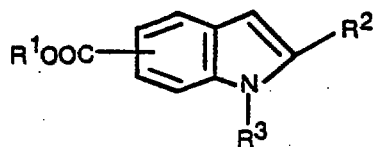
(wherein R^{1'} and R³ are as hereinbefore defined) with a compound of the general formula:—



(wherein R^{2''} and R⁴ are as hereinbefore defined) at a temperature between -65°C and ambient temperature in an inert organic solvent e.g. methylene chloride, in the presence of *tert.*-butyl hypochlorite and of organic base e.g. triethylamine.

Compounds of general formula IX may be prepared by the reaction of a compound of the general formula:—

5



XXI

10 (wherein R¹ and R³ are as hereinbefore defined and the depicted symbol R² is as hereinbefore defined for general formula IX) with a compound of the general formula:—

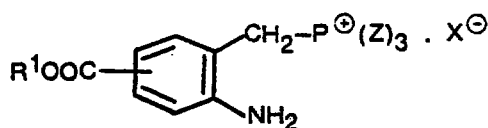


XXII

15 (wherein R⁴ and R⁵ are as hereinbefore defined) in the presence of phosphorus oxychloride at an elevated temperature, e.g. at a temperature between 50°C and 90°C.

Compounds of general formula X may be prepared by reacting a compound of the general formula:—

20



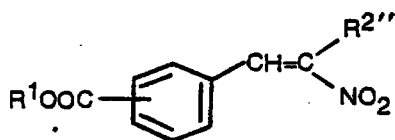
XXIII

25

(wherein R¹, X⁻ and X are as hereinbefore defined) with a compound of general formula XVIII.

Compounds of general formula XI may be prepared by nitrating a compound of the general formula:—

30



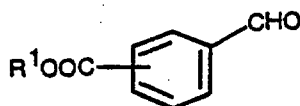
XXIV

35

wherein R¹ and R²'' are as hereinbefore defined.

Compounds of general formula XXIV may be prepared by reacting a compound of general formula:—

40



XXV

(wherein R¹ is as hereinbefore defined) with a compound of general formula:—

45



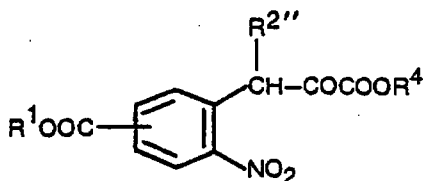
XXVI

(wherein R²'' is as hereinbefore defined) in the presence of an organic base at the reflux temperature of the reaction mixture with continuous removal of the water produced.

50

Compounds of general formula XII may be prepared from compounds of the general formula:—

55



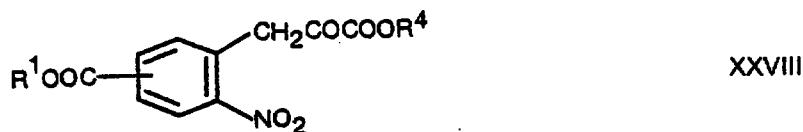
XXVII

60 (wherein R¹, R²'' and R⁴ are as hereinbefore defined) by reduction either by chemical means or by catalytic hydrogenation, followed if necessary by N-alkylation of the resulting indole compound by known methods.

Chemical reduction may be effected by zinc dust in acetic acid at an elevated temperature.

65 Catalytic hydrogenation may be effected using, for example, palladium on charcoal as catalyst in an organic solvent or mixtures thereof.

Compounds of general formula XXVII may be prepared by R²'-alkylation of the corresponding compounds of the general formula:—



10 (wherein R¹ and R⁴ are as hereinbefore defined) by the application or adaptation of known methods.
Compounds of general formula XXVIII may be prepared by reacting a compound of the general formula:



20 (wherein R¹ is as hereinbefore defined) with oxalic acid dialkyl ester in the presence of alkali metal alkoxide.

It will be understood by those skilled in the art that in the performance of the processes described above of the present invention it may be desirable to introduce chemical protecting groups into the reactants in order to avoid secondary reactions taking place, for example, in the methods of preparation of indole derivatives hereinbefore described hydroxy substituent(s) on an alkyl group R¹ as defined in relation to general formula I may have been converted into benzyloxy groups before reaction as described with subsequent removal of the protecting benzyl groups.

The following Examples illustrate the preparation of the compounds of the present invention.

Example 1

30 Compound D

A mixture of 3-(n-hexadecanamido)-4-methylbenzoic acid (6.0 g) and potassium *tert*-butoxide (22.0 g) was placed in a preheated Woods Metal bath (temperature range 240—260°C). The temperature of the bath was rapidly raised to between 290 and 305°C and was maintained within this region for 15 minutes. The mixture was then left to cool to room temperature. Water (100 ml) was added to the mixture and the resultant suspension was treated with dilute hydrochloric acid (100 ml of strength 2N) and the mixture was extracted with diethyl ether (3 x 100 ml). The organic extract was washed with water (2 x 100 ml), dried over magnesium sulphate and was evaporated *in vacuo* to give a solid. The solid was recrystallised from glacial acetic acid and then toluene to give 2-(n-pentadecyl)-indole-6-carboxylic acid (3.05 g), in the form of an off-white solid, m.p. 140—142°C.

40 (i) The 3-(n-hexadecanamido)-4-methylbenzoic acid, used as starting material, was prepared as follows:—

A stirred solution of 3-amino-4-methylbenzoic acid (15.1 g) in dry dimethylformamide (150 ml), containing triethylamine (20.2 g) was treated with n-hexadecanoyl chloride (27.5 g) during 30 minutes. The temperature of the reaction mixture was maintained at 25—45°C during the addition by water cooling. The mixture was then stirred for a further hour and was poured into water (1000 ml). The mixture was adjusted to pH 1 by the addition of concentrated hydrochloric acid (strength 36% w/v). The solid was collected, was washed with water and was recrystallised from ethanol (1500 ml) to give 3-(n-hexadecanamido)-4-methylbenzoic acid (22.0 g), in the form of a white solid, m.p. 238—240°C.

50 Example 2

Compound G

A mixture of 4-(n-hexadecanamido)-3-methylbenzoic acid (6.3 g) and potassium *tert*-butoxide (25 g) was treated in a similar manner to that described hereinbefore in Example 1 to give 2-(n-pentadecyl)indole-5-carboxylic acid (3.6 g), in the form of a white solid, m.p. 110—112°C.

55 (i) The 4-(n-hexadecanamido)-3-methylbenzoic acid, used as starting material, was prepared as follows:—

A stirred solution of 4-amino-3-methylbenzoic acid (30.2 g), in dry dimethylformamide (300 ml), containing tributylamine (55 ml) was treated with n-hexadecanoyl chloride (61.0 g) in a similar manner to that described in Example 1(i) to give 4-(n-hexadecanamido)-3-methylbenzoic acid (21 g), in the form of white needles, m.p. 194—196°C.

Example 3

Compound J

65 A mixture of 3-(n-hexadecanamido)-2-methylbenzoic acid (6.0 g) and potassium *tert*-butoxide

(23 g) was treated in a similar manner to that described hereinbefore in Example 1 to give 2-(n-pentadecyl)indole-4-carboxylic acid (3.1 g), in the form of a cream solid, m.p. 114—117°C.

(i) The 3-(n-hexadecanamido)-2-methylbenzoic acid, used as starting material, was prepared as follows:—

- 5 A stirred solution of ethyl 3-amino-2-methylbenzoate (17.9 g) in chloroform (150 ml), containing triethylamine (15 ml), was treated with a solution of n-hexadecanoyl chloride (28 g) in chloroform (50 ml), during 30 minutes. The temperature of the reaction mixture was maintained at 0—10°C during the addition by ice cooling. The mixture was then refluxed for 90 minutes, washed with water (2 x 150 ml) and was dried over magnesium sulphate. The solvent was removed *in vacuo* to give a
10 white solid, which was crystallised from ethanol. The solid was dissolved in warm ethanol (500 ml) and the solution was treated with sodium hydroxide (10 g) in water (50 ml). The mixture was then refluxed for one hour and was poured onto a mixture of crushed ice and dilute hydrochloric acid (150 ml of strength 2N). The solid was collected and was recrystallised from ethanol (1000 ml) to give 3-(n-hexadecanamido)-2-methylbenzoic acid (28 g), in the form of a white solid, m.p. 163—165°C.

15

Example 4

Compound I

- A mixture of 2-(n-hexadecanamido)-3-methylbenzoic acid (5.0 g) and potassium *tert*-butoxide (20 g) was treated in a similar manner to that described in Example 1 to give a solid, which was
20 recrystallised from methanol to give 2-(n-pentadecyl)indole-7-carboxylic acid (4.25 g), in the form of a white solid, m.p. 93—99°C.

The 2-(n-hexadecanamido)-3-methylbenzoic acid, used as starting material, was prepared as follows:—

- A stirred solution of 2-amino-3-methylbenzoic acid (31.4 g) in dry dimethylformamide (300 ml),
25 containing tributylamine (60 ml) was treated in a similar manner to that described in Example 1(i) to give 2-(n-hexadecanamido)-3-methylbenzoic acid (8.7 g), in the form of a white solid, m.p. 106—113°C.

Example 5

Compound L

- 30 A mixture of 3-(n-decanamido)-4-methylbenzoic acid (6.0 g) and potassium *tert*-butoxide (23.5 g) was treated in a similar manner to that described hereinbefore in Example 1 to give a solid which was recrystallised from ethanol to give 2-(n-nonyl)indole-6-carboxylic acid (4.1 g), in the form of colourless crystals, m.p. 166—169°C.

- (i) The 3-(n-decanamido)-4-methylbenzoic acid, used as starting material, was prepared as
35 follows:—

- A solution of 3-amino-4-methylbenzoic acid (15.1 g) and n-decanoyl chloride (19.4 g) in dry dimethylformamide (150 ml) was heated on a steam bath for 90 minutes. The solution was poured into water and the solid was collected, and recrystallised from ethanol (600 ml) to give 3-(n-decanamido)-
40 4-methylbenzoic acid (22.5 g), in the form of a white powder, m.p. 246—250°C.

Example 6

Compound A

- By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid
45 by 3-(n-tetradecanamido)-4-methylbenzoic acid, there was prepared 2-(n-tridecyl)indole-6-carboxylic acid, in the form of colourless plates, m.p. 151—153°C.

- By proceeding in a similar manner to that hereinbefore described in Example 1(i) for the preparation of 3-(n-hexadecanamido)-4-methylbenzoic acid but replacing n-hexadecanoyl chloride by n-tetradecanoyl chloride and triethylamine by tributylamine, there was prepared 3-(n-tetra-
50 decanamido)-4-methylbenzoic acid, in the form of a colorless solid, m.p. 233—235°C, used in the preparation above.

Example 7

Compound B

- By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation
55 of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 3-(n-octadecanamido)-4-methylbenzoic acid, there was prepared 2-(n-heptadecyl)indole-6-carboxylic acid, in the form of colourless crystals, m.p. 134—136°C.

- By proceeding in a similar manner to that hereinbefore described in Example 1(i) for the preparation of 3-(n-hexadecanamido)-4-methylbenzoic acid but replacing n-hexadecanoyl chloride by
60 n-octadecanoyl chloride and triethylamine by tributylamine, there was prepared 3-(n-octadecanamido)-4-methylbenzoic acid, in the form of a white powder, m.p. 228—231°C, used in the preparation above.

Example 8

Compound C

- 65 By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation

of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 3-(n-dodecanamido)-4-methylbenzoic acid, there was prepared 2-(n-undecyl)indole-6-carboxylic acid, in the form of colourless plates, m.p. 156—159°C.

- 5 By proceeding in a similar manner to that hereinbefore described in Example 3(i) for the preparation of 3-(n-hexadecanamido)-2-methylbenzoic acid but replacing ethyl 3-amino-2-methylbenzoic acid by ethyl 3-amino-4-methylbenzoic acid, n-hexadecanoyl chloride by n-dodecanoyl chloride and triethylamine by tributylamine, there was prepared 3-(n-dodecanamido)-4-methylbenzoic acid, in the form of colourless crystals, m.p. 240—243°C, used in the preparation above.

10

Example 9

Compound E

- By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 4-(n-octadecanamido)-3-methylbenzoic acid, there was prepared 2-(n-heptadecyl)indole-5-carboxylic acid, in the form of a white solid, m.p. 108—111°C.

- 15 By proceeding in a similar manner to that hereinbefore described in Example 2(i) for the preparation of 4-(n-hexadecanamido)-3-methylbenzoic acid but replacing n-hexadecanoyl chloride by n-octadecanoyl chloride, there was prepared 4-(n-octadecanamido)-3-methylbenzoic acid, in the form of a white powder, m.p. 192—196°C, used in the preparation above.

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Example 10

Compound F

- By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 4-(n-dodecanamido)-3-methylbenzoic acid, there was prepared 2-(n-undecyl)indole-5-carboxylic acid, in the form of light brown crystals, m.p. 124—126°C.

- 25 By proceeding in a similar manner to that hereinbefore described in Example 2(i) for the preparation of 4-(n-hexadecanamido)-3-methylbenzoic acid but replacing n-hexadecanoyl chloride by n-dodecanoyl chloride and tributylamine by triethylamine, there was prepared 4-(n-dodecanamido)-3-methylbenzoic acid, in the form of a colourless solid, m.p. 192—196°C, used in the preparation above.

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Example 11

Compound H

- By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 4-(n-tetradecanamido)-3-methylbenzoic acid, there was prepared 2-(n-tridecyl)indole-5-carboxylic acid, in the form of light brown crystals, m.p. 124—126°C.

- 35 By proceeding in a similar manner to that hereinbefore described in Example 2(i) for the preparation of 4-(n-hexadecanamido)-3-methylbenzoic acid but replacing n-hexadecanoyl chloride by n-tetradecanoyl chloride there was prepared 4-(n-tetradecanamido)-3-methylbenzoic acid, in the form of a white powder, m.p. 197—200°C, used in the preparation above.

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Example 12

Compound M

- By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 4-(n-undecanamido)-3-methylbenzoic acid, there was prepared 2-(n-decyl)indole-5-carboxylic acid, in the form of a light orange solid, m.p. 127—130°C.

- 50 By proceeding in a similar manner to that hereinbefore described in Example 2(i) for the preparation of 4-(n-hexadecanamido)-3-methylbenzoic acid but replacing n-hexadecanoyl chloride by n-undecanoyl chloride, there was prepared 4-(n-undecanamido)-3-methylbenzoic acid, in the form of a white solid, m.p. 197—200°C, used in the preparation above.

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Example 13

Compound N

- By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 3-(n-undecanamido)-4-methylbenzoic acid, there was prepared 2-(n-decyl)indole-6-carboxylic acid, in the form of a cream solid, m.p. 160—164°C.

- 60 By proceeding in a similar manner to that hereinbefore described in Example 1(i) for the preparation of 3-(n-hexadecanamido)-4-methylbenzoic acid but replacing n-hexadecanoyl chloride by n-undecanoyl chloride and triethylamine by tributylamine, there was prepared 3-(n-undecanamido)-4-methylbenzoic acid, in the form of a white solid, m.p. 242—246°C, used in the preparation above.

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Example 14

Compound O

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 4-(n-decanamido)-3-methylbenzoic acid, there was prepared 2-(n-nonyl)indole-5-carboxylic acid, in the form of a light brown solid, m.p. 137—141°C.

By proceeding in a similar manner to that hereinbefore described in Example 2(i) for the preparation of 4-(n-hexadecanamido)-3-methylbenzoic acid but replacing n-hexadecanoyl chloride by n-decanoyl chloride, there was prepared 4-(n-decanamido)-3-methylbenzoic acid, in the form of a colourless powder, m.p. 196—199°C, used in the preparation above.

Example 15

Compound P

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 3-(n-nonanamido)-4-methylbenzoic acid, there was prepared 2-(n-octyl)indole-6-carboxylic acid, in the form of colourless crystals, m.p. 166—169°C.

By proceeding in a similar manner to that hereinbefore described in Example 1(i) for the preparation of 3-(n-hexadecanamido)-4-methylbenzoic acid but replacing n-hexadecanoyl chloride by n-nonanoyl chloride, there was prepared 3-(n-nonanamido)-4-methylbenzoic acid, in the form of a white solid, m.p. 247—250°C, used in the preparation above.

Example 16

Compound Q

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 4-(n-octanamido)-3-methylbenzoic acid, there was prepared 2-(n-heptyl)indole-5-carboxylic acid, in the form of a light brown solid, m.p. 152—155°C.

By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing 3-amino-4-methylbenzoic acid by 4-amino-3-methylbenzoic acid and n-decanoyl chloride by n-octanoyl chloride, there was prepared 4-(n-octanamido)-3-methylbenzoic acid, in the form of colourless needles, m.p. 221—224°C, used in the preparation above.

Example 17

Compound R

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 3-(n-octanamido)-4-methylbenzoic acid, there was prepared 2-(n-heptyl)indole-6-carboxylic acid, in the form of a cream solid, m.p. 169—172°C.

By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing n-decanoyl chloride by n-octanoyl chloride, there was prepared 3-(n-octanamido)-4-methylbenzoic acid, in the form of a white solid, m.p. 246—250°C, used in the preparation above.

Example 18

Compound K

2-n-Pentadecylindole-6-carboxylic acid (16.0 g) was dissolved in a mixture of tetrahydrofuran (400 ml) and ethanol (100 ml), containing aqueous fluoroboric acid (100 ml, of strength 40% w/v). The stirred mixture was hydrogenated over platinum oxide (2.0 g) at room temperature and atmospheric pressure. After 6 hours the mixture was filtered, the residue was washed with diethyl ether (100 ml) and the combined filtrates were concentrated *in vacuo* until a solid separated. The mixture was adjusted to pH 7 by treatment with an aqueous solution of sodium hydroxide (strength 50% w/v) and was then adjusted to pH 4—5 with glacial acetic acid. The mixture was extracted with diethyl ether (3 x 100 ml), and the ether solution was dried over magnesium sulphate and, on evaporation *in vacuo*, gave a solid. The solid was recrystallised from a mixture of toluene and hexane (equal parts by volume) to give (RS)-2-(n-pentadecyl)indoline-6-carboxylic acid (7.3 g), in the form of a colourless solid, m.p. 119—122°C.

The corresponding hydrochloride salt was prepared as follows:—

A solution of (RS)-2-(n-pentadecyl)indoline-6-carboxylic acid (3.0 g) in ethanol (30 ml), was treated with a saturated solution of hydrogen chloride gas in ethanol (50 ml of strength 34% w/v). Anhydrous diethyl ether was then added to the mixture until a solid separated. The solid was collected and was washed with diethyl ether (2 x 100 ml) to give (RS)-2-(n-pentadecyl)indoline-6-carboxylic acid hydrochloride (2.7 g), in the form of a colourless solid, m.p. 230—240°C (with decomposition).

The sodium salt of (RS)-2-(n-pentadecyl)indoline-6-carboxylic acid was prepared as follows:—
(RS)-2-(n-pentadecyl)indoline-6-carboxylic acid (10.0 g) in hot ethanol (250 ml) was treated with

an aqueous sodium hydroxide solution (20 ml, of strength 10% w/v). The mixture was left to cool and a solid precipitated and was collected. The solid was washed with a little water and then acetone and was recrystallised from a mixture of ethanol and water (95:5) to give sodium (RS)-2-(n-pentadecyl)indoline-6-carboxylate (4.9 g), in the form of colourless crystals, m.p. greater than 320°C (with decomposition).

Example 19

Compound S

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 3-(n-tridecanamido)-4-methylbenzoic acid, there was prepared 2-(n-dodecyl)indole-6-carboxylic acid, in the form of a white solid, m.p. 153—156°C.

By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing n-decanoyl chloride by n-tridecanoyl chloride there was prepared 3-(n-tridecanamido)-4-methylbenzoic acid, in the form of a white solid, m.p. 243—247°C, used in the preparation above.

Example 20

Compound T

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 4-(n-nonadecanamido)-3-methylbenzoic acid, there was prepared 2-(n-octadecyl)indole-5-carboxylic acid, in the form of a white solid m.p. 116—118°C.

By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing 3-amino-4-methylbenzoic acid by 4-amino-3-methylbenzoic acid and n-decanoyl chloride by n-nonadecanoyl chloride there was prepared 4-(n-nonadecanamido)-3-methylbenzoic acid, in the form of colourless plates, m.p. 197—199°C, used in the preparation above.

Example 21

Compound U

A solution of 2-(n-undecyl)indole-5-carboxylic acid (15.0 g) in ethanol (50 ml) containing a solution of hydrogen chloride gas in ethanol (100 ml of strength 34% w/v) was refluxed for 3 hours. The solution was poured onto a mixture of crushed ice and water and the precipitated solid was collected. Recrystallisation from ethanol (100 ml) with charcoal treatment gave ethyl 2-(n-undecyl)indole-5-carboxylate (7.5 g), in the form of white crystals, m.p. 76—77°C.

Example 22

Compound AA

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 4-(n-heneicosanamido)-3-methylbenzoic acid, there was prepared 2-(n-eicosyl)indole-5-carboxylic acid, in the form of a buff solid, m.p. 110—112°C.

By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing 3-amino-4-methylbenzoic acid by 4-amino-3-methylbenzoic acid and n-decanoyl chloride by n-heneicosanoyl chloride, there was prepared 4-(n-heneicosanamido)-3-methylbenzoic acid, in the form of a buff solid, m.p. 189—193°C, used in the preparation above.

Example 23

Compound V

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 3-(n-nonadecanamido)-4-methylbenzoic acid there was prepared 2-(n-octadecyl)indole-6-carboxylic acid, in the form of a pale yellow solid, m.p. 129—131°C.

By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing n-decanoyl chloride by a n-nonadecanoyl chloride there was prepared 3-(n-nonadecanamido)-4-methylbenzoic acid, in the form of a buff solid m.p. 233—236°C, used in the preparation above.

Example 24

Compound W

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 3-(n-dodecanamido)-2-methylbenzoic acid, there was prepared 2-(n-undecyl)indole-4-carboxylic acid, in the form of a cream solid, m.p. 108—111°C.

By proceeding in a similar manner to that hereinbefore described in Example 3(i) for the preparation of 3-(n-hexadecanamido)-2-methylbenzoic acid but replacing n-hexadecanoyl chloride by n-dodecanoyl chloride, there was prepared 3-(n-dodecanamido)-2-methylbenzoic acid, in the form of a white powder, m.p. 162—166°C, used in the preparation above.

Example 25

Compound X

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 4-(n-nonanamido)-3-methylbenzoic acid, there was prepared 2-(n-octyl)indole-5-carboxylic acid, in the form of a cream solid, m.p. 136—138°C.

By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing 3-amino-4-methylbenzoic acid by 4-amino-3-methylbenzoic acid and n-decanoyl chloride by n-nonanoyl chloride there was prepared 4-(n-nonanamido)-3-methylbenzoic acid, in the form of a white crystalline solid, m.p. 196—199°C, used in the preparation above.

Example 26

Compound Y

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 4-(n-tridecanamido)-3-methylbenzoic acid, there was prepared 2-(n-dodecyl)indole-5-carboxylic acid, in the form of a cream solid, m.p. 114—117°C.

By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing 3-amino-4-methylbenzoic acid by 4-amino-3-methylbenzoic acid and n-decanoyl chloride by n-tridecanoyl chloride, there was prepared 4-(n-tridecanamido)-3-methylbenzoic acid, in the form of a white crystalline solid, m.p. 201—203°C, used in the preparation above.

Example 27

Compound Z

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 3-(n-decanamido)-2-methylbenzoic acid, there was prepared 2-(n-nonyl)indole-4-carboxylic acid, in the form of a pale yellow solid, m.p. 92—94°C.

By proceeding in a similar manner to that hereinbefore described in Example 3(i) for the preparation of 3-(n-hexadecanamido)-2-methylbenzoic acid but replacing n-hexadecanoyl chloride by n-decanoyl chloride there was prepared 3-(n-decanamido)-2-methylbenzoic acid, in the form of a cream solid, m.p. 160—164°C, used in the preparation above.

Example 28

Compound CC

A solution of 2-(n-dodecyl)indole-6-carboxylic acid (14.0 g) in ethanol (70 ml) containing a solution of hydrogen chloride gas in ethanol (100 ml, of strength 35% w/v) was refluxed for 5 hours. The solid, which crystallised on cooling, was collected, washed with light petroleum ether (b.p. 40°—60°C) and was recrystallised from ethanol to give ethyl 2-(n-dodecyl)indole-6-carboxylate (9.1 g), in the form of a pale pink solid, m.p. 83—86°C.

Example 29

Compound DD

A solution of 2-(n-heptyl)indole-5-carboxylic acid (18.4 g) in ethanol (80 ml) containing a solution of hydrogen chloride gas in ethanol (110 ml, of strength 34% w/v) was refluxed for 6 hours. The solution was poured into water and the solid was collected and was recrystallised from methanol to give ethyl 2-(n-heptyl)indole-5-carboxylate (10.7 g), in the form of buff crystals, m.p. 66—69°C.

Example 30

Compound EE

A solution of 2-(n-pentadecyl)indole-4-carboxylic acid (15 g) in ethanol (100 ml) containing a solution of hydrogen chloride gas in ethanol (100 ml, of strength 35% w-v) was refluxed for 6 hours. After cooling, the solution was poured into water and the solid was collected and was recrystallised from methanol to give ethyl 2-(n-pentadecyl)indole-4-carboxylate (12.4 g), in the form of a pale yellow solid, m.p. 42—45°C.

Example 31

Compound JJ

A solution of 2-(n-undecyl)indole-6-carboxylic acid (15.0 g) in methanol (200 ml) containing aqueous hydrochloric acid (10 ml) of strength 36.5% w/v) was refluxed for 8 hours. The solution was

concentrated *in vacuo* to about one half of its volume, diluted with diethyl ether (300 ml) and washed with water. The solution was dried over magnesium sulphate, then evaporated *in vacuo* and the residue was recrystallised from methanol to give methyl 2-(n-undecyl)indole-6-carboxylate (10.5 g), in the form of an off-white powder, m.p. 84—86°C.

5

Example 32

Compound KK

A solution of 2-(n-dodecyl)indole-5-carboxylic acid (15.0 g) in n-butanol (100 ml) containing aqueous hydrochloric acid (10 ml of strength 36.5% w/v) was heated on a steam bath for 8 hours. The solution was concentrated *in vacuo* to about one half of its volume, diethyl ether (300 ml) was added, and the solution was washed with water and was dried over magnesium sulphate. Evaporation of the solvent *in vacuo* gave a residue which was recrystallised from methanol to give n-butyl 2-(n-dodecyl)indole-5-carboxylate (9.6 g), in the form of an off-white powder, m.p. 74—76°C.

15

Example 33

Compound II

A solution of 2-(n-dodecyl)indole-5-carboxylic acid (13.8 g) in ethanol (80 ml) containing a solution of hydrogen chloride gas in ethanol (100 ml of strength 39% w/v) was refluxed for 6 hours. The solid which separated on cooling was collected and was recrystallised from ethanol to give ethyl 2-(n-dodecyl)indole-5-carboxylate (11.2 g), in the form of a buff powder, m.p. 77—79°C.

20

Example 34

Compound HH

A solution of 2-(n-pentadecyl)indole-5-carboxylic acid (17.4 g) in n-butanol (100 ml) containing aqueous hydrochloric acid (10 ml of strength 36.5% w/v) was heated in a steam bath for 18 hours. The solution was concentrated *in vacuo* to about one half of its volume and the residue was dissolved in diethyl ether. The ethereal solution was washed with water (2 x 50 ml) and was dried over magnesium sulphate. Evaporation of the solvent *in vacuo* gave a solid, which was recrystallised from light petroleum ether (b.p. 40—60°C) and then from methanol to give n-butyl 2-(n-pentadecyl)indole-5-carboxylate (12.2 g), in the form of a white powder, m.p. 79—80°C.

30

Example 35

Compound GG

A solution of 2-(n-undecyl)indole-6-carboxylic acid (15.0 g) in n-butanol (100 ml) containing aqueous hydrochloric acid (10 ml, of strength 36.5% w/v) was heated on a steam bath for 16 hours. The solution was concentrated *in vacuo* to approximately half of its volume and the solid which crystallised on cooling was collected and washed with light petroleum ether (b.p. 40°—60°C) to give n-butyl 2-(n-undecyl)indole-6-carboxylate (11.3 g), in the form of white crystals, m.p. 73—76°C.

40

Example 36

Compound FF

A solution of 2-(n-undecyl)indole-6-carboxylic acid (11.9 g) in ethanol (50 ml) containing a solution of hydrogen chloride gas in ethanol (75 ml, of strength 39% w/v) was refluxed for 4.5 hours. The solution was cooled and a solid was collected which was dissolved in diethyl ether, and the ethereal solution was washed with water (2 x 100 ml) and dried over magnesium sulphate. The solvent was removed *in vacuo* to give a residue which was recrystallised from methanol to give ethyl 2-(n-undecyl)indole-6-carboxylic acid (6.2 g), in the form of very pale yellow needles, m.p. 84—86°C.

50

Example 37

Compound LL

A solution of 2-(n-pentadecyl)indole-5-carboxylic acid (15.0 g) in methanol (100 ml) containing aqueous hydrochloric acid (10 ml, of strength 36.5% w/v) was refluxed for 5 hours. After cooling, the mixture was dissolved in a mixture of diethyl ether and tetrahydrofuran (1:1). The solution was washed with water (2 x 50 ml), dried over sodium sulphate, evaporated *in vacuo*, and the residue was recrystallised from methanol to give methyl 2-(n-pentadecyl)indole-5-carboxylate (12.2 g), in the form of an off-white powder, m.p. 89—92°C.

60

Example 38

Compound BB

By proceeding in a similar manner to that hereinbefore described in Example 33 for the preparation of ethyl 2-(n-dodecyl)indole-5-carboxylate but replacing 2-(n-dodecyl)indole-5-carboxylic acid by 2-(n-pentadecyl)indole-5-carboxylic acid, there was prepared ethyl 2-(n-pentadecyl)indole-5-carboxylate, in the form of off-white crystals m.p. 88—91°C.

65

Example 39

Compound D

- 5 A solution of 2-(n-pentadecyl)indole-6-carboxylic acid (15.0 g) in hot ethanol (100 ml) was treated with a solution of sodium hydroxide (2.0 g) in water (50 ml), and a white precipitate was obtained. The precipitate was recrystallised from aqueous ethanol (1:1) (300 ml) to give sodium 2-(n-pentadecyl)indole-6-carboxylate (14.8 g), in the form of white crystals, m.p. greater than 340°C.

Example 40

Compound C

- 10 By proceeding in a similar manner to that hereinbefore described in Example 39 for the preparation of sodium 2-(n-pentadecyl)indole-6-carboxylate but replacing 2-(n-pentadecyl)indole-6-carboxylic acid by 2-(n-undecyl)indole-6-carboxylic acid there was prepared sodium 2-(n-undecyl)indole-6-carboxylate, in the form of colourless needles, m.p. greater than 340°C.

Example 41

Compound MM

- 15 By proceeding in a similar manner to that hereinbefore described in Example 35 for the preparation of n-butyl 2-(n-undecyl)indole-6-carboxylate but replacing 2-(n-undecyl)indole-6-carboxylic acid by 2-(n-pentadecyl)indole-4-carboxylic acid, there was prepared n-butyl 2-(n-pentadecyl)indole-4-carboxylate, in the form of an off-white solid, m.p. 40—42°C.

Example 42

Compound NN

- 25 By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 4-(n-pentadecanamido)-3-methylbenzoic acid, there was prepared 2-(n-tetradecyl)indole-5-carboxylic acid, in the form of a buff solid, m.p. 117—120°C.

- 30 By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing n-decanoyl chloride by n-pentadecanoyl chloride and 3-amino-4-methylbenzoic acid by 4-amino-3-methylbenzoic acid, there was prepared 4-(n-pentadecanamido)-3-methylbenzoic acid, in the form of a white solid, m.p. 198—201°C, used in the preparation above.

Example 43

Compound OO

- 35 By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 4-(n-heptadecanamido)-3-methylbenzoic acid, there was prepared 2-(n-hexadecyl)indole-5-carboxylic acid, in the form of a buff solid, m.p. 108—110°C.

- 40 By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing n-decanoyl chloride by n-heptadecanoyl chloride and 3-amino-4-methylbenzoic acid by 4-amino-3-methylbenzoic acid, there was prepared 4-(n-heptadecanamido)-3-methylbenzoic acid, in the form of an off-white solid, m.p. 197—200°C, used in the preparation above.

45

Example 44

Compound PP

- 50 By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 4-(n-eicosanamido)-3-methylbenzoic acid, there was prepared 2-(n-nonadecyl)indole-5-carboxylic acid, in the form of a white solid, m.p. 110—111°C.

- 55 By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing n-decanoyl chloride by n-eicosanoyl chloride and 3-amino-4-methylbenzoic acid by 4-amino-3-methylbenzoic acid, there was prepared 4-(n-eicosanamido)-3-methylbenzoic acid, in the form of a white solid, m.p. 193—196°C, used in the preparation above.

Example 45

Compound QQ

- 60 By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 4-(n-tetracosanamido)-3-methylbenzoic acid, there was prepared 2-(n-tricosyl)indole-5-carboxylic acid, in the form of a buff solid, m.p. 112—114°C.

- 65 By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing n-decanoyl chloride by n-tetra-

cosanoyl chloride and 3-amino-4-methylbenzoic acid by 4-amino-3-methylbenzoic acid, there was prepared 4-(n-tetracosanamido)-3-methylbenzoic acid, in the form of a buff solid, m.p. 184—189°C, used in the preparation above.

5

Example 46

Compound RR

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by (RS)-4-(2-methylundecanamido)-3-methylbenzoic acid, there was prepared (RS)-2-(1-methyl-
10 decyl)indole-5-carboxylic acid, in the form of a cream solid, m.p. 103—106°C.

By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing n-decanoyl chloride by (RS)-2-methylundecanoyl chloride and 3-amino-4-methylbenzoic acid by 4-amino-3-methylbenzoic acid there was prepared (RS)-4-(2-methylundecanamido)-3-methylbenzoic acid, in the form of an off-white solid,
15 m.p. 186—190°C, used in the preparation above.

Example 47

Compound SS

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 3-(n-pentadecanamido)-4-methylbenzoic acid, there was prepared 2-(n-tetradecyl)indole-6-
20 carboxylic acid, in the form of an off-white solid, m.p. 147—150°C.

By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing n-decanoyl chloride by n-penta-
25 decanoyl chloride, there was prepared 3-(n-pentadecanamido)-4-methylbenzoic acid, in the form of an off-white solid, m.p. 238—241°C, used in the preparation above.

Example 48

Compound TT

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 3-(n-heptadecanamido)-4-methylbenzoic acid, there was prepared 2-(n-hexadecyl)indole-6-
30 carboxylic acid, in the form of a yellow solid, m.p. 136—140°C.

By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing n-decanoyl chloride by n-hepta-
35 decanoyl chloride, there was prepared 3-(n-heptadecanamido)-4-methylbenzoic acid, in the form of a white solid, m.p. 238—240°C, used in the preparation above.

Example 49

Compound UU

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 3-(n-heneicosanamido)-4-methylbenzoic acid, there was prepared 2-(n-eicosyl)indole-6-carboxylic
40 acid, in the form of an off-white solid, m.p. 133—135°C.

By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing n-decanoyl chloride by n-heneico-
45 sanoyl chloride there was prepared 3-(n-heneicosanamido)-4-methylbenzoic acid, in the form of a white solid, m.p. 230—234°C, used in the preparation above.

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Example 50

Compound VV

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by (RS)-3-(2-methylundecanamido)-4-methylbenzoic acid, there was prepared (RS)-2-(1-methyl-
55 decyl)indole-6-carboxylic acid, in the form of a cream solid, m.p. 81—84°C.

By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing n-decanoyl chloride by (RS)-2-methylundecanoyl chloride, there was prepared (RS)-3-(2-methylundecanamido)-4-methylbenzoic acid,
60 in the form of a white solid, m.p. 233—236°C, used in the preparation above.

Example 51

Compound WW

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid
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by 2-(n-decanamido)-3-methylbenzoic acid, there was prepared 2-(n-nonyl)indole-7-carboxylic acid, in the form of a white solid, m.p. 152—155°C.

- By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing 3-amino-4-methylbenzoic acid by 2-amino-3-methylbenzoic acid, there was prepared 2-(n-decanamido)-3-methylbenzoic acid, in the form of a white solid, m.p. 114—116°C, used in the preparation above.

Example 52

Compound XX

- By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by 2-(n-dodecanamido)-3-methylbenzoic acid, there was prepared 2-(n-undecyl)indole-7-carboxylic acid, in the form of a white solid, m.p. 155—159°C.

- By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing n-decanoyl chloride by n-dodecanoyl chloride and 3-amino-4-methylbenzoic acid by 2-amino-3-methylbenzoic acid, there was prepared 2-(n-dodecanamido)-3-methylbenzoic acid, in the form of a white solid, m.p. 114—116°C, used in the preparation above.

Example 53

Compound S

- By proceeding in a similar manner to that hereinbefore described in Example 39 for the preparation of sodium 2-(n-pentadecyl)indole-6-carboxylate but replacing 2-(n-pentadecyl)indole-6-carboxylic acid by 2-(n-dodecyl)indole-6-carboxylic acid, there was prepared sodium 2-(n-dodecyl)indole-6-carboxylate hydrate in the form of colourless needles, m.p. greater than 340°C.

Example 54

Compound L

- By proceeding in a similar manner to that hereinbefore described in Example 39 for the preparation of sodium 2-(n-pentadecyl)indole-6-carboxylate but replacing 2-(n-pentadecyl)indole-6-carboxylic acid by 2-(n-nonyl)indole-6-carboxylic acid, there was prepared sodium 2-(n-nonyl)indole-6-carboxylate, in the form of colourless needles, m.p. greater than 340°C.

Example 55

Compound G

- By proceeding in a similar manner to that hereinbefore described in Example 39 for the preparation of sodium 2-(n-pentadecyl)indole-6-carboxylate but replacing 2-(n-pentadecyl)indole-6-carboxylic acid by 2-(n-pentadecyl)indole-5-carboxylic acid and ethanol by acetone, there was prepared sodium 2-(n-pentadecyl)indole-5-carboxylate, in the form of colourless needles, m.p. greater than 320°C.

Example 56

Compound YY

- 2-(n-Undecyl)indole-5-carboxylic acid (45 g) was added to a mixture of tetrahydrofuran (250 ml), glacial acetic acid (50 ml) and perchloric acid (25 ml of strength 70% w/v). The mixture was hydrogenated over palladium on charcoal (5% w/w, 5 g) at room temperature and atmospheric pressure. When hydrogen uptake had ceased (after 6 hours), the mixture was filtered through diatomaceous earth, and the residue was washed with tetrahydrofuran (2 x 50 ml). The combined filtrates were adjusted to pH 4 by treatment with an aqueous solution of sodium hydroxide (strength 50% w/v). The mixture was diluted with water (200 ml) and was extracted with diethyl ether (3 x 200 ml). The diethyl ether solution was dried over magnesium sulphate and, on evaporation *in vacuo* gave a solid. The solid was dissolved in diethyl ether (100 ml) and the solution was treated with an excess of a solution of hydrogen chloride in ethanol (strength 38% w/v, 30 ml). The mixture was diluted with diethyl ether (1000 ml) and a solid was collected. The solid was recrystallised from isopropanol to give (RS)-2-(n-undecyl)indoline-5-carboxylic acid hydrochloride (27.6 g), in the form of a white solid m.p. 175—179°C (with decomposition).

The corresponding parent indoline was prepared as follows:—

- (RS)-2-(n-undecyl)indoline-5-carboxylic acid hydrochloride (32.9 g) in ethanol (150 ml) containing sodium hydroxide (10 g) and water (38 ml) was stirred and refluxed for 1.5 hours. Glacial acetic acid (15 ml) was added to the hot solution and the mixture was cooled to 0°C and then diluted with water (600 ml). The solid was collected and was recrystallised from methanol to give (RS)-2-(n-undecyl)indoline-5-carboxylic acid (25.7 g), in the form of a white solid, m.p. 99—103°C.

- By proceeding in a similar manner to that hereinbefore described in Example 18 for the preparation of sodium (RS)-2-(n-pentadecyl)indoline-6-carboxylate but replacing (RS)-2-(n-pentadecyl)indoline-6-carboxylic acid by (RS)-2-(n-undecyl)indoline-5-carboxylic acid there was prepared sodium (RS)-2-(n-undecyl)indoline-5-carboxylate, in the form of a buff solid, m.p. greater than 300°C.

Example 57

Compound ZZ

A mixture of 2-(n-decyl)indole-6-carboxylic acid (62.5 g), perchloric acid (40 ml of strength 70% w/v) and glacial acetic acid (400 ml) were hydrogenated over palladium on charcoal (5% w/w, 8.0 g) at 80—90°C and atmospheric pressure. When hydrogen uptake had ceased (after 4 hours) the hot mixture was filtered and the residue was washed with hot (80°C) glacial acetic acid (500 ml). The combined filtrates were concentrated *in vacuo* to 450 ml and were poured onto ice (1000 g). The mixture was adjusted to pH 9 by treatment with an aqueous solution of sodium hydroxide (strength 50% w/v) and was then adjusted to pH 4—5 with glacial acetic acid. The solid was collected, was washed with water (3 x 100 ml) and was dried. The solid was dissolved in boiling ethanol, treated with charcoal, and the solution was filtered. The filtrate was treated with an excess of a solution of hydrogen chloride in ethanol (90 ml of strength 37% w/v) and then the mixture was cooled and diluted with diethyl ether (750 ml). The solid was collected and treated as in Example 56 to give (RS)-2-(n-decyl)-indoline-6-carboxylic acid (47.4 g), in the form of a buff solid, m.p. 123—125°C.

By proceeding in a similar manner to that hereinbefore described in Example 18 for the preparation of (RS)-2-(n-pentadecyl)indoline-6-carboxylic acid hydrochloride but replacing (RS)-2-(n-pentadecyl)indoline-6-carboxylic acid by (RS)-2-(n-decyl)indoline-6-carboxylic acid there was prepared (RS)-2-(n-decyl)indoline-6-carboxylic acid hydrochloride, in the form of a white solid, m.p. 247—250°C with decomposition.

Example 58

Compound AAA

Perchloric acid (3 ml) was added to a hot solution of 2-(n-pentadecyl)indole-5-carboxylic acid in glacial acetic acid (60 ml) and the mixture was hydrogenated at normal pressure using palladium on charcoal (5% w/w, 0.7 g) as catalyst. After 3.5 hours the hot mixture was filtered and the residue was washed with hot glacial acetic acid (30 ml). The pH of the combined filtrates was adjusted to 6 with 10% w/v sodium hydroxide solution. The mixture was extracted with diethyl ether (2 x 75 ml) and the ether solution was dried over magnesium sulphate. The solution was treated with a saturated solution of hydrogen chloride gas in ethanol to precipitate the hydrochloride. The solid was collected and recrystallised from isopropanol to give (RS)-2-(n-pentadecyl)indoline-5-carboxylic acid hydrochloride (5.6 g) as a white solid, m.p. 165—170°C with decomposition.

(RS)-2-(n-pentadecyl)indoline-5-carboxylic acid was prepared by treating a stirred suspension of hydrochloride salt (12.3 g) in water (100 ml) with a solution of sodium bicarbonate (3 g) in water (100 ml). The mixture was extracted with diethyl ether (2 x 100 ml) and the ether solution was dried over magnesium sulphate. Evaporation of the ether solution *in vacuo* gave (RS)-2-(n-pentadecyl)indoline-5-carboxylic acid (10.7 g) as a white solid m.p. 102—104°C.

Example 59

Compound ABB

By proceeding in a similar manner to that hereinbefore described in Example 57 for the preparation of (RS)-2-(n-decyl)indoline-6-carboxylic acid but replacing 2-(n-decyl)indole-6-carboxylic acid by 2-(n-heptyl)indole-5-carboxylic acid, there was prepared (RS)-2-(n-heptyl)indoline-5-carboxylic acid, in the form of a white solid, m.p. 109—112°C.

Example 60

Compound ACC

By proceeding in a similar manner to that hereinbefore described in Example 57 for the preparation of (RS)-2-(n-decyl)indoline-6-carboxylic acid but replacing 2-(n-decyl)indole-6-carboxylic acid by 2-(n-decyl)indole-5-carboxylic acid there was prepared (RS)-2-(n-decyl)indoline-5-carboxylic acid, in the form of a buff solid, m.p. 110—112°C.

By proceeding in a similar manner to that hereinbefore described in Example 18 for the preparation of (RS)-2-(n-pentadecyl)indoline-6-carboxylic acid hydrochloride but replacing (RS)-2-(n-pentadecyl)indoline-6-carboxylic acid by (RS)-2-(n-decyl)indoline-5-carboxylic acid, there was prepared (RS)-2-(n-decyl)indoline-5-carboxylic acid hydrochloride, in the form of a white solid, m.p. 182—184°C with decomposition.

Example 61

Compound ADD

By proceeding in a similar manner to that hereinbefore described in Example 56 for the preparation of (RS)-2-(n-undecyl)indoline-5-carboxylic acid hydrochloride but replacing 2-(n-undecyl)indole-5-carboxylic acid by 2-(n-heptyldecyl)indole-5-carboxylic acid there was prepared (RS)-2-(n-heptadecyl)indoline-5-carboxylic acid, in the form of a tan solid, m.p. 101—103°C.

Example 62

Compound AEE

By proceeding in a similar manner to that hereinbefore described in Example 57 for the

preparation of (RS)-2-(n-decyl)indoline-6-carboxylic acid but replacing 2-(n-decyl)indole-6-carboxylic acid by 2-(n-heptyl)indole-6-carboxylic acid there was prepared (RS)-2-(n-heptyl)indoline-6-carboxylic acid, in the form of a cream solid, m.p. 139—142°C.

- By proceeding in a similar manner to that hereinbefore described in Example 18 for the preparation of (RS)-2-(n-pentadecyl)indoline-6-carboxylic acid hydrochloride but replacing (RS)-2-(n-pentadecyl)indoline-6-carboxylic acid by (RS)-2-(n-heptyl)indoline-6-carboxylic acid, there was prepared (RS)-2-(n-heptyl)indoline-6-carboxylic acid hydrochloride, in the form of a white solid, m.p. 255—260°C with decomposition.

10 Example 63

Compound AFF

- By proceeding in a similar manner to that hereinbefore described in Example 56 for the preparation of (RS)-2-(n-undecyl)indoline-5-carboxylic acid hydrochloride but replacing 2-(n-undecyl)indole-5-carboxylic acid by 2-(n-undecyl)indole-6-carboxylic acid there was prepared (RS)-2-(n-undecyl)indoline-6-carboxylic acid, in the form of a pale orange solid, m.p. 120—123°C.

- By proceeding in a similar manner to that hereinbefore described in Example 18 for the preparation of (RS)-2-(n-pentadecyl)indoline-6-carboxylic acid hydrochloride but replacing (RS)-2-(n-pentadecyl)indoline-6-carboxylic acid by (RS)-2-(n-undecyl)indoline-6-carboxylic acid there was prepared (RS)-2-(n-undecyl)indoline-6-carboxylic acid hydrochloride, in the form of a white solid, m.p. 232—234°C with decomposition.

- By proceeding in a similar manner to that hereinbefore described in Example 18 for the preparation of sodium (RS)-2-(n-pentadecyl)indoline-6-carboxylate but replacing (RS)-2-(n-pentadecyl)indoline-6-carboxylic acid by (RS)-2-(n-undecyl)indoline-6-carboxylic acid there was prepared sodium (RS)-2-(n-undecyl)indoline-6-carboxylate, in the form of a white powder, m.p. greater than 300°C.

Example 64

Compound AGG

- By proceeding in a similar manner to that hereinbefore described in Example 56 for the preparation of (RS)-2-(n-undecyl)indoline-5-carboxylic acid hydrochloride but replacing 2-(n-undecyl)indole-5-carboxylic acid by 2-(n-tetradecyl)indole-6-carboxylic acid, there was prepared (RS)-2-(n-tetradecyl)indoline-6-carboxylic acid, in the form of a pale yellow solid, m.p. 117—119°C.

- By proceeding in a similar manner to that hereinbefore described in Example 18 for the preparation of (RS)-2-(n-pentadecyl)indoline-6-carboxylic acid hydrochloride but replacing (RS)-2-(n-pentadecyl)indoline-6-carboxylic acid by (RS)-2-(n-tetradecyl)indoline-6-carboxylic acid, there was prepared (RS)-2-(n-tetradecyl)indoline-6-carboxylic acid hydrochloride, in the form of a white solid, m.p. 244—250°C with decomposition.

Example 65

Compound AHH

- By proceeding in a similar manner to that hereinbefore described in Example 33 for the preparation of ethyl 2-(n-dodecyl)indole-5-carboxylate but replacing 2-(n-dodecyl)indole-5-carboxylic acid by (RS)-2-(n-undecyl)indoline-6-carboxylic acid (prepared as described hereinbefore in Example 63), there was prepared (RS)-ethyl 2-(n-undecyl)indoline-6-carboxylate hydrochloride, in the form of a pale pink solid, m.p. 136—138°C.

Example 66

Compound All

- By proceeding in a similar manner to that hereinbefore described in Example 31 for the preparation of methyl 2-(n-undecyl)indole-6-carboxylate but replacing 2-(n-undecyl)indole-6-carboxylic acid by 2-(n-heptyl)indole-6-carboxylic acid, there was prepared methyl 2-(n-heptyl)indole-6-carboxylate, in the form of an off-white solid, m.p. 86—89°C.

Example 67

Compound AJJ

- By proceeding in a similar manner to that hereinbefore described in Example 33 for the preparation of ethyl 2-(n-dodecyl)indole-5-carboxylate but replacing 2-(n-dodecyl)indole-5-carboxylic acid by 2-(n-heptyl)indole-6-carboxylic acid there was prepared ethyl 2-(n-heptyl)indole-6-carboxylate, in the form of a yellow solid, m.p. 83—86°C.

60 Example 68

Compound AKK

- By proceeding in a similar manner to that hereinbefore described in Example 35 for the preparation of n-butyl 2-(n-undecyl)indole-6-carboxylate but replacing 2-(n-undecyl)indole-6-carboxylic acid by 2-(n-heptyl)indole-6-carboxylic acid, there was prepared n-butyl 2-(n-heptyl)indole-6-carboxylate, in the form of an off-white solid, m.p. 79—83°C.

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Example 69

Compound ALL

By proceeding in a similar manner to that hereinbefore described in Example 35 for the preparation of n-butyl 2-(n-undecyl)indole-6-carboxylate but replacing 2-(n-undecyl)indole-6-carboxylic acid by 2-(n-dodecyl)indole-6-carboxylic acid, there was prepared n-butyl 2-(n-dodecyl)indole-6-carboxylate, in the form of an off-white solid, m.p. 72—74°C.

Example 70

Compound AMM

By proceeding in a similar manner to that hereinbefore described in Example 33 for the preparation of ethyl 2-(n-dodecyl)indole-5-carboxylate but replacing 2-(n-dodecyl)indole-5-carboxylic acid by 2-(n-tridecyl)indole-6-carboxylic acid, there was prepared ethyl 2-(n-tridecyl)indole-6-carboxylate, in the form of a buff solid, m.p. 83—85°C.

Example 71

Compound ANN

By proceeding in a similar manner to that hereinbefore described in Example 31 for the preparation of methyl 2-(n-undecyl)indole-6-carboxylate but replacing 2-(n-undecyl)indole-6-carboxylic acid by 2-(n-pentadecyl)indole-6-carboxylic acid, there was prepared methyl 2-(n-pentadecyl)indole-6-carboxylate, in the form of a white solid, m.p. 90—91°C.

Example 72

Compound AOO

By proceeding in a similar manner to that hereinbefore described in Example 33 for the preparation of ethyl 2-(n-dodecyl)indole-5-carboxylate but replacing 2-(n-dodecyl)indole-5-carboxylic acid by 2-(n-pentadecyl)indole-6-carboxylic acid, there was prepared ethyl 2-(n-pentadecyl)indole-6-carboxylate, in the form of a white solid, m.p. 90—92°C.

Example 73

Compound APP

By proceeding in a similar manner to that hereinbefore described in Example 35 for the preparation of n-butyl 2-(n-undecyl)indole-6-carboxylate but replacing 2-(n-undecyl)indole-6-carboxylic acid by 2-(n-pentadecyl)indole-6-carboxylic acid, there was prepared n-butyl 2-(n-pentadecyl)indole-6-carboxylate, in the form of a white solid, m.p. 76—79°C.

Example 74

Compound AQQ

By proceeding in a similar manner to that hereinbefore described in Example 35 for the preparation of n-butyl 2-(n-undecyl)indole-6-carboxylate but replacing 2-(n-undecyl)indole-6-carboxylic acid by 2-(n-eicosyl)indole-6-carboxylic acid, there was prepared n-butyl 2-(n-eicosyl)indole-6-carboxylate, in the form of a white solid, m.p. 91—94°C.

Example 75

Compound ARR

By proceeding in a similar manner to that hereinbefore described in Example 35 for the preparation of n-butyl 2-(n-undecyl)indole-6-carboxylate but replacing 2-(n-undecyl)indole-6-carboxylic acid by 2-(n-heptyl)indole-5-carboxylic acid, there was prepared n-butyl 2-(n-heptyl)indole-5-carboxylate, in the form of an off-white solid, m.p. 71—74°C.

Example 76

Compound ASS

By proceeding in a similar manner to that hereinbefore described in Example 31 for the preparation of methyl 2-(n-undecyl)indole-6-carboxylate but replacing 2-(n-undecyl)indole-6-carboxylic acid by 2-(n-heptyl)indole-5-carboxylic acid, there was prepared methyl 2-(n-heptyl)indole-5-carboxylate, in the form of an off-white solid, m.p. 85—88°C.

Example 77

Compound ATT

By proceeding in a similar manner to that hereinbefore described in Example 31 for the preparation of methyl 2-(n-undecyl)indole-6-carboxylate but replacing 2-(n-undecyl)indole-6-carboxylic acid by 2-(n-undecyl)indole-5-carboxylic acid, there was prepared methyl 2-(n-undecyl)indole-5-carboxylate, in the form of an off-white solid, m.p. 78—81°C.

Example 78

Compound AUU

By proceeding in a similar manner to that hereinbefore described in Example 35 for the

preparation of *n*-butyl 2-(*n*-undecyl)indole-6-carboxylate but replacing 2-(*n*-undecyl)indole-6-carboxylic acid by 2-(*n*-undecyl)indole-5-carboxylic acid, there was prepared *n*-butyl 2-(*n*-undecyl)indole-5-carboxylate, in the form of a buff solid, m.p. 68—70°C.

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Example 79

Compound AVV

By proceeding in a similar manner to that hereinbefore described in Example 31 for the preparation of methyl 2-(*n*-undecyl)indole-6-carboxylate but replacing 2-(*n*-undecyl)indole-6-carboxylic acid by 2-(*n*-dodecyl)indole-5-carboxylic acid, there was prepared methyl 2-(*n*-dodecyl)indole-5-carboxylate, in the form of an off-white solid, m.p. 80—83°C.

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Example 80

Compound AWW

By proceeding in a similar manner to that hereinbefore described in Example 31 for the preparation of methyl 2-(*n*-undecyl)indole-6-carboxylate but replacing 2-(*n*-undecyl)indole-6-carboxylic acid by 2-(*n*-heptadecyl)indole-5-carboxylic acid, there was prepared methyl 2-(*n*-heptadecyl)indole-5-carboxylate, in the form of an off-white solid, m.p. 95—97°C.

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Example 81

Compound AXX

Sodium hydride (0.32 g of a 50% oil dispersion) was added to a stirred solution of (RS)-2-(*n*-decyl)indoline-6-carboxylic acid (2 g; prepared as described hereinbefore in Example 57) in dry dimethylformamide (50 ml). When the addition was complete, the mixture was warmed on the steam bath for 1 hour with stirring, and 3-chloro-1,2-propanediol (0.8 g) was added. The mixture was warmed on the steam bath for 20 hours with stirring. The solvent was then evaporated to dryness and the residue was dissolved in dichloromethane. The solution in dichloromethane was washed with water, dried over magnesium sulphate and filtered, and the solvent evaporated to dryness to give an oil which slowly solidified. This solid was washed with petroleum ether (b.p. 60—80°C), filtered off and dried in air to give (RS)(RS)-2,3-dihydroxypropyl-1-yl 2-(*n*-decyl)indoline-6-carboxylate (1.5 g), in the form of an off-white powder m.p. 102—110°C.

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Example 82

Compound BB

Raney nickel (5 g) was added to a solution of ethyl 2-(*n*-pentadecyl)-3-methylthioindole-5-carboxylate (0.5 g) in dioxan (25 ml) and the mixture was heated on a steam bath for 1 hour. The mixture was filtered hot and the filtrate was evaporated *in vacuo* to give a white solid. This solid was recrystallised from petroleum ether (b.p. 60—80°C) to give ethyl 2-(*n*-pentadecyl)indole-5-carboxylate (0.35 g), m.p. 89—91°C.

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Ethyl 2-(*n*-pentadecyl)-3-methylthioindole-5-carboxylate used as starting material was prepared as follows:—

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A solution of *tert*-butyl hypochlorite (5.4 g) in methylene chloride (30 ml) was added dropwise to a stirred solution of ethyl 4-aminobenzoate (8.3 g) in methylene chloride (100 ml) at -65°C. After 15 minutes, a solution of 1-methylthioheptadecan-2-one (15 g) in methylene chloride (60 ml) was added. The stirring at -65°C was continued for 1 hour and a solution of triethylamine (5 g) in methylene chloride (20 ml) was then added. The reaction mixture was allowed to warm to room temperature. Water (50 ml) was added, and the organic layer was separated, dried over magnesium sulphate and evaporated *in vacuo*. The residue was dissolved in chloroform (20 ml) and chromatographed on a silica column (3.5 cm diameter x 45 cm) using chloroform as the eluant. The crude ethyl 2-(*n*-pentadecyl)-3-methylthioindole-5-carboxylate (4.2 g) was obtained as an orange solid, m.p. 55—60°C.

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1-Methylthioheptadecan-2-one was synthesised as follows:—

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(i) A stirred mixture of 1-methylsulphinylheptadecan-2-one (10 g), water (100 ml), sodium metabisulphate (50 g) and dioxan (50 ml) was heated on a steam bath for 18 hours. The mixture was cooled to room temperature and extracted with diethyl ether (2 x 100 ml). The ether extract was dried over magnesium sulphate and was evaporated to give 1-methylthioheptadecan-2-one (5.7 g) as a white solid, m.p. 38—40°C.

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(ii) A solution of trifluoroacetic anhydride (1.68 g) in acetone (5 ml) was added to a stirred mixture of 1-methylsulphinylheptadecan-2-one (1.58 g) and sodium iodide (1.8 g) in acetone (10 ml) cooled in an ice bath. The mixture was stirred for a further 10 minutes and then evaporated. Water (50 ml) was added to the residue and the mixture was extracted with diethyl ether (2 x 40 ml). The ether extract was washed with a solution of sodium thiosulphate (3 g) in water (50 ml), dried over magnesium sulphate and evaporated to give 1-methylthioheptadecan-2-one (1.3 g), m.p. 40°C.

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Example 83

Compound G

A stirred mixture of 4-(*n*-hexadecanamido)-3-methylbenzoic acid (4 g), potassium *tert*-butoxide (4

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g) and diethylaniline (10 ml) was refluxed for 3.5 hours. The fraction boiling at less than 200°C during the reaction was collected. The reaction mixture was left to cool to room temperature and was then acidified with 10% w/v hydrochloric acid. The solid was filtered off, dried and recrystallised from toluene to give 2-(n-pentadecyl)indole-5-carboxylic acid (2.7 g), m.p. 108—110°C.

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Example 84

Compound C

A mixture of 3-(n-dodecanamido)-4-methylbenzoic acid (4 g), potassium *tert*-butoxide (4 g) and diethylaniline (10 ml) was treated in a similar manner to that hereinbefore described in Example 83 to give 2-(n-undecyl)indole-6-carboxylic acid (2.6 g), m.p. 156—158°C.

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Example 85

Compound AYY

A solution of borane in tetrahydrofuran (134 ml, of strength 1M) in portions (13 x 10 ml) was added during 20 minutes to a stirred solution of methyl 3-(n-dodecanoyl)indole-6-carboxylate (19.9 g) in a mixture of dry tetrahydrofuran (330 ml) and dry ethyl acetate (330 ml), the temperature of the reaction being maintained at 50°C by external warming. The mixture was stirred and refluxed for 1.5 hours and then methanol (330 ml) was added to the refluxing mixture during 10 minutes. The mixture was refluxed for a further 30 minutes and water (50 ml) was added. The mixture was distilled at atmospheric pressure to remove the organic solvents to give a yellow residue. The residue was triturated with water (50 ml) to give a solid, which was collected and washed with water (100 ml). The solid was recrystallised from methanol (100 ml) (with treatment with charcoal) and then from toluene to give methyl 3-(n-dodecyl)indole-6-carboxylate (10 g), in the form of a white solid, m.p. 85—89°C.

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(i) The methyl 3-(n-dodecanoyl)indole-6-carboxylate, used as starting material, was prepared as follows:—

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Phosphorus oxychloride (27.5 ml) was added dropwise during 20 minutes to stirred N,N-dimethyldodecanamide (84.9 g) at room temperature. The temperature of the mixture rose during the addition to 50°C. The mixture was stirred and heated at 90°C for 15 minutes and then methyl indole-6-carboxylate (33.4 g) was added portionwise to the stirred mixture during 10 minutes, the temperature of the mixture being maintained at 90°C during the addition. The mixture was then stirred for 2 hours at 90°C and was then poured onto ice. The aqueous mixture was extracted with chloroform (3 x 300 ml) and the extract was dried over magnesium sulphate and was evaporated to give a red brown oil. The oil was dissolved in boiling methanol (100 ml), the solution was treated with charcoal and the solution was filtered and cooled (0°C) to give methyl 3-(n-dodecanoyl)indole-6-carboxylate (26.7 g), in the form of a buff solid, m.p. 167—169°C.

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Example 86

Compound AZZ

By proceeding in a similar manner to that hereinbefore described in Example 85 for the preparation of methyl 3-(n-dodecyl)indole-6-carboxylate but replacing methyl 3-(n-dodecanoyl)indole-6-carboxylate by methyl 3-(n-octanoyl)indole-6-carboxylate, there was prepared methyl 3-(n-octyl)indole-6-carboxylate, in the form of a white solid, m.p. 78—79°C.

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By proceeding in a similar manner to that hereinbefore described in Example 85(i) for the preparation of methyl 3-(n-dodecanoyl)indole-6-carboxylate but replacing N,N-dimethyldodecanamide by N,N-dimethyloctanamide, there was prepared methyl 3-(n-octanoyl)indole-6-carboxylate in the form of a white solid, m.p. 205—208°C after recrystallisation from glacial acetic acid, used in the preparation above.

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Example 87

Compound BAA

By proceeding in a similar manner to that hereinbefore described in Example 85 for the preparation of methyl 3-(n-dodecyl)indole-6-carboxylate but replacing methyl 3-(n-dodecanoyl)indole-6-carboxylate by methyl 3-(n-hexadecanoyl)indole-6-carboxylate, there was prepared methyl 3-(n-hexadecyl)indole-6-carboxylate in the form of a white solid, m.p. 89—94°C after recrystallisation from methanol.

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By proceeding in a similar manner to that hereinbefore described in Example 85(i) for the preparation of methyl 3-(n-dodecanoyl)indole-6-carboxylate but replacing N,N-dimethyldodecanamide by N,N-dimethylhexadecanamide, there was prepared methyl 3-(n-hexadecanoyl)indole-6-carboxylate in the form of a white solid, m.p. 156—158°C after recrystallisation from ethyl acetate, used in the preparation above.

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Example 88

Compound BBB

By proceeding in a similar manner to that hereinbefore described in Example 85 for the preparation of methyl 3-(n-dodecyl)indole-6-carboxylate but replacing methyl 3-(n-dodecanoyl)indole-6-carboxylate by methyl 3-(n-octadecanoyl)indole-6-carboxylate, there was prepared methyl 3-(n-octa-

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decyl)indole-6-carboxylate in the form of a white solid, m.p. 92—94°C after recrystallisation from methanol.

By proceeding in a similar manner to that hereinbefore described in Example 85(i) for the preparation of methyl 3-(n-dodecanoyl)indole-6-carboxylate but replacing N,N-dimethyldodecanamide by N,N-dimethyloctadecanamide, there was prepared methyl 3-(n-octadecanoyl)indole-6-carboxylate in the form of a cream solid, m.p. 153—155°C after recrystallisation from ethyl acetate, used in the preparation above.

Example 89

Compound BCC

By proceeding in a similar manner to that hereinbefore described in Example 85 for the preparation of methyl 3-(n-dodecyl)indole-6-carboxylate but replacing methyl 3-(n-dodecanoyl)indole-6-carboxylate by methyl 3-(n-hexadecanoyl)indole-5-carboxylate, there was prepared methyl 3-(n-hexadecyl)indole-5-carboxylate in the form of a white solid, m.p. 85—87°C after recrystallisation from methanol.

By proceeding in a similar manner to that hereinbefore described in Example 85(i) for the preparation of methyl 3-(n-dodecanoyl)indole-6-carboxylate but replacing methyl indole-6-carboxylate by methyl indole-5-carboxylate and N,N-dimethyldodecanamide by N,N-dimethylhexadecanamide, there was prepared methyl 3-(n-hexadecanoyl)indole-5-carboxylate in the form of a cream solid, m.p. 158—160°C after recrystallisation from ethyl acetate, used in the preparation above.

Example 90

Compound BDD

A solution of sodium hydroxide (15 g) in water (100 ml) was added dropwise during 30 minutes to a refluxing solution of methyl 3-(n-dodecyl)indole-6-carboxylate (12.8 g prepared as hereinbefore described in Example 85) in methanol (800 ml). The mixture was stirred and refluxed for 12 hours. The mixture was then concentrated to 500 ml volume and water (400 ml) was added. After cooling to 0°C, a solid was collected and was dissolved in hot glacial acetic acid (300 ml). The solution was then poured into water (800 ml) and a solid was collected, washed with water (4 x 100 ml) and dried at 60°C. Recrystallisation of the solid from methanol gave 3-(n-dodecyl)indole-6-carboxylic acid (9.0 g), in the form of a white solid, m.p. 181—184°C.

Example 91

Compound BEE

By proceeding in a similar manner to that hereinbefore described in Example 90 for the preparation of 3-(n-dodecyl)indole-6-carboxylic acid but replacing methyl 3-(n-dodecyl)indole-6-carboxylate by methyl 3-(n-octyl)indole-6-carboxylate, there was prepared 3-(n-octyl)indole-6-carboxylic acid in the form of a white solid, m.p. 195—197°C after recrystallisation from toluene.

Example 92

Compound BFF

By proceeding in a similar manner to that hereinbefore described in Example 90 for the preparation of 3-(n-dodecyl)indole-6-carboxylic acid but replacing methyl 3-(n-dodecyl)indole-6-carboxylate by methyl 3-(n-hexadecyl)indole-6-carboxylate, there was prepared 3-(n-hexadecyl)indole-6-carboxylic acid in the form of a white solid, m.p. 174—178°C after recrystallisation from ethyl acetate.

Example 93

Compound BGG

By proceeding in a similar manner to that hereinbefore described in Example 90 for the preparation of 3-(n-dodecyl)indole-6-carboxylic acid but replacing methyl 3-(n-dodecyl)indole-6-carboxylate by methyl 3-(n-octadecyl)indole-6-carboxylate, there was prepared 3-(n-octadecyl)indole-6-carboxylic acid in the form of a white solid, m.p. 172—174°C after recrystallisation from ethyl acetate.

Example 94

Compound BHH

By proceeding in a similar manner to that hereinbefore described in Example 90 for the preparation of 3-(n-dodecyl)indole-6-carboxylic acid but replacing methyl 3-(n-dodecyl)indole-6-carboxylate by methyl 3-(n-hexadecyl)indole-5-carboxylate, there was prepared 3-(n-hexadecyl)indole-5-carboxylic acid in the form of an off-white solid, m.p. 114—116°C after recrystallisation from glacial acetic acid.

Example 95

Compound BII

A mixture of (RS)-2-(n-undecyl)indoline-6-carboxylic acid (13.3 g), sodium hydroxide (13.3 g), water (40 ml), ethanol (160 ml) and methyl iodide (15 ml) was heated under reflux for 1 hour. Methyl iodide (5 ml) was added and the mixture was heated for 1 hour, then poured into water, and acidified

with acetic acid. The product was collected and recrystallised from methanol to give (RS)-1-methyl-2-(n-undecyl)indoline-6-carboxylic acid (8.9 g), in the form of white needles, m.p. 121—124°C.

Example 96

5 Compound BJJ

A mixture of (RS)-2-(n-undecyl)indoline-5-carboxylic acid hydrochloride (6.8 g), sodium hydroxide (6.8 g), water (25 ml), ethanol (75 ml) and methyl iodide (10 ml) was heated under reflux for 1 hour. Methyl iodide (5 ml) was added and the mixture was heated for 30 minutes, then poured into water and acidified with acetic acid. The product was collected and recrystallised from methanol to give (RS)-1-methyl-2-(n-undecyl)indoline-5-carboxylic acid (3.0 g), in the form of white needles, m.p. 102—104°C.

Example 97

Compound BKK

15 Methyl 3-(n-octadecanoyl)indole-5-carboxylate (17.30 g) was suspended in glacial acetic acid (400 ml), containing perchloric acid (11 ml, 70% w/v), and was hydrogenated over palladium on charcoal (5% w/w, 15 g) at atmospheric pressure and at a temperature of 80—90°C. The mixture was then hot filtered through diatomaceous earth and was poured into water (150 ml) to give an off-white solid. The solid was collected, washed with water (2 x 100 ml) and was dissolved in ethyl acetate 20 (1000 ml). The ethyl acetate solution was washed with an aqueous solution of sodium carbonate (of strength 2N, 150 ml) and the organic layer was separated and was dried over magnesium sulphate. The organic solvent was removed *in vacuo* to give (RS)-methyl-3-(n-octadecyl)indoline-5-carboxylate in the form of an off-white solid, which was used without purification.

By proceeding in a similar manner to that hereinbefore described in Example 85(i) for the 25 preparation of methyl 3-(n-dodecanoyl)indole-6-carboxylate but replacing N,N-dimethyldodecanamide by N,N-dimethyloctadecanamide and methyl indole-6-carboxylate by methyl indole-5-carboxylate, there was prepared methyl 3-(n-octadecanoyl)indole-5-carboxylate in the form of an off-white solid, used in the preparation above, without further purification.

Example 98

Compound BLL

By proceeding in a similar manner to that hereinbefore described in Example 97 for the preparation of (RS)-methyl 3-(n-octadecyl)indoline-5-carboxylate but replacing methyl 3-(n-octadecanoyl)indole-5-carboxylate by methyl 3-(n-decanoyl)indole-5-carboxylate, there was prepared (RS)- 35 methyl 3-(n-decyl)indoline-5-carboxylate in the form of an off-white solid, m.p. 53—55°C after recrystallisation from methanol.

By proceeding in a similar manner to that hereinbefore described in Example 85(i) for the preparation of methyl 3-(n-dodecanoyl)indole-6-carboxylate but replacing N,N-dimethyldodecanamide by N,N-dimethyldecanamide and methyl indole-6-carboxylate by methyl indole-5-carboxylate, there 40 was prepared methyl 3-(n-decanoyl)indole-5-carboxylate in the form of a white solid, m.p. 173—175°C after recrystallisation from methanol, used in the preparation above.

Example 99

Compound BMM

45 By proceeding in a similar manner to that hereinbefore described in Example 97 for the preparation of (RS)-methyl 3-(n-octadecyl)indoline-5-carboxylate but replacing methyl 3-(n-octadecanoyl)indole-5-carboxylate by methyl 3-(n-octanoyl)indole-5-carboxylate, there was prepared (RS)-methyl 3-(n-octyl)indoline-5-carboxylate in the form of a solid, having a low melting point.

By proceeding in a similar manner to that hereinbefore described in Example 85(i) for the 50 preparation of methyl 3-(n-dodecanoyl)indole-6-carboxylate but replacing N,N-dimethyldodecanamide by N,N-dimethyloctanamide and methyl indole-6-carboxylate by methyl indole-5-carboxylate, there was prepared methyl 3-(n-octanoyl)indole-5-carboxylate in the form of a solid, m.p. 102—105°C after recrystallisation from ethyl acetate, used in the preparation above.

Example 100

Compound BNN

By proceeding in a similar manner to that hereinbefore described in Example 97 for the preparation of (RS)-methyl 3-(n-octadecyl)indoline-5-carboxylate but replacing methyl 3-(n-octadecanoyl)indole-5-carboxylate by methyl 3-(n-hexadecanoyl)indole-5-carboxylate, there was prepared 60 (RS)-methyl 3-(hexadecyl)indoline-5-carboxylate in the form of an off-white solid, m.p. 69—71°C.

By proceeding in a similar manner to that hereinbefore described in Example 85(i) for the preparation of methyl 3-(n-dodecanoyl)indole-6-carboxylate but replacing N,N-dimethyldodecanamide by N,N-dimethylhexadecanamide and methyl indole-6-carboxylate by methyl indole-5-carboxylate, there was prepared methyl 3-(n-hexadecanoyl)indole-5-carboxylate in the form of a solid, m.p. 65 158—160°C after recrystallisation from ethyl acetate, used in the preparation above.

Example 101

Compound BOO

(RS)-Methyl 3-(n-octadecyl)indoline-5-carboxylate (13.6 g) in ethanol (380 ml), containing potassium hydroxide (2.7 g) and water (50 ml), was refluxed with stirring for 24 hours. The solvent was removed *in vacuo* to give an off-white solid. The solid was dissolved in water, and the solution treated with charcoal and filtered through diatomaceous earth. Glacial acetic acid (50 ml) was slowly added to the stirred solution and an off-white solid was collected, which was recrystallised from ethyl acetate to give (RS)-3-(n-octadecyl)indoline-5-carboxylic acid (9.1 g), in the form of a white solid, m.p. 84—87°C.

Example 102

Compound BPP

By proceeding in a similar manner to that hereinbefore described in Example 101 for the preparation of (RS)-3-(n-octadecyl)indoline-5-carboxylic acid but replacing (RS)-methyl 3-(n-octadecyl)indoline-5-carboxylate by (RS)-methyl 3-(n-decyl)indoline-5-carboxylate, there was prepared (RS)-3-(n-decyl)indoline-5-carboxylic acid in the form of a cream solid, m.p. 88—90°C after recrystallisation from petroleum ether (b.p. 60—80°C).

Example 103

Compound BQQ

By proceeding in a similar manner to that hereinbefore described in Example 101 for the preparation of (RS)-3-(n-octadecyl)indoline-5-carboxylic acid but replacing (RS)-methyl 3-(n-octadecyl)indoline-5-carboxylate by (RS)-methyl 3-(n-octyl)indoline-5-carboxylate, there was prepared (RS)-3-(n-octyl)indoline-5-carboxylic acid in the form of a white solid, m.p. 128—130°C after recrystallisation from ethyl acetate.

Example 104

Compound BRR

By proceeding in a similar manner to that hereinbefore described in Example 101 for the preparation of (RS)-3-(n-octadecyl)indoline-5-carboxylic acid but replacing (RS)-methyl 3-(n-octadecyl)indoline-5-carboxylate by (RS)-methyl 3-(n-hexadecyl)indoline-5-carboxylate, there was prepared (RS)-3-(n-hexadecyl)indoline-5-carboxylic acid in the form of a white solid, m.p. 78—80°C after recrystallisation from petroleum ether (b.p. 40—60°C).

Example 105

Compound BRR

The free base (8.7 g; prepared as hereinbefore described in Example 104) was dissolved in diethyl ether (200 ml) and the solution was filtered through diatomaceous earth. The solution was treated with aqueous hydrochloric acid (3 ml, of strength 36.5% w/v) and the precipitated solid was collected. The solid was recrystallised from ethyl acetate to give (RS)-3-(n-hexadecyl)indoline-5-carboxylic acid hydrochloride (7.4 g), in the form of a white solid, m.p. 141—143°C.

Example 106

Compound BSS

(RS)-3-(n-Octadecyl)indoline-5-carboxylic acid (2.0 g) in mesitylene (20 ml) was treated with palladium on charcoal (5% w/w, 0.15 g) and the mixture was refluxed for 2 hours. The catalyst was removed by hot filtration and the solvent was evaporated *in vacuo* to give a solid. The solid was recrystallised from methanol to give 3-(n-octadecyl)indole-5-carboxylic acid (1.10 g) in the form of a buff solid (m.p. 110—112°C).

Example 107

Compound BTT

By proceeding in a similar manner to that hereinbefore described in Example 106 for the preparation of 3-(n-octadecyl)indole-5-carboxylic acid but replacing (RS)-3-(n-octadecyl)indoline-5-carboxylic acid by (RS)-3-(n-octyl)indoline-5-carboxylic acid, there was prepared 3-(n-octyl)indole-5-carboxylic acid in the form of an off-white solid, m.p. 151—154°C.

Example 108

Compound BUU

By proceeding in a similar manner to that hereinbefore described in Example 97 for the preparation of (RS)-methyl 3-(n-octadecyl)indoline-5-carboxylate but replacing methyl 3-(n-octadecanoyl)indole-5-carboxylate by methyl 3-(n-undecanoyl)indole-6-carboxylate, there was prepared (RS)-methyl 3-(n-undecyl)indoline-6-carboxylate in the form of a white solid.

By proceeding in a similar manner to that hereinbefore described in Example 85(i) for the preparation of methyl 3-(n-dodecanoyl)indole-6-carboxylate but replacing N,N-dimethyldodecanamide by N,N-dimethylundecanamide there was prepared methyl 3-(n-undecanoyl)indole-6-carboxylate in the

form of a white solid, m.p. 173—176°C after recrystallisation from ethyl acetate, used in the preparation above.

Example 109

5 *Compound BVV*

By proceeding in a similar manner to that hereinbefore described in Example 97 for the preparation of (RS)-methyl 3-(n-octadecyl)indoline-5-carboxylate but replacing methyl 3-(n-octadecanoyl)indole-5-carboxylate by methyl 3-(n-decanoyl)indole-6-carboxylate, there was prepared (RS)-methyl 3-(n-decyl)indoline-6-carboxylate in the form of a white solid, m.p. 63—65°C after re-

10 crystallisation from methanol.

By proceeding in a similar manner to that hereinbefore described in Example 85(i) for the preparation of methyl 3-(n-dodecanoyl)indole-6-carboxylate but replacing N,N-dimethyldodecanamide by N,N-dimethyldecanamide, there was prepared methyl 3-(n-decanoyl)indole-6-carboxylate in the form of a white solid, m.p. 172—173°C after recrystallisation from ethyl acetate, used in the

15 preparation above.

Example 110

Compound BWW

By proceeding in a similar manner to that hereinbefore described in Example 97 for the preparation of (RS)-methyl 3-(n-octadecyl)indoline-5-carboxylate but replacing methyl 3-(n-octadecanoyl)indole-5-carboxylate by methyl 3-(n-pentadecanoyl)indole-6-carboxylate, there was prepared (RS)-methyl 3-(n-pentadecyl)indoline-6-carboxylate in the form of an off-white solid, m.p. 90—92°C after recrystallisation from methanol.

By proceeding in a similar manner to that hereinbefore described in Example 85(i) for the preparation of methyl 3-(n-dodecanoyl)indole-6-carboxylate but replacing N,N-dimethyldodecanamide by N,N-dimethylpentadecanamide, there was prepared methyl 3-(n-pentadecanoyl)indole-6-carboxylate in the form of an off-white solid, m.p. 154—156°C after recrystallisation from ethyl acetate, used in the preparation above.

Example 111

Compound BXX

30 (RS)-Methyl 3-(n-undecyl)indoline-6-carboxylate (12.4 g) in ethanol (350 ml), containing potassium hydroxide (3.33 g) and water (45 ml), was stirred and refluxed for 24 hours. The solvent was removed *in vacuo* to give an off-white solid. The solid was dissolved in water, and the solution was treated with charcoal and filtered through diatomaceous earth. Glacial acetic acid (50 ml) was slowly added to the stirred solution and an off-white solid was collected and recrystallised from ethyl acetate

35 to give (RS)-3-(n-undecyl)indoline-6-carboxylic acid (11.9 g), in the form of a white solid, m.p. 107—111°C.

Example 112

Compound BYY

40 By proceeding in a similar manner to that hereinbefore described in Example 111 for the preparation of (RS)-3-(n-undecyl)indoline-6-carboxylic acid but replacing (RS)-methyl 3-(n-undecyl)indoline-6-carboxylate by (RS)-methyl 3-(n-decyl)indoline-6-carboxylate, there was prepared (RS)-3-(n-decyl)indoline-6-carboxylic acid in the form of a white solid, m.p. 115—117°C after recrystallisation from ethyl acetate.

Example 113

45 *Compound BZZ*

By proceeding in a similar manner to that hereinbefore described in Example 111 for the preparation of (RS)-3-(n-undecyl)indoline-6-carboxylic acid but replacing (RS)-methyl 3-(n-undecyl)indole-6-carboxylate by (RS)-methyl 3-(n-pentadecyl)indoline-6-carboxylate, there was prepared (RS)-3-(n-pentadecyl)indoline-6-carboxylic acid in the form of an off-white solid, m.p. 105—109°C.

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Example 114

Compound CAA

3-(n-Dodecyl)indole-6-carboxylic acid (16.1 g) in suspension in glacial acetic acid (200 ml), containing perchloric acid (12.2 ml; of strength (70% w/v) was hydrogenated over palladium on charcoal (1.8 g of 5% w/w) at atmospheric pressure and at a temperature of 80—90°C. The mixture was then hot filtered through diatomaceous earth and was poured into water (1500 ml) to give an off-white solid. The solid was collected, washed with water (2 x 100 ml) and was dissolved in ethyl acetate (1000 ml). The ethyl acetate solution was washed with an aqueous solution of sodium carbonate (of strength 2N, 150 ml) and the organic layer was separated and was dried over magnesium sulphate. The organic solvent was removed *in vacuo* to give (RS)-3-(n-dodecyl)indoline-6-carboxylic acid (7.9 g), in the form of a white solid (m.p. 100—102°C).

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Example 115

Compound CBB

65 3-(n-Octadecanoyl)indole-6-carboxylic acid (20.5 g) in glacial acetic acid (300 ml), containing

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perchloric acid (13 ml, of strength 70% w/v), was hydrogenated over palladium on charcoal (3 g of 5% w/w) at atmospheric pressure and at a temperature of 80—90°C. The mixture was then hot filtered through diatomaceous earth and was poured into water (1500 ml) to give an off-white solid. The solid was collected, washed with water (2 x 100 ml) and was dissolved in ethyl acetate (100 ml). The ethyl acetate solution was washed with an aqueous solution of sodium carbonate (of strength 2N, 150 ml) and the organic layer was separated and was dried over magnesium sulphate. The organic solvent was removed *in vacuo* to give (RS)-3-(n-octadecyl)indoline-6-carboxylic acid (8.5 g), in the form of an off-white solid, m.p. 112—114°C.

(i) The 3-(n-octadecanoyl)indole-6-carboxylic acid used as starting material was prepared as follows:—

Methyl 3-(n-octadecanoyl)indole-6-carboxylate (35.2 g) in methanol (1620 ml), containing sodium hydroxide (32 g) and water (49 ml), was stirred and refluxed for 2 hours. The solution was cooled to room temperature and the solid was collected. The solid was suspended in water (500 ml) and aqueous hydrochloric acid (20 ml, of strength 36% w/v) was added to the suspension with rapid stirring. The solid was collected and was recrystallised from glacial acetic acid to give 3-(n-octadecanoyl)indole-6-carboxylic acid (28 g), in the form of a white solid, m.p. 268—270°C.

Example 116

Compound CCC

3-(n-Octanoyl)indole-6-carboxylic acid (39.4 g) in glacial acetic acid (860 ml), containing perchloric acid (37 ml, of strength 70% w/v), was hydrogenated over palladium on charcoal (17 g of 5% w/w) at atmospheric pressure and at a temperature between 80—90°C. The catalyst was removed by hot filtration through diatomaceous earth and on cooling a solid separated which was collected. The solid was washed with diethyl ether (2 x 100 ml) and was dissolved in ethyl acetate. The ethyl acetate solution was washed with an aqueous solution of sodium carbonate (2 x 100 ml of strength 2N) and was dried over magnesium sulphate and on evaporation *in vacuo* gave an off-white solid. The solid was dissolved in ethyl acetate (200 ml) and hydrogen chloride gas was bubbled through the solution. The resulting solid was collected and was washed with diethyl ether (2 x 200 ml) to give (RS)-3-(n-octyl)indoline-6-carboxylic acid hydrochloride (14.5 g), in the form of an off-white solid, m.p. 233—234°C with decomposition.

By proceeding in a similar manner to that hereinbefore described in Example 115(i) for the preparation of 3-(n-octadecanoyl)indole-6-carboxylic acid but replacing methyl 3-(n-octadecanoyl)indole-6-carboxylate by methyl 3-(n-octanoyl)indole-6-carboxylate, there was prepared 3-(n-octanoyl)indole-6-carboxylic acid in the form of a white solid, m.p. 283—286°C after recrystallisation from glacial acetic acid, used in the preparation above.

Example 117

Compound CDD

By proceeding in a similar manner to that hereinbefore described in Example 116 for the preparation of (RS)-3-(n-octyl)indoline-6-carboxylic acid hydrochloride but replacing 3-(n-octanoyl)indole-6-carboxylic acid by 3-(n-hexadecanoyl)indole-6-carboxylic acid, there was prepared (RS)-3-(n-hexadecyl)indoline-6-carboxylic acid hydrochloride in the form of a white solid, m.p. 204—207°C.

By proceeding in a similar manner to that hereinbefore described in Example 115(i) for the preparation of 3-(n-octadecanoyl)indole-6-carboxylic acid but replacing methyl 3-(n-octadecanoyl)indole-6-carboxylate by methyl 3-(n-hexadecanoyl)indole-6-carboxylate, there was prepared 3-(n-hexadecanoyl)indole-6-carboxylic acid in the form of a white solid, m.p. 273—275°C after recrystallisation from glacial acetic acid, used in the preparation above.

Example 118

Compound CEE

(RS)-3-(n-Octyl)indoline-6-carboxylic acid hydrochloride (7.5 g) in methanol (500 ml), containing hydrochloric acid (50 ml, of strength 36% w/v), was refluxed for 18 hours. The solvent was removed *in vacuo* and water (100 ml) was added to the residue to give a solid, which was collected, washed with water (2 x 200 ml) and dried. The solid was dissolved in dichloromethane and was washed with an aqueous solution of sodium bicarbonate (100 ml of strength 2% w/v) and then water (100 ml) and was dried over sodium sulphate. The solvent was removed *in vacuo* to give a pale yellow oil, which solidified. The solid was recrystallised from a mixture (4:1) of methanol and water to give (RS)-methyl 3-(n-octyl)indoline-6-carboxylate (4.8 g), in the form of a white solid, m.p. 57—60°C.

Example 119

Compound CFF

By proceeding in a similar manner to that hereinbefore described in Example 118 for the preparation of (RS)-methyl 3-(n-octyl)indoline-6-carboxylate but replacing (RS)-3-(n-octyl)indoline-6-carboxylic acid by (RS)-3-(n-hexadecyl)indoline-6-carboxylic acid there was prepared (RS)-methyl 3-(n-hexadecyl)indoline-6-carboxylate, in the form of an off-white solid, m.p. 76—77°C.

Example 120

Compound JJ

A mixture of [4-methoxycarbonyl-2-(n-dodecanamido)benzyl]triphenylphosphonium bromide (23.8 g) and potassium *tert.*-butoxide (3.9 g) were added to dry toluene (680 ml). The stirred mixture was heated to reflux for 15 minutes and cooled to room temperature. Ethyl acetate (1.5 litre) and saturated brine (750 ml) were added; the mixture was shaken and the organic phase separated. The organic extract was dried over magnesium sulphate and was evaporated *in vacuo* to give an oil. The oil was purified by chromatography on a silica column using chloroform as eluant to give a crude solid which was recrystallised from methanol to give methyl 2-(n-undecyl)indole-6-carboxylate (4.1 g) as an off-white solid, m.p. 83—85°C.

The [4-methoxycarbonyl-2-(n-dodecanamido)benzyl]triphenylphosphonium bromide, used as starting material, was prepared as follows:—

n-Dodecanol chloride (9.9 g) was added dropwise to a stirred suspension of (2-amino-4-methoxycarbonylbenzyl)triphenylphosphonium bromide (22.9 g) in dry dimethylformamide (225 ml) and stirring continued for 3 hours. The resulting solution was evaporated *in vacuo* to give an orange-brown oil which on treatment with water gave a solid. The solid was collected, washed with water, dried, washed with diethyl ether and collected to give [4-methoxycarbonyl-2-(n-dodecanamido)benzyl]triphenylphosphonium bromide (22.9 g) in the form of a pale yellow solid, m.p. 142—145°C.

Example 121

Compound CGG

(RS)-2-(n-Tetradecyl)indoline-6-carboxylic acid (10.5 g) and sodium hydroxide (5.0 g) were refluxed together in a mixture of water (30 ml) and methanol (70 ml) for 1.5 hours, then methyl iodide (5 ml) was added. Water (30 ml) was added and the mixture was refluxed for 1 hour. The mixture was filtered, and the filtrate was diluted with water and acidified with acetic acid. The product was collected and recrystallised from a mixture of methanol and ethanol to give (RS)-1-methyl-2-(n-tetradecyl)indoline-6-carboxylic acid (7.0 g) in the form of off-white crystals, m.p. 115—118°C.

Example 122

Compound CHH and its methyl ester

Potassium hydroxide (9.0 g) was added to a solution of 2-(n-undecyl)indole-6-carboxylic acid (22.1 g) in dimethylsulphoxide (100 ml) and hot water (5 ml), and the mixture was stirred and warmed on a steam bath to give a suspension. After 15 minutes the suspension was removed from the steam bath, methyl iodide (15 ml) was added, and the mixture was stirred for 2 hours with occasional warming. Methyl iodide (10 ml) was added and the mixture was stirred for 1 hour. The mixture was left to cool overnight and was then poured into water and acidified with 2N hydrochloric acid. The product was collected and washed. This product was then added to a mixture of ethanol (150 ml), water (50 ml), and sodium hydroxide (6.5 g), and the mixture was heated under reflux for 1 hour and then poured into water containing acetic acid (50 ml). The product was twice recrystallised from ethanol to give 1-methyl-2-(n-undecyl)indole-6-carboxylic acid (9.6 g), in the form of a white powder, m.p. 165—168°C.

Example 123

Compound CII and its methyl ester

Potassium hydroxide (16.5 g) was warmed in dry dimethylsulphoxide (150 ml) with stirring for 10 minutes. Water (7 ml) was added, followed, after 5 minutes, by 2-(n-pentadecyl)indole-5-carboxylic acid (27.0 g). The mixture was cooled to room temperature and methyl iodide (15 ml) was added, producing an exothermic reaction. The mixture was stirred without heating for 1 hour, then poured into the water (approx. 500 ml) containing concentrated hydrochloric acid (40 ml). The product was collected, washed with water, dissolved in a mixture of chloroform, diethyl ether and tetrahydrofuran, and the solution was dried over sodium sulphate. The solvent was evaporated *in vacuo* and the residue was recrystallised from toluene. The resulting crystals were dried by suction to give a solid (11.7 g) in the form of needles, m.p. 77—79°C.

This solid (methyl ester of compound CII) was heated under reflux in ethanol (100 ml) and water (20 ml) with sodium hydroxide (2.0 g) for 2 hours. The hot solution was acidified with acetic acid, the product was filtered off, washed with water, ethanol, and petroleum ether (b.p. 40—60°C), and recrystallised from toluene to give 1-methyl-2-(n-pentadecyl)indole-5-carboxylic acid (10.0 g), in the form of a white powder, m.p. 127—128°C.

Example 124

Compound CJJ

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by (RS)-3-(2-methyloctadecanamido)-4-methylbenzoic acid, there was prepared (RS)-2-(1-methylheptadecyl)indole-6-carboxylic acid, in the form of a buff solid, m.p. 84—88°C.

By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation

of 3-(n-decanamido)-4-methylbenzoic acid but replacing n-decanoyl chloride by (RS)-2-methyloctadecanoyl chloride, there was prepared (RS)-3-(2-methyloctadecanamido)-4-methylbenzoic acid in the form of colourless needles, m.p. 220—223°C after recrystallisation from isopropanol, used in the preparation above.

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Example 125

Compound CKK

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by (RS)-4-(2-methyloctadecanamido)-3-methylbenzoic acid, there was prepared (RS)-2-(1-methylheptadecyl)indole-5-carboxylic acid, in the form of an off-white solid, m.p. 68—72°C.

By proceeding in a similar manner to that hereinbefore described in Example 5(i) for the preparation of 3-(n-decanamido)-4-methylbenzoic acid but replacing n-decanoyl chloride by (RS)-2-methyloctadecanoylchloride and 3-amino-4-methylbenzoic acid by 4-amino-3-methylbenzoic acid, there was prepared (RS)-4-(2-methyloctadecanamido)-3-methylbenzoic acid, in the form of a colourless solid, m.p. 193—195°C after recrystallisation from isopropanol, used in the preparation above.

Example 126

Compound CLL

By proceeding in a similar manner to that hereinbefore described in Example 57 for the preparation of (RS)-2-(n-decyl)indoline-6-carboxylic acid but replacing 2-(n-decyl)indole-6-carboxylic acid by (RS)-2-(1-methylheptadecyl)indole-6-carboxylic acid, there was prepared (RS)(RS)-2-(1-methylheptadecyl)indoline-6-carboxylic acid, in the form of a buff solid, m.p. 80—86°C.

25

Example 127

Compound CMM

By proceeding in a similar manner to that hereinbefore described in Example 57 for the preparation of (RS)-2-(n-decyl)indoline-6-carboxylic acid but replacing 2-(n-decyl)indole-6-carboxylic acid by (RS)-2-(1-methylheptadecyl)indole-5-carboxylic acid, there was prepared (RS)(RS)-2-(1-methylheptadecyl)indoline-5-carboxylic acid, in the form of a buff solid, m.p. 69—76°C.

Example 128

Compound CNN

With external steam heating, a mixture of methyl 3-formyl-2-(n-undecyl)indole-6-carboxylate (20.0 g) and palladium on charcoal (5% w/w, 4.0 g) in glacial acetic acid (150 ml) and perchloric acid (72% w/v, 15 ml) was shaken under hydrogen. When the uptake stopped, the mixture was filtered, the residue was washed with hot acetic acid (100 ml) and the filtrate was concentrated *in vacuo* to about 50 ml. This mixture was diluted with ethanol (200 ml), 50% w/w aqueous sodium hydroxide (100 ml) was added, followed by water (200 ml), and the mixture was refluxed for 2 hours. The hot solution was filtered, and the filtrate was poured into cold water (1500 ml). Acetic acid was added until pH 5, and the product was collected and recrystallised from methanol to yield 2(RS),3(RS)-2-(n-undecyl)-3-methylindoline-6-carboxylic acid (13.7 g), in the form of buff needles, m.p. 107—110°C.

Methyl 3-formyl-2-(n-undecyl)indole-6-carboxylate, used as starting material, was prepared as follows:—

A solution of phosphorus oxychloride (20 ml) in dimethylformamide (80 ml) was added to a solution of methyl 2-(n-undecyl)indole-6-carboxylate (58.3 g) in dimethylformamide (250 ml) and the mixture was stirred at a temperature of 55—90°C for 2 hours. After cooling, the mixture was poured into rapidly stirred water. Aqueous sodium hydroxide (50% w/v) was added until pH 12, the mixture was stirred for 10 minutes, and then glacial acetic acid was added to pH 5. The mixture was stirred until the gummy product solidified. The solid was then collected and recrystallised from ethanol to give methyl 3-formyl-2-(n-undecyl)indole-6-carboxylate (52.5 g), in the form of a buff powder, m.p. 147—149°C.

Example 129

Compound COO

By proceeding in a similar manner to that hereinbefore described in Example 128 for the preparation of 2(RS),3(RS)-2-(n-undecyl)-3-methylindoline-6-carboxylic acid but replacing methyl 3-formyl-2-(n-undecyl)indole-6-carboxylate by methyl 3-formyl-2-(n-undecyl)indole-5-carboxylate, there was prepared 2(RS),3(RS)-2-(n-undecyl)-3-methylindoline-5-carboxylic acid, in the form of an off-white solid, m.p. 102—105°C.

Methyl 3-formyl-2-(n-undecyl)indole-5-carboxylate, used as starting material, was prepared as follows:—

A solution of phosphorus oxychloride (21.5 ml) in dimethylformamide (80 ml) was added to a solution of methyl 2-(n-undecyl)indole-5-carboxylate (36.9 g) in dimethylformamide (320 ml) and the mixture was stirred at a temperature of 60—70°C for 2 hours. After cooling the mixture was poured into water (500 ml). An aqueous solution of sodium hydroxide (50% w/v) was added to the mixture to

adjust the pH to 12. Glacial acetic acid was then added to the stirred mixture to readjust the pH to 5. The resultant solid was collected and on recrystallisation from ethanol gave methyl 3-formyl-2-(n-undecyl)indole-5-carboxylate (34.8 g), m.p. 162—165°C.

5

Example 130

Compound CPP

A mixture of 2(RS),3(RS)-2-(n-undecyl)-3-methylindoline-6-carboxylic acid (23.0 g) and palladium on charcoal (5% w/w; 3.0 g) was stirred in refluxing mesitylene (150 ml) for 3.5 hours. The hot suspension was filtered, the residue was washed with hot mesitylene (50 ml) and the filtrate was set
10 aside to cool. The product crystallised directly from the filtrate yielding 2-(n-undecyl)-3-methylindole-6-carboxylic acid (20.6 g) in the form of lustrous, white plates, m.p. 153—156°C.

Example 131

Compound CQQ

15 By proceeding in a similar manner to that hereinbefore described in Example 130 for the preparation of 2-(n-undecyl)-3-methylindole-6-carboxylic acid but replacing 2(RS),3(RS)-2-(n-undecyl)-3-methylindoline-6-carboxylic acid by 2(RS),3(RS)-2-(n-undecyl)-3-methylindoline-5-carboxylic acid, there was prepared 2-(n-undecyl)-3-methylindole-5-carboxylic acid in the form of a white solid, m.p. 102—105°C.

20

Example 132

Compound CRR

A mixture containing 2-(n-undecyl)indole-4-carboxylic acid (25.8 g), palladium on charcoal (5% w/w, 5.2 g), 72% w/v aqueous perchloric acid (26 ml) and glacial acetic acid (200 ml) was heated by
25 external application of steam while being shaken under an atmosphere of hydrogen. When the required hydrogen had been taken up, the hot mixture was filtered through diatomaceous earth, the residue was washed with fresh hot glacial acetic acid (200 ml), and the combined filtrates were concentrated *in vacuo* to about 75 ml. The residue was poured onto crushed ice and water, and 50% w/v aqueous sodium hydroxide was added to pH 12. Acetic acid was added to pH 4—5 and the product was
30 collected by filtration and washed with water. Recrystallisation from methanol yielded (RS)-2-(n-undecyl)-indoline-4-carboxylic acid (9.1 g) in the form of a buff solid, m.p. 105—108°C.

Example 133

Compound CRR

35 A solution of hydrogen chloride in ethanol (37% w/v, 20 ml) was added to a solution of (RS)-2-(n-undecyl)indoline-4-carboxylic acid (15.0 g) in ethanol (80 ml) and acetone (170 ml). After 30 seconds, anhydrous diethyl ether (800 ml) was added and the product was collected and washed with fresh anhydrous diethyl ether to give (RS)-2-(n-undecyl)indoline-4-carboxylic acid hydrochloride (14.2 g) in the form of a white powder, m.p. 220—230°C (with decomposition).

40

Example 134

Compound CSS

A mixture containing 2-(n-eicosyl)indole-5-carboxylic acid (12.8 g), 5% w/w palladium on charcoal (2.0 g), 72% w/v aqueous perchloric acid (10 ml) and glacial acetic acid (150 ml) was heated
45 by steam whilst shaken under hydrogen. Afterwards the mixture was filtered hot through diatomaceous earth, the residue was washed with hot glacial acetic acid (400 ml), and the combined filtrates were concentrated *in vacuo* to about 100 ml. The residue was poured into a mixture of ice and water, 50% w/v aqueous sodium hydroxide was added to pH 12 and acetic acid was then added to pH 4—5. The product was collected and recrystallised from methanol to give (RS)-2-(n-eicosyl)indoline-5-carboxylic acid hemimethanolate (4.8 g) as a pale brown solid. m.p. 110—115°C.

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Example 135

Compound CTT

A mixture containing methyl 3-formyl-2-(n-heptyl)indole-6-carboxylate (64.5 g), palladium on
55 charcoal (5% w/w, 12.4 g), 72% w/v aqueous perchloric acid (45 ml), and glacial acetic acid (450 ml) was externally heated with steam and shaken under an atmosphere of hydrogen. When the required hydrogen uptake had occurred, the mixture was filtered through diatomaceous earth, the residue was washed with hot glacial acetic acid (400 ml), and the filtrate was concentrated *in vacuo* to about 200 ml. The residue was poured into water (200 ml), ethanol (400 ml) was added, followed by a solution of
60 sodium hydroxide (140 g) in water (400 ml), and the mixture was refluxed for 2.5 hours. The hot solution was poured into water (2 litres) and acidified to pH 4—5 with an acetic acid. The solid product was recrystallised from acetonitrile to yield 2(RS),3(RS)-2-(n-heptyl)-3-methylindoline-6-carboxylic acid (32.5 g) in the form of off-white crystals, m.p. 121—124°C.

Methyl 3-formyl-2-(n-heptyl)indole-6-carboxylate, used as starting material, was prepared as
65 follows:—

A solution of phosphorus oxychloride (35 ml) in dimethylformamide (150 ml) was added to a solution of methyl 2-(n-heptyl)indole-6-carboxylate (67.5 g) in dimethylformamide (250 ml) and the resulting solution was stirred at between 70° and 85°C for 2 hours. The mixture was then stirred for 30 minutes while the temperature dropped to 50°C and was then poured into water (2 litres). Ice was added to reduce the temperature to 25°C and a 50% w/v aqueous sodium hydroxide solution was added until the pH reached 11. After stirring for 10 minutes, acetic acid was added to pH 5 and the mixture was stirred until the product had solidified. Recrystallisation from methanol yielded methyl 3-formyl-2-(n-heptyl)indole-6-carboxylate (65.0 g) in the form of colourless, lustrous needles, m.p. 177—180°C.

Example 136

Compound CUU

By proceeding in a similar manner to that hereinbefore described in Example 1 for the preparation of 2-(n-pentadecyl)indole-6-carboxylic acid but replacing 3-(n-hexadecanamido)-4-methylbenzoic acid by (RS)-3-(2-ethylundecanamido)-4-methylbenzoic acid, there was prepared (RS)-2-(1-ethyldecyl)indole-6-carboxylic acid, in the form of an off-white solid, m.p. 70—73°C after chromatography of the oil obtained.

The 3-(2-ethylundecanamido)-4-methylbenzoic acid used as starting material was prepared as follows:—

A mixture of (RS)-2-ethylundecanoyl chloride (1.16 g) and 3-amino-4-methylbenzoic acid (0.75 g) was placed in an oil bath at 90°C and the temperature was gradually raised to 140°C for 2 hours. After cooling, the solid was recrystallised from a mixture of ethanol (25 ml) and water (1 ml) to yield (RS)-3-(2-ethylundecanamido)-4-methylbenzoic acid (1.65 g) in the form of a white solid, m.p. 217—220°C.

Example 137

Compound CVV

A mixture of sodium 2-(n-undecyl)indole-6-carboxylate (5.0 g) and 3-chloro-1,2-propanediol (1.64 g) in diglyme (50 ml) was refluxed for 30 minutes. Potassium iodide (2.5 g) was added and the mixture refluxed for 48 hours. The mixture was cooled, water (50 ml) was added and the resulting emulsion was extracted with dichloromethane (2 x 100 ml). The combined extracts were dried over anhydrous magnesium sulphate, filtered, and the solvent evaporated to dryness. The solid residue was recrystallised from cyclohexane, filtered off and dried to give (RS)-2,3-dihydroxyprop-1-yl-2-(n-undecyl)indole-6-carboxylate (1.5 g) in the form of a white solid, m.p. 110—112°C.

The following Example illustrates the preparation of the compounds of general formula XXL some of which are compounds of general formula I and others are intermediates in the preparation of other compounds of general formula I.

Example 138

Compound of formula XXI

A suspension of 1-(4-carboxy-2-nitrophenyl)-2-nitropropene (14.78 g), palladium on charcoal catalyst (2.2 g; 5% w/w) and diatomaceous earth (3 g) in ethyl acetate (275 ml) containing glacial acetic acid (3.12 g) was shaken under an atmosphere of hydrogen at room temperature for 3 hours. The temperature of the reaction mixture rose slightly during this period. When hydrogen uptake was complete (96% of theory), the mixture was filtered through diatomaceous earth to remove the catalyst and the filtrate was washed with water (100 ml) and dried over magnesium sulphate. The ethyl acetate solution was concentrated *in vacuo* to give a pale yellow solid (7.36 g). The solid was dissolved in hot glacial acetic acid (100 ml) and water was added until a slight clouding occurred. The hot solution was treated with charcoal and then filtered. The resulting filtrate was cooled and the pale yellow solid which appeared was filtered off to give 2-methylindole-6-carboxylic acid (3.3 g), m.p. 200—202°C (with decomposition).

The 1-(4-carboxy-2-nitrophenyl)-2-nitropropene, used as starting material above, was prepared as follows:—

Fuming nitric acid (95—98% w/w, 3.7 ml) was added dropwise with stirring to concentrated sulphuric acid (98% w/w, 30 ml), whilst maintaining the temperature at 0—10°C. 1-(4-Carboxyphenyl)-2-nitropropene (15.3 g) was then added in portions with vigorous stirring over 15 minutes, whilst maintaining the temperature at 0—10°C. The mixture was stirred for 30 minutes at the same temperature. The viscous reaction mixture was poured into an ice/water mixture (600 ml) and the resulting yellow solid was filtered off and washed with water to give 1-(4-carboxy-2-nitrophenyl)-2-nitropropene (17.17 g), m.p. 200—202°C (with decomposition).

The 1-(4-carboxyphenyl)-2-nitropropene, used as starting material above, was prepared as follows:—

A solution of 4-carboxybenzaldehyde (38.44 g) in nitroethane (360 ml) and butylamine (2 ml) was heated at reflux for 2 hours with azeotropic distillation of water using a Dean and Stark apparatus. The solution was cooled to room temperature and the resulting solid was collected and recrystallised from isopropanol (250 ml) with hot filtration to give 1-(4-carboxyphenyl)-2-nitropropene (31.57 g) in the form of a yellow crystalline solid, m.p. 212—214°C.

Compounds of general formula I may be prepared in a similar manner to that described above but replacing 1-(4-carboxy-2-nitrophenyl)-2-nitropropene by the appropriate 1-(carboxy-2-nitrophenyl)-2-nitroalkene.

The present invention includes within its scope pharmaceutical compositions which comprise at least one of the compounds of general formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier or coating. In clinical practice the compounds of the present invention may be administered parenterally, but are preferably administered rectally or, more preferably, orally.

Solid compositions for oral administration include compressed tablets, pills, powders and granules. In such solid compositions, one or more of the active compounds is, or are, admixed with at least one inert diluent such as starch, sucrose or lactose. The compositions may also comprise, as is normal practice, additional substances other than inert diluents, e.g. lubricating agents, such as magnesium stearate.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as water and liquid paraffin. Besides inert diluents such compositions may comprise adjuvants, such as wetting, and suspending agents, and sweetening, flavouring, perfuming and preserving agents. The compositions according to the invention for oral administration also include capsules of absorbable material such as gelatin, containing one or more of the active substances with or without the addition of diluents or excipients.

Preparations according to the invention for parenteral administration include sterile aqueous, aqueous-organic, and organic solutions, suspensions and emulsions. Examples of organic solvents or suspending media are propylene glycol, polyethylene glycol, vegetable oils such as olive oil and injectable organic esters such as ethyl oleate. The compositions may also contain adjuvants such as stabilising, preserving, wetting, emulsifying and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporation in the compositions of sterilizing agents, by irradiation or by heating. They may also be manufactured in the form of sterile solid compositions, which can be dissolved in sterile water or some other sterile injectable medium immediately before use.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing one or more of the compounds of formula I or a pharmaceutically acceptable salt thereof.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally between 0.1 and 50 mg/kg body weight per day by oral administration. For example, as hypolipidaemic agents and in associated cardiovascular diseases between 10 and 50 mg/kg body weight per day by oral administration, and in the treatment of diabetes between 5 and 40 mg/kg body weight per day by oral administration.

The following Example illustrates pharmaceutical compositions according to the present invention.

Example 139

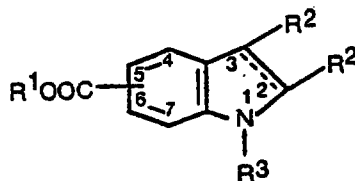
No. 2 size gelatin capsules each containing:—

	2-(n-pentadecyl)indole-6-carboxylic acid	20 mg
	lactose	100 mg
	starch	60 mg
	dextrin	40 mg
	magnesium stearate	1 mg

were prepared in accordance with the usual procedure.

Claims for the Contracting States: BE CH DE FR GB IT LU LI NL SE

1. Indole and indoline derivatives of the general formula:—



wherein — indicates a double bond or a single bond between carbon atoms, R¹ represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms (which may be substituted by one or more than one of the same type of substituents selected from the hydroxy group, alkenyl groups containing from 2 to 5 carbon atoms, and alkanoyloxy groups containing from 2 to 7 carbon atoms) or a hydrogen atom, and one of the symbols R² represents a straight- or branched-chain alkyl group containing from 7 to 24 carbon atoms and the other symbol R² represents a straight- or branched-chain alkyl group containing from 1 to 24 carbon atoms, or a hydrogen atom, and R³ represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms or a hydrogen atom, and pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1 wherein the group R¹OOC— is attached to the 5 or 6 position of the indole or indoline ring system.

3. Compounds according to claim 1 or 2 wherein R¹ represents a hydrogen atom.

4. Compounds according to claim 1, 2 or 3 wherein one of the symbols R² represents a straight- or branched-chain alkyl group containing from 7 to 20 carbon atoms, and the other symbol R² represents a straight- or branched-chain alkyl group containing from 1 to 24 carbon atoms or a hydrogen atom.

5. Compounds according to any one of claims 1 to 4 wherein the second symbol R² represents a hydrogen atom.

6. Compounds according to claim 4 wherein the second symbol R² represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms.

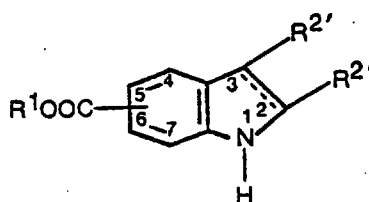
7. Compounds according to any one of the preceding claims wherein one of the symbols R² represents a hydrogen or a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms, and that particular symbol is attached to the 3 position of the indole or indoline ring system.

8. Compounds according to claim 7 wherein the symbol R² attached to the 3 position of the indole or indoline ring system represents methyl.

9. Compounds according to any one of claims 1, 2 and 4 to 8 wherein R¹ represents a methyl, ethyl, butyl, 2,3-dihydroxyprop-1-yl, allyl or pivaloyloxymethyl group.

10. Compounds according to any one of the preceding claims wherein the symbol R³ in the general formula depicted in claim 1 represents hydrogen.

11. Indole and indoline derivatives according to claim 1 of the general formula:—



wherein — indicates a double bond or a single bond between carbon atoms, the group R¹OOC— is attached to the 5 or 6 position of the indole or indoline ring system, R¹ represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms or a hydrogen atom, and one of the symbols R²' represents a straight- or branched-chain alkyl group containing from 7 to 24 carbon atoms and the other symbol R²' represents a straight- or branched-chain alkyl group containing from 1 to 24 carbon atoms, and pharmaceutically acceptable salts thereof.

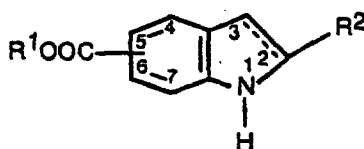
12. Compounds according to claim 11 wherein R¹ represents a hydrogen atom.

13. Compounds according to claim 11 or 12 wherein one of the symbols R²' represents a straight- or branched-chain alkyl group containing from 7 to 20 carbon atoms, and the other symbol R²' represents a straight- or branched-chain alkyl group containing from 1 to 24 carbon atoms.

14. Compounds according to claim 11, 12 or 13 wherein the second symbol R²' represents an alkyl group containing from 1 to 6 carbon atoms and that particular symbol is attached to the 3 position of the indole or indoline ring system.



15. Indole and indoline derivatives according to claim 1 of the general formula:—

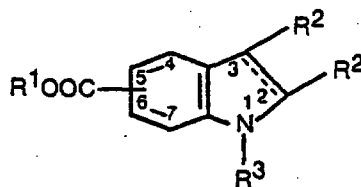


III

wherein — indicates a double bond or a single bond between carbon atoms, the group R¹OOC— is attached to the 5 or 6 position of the indole or indoline ring system, R¹ represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms or a hydrogen atom, and R² represents a straight- or branched-chain alkyl group containing from 7 to 24 carbon atoms, and pharmaceutically acceptable salts thereof.

16. Compounds according to claim 15 wherein R¹ represents a hydrogen atom.
17. Compounds according to claim 15 or 16 wherein R² represents a straight- or branched-chain alkyl group containing from 7 to 20 carbon atoms.
18. Compounds according to claim 11, 13, 14 or 15 wherein R¹ represents a methyl, ethyl or butyl group.
19. A Compounds according to claim 1 which is 2-(n-octadecyl)indole-5-carboxylic acid and pharmaceutically acceptable salts thereof.
20. A compound according to claim 1 which is 2-(n-undecyl)indole-6-carboxylic acid and pharmaceutically acceptable salts thereof.
21. A compound according to claim 1 which is 2-(n-pentadecyl)indole-5-carboxylic acid and pharmaceutically acceptable salts thereof.
22. A compound according to claim 1 which is 2-(n-undecyl)indole-5-carboxylic acid and pharmaceutically acceptable salts thereof.
23. A compound according to claim 1 which is 2-(n-pentadecyl)indole-6-carboxylic acid and pharmaceutically acceptable salts thereof.
24. A compound according to claim 1 which is 2-(1-methyldecyl)indole-6-carboxylic acid and pharmaceutically acceptable salts thereof.
25. A compound according to claim 1 which is 2-(n-undecyl)indoline-5-carboxylic acid and pharmaceutically acceptable salts thereof.
26. A compound according to claim 1 which is 2-(n-decyl)indoline-5-carboxylic acid and pharmaceutically acceptable salts thereof.
27. A compound according to claim 1 which is 2-(n-undecyl)indoline-6-carboxylic acid and pharmaceutically acceptable salts thereof.
28. A compound according to claim 1 which is 2-(n-undecyl)-3-methylindoline-6-carboxylic acid and pharmaceutically acceptable salts thereof.
29. A compound according to claim 1 which is 2-n-heptadecylindole-5-carboxylic acid and pharmaceutically acceptable salts thereof.
30. A compound according to claim 1 which is 2-n-octylindole-6-carboxylic acid and pharmaceutically acceptable salts thereof.
31. A compound according to claim 1 which is 2-n-dodecylindole-6-carboxylic acid and pharmaceutically acceptable salts thereof.
32. A compound according to claim 1 which is 2-n-hexadecylindole-5-carboxylic acid and pharmaceutically acceptable salts thereof.

33. Process for the preparation of an indoline compound of the general formula depicted in claim 1, wherein — represents a single bond between carbon atoms and R¹, R² and R³ are as defined in claim 1, which comprises the reduction of the C₂—C₃ double bond of a corresponding indole compound of the general formula:—



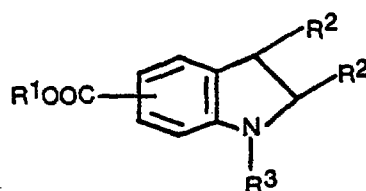
V

(wherein the symbols R¹, R² and R³ are as defined in claim 1) by catalytic hydrogenation.

34. Process for the preparation of an indole compound of the general formula depicted in claim 1, wherein — represents a double bond between carbon atoms and R¹, R² and R³ are as defined in



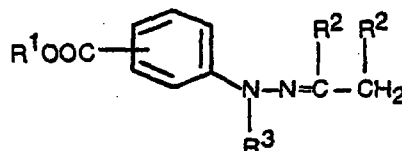
claim 1, which comprises the catalytic dehydrogenation of a corresponding indoline compound of the general formula:—



IV

wherein R¹, R² and R³ are as defined in claim 1.

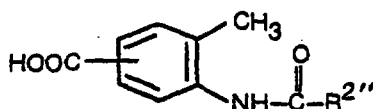
35. Process for the preparation of an indole compound of the general formula depicted in claim 1, wherein — represents a double bond between carbon atoms, and R¹, R² and R³ are as defined in claim 1, which comprises the cyclisation of a compound of the general formula:—



VI

(wherein R¹, R² and R³ are as defined in claim 1) by reaction with an inorganic acid or some other Lewis acid, at an elevated temperature optionally in the presence of an inert organic solvent.

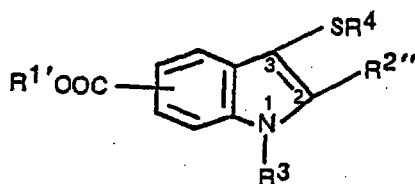
36. Process for the preparation of an indole compound of the general formula depicted in claim 1, wherein — represents a double bond between carbon atoms, the symbol R² attached to the 2 position of the indole ring system represents a straight- or branched-chain alkyl group containing from 7 to 24 carbon atoms, the symbol R² attached to the 3-position represents a hydrogen atom, and R¹ and R³ represents hydrogen atoms, which comprises the cyclisation of a compound of the general formula:—



VII

(wherein R²'' represents a straight- or branched-chain alkyl group containing 7 to 24 carbon atoms) in the presence of a base at an elevated temperature with or without an inert organic solvent.

37. Process for the preparation of an indole compound of the general formula depicted in claim 1, wherein — represents a double bond between carbon atoms, R¹ represents an optionally substituted alkyl group as defined in claim 1, the symbol R² attached to the 2 position of the indole ring system represents a straight- or branched-chain alkyl group containing from 7 to 24 carbon atoms, the symbol R² attached to the 3 position represents a hydrogen atom, and R³ is as defined in claim 1, which comprises the reaction of a 3-alkylthio-indole derivative of the general formula:—



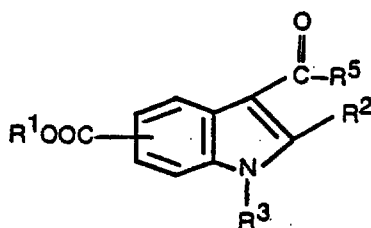
VIII

(wherein R²'' and R³ are as defined in claim 36 and claim 1 respectively, R¹' represents an optionally substituted alkyl group as defined for R¹ in claim 1, and R⁴ represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms) with Raney nickel in the presence of an inert organic solvent to replace the 3-alkylthio substituent by a hydrogen atom.

38. Process for the preparation of an indole or indoline compound of the general formula depicted in claim 1, wherein the symbol R² in the 3 position of the indole or indoline ring system represents a straight- or branched-chain alkyl group containing from 1 to 24 carbon atoms, the symbol R² attached to the 2 position represents a straight- or branched-chain alkyl group containing 7 to 24 carbon atoms, or a hydrogen atom or a straight- or branched-chain alkyl group containing 1 to 6 carbon atoms when R² in the 3 position is an alkyl group containing from 7 to 24 carbon atoms, and R¹ and R³ are as



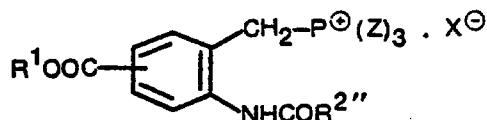
defined in claim 1, which comprises the reduction of the carbonyl radical of a compound of the general formula:—



IX

(wherein R¹ and R³ are as defined in claim 1, R⁵ represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 23 carbon atoms, and R² represents a hydrogen atom or an alkyl group as appropriate to fit the general formula depicted in claim 1) to methylene using borane when it is desired to obtain an indole product of the general formula depicted in claim 1 wherein — represents a double bond between carbon atoms, or catalytic hydrogenation when it is desired to obtain an indoline product of the general formula depicted in claim 1 wherein — represents a single bond between carbon atoms.

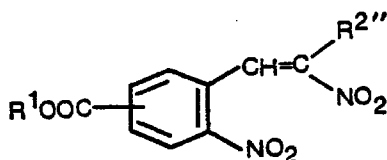
39. Process for the preparation of an indole compound of the general formula depicted in claim 1, wherein — represents a double bond between carbon atoms, R¹ is as defined in claim 1, the symbol R² attached to the 2 position of the indole ring system represents a straight- or branched-chain alkyl group containing from 7 to 24 carbon atoms, the symbol R² attached to the 3 position represents a hydrogen atom, and R³ represents a hydrogen atom, which comprises the cyclisation of a compound of the general formula:—



X

(wherein X⁻ represents an anion, Z represents an optionally substituted phenyl group, and R¹ and R²'' are as defined in claim 1 and claim 4 respectively) in an inert organic solvent in the presence of a base, preferably at an elevated temperature.

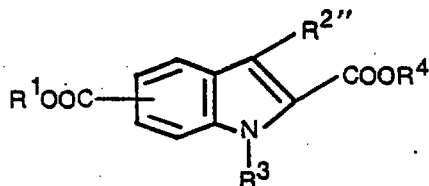
40. Process for the preparation of an indole compound of the general formula depicted in claim 1, wherein — represents a double bond between carbon atoms, R¹ is as defined in claim 1, symbol R² attached to the 2 position of the indole ring system represents a straight- or branched-chain alkyl group containing from 7 to 24 carbon atoms, the symbol R² attached to the 3 position represents a hydrogen atom, and R³ represents a hydrogen atom, which comprises the catalytic hydrogenation of a compound of the general formula:—



XI

(wherein R¹ and R²'' are as defined in claim 1 and claim 36 respectively), followed by cyclisation of the amine intermediate so obtained.

41. Process for the preparation of an indole compound of the general formula depicted in claim 1, wherein — represents a double bond between carbon atoms, R¹ is as defined in claim 1, the symbol R² attached to the 3 position of the indole ring system represents a straight- or branched-chain alkyl group containing from 7 to 24 carbon atoms, the symbol R² attached to the 2-position represents a hydrogen atom and R³ is as defined in claim 1, which comprises the decarboxylation by heating of a 2-alkoxycarbonyl-indole derivative of the general formula:—



XII

wherein R¹ and R³ are as defined in claim 1, and R²'' and R⁴ are as defined in claim 36 and claim 37 respectively.

42. Process for the preparation of an indole or indoline derivative of the general formula depicted



in claim 1, wherein R¹ represents a hydrogen atom and R² and R³ are as defined in claim 1, which comprises the hydrolysis of a corresponding ester of the general formula depicted in claim 1 wherein R² and R³ are as defined in claim 1 and R¹ represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms optionally substituted as stated in claim 1.

43. Process for the preparation of an ester of an indole or indoline derivative of the general formula depicted in claim 1, wherein R¹ represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms (which may be substituted by one or more than one of the same type of substituents selected from the hydroxy group, alkenyl groups containing 2 to 5 carbon atoms and alkanoyloxy groups containing from 2 to 7 carbon atoms) which comprises the esterification of a corresponding carboxylic acid wherein R¹ in the general formula depicted in claim 1 represents a hydrogen atom, and R² and R³ are as defined in claim 1.

44. Process for the preparation of an indole or indoline derivative of the general formula depicted in claim 1, wherein R³ represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms and R¹ and R² are as defined in claim 1, which comprises the N-(C₁—C₆)alkylation of a corresponding compound of the general formula depicted in claim 1 wherein R³ represents a hydrogen atom.

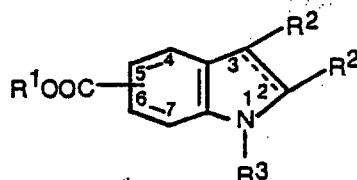
45. Process according to any one of the claims 33 to 44 followed by the step of converting an indole or indoline compound of the general formula depicted in claim 1 so obtained — when appropriate — into a pharmaceutically acceptable salt.

46. Pharmaceutical compositions which comprise, as active ingredient, at least one of the indole or indoline derivatives of the general formula depicted in claim 1, wherein — and the symbols R¹, R² and R³ are as defined in claim 1, or — when appropriate — a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier or coating.

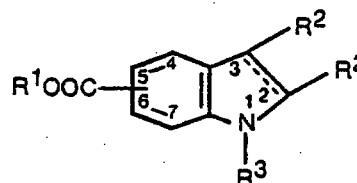
47. Indole or indoline derivatives of the general formula depicted in claim 1, wherein — and the symbols R¹, R² and R³ are as defined in claim 1, and — when appropriate — pharmaceutically acceptable salts thereof, for use in the prevention or treatment of diabetes mellitus, hyperlipoproteinaemic states, of atherosclerosis, and of angina, myocardial infarction, cerebral vascular occlusion, arterial aneurism, peripheral vascular disease, recurrent pancreatitis and xanthomas.

Claims for the contracting state: AT

1. Process for the preparation of an indoline compound of the general formula:



wherein — represents a single bond between carbon atoms, R¹ represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms (which may be substituted by one or more than one of the same type of substituents selected from the hydroxy group, alkenyl groups containing from 2 to 5 carbon atoms, and alkanoyloxy groups containing from 2 to 7 carbon atoms) or a hydrogen atom, and one of the symbols R² represents a straight- or branched-chain alkyl group containing from 7 to 24 carbon atoms and the other symbol R² represents a straight- or branched-chain alkyl group containing from 1 to 24 carbon atoms, or a hydrogen atom, and R³ represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms or a hydrogen atom, which comprises the reduction of the C₂—C₃ double bond of a corresponding indole compound of the general formula:—

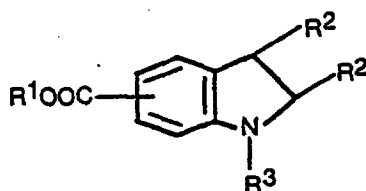


(wherein the symbols R¹, R² and R³ are as hereinbefore defined) by catalytic hydrogenation.

2. Process for the preparation of an indole compound of the general formula depicted in claim 1, wherein — represents a double bond between carbon atoms and R¹, R² and R³ are as defined in



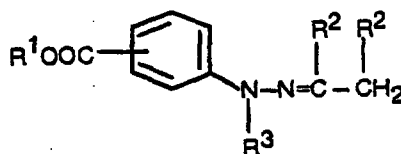
claim 1, which comprises the catalytic dehydrogenation of a corresponding indoline compound of the general formula:—



IV

wherein R^1 , R^2 and R^3 are as defined in claim 1.

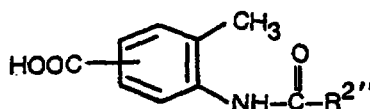
3. Process for the preparation of an indole compound of the general formula depicted in claim 1, wherein — represents a double bond between carbon atoms, and R^1 , R^2 and R^3 are as defined in claim 1, which comprises the cyclisation of a compound of the general formula:—



VI

(wherein R^1 , R^2 and R^3 are as defined in claim 1) by reaction with an inorganic acid or some other Lewis acid, at an elevated temperature optionally in the presence of an inert organic solvent.

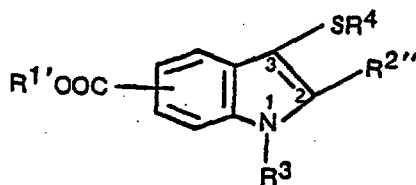
4. Process for the preparation of an indole compound of the general formula depicted in claim 1, wherein — represents a double bond between carbon atoms, the symbol R^2 attached to the 2 position of the indole ring system represents a straight- or branched-chain alkyl group containing from 7 to 24 carbon atoms, the symbol R^2 attached to the 3-position represents a hydrogen atom, and R^1 and R^3 represent hydrogen atoms, which comprises the cyclisation of a compound of the general formula:—



VII

(wherein $R^{2''}$ represents a straight- or branched-chain alkyl group containing 7 to 24 carbon atoms) in the presence of a base at an elevated temperature with or without an inert organic solvent.

5. Process for the preparation of an indole compound of the general formula depicted in claim 1, wherein — represents a double bond between carbon atoms, R^1 represents an optionally substituted alkyl group as defined in claim 1, the symbol R^2 attached to the 2 position of the indole ring system represents a straight- or branched-chain alkyl group containing from 7 to 24 carbon atoms, the symbol R^2 attached to the 3 position represents a hydrogen atom, and R^3 is as defined in claim 1, which comprises the reaction of a 3-alkylthio-indole derivative of the general formula:—



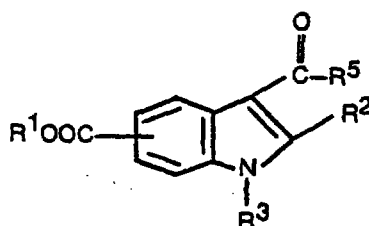
VIII

(wherein $R^{2''}$ and R^3 are as defined in claim 4 and claim 1 respectively, R^1 represents an optionally substituted alkyl group as defined for R^1 in claim 1, and R^4 represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms) with Raney nickel in the presence of an inert organic solvent to replace the 3-alkylthio substituent by a hydrogen atom.

6. Process for the preparation of an indole or indoline compound of the general formula depicted in claim 1, wherein the symbol R^2 in the 3 position of the indole or indoline ring system represents a straight- or branched-chain alkyl group containing from 1 to 24 carbon atoms, the symbol R^2 attached to the 2 position represents a straight- or branched-chain alkyl group containing 7 to 24 carbon atoms, or a hydrogen atom or a straight- or branched-chain alkyl group containing 1 to 6 carbon atoms when R^2 in the 3 position is an alkyl group containing from 7 to 24 carbon atoms, and R^1 and R^3 are as



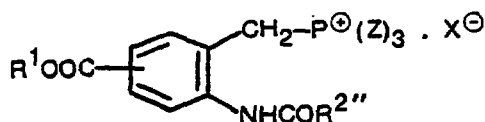
defined in claim 1, which comprises the reduction of the carbonyl radical of a compound of the general formula:—



IX

(wherein R¹ and R³ are as defined in claim 1, R⁵ represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 23 carbon atoms, and R² represents a hydrogen atom or an alkyl group as appropriate to fit the general formula depicted in claim 1) to methylene using borane when it is desired to obtain an indole product of the general formula depicted in claim 1 wherein — represents a double bond between carbon atoms, or catalytic hydrogenation when it is desired to obtain an indoline product of the general formula depicted in claim 1 wherein — represents a single bond between carbon atoms.

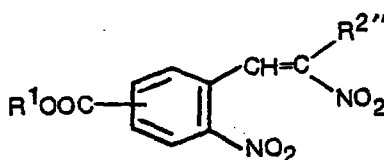
7. Process for the preparation of an indole compound of the general formula depicted in claim 1, wherein — represents a double bond between carbon atoms, R¹ is as defined in claim 1, the symbol R² attached to the 2 position of the indole ring system represents a straight- or branched-chain alkyl group containing from 7 to 24 carbon atoms, the symbol R² attached to the 3 position represents a hydrogen atom, and R³ represents a hydrogen atom, which comprises the cyclisation of a compound of the general formula:—



X

(wherein X⁻ represents an anion, Z represents an optionally substituted phenyl group, and R¹ and R² are as defined in claim 1 and claim 4 respectively) in an inert organic solvent in the presence of a base, preferably at an elevated temperature.

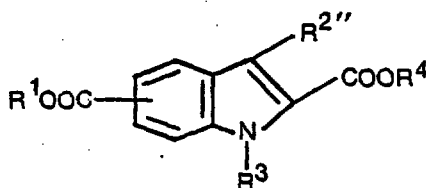
8. Process for the preparation of an indole compound of the general formula depicted in claim 1, wherein — represents a double bond between carbon atoms, R¹ is as defined in claim 1, symbol R² attached to the 2 position of the indole ring system represents a straight- or branched-chain alkyl group containing from 7 to 24 carbon atoms, the symbol R² attached to the 3 position represents a hydrogen atom, and R³ represents a hydrogen atom, which comprises the catalytic hydrogenation of a compound of the general formula:—



XI

(wherein R¹ and R² are as defined in claim 1 and claim 4 respectively), followed by cyclisation of the amine intermediate so obtained.

9. Process for the preparation of an indole compound of the general formula depicted in claim 1, wherein — represents a double bond between carbon atoms, R¹ is as defined in claim 1, the symbol R² attached to the 3 position of the indole ring system represents a straight- or branched-chain alkyl group containing from 7 to 24 carbon atoms, the symbol R² attached to the 2-position represents a hydrogen atom and R³ is as defined in claim 1, which comprises the decarboxylation by heating of a 2-alkoxycarbonyl-indole derivative of the general formula:—



XII

wherein R¹ and R³ are as defined in claim 1, and R² and R⁴ are as defined in claim 4 and claim 5 respectively.

10. Process for the preparation of an indole or indoline derivative of the general formula depicted



in claim 1, wherein R^1 represents a hydrogen atom and R^2 and R^3 are as defined in claim 1, which comprises the hydrolysis of a corresponding ester of the general formula depicted in claim 1 wherein R^2 and R^3 are as defined in claim 1 and R^1 represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms optionally substituted as stated in claim 1.

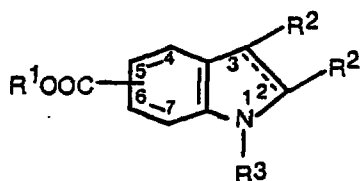
11. Process for the preparation of an ester of an indole or indoline derivative of the general formula depicted in claim 1, wherein R^1 represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms (which may be substituted by one or more than one of the same type of substituents selected from the hydroxy group, alkenyl groups containing 2 to 5 carbon atoms and alkanoyloxy groups containing from 2 to 7 carbon atoms) which comprises the esterification of a corresponding carboxylic acid wherein R^1 in the general formula depicted in claim 1 represents a hydrogen atom, and R^2 and R^3 are as defined in claim 1.

12. Process for the preparation of an indole or indoline derivative of the general formula depicted in claim 1, wherein R^3 represents a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms and R^1 and R^2 are as defined in claim 1, which comprises the $N-(C_1-C_6)$ alkylation of a corresponding compound of the general formula depicted in claim 1 wherein R^3 represents a hydrogen atom.

13. Process according to any one of the preceding claims followed by the step of converting an indole or indoline compound of the general formula depicted in claim 1 so obtained — when appropriate — into a pharmaceutically acceptable salt.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Indol- und Indolin-Derivate der allgemeinen Formel I



worin — eine Doppelbindung oder eine Einfachbindung zwischen Kohlenstoffatomen anzeigt, R^1 eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen (welche durch einen oder mehrere Substituenten vom gleichen Typ, ausgewählt unter der Hydroxygruppe, Alkenylgruppen mit 2 bis 5 Kohlenstoffatomen und Alkanoyloxygruppen mit 2 bis 7 Kohlenstoffatomen, substituiert sein kann) oder ein Wasserstoffatom bedeutet und eines der Symbole R^2 eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 24 Kohlenstoffatomen und das andere Symbol R^2 eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 24 Kohlenstoffatomen oder ein Wasserstoffatom bedeutet und R^3 eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen oder ein Wasserstoffatom bedeutet, und pharmazeutisch annehmbare Salze davon.

2. Verbindungen gemäß Anspruch 1, worin die Gruppe R^1OOC- in der 5- oder 6-Stellung des Indol- oder Indolin-Ringsystems verknüpft ist.

3. Verbindungen gemäß Anspruch 1 oder 2, worin R^1 ein Wasserstoffatom bedeutet.

4. Verbindungen gemäß Anspruch 1, 2 oder 3, worin eines der Symbole R^2 eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 20 Kohlenstoffatomen und das andere Symbol R^2 eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 24 Kohlenstoffatomen oder ein Wasserstoffatom bedeutet.

5. Verbindungen gemäß einen der Ansprüche 1 bis 4, worin das zweite Symbol R^2 ein Wasserstoffatom bedeutet.

6. Verbindungen gemäß Anspruch 4, worin das zweite Symbol R^2 eine geradkettige oder verzweigt-kettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen bedeutet.

7. Verbindungen gemäß einem der vorhergehenden Ansprüche, worin eines der Symbole R^2 ein Wasserstoffatom oder eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen bedeutet und dieses besondere Symbol mit der 3-Stellung des Indol- oder Indolin-Ringsystems verknüpft ist.

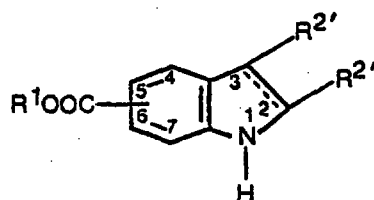
8. Verbindung gemäß Anspruch 7, worin das Symbol R^2 , das mit der 3-Stellung des Indol- oder Indolin-Ringsystems verknüpft ist, Methyl bedeutet.

9. Verbindungen gemäß einem der Ansprüche 1, 2 und 4 bis 8, worin R^1 eine Methyl-, Ethyl-, Butyl-, 2,3-Dihydroxyprop-1-yl-, Allyl- oder Pivaloyloxymethylgruppe bedeutet.

10. Verbindungen gemäß einen der vorhergehenden Ansprüche, worin das Symbol R^3 in der allgemeinen Formel, dargestellt in Anspruch 1, Wasserstoff bedeutet.



11. Indol- und Indolin-Derivative gemäß Anspruch 1 der allgemeinen Formel II



II

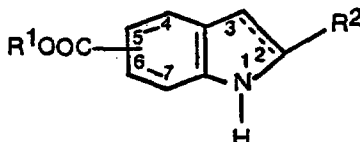
worin --- eine Doppelbindung oder eine Einfachbindung zwischen Kohlenstoffatomen anzeigt, die Gruppe $\text{R}^1\text{OOC-}$ mit der 5- oder 6-Stellung des Indol- oder Indolin-Ringsystems verknüpft ist, R^1 eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen oder ein Wasserstoffatom bedeutet und eines der Symbole $\text{R}^{2'}$ eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 24 Kohlenstoffatomen und das andere Symbol $\text{R}^{2'}$ eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 24 Kohlenstoffatomen bedeutet, und pharmazeutisch annehmbare Salze davon.

12. Verbindungen gemäß Anspruch 11, worin R^1 ein Wasserstoffatom bedeutet.

13. Verbindung gemäß Anspruch 11 oder 12, worin eines der Symbole $\text{R}^{2'}$ eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 20 Kohlenstoffatom und das andere Symbol $\text{R}^{2'}$ eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 24 Kohlenstoffatomen bedeutet.

14. Verbindungen gemäß Anspruch 11, 12 oder 13, worin das zweite Symbol $\text{R}^{2'}$ eine Alkylgruppe mit 1 bis 6 Kohlenstoffatomen bedeutet und dieses besondere Symbol mit der 3-Stellung des Indol- oder Indolin-Ringsystems verknüpft ist.

15. Indol- und Indolin-Derivate gemäß Anspruch 1 der allgemeinen Formel III



III

worin --- eine Doppelbindung oder eine Einfachbindung zwischen Kohlenstoffatomen anzeigt, die Gruppe $\text{R}^1\text{OOC-}$ mit der 5- oder 6- Stellung des Indol- oder Indolin-Ringsystems verknüpft ist, R^1 eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen oder ein Wasserstoffatom bedeutet und R^2 eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 24 Kohlenstoffatomen bedeutet, und pharmazeutisch annehmbare Salze davon.

16. Verbindungen gemäß Anspruch 15, worin R^1 ein Wasserstoffatom bedeutet.

17. Verbindungen gemäß Anspruch 15 oder 16, worin R^2 eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 20 Kohlenstoffatomen bedeutet.

18. Verbindung gemäß Anspruch 11, 13, 14 oder 15, worin R^1 eine Methyl-, Ethyl- oder Butylgruppe bedeutet.

19. Eine Verbindung gemäß Anspruch 1, welche 2-(n-Octadecyl)-indol-5-carbonsäure ist und pharmazeutisch annehmbare Salze davon.

20. Eine Verbindung gemäß Anspruch 1, welche 2-(n-Undecyl)-indol-6-carbonsäure ist und pharmazeutisch annehmbare Salze davon.

21. Eine Verbindung gemäß Anspruch 1, welche 2-(n-Pentadecyl)-indol-5-carbonsäure ist und pharmazeutisch annehmbare Salze davon.

22. Eine Verbindung gemäß Anspruch 1, welche 2-(n-Undecyl)-indol-5-carbonsäure ist und pharmazeutisch annehmbare Salze davon.

23. Eine Verbindung gemäß Anspruch 1, welche 2-(n-Pentadecyl)-indol-6-carbonsäure ist und pharmazeutisch annehmbare Salze davon.

24. Eine Verbindung gemäß Anspruch 1, welche 2-(1-Methyldecyl)-indol-6-carbonsäure ist und pharmazeutisch annehmbare Salze davon.

25. Eine Verbindung gemäß Anspruch 1, welche 2-(n-Undecyl)-indolin-5-carbonsäure ist und pharmazeutisch annehmbare Salze davon.

26. Eine Verbindung gemäß Anspruch 1, welche 2-(n-Decyl)-indolin-5-carbonsäure ist und pharmazeutisch annehmbare Salze davon.

27. Eine Verbindung gemäß Anspruch 1, welche 2-(n-Undecyl)-indolin-6-carbonsäure ist und pharmazeutisch annehmbare Salze davon.

28. Eine Verbindung gemäß Anspruch 1, welche 2-(n-Undecyl)-3-methylindolin-6-carbonsäure ist und pharmazeutisch annehmbare Salze davon.

29. Eine Verbindung gemäß Anspruch 1, welche 2-n-Heptadecylindol-5-carbonsäure ist und pharmazeutisch annehmbare Salze davon.

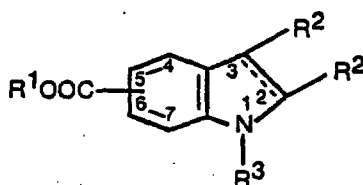
30. Eine Verbindung gemäß Anspruch 1, welche 2-n-Octylindol-6-carbonsäure ist und pharmazeutisch annehmbare Salze davon.



31. Eine Verbindung gemäß Anspruch 1, welche 2-n-Dodecylindol-6-carbonsäure ist und pharmazeutisch annehmbare Salze davon.

32. Eine Verbindung gemäß Anspruch 1, welche 2-n-Hexadecylindol-5-carbonsäure ist und pharmazeutisch annehmbare Salze davon.

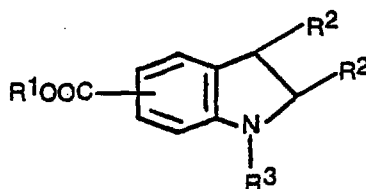
33. Verfahren zur Herstellung einer Indolinverbindung der allgemeinen Formel, dargestellt in Anspruch 1, worin --- eine Einfachbindung zwischen Kohlenstoffatomen bedeutet und R^1 , R^2 und R^3 wie in Anspruch 1 definiert sind, gekennzeichnet durch die Reduktion der $C_2\text{---}C_3$ -Doppelbindung einer entsprechenden Indolverbindung der allgemeinen Formel V



V

(worin die Symbole R^1 , R^2 und R^3 wie in Anspruch 1 definiert sind) durch katalytische Hydrierung.

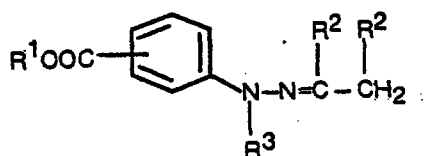
34. Verfahren zur Herstellung einer Indolverbindung der allgemeinen Formel, dargestellt in Anspruch 1, worin --- eine Doppelbindung zwischen Kohlenstoffatomen bedeutet und R^1 , R^2 und R^3 wie in Anspruch 1 definiert sind, gekennzeichnet durch die katalytische Dehydrierung einer entsprechenden Indolinverbindung der allgemeinen Formel IV



IV

worin R^1 , R^2 und R^3 wie in Anspruch 1 definiert sind.

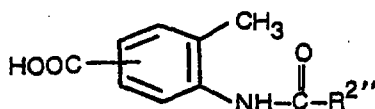
35. Verfahren zur Herstellung einer Indolverbindung der allgemeinen Formel, dargestellt in Anspruch 1, worin --- eine Doppelbindung zwischen Kohlenstoffatomen bedeutet und R^1 , R^2 und R^3 wie in Anspruch 1 definiert sind, gekennzeichnet durch die Cyclisierung einer Verbindung der allgemeinen Formel VI



VI

(worin R^1 , R^2 und R^3 wie in Anspruch 1 definiert sind) durch Reaktion mit einer anorganischen Säure oder einer anderen Lewisäure bei erhöhter Temperatur, gegebenenfalls in Gegenwart eines inerten, organischen Lösungsmittels.

36. Verfahren zur Herstellung einer Indolverbindung der allgemeinen Formel, dargestellt in Anspruch 1, worin --- eine Doppelbindung zwischen Kohlenstoffatomen bedeutet, das Symbol R^2 , das mit der 2-Stellung des Indol-Ringsystems verknüpft ist, eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 24 Kohlenstoffatomen bedeutet, das Symbol R^2 , das mit der 3-Stellung verknüpft ist, ein Wasserstoffatom bedeutet und R^1 und R^3 Wasserstoffatome bedeuten, gekennzeichnet durch die Cyclisierung einer Verbindung der allgemeinen Formel VII



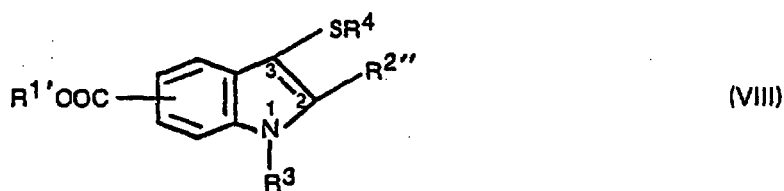
VII

(worin $R^{2''}$ eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 24 Kohlenstoffatomen bedeutet) in Anwesenheit einer Base bei erhöhter Temperatur mit oder ohne inertes, organisches Lösungsmittel.

37. Verfahren zur Herstellung einer Indolverbindung der allgemeinen Formel, dargestellt in Anspruch 1, worin --- eine Doppelbindung zwischen Kohlenstoffatomen bedeutet, R^1 eine gegebenenfalls substituierte Alkylgruppe, wie in Anspruch 1 definiert, bedeutet, das Symbol R^2 , das mit der 2-Stellung des Indol-Ringsystems verknüpft ist, eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 24 Kohlenstoffatomen bedeutet, das mit der 3-Stellung verknüpfte Symbol R^2 ein Wasserstoffatom be-

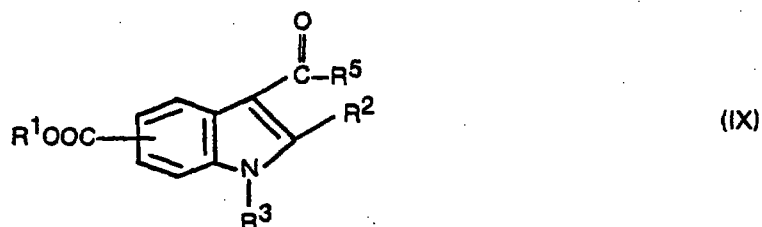


deutet und R^3 wie in Anspruch 1 definiert ist, gekennzeichnet durch die Reaktion eines 3-Alkylthioindol-Derivats der allgemeinen Formel VIII



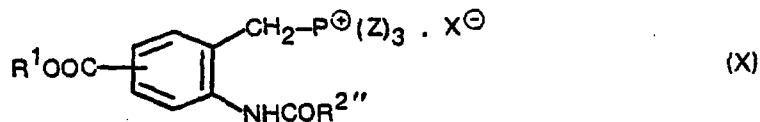
(worin $R^{2''}$ und R^3 wie in Anspruch 36 bzw. Anspruch 1 definiert sind, R^1' eine gegebenenfalls substituierte Alkylgruppe, wie für R^1 in Anspruch 1 definiert, bedeutet und R^4 eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen bedeutet) mit Raneynickel in Gegenwart eines inerten, organischen Lösungsmittels, um den 3-Alkylthio-Substituenten durch ein Wasserstoffatom auszutauschen.

38. Verfahren zur Herstellung einer Indol- oder Indolin-Verbindung der allgemeinen Formel, dargestellt in Anspruch 1, worin das Symbol R^2 in der 3-Stellung des Indol- oder Indolin-Ringsystems eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 24 Kohlenstoffatomen, das mit der 2-Stellung verknüpfte Symbol R^2 eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 24 Kohlenstoffatomen, oder ein Wasserstoffatom oder eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen bedeutet, wenn R^2 in der 3-Stellung eine Alkylgruppe mit 7 bis 24 Kohlenstoffatomen ist, und R^1 und R^3 wie in Anspruch 1 definiert sind, gekennzeichnet durch die Reduktion des Carbonylrestes einer Verbindung der allgemeinen Formel IX



(worin R^1 und R^3 wie in Anspruch 1 definiert sind, R^5 ein Wasserstoffatom oder eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 23 Kohlenstoffatomen bedeutet und R^2 ein Wasserstoffatom oder eine Alkylgruppe, geeignet zur Bildung der allgemeinen Formel, dargestellt in Anspruch 1, bedeutet) zu Methylen unter Verwendung von Boran, wenn es gewünscht ist, ein Indolprodukt der allgemeinen Formel, dargestellt in Anspruch 1, zu erhalten, worin — eine Doppelbindung zwischen Kohlenstoffatomen bedeutet, oder katalytische Hydrierung, wenn es gewünscht ist, ein Indolinprodukt der allgemeinen Formel, dargestellt in Anspruch 1, zu erhalten, worin — eine Einfachbindung zwischen Kohlenstoffatomen bedeutet.

39. Verfahren zur Herstellung einer Indolverbindung der allgemeinen Formel, dargestellt in Anspruch 1, worin — eine Doppelbindung zwischen Kohlenstoffatomen bedeutet, R^1 wie in Anspruch 1 definiert ist, das Symbol R^2 , das mit der 2-Stellung des Indol-Ringsystems verknüpft ist, eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 24 Kohlenstoffatomen bedeutet, das mit der 3-Stellung verknüpfte Symbol R^2 ein Wasserstoffatom bedeutet und R^3 ein Wasserstoffatom bedeutet, gekennzeichnet durch die Cyclisierung einer Verbindung der allgemeinen Formel X

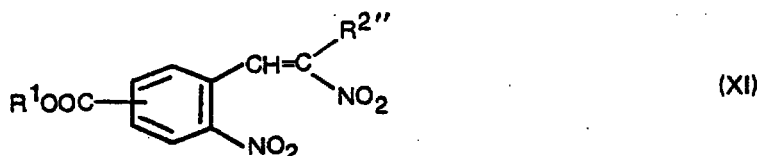


(worin X^- ein Anion bedeutet, Z eine gegebenenfalls substituierte Phenylgruppe bedeutet und R^1 und $R^{2''}$ wie in Anspruch 1 bzw. Anspruch 36 definiert sind) in einem inerten, organischen Lösungsmittel in Gegenwart einer Base, vorzugsweise bei erhöhter Temperatur.

40. Verfahren zur Herstellung einer Indolverbindung der allgemeinen Formel, dargestellt in Anspruch 1, worin — eine Doppelbindung zwischen Kohlenstoffatomen bedeutet, R^1 wie in Anspruch 1 definiert ist, das Symbol R^2 , das mit der 2-Stellung des Indol-Ringsystems verknüpft ist, eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 24 Kohlenstoffatomen bedeutet, das mit der 3-Stellung

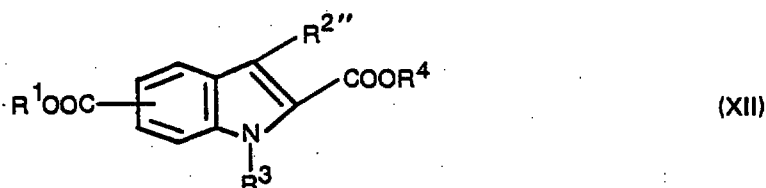


verknüpfte Symbol R^2 ein Wasserstoffatom bedeutet und R^3 ein Wasserstoffatom bedeutet, gekennzeichnet durch die katalytische Hydrierung einer Verbindung der allgemeinen Formel XI



10 (worin R^1 und $R^{2''}$ wie in Anspruch 1 bzw. Anspruch 36 definiert sind), danach durch Cyclisierung der so erhaltenen Amin-Zwischenverbindung.

41. Verfahren zur Herstellung einer Indolverbindung der allgemeinen Formel, dargestellt in Anspruch 1, worin — eine Doppelbindung zwischen Kohlenstoffatomen bedeutet, R^1 wie in Anspruch 1 definiert ist, das Symbol R^2 , das mit der 3-Stellung des Indol-Ringsystems verknüpft ist, eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 24 Kohlenstoffatomen bedeutet, das mit der 2-Stellung verknüpfte Symbol R^2 ein Wasserstoffatom bedeutet und R^3 wie in Anspruch 1 definiert ist, gekennzeichnet durch die Decarboxylierung durch Erhitzen eines 2-Alkoxycarbonylindol-Derivats der allgemeinen Formel XII



25 worin R^1 und R^3 wie in Anspruch 1 definiert sind und $R^{2''}$ und R^4 wie in Anspruch 36 bzw. Anspruch 37 definiert sind.

30 42. Verfahren zur Herstellung einer Indol- oder Indolin-Derivats der allgemeinen Formel, dargestellt in Anspruch 1, worin R^1 ein Wasserstoffatom bedeutet und R^2 und R^3 wie in Anspruch 1 definiert sind, gekennzeichnet durch die Hydrolyse eines entsprechenden Esters der allgemeinen Formel, dargestellt in Anspruch 1, worin R^2 und R^3 wie in Anspruch 1 definiert sind und R^1 eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, gegebenenfalls substituiert wie in Anspruch 1 angegeben, bedeutet.

43. Verfahren zur Herstellung eines Esters eines Indol- oder Indolin-Derivats der allgemeinen Formel, dargestellt in Anspruch 1, worin R^1 eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen (welche durch einen oder mehr als einen vom gleichen Typ von Substituenten, ausgewählt unter der Hydroxygruppe, Alkenylgruppen mit 2 bis 5 Kohlenstoffatomen und Alkanoyloxygruppen mit 2 bis 7 Kohlenstoffatomen, substituiert sein kann) bedeutet, gekennzeichnet durch die Veresterung einer entsprechenden Carbonsäure, worin R^1 in der allgemeinen Formel, dargestellt in Anspruch 1, ein Wasserstoffatom bedeutet und R^2 und R^3 wie in Anspruch 1 definiert sind.

44. Verfahren zur Herstellung einer Indol- oder Indolin-Derivats der allgemeinen Formel, dargestellt in Anspruch 1, worin R^3 eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen bedeutet und R^1 und R^2 wie in Anspruch 1 definiert sind, gekennzeichnet durch die N-(C_1-C_6)-Alkylierung einer entsprechenden Verbindung der allgemeinen Formel dargestellt in Anspruch 1, worin R^3 ein Wasserstoffatom bedeutet.

45. Verfahren gemäß einem der Ansprüche 33 bis 44, gekennzeichnet durch den anschließenden Schritt der Überführung einer so erhaltenen Indol- oder Indolin-Verbindung der allgemeinen Formel, dargestellt in Anspruch 1, — falls geeignet — in ein pharmazeutisch annehmbares Salz.

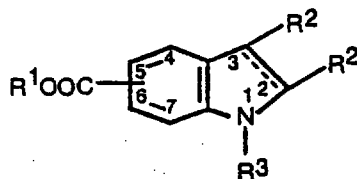
46. Pharmazeutische Zusammensetzungen, welche als aktiven Bestandteil wenigstens eine der Indol- oder Indolin-Derivate der allgemeinen Formel, dargestellt in Anspruch 1, worin — und die Symbole R^1 , R^2 und R^3 wie in Anspruch 1 definiert sind, oder — falls geeignet — ein pharmazeutisch annehmbares Salz davon zusammen mit einem pharmazeutisch annehmbaren Träger oder Überzug umfassen.

47. Indol- oder Indolin-Derivate der allgemeinen Formel, dargestellt in Anspruch 1, worin — und die Symbole R^1 , R^2 und R^3 wie in Anspruch 1 definiert sind, und — falls geeignet — pharmazeutisch annehmbare Salze davon zur Verwendung bei der Vorbeugung oder Behandlung von Diabetes mellitus, hyperlipoproteinämischen Zuständen, von Atherosklerose und von Angina, Myokardinfarkt, cerebraler Vaskuläroclulsion, arteriellem Aneurisma, peripherer Gefäßerkrankung, recurrierender Pankreatitis und Xanthom.



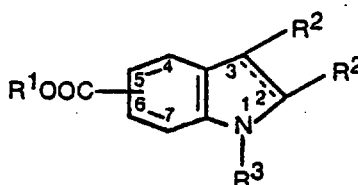
Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer Indolverbindung der allgemeinen Formel:



(II)

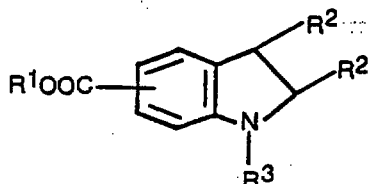
worin --- eine Einfachbindung zwischen Kohlenstoffatomen darstellt, R^1 eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen (die durch einen oder mehrere gleichartige Substituenten, ausgewählt aus der Hydroxygruppe, Alkenylgruppen mit 2 bis 5 Kohlenstoffatomen und Alkanoyloxygruppen mit 2 bis 7 Kohlenstoffatomen, substituiert sein kann) oder ein Wasserstoffatom darstellt und eines der Symbole R^2 eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 24 Kohlenstoffatomen darstellt und das andere Symbol R^2 eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 24 Kohlenstoffatomen oder ein Wasserstoffatom darstellt und R^3 eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen oder ein Wasserstoffatom darstellt, welches die Reduktion der C_2-C_3 -Doppelbindung einer entsprechenden Indolverbindung der allgemeinen Formel:



(V)

(worin die Symbole R^1 , R^2 und R^3 die obige Bedeutung haben) durch katalytische Hydrierung umfaßt.

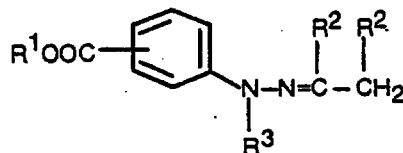
2. Verfahren zur Herstellung einer Indolverbindung der in Anspruch 1 dargestellten allgemeinen Formel, worin = eine Doppelbindung zwischen Kohlenstoffatomen darstellt und R^1 , R^2 und R^3 die in Anspruch 1 angegebene Bedeutung haben, welches die katalytische Dehydrogenierung einer entsprechenden Indolinverbindung der allgemeinen Formel:



(IV)

in welcher R^1 , R^2 und R^3 die in Anspruch 1 angegebene Bedeutung haben, umfaßt.

3. Verfahren zur Herstellung einer Indolverbindung der in Anspruch 1 dargestellten allgemeinen Formel, worin = eine Doppelbindung zwischen Kohlenstoffatomen darstellt und R^1 , R^2 und R^3 die in Anspruch 1 angegebene Bedeutung haben, welches die Cyclisierung einer Verbindung der allgemeinen Formel:



(VI)

(worin R^1 , R^2 und R^3 die in Anspruch 1 angegebene Bedeutung haben), durch Reaktion mit einer anorganischen Säure oder einer anderen Lewis-Säure bei erhöhter Temperatur, gegebenenfalls in Gegenwart eines inerten organischen Lösungsmittels umfaßt.

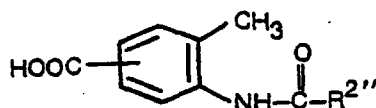
4. Verfahren zur Herstellung einer Indolverbindung der in Anspruch 1 dargestellten allgemeinen Formel, worin = eine Doppelbindung zwischen Kohlenstoffatomen darstellt, das in 2-Stellung des Indolringsystems gebundene Symbol R^2 eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 24 Kohlenstoffatomen darstellt, das in 3-Stellung gebundene Symbol R^2 ein Wasserstoffatom darstellt und



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R¹ und R³ Wasserstoffatome darstellen, welches die Cyclisierung einer Verbindung der allgemeinen Formel

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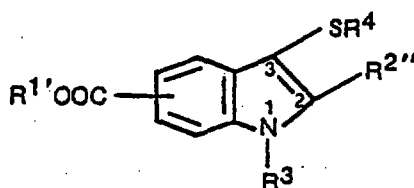


(VII)

(worin R^{2''} eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 24 Kohlenstoffatomen darstellt) in Gegenwart einer Base bei erhöhter Temperatur in An- oder Abwesenheit eines inerten organischen Lösungsmittels umfaßt.

5. Verfahren zur Herstellung einer Indolverbindung der in Anspruch 1 dargestellten allgemeinen Formel, worin --- eine Doppelbindung zwischen Kohlenstoffatomen darstellt, R¹ eine gegebenenfalls substituierte Alkylgruppe wie in Anspruch 1 angegeben bedeutet, das in 2-Stellung an das Indolring-system gebundene Symbol R² eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 24 Kohlenstoffatomen darstellt, das in 3-Stellung gebunden Symbol R² ein Wasserstoffatom bedeutet und R³ die in Anspruch 1 angegebene Bedeutung hat, welches die Reaktion eines 3-Alkylthioindolderivats der allgemeinen Formel

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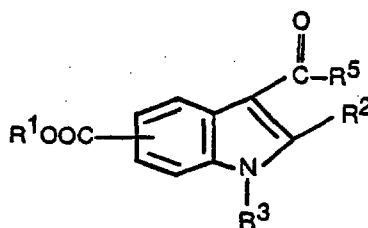
(VIII)

25

(worin R^{2''} und R³ die in Anspruch 4 bzw. Anspruch 1 angegebene Bedeutung haben, R^{1'} eine gegebenenfalls substituierte Alkylgruppe wie für R¹ in Anspruch 1 angegeben darstellt und R⁴ eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen bedeutet) mit Raney-Nickel in Gegenwart eines inerten organischen Lösungsmittels umfaßt, wobei der 3-Alkylthiosubstituent durch ein Wasserstoffatom ersetzt wird.

6. Verfahren zur Herstellung einer Indol- oder Indolverbindung der in Anspruch 1 dargestellten allgemeinen Formel, worin das Symbol R² in der 3-Stellung des Indol- oder Indolinringsystems eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 24 Kohlenstoffatomen darstellt, das in 2-Stellung gebundene Symbol R² eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 24 Kohlenstoffatomen oder ein Wasserstoffatom oder eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, wenn R² in der 3-Stellung eine Alkylgruppe mit 7 bis 25 Kohlenstoffatomen ist, darstellt und R¹ und R³ die in Anspruch 1 angegebene Bedeutung haben, welches die Reduktion des Carbonyl-rests einer Verbindung der allgemeinen Formel

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(IX)

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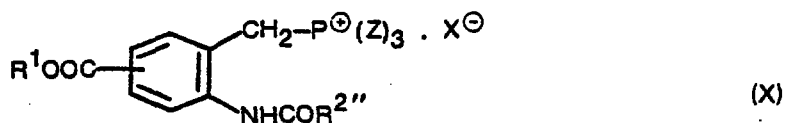
(worin R¹ und R³ die in Anspruch 1 angegebene Bedeutung haben, R⁵ ein Wasserstoffatom oder eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 23 Kohlenstoffatomen darstellt und R² ein Wasserstoffatom oder eine Alkylgruppe die in die in Anspruch 1 dargestellte Formel paßt, darstellt) zu Methylen unter Verwendung von Boran, wenn eine Indolverbindung der in Anspruch 1 dargestellten allgemeinen Formel, worin --- eine Doppelbindung zwischen Kohlenstoffatomen darstellt, hergestellt werden soll, oder durch katalytische Hydrierung, wenn eine Indolinverbindung der in Anspruch 1 dargestellten allgemeinen Formel, worin --- eine Einfachbindung zwischen Kohlenstoffatomen bedeutet, hergestellt werden soll, umfaßt.

7. Verfahren zur Herstellung einer Indolverbindung der in Anspruch 1 dargestellten allgemeinen Formel, worin --- eine Doppelbindung zwischen Kohlenstoffatomen darstellt, R¹ die in Anspruch 1 angegebene Bedeutung hat, das in 2-Stellung des Indolring-systems gebundene Symbol R² eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 24 Kohlenstoffatomen darstellt, das in 3-Stellung gebun-

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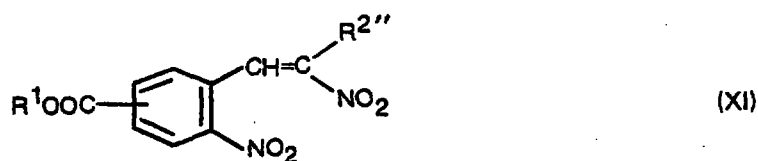


dene Symbol R^2 ein Wasserstoffatom darstellt und R^3 ein Wasserstoffatom darstellt, welches die Cyclisierung einer Verbindung der allgemeinen Formel:



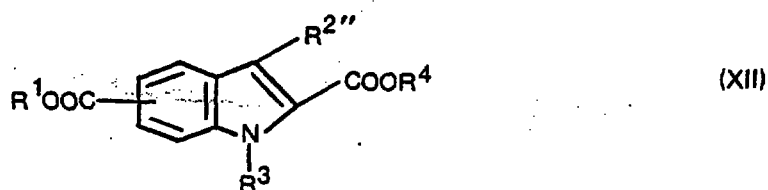
10 (worin $X^\ominus$ ein Anion darstellt, Z eine gegebenenfalls substituierte Phenylgruppe darstellt und R^1 und $R^{2''}$ die in Anspruch 1 bzw. Anspruch 4 angegebene Bedeutung haben) in einem inerten organischen Lösungsmittel in Anwesenheit einer Base, vorzugsweise bei erhöhter Temperatur, umfaßt.

8. Verfahren zur Herstellung einer Indolverbindung der in Anspruch 1 dargestellten allgemeinen Formel, worin --- eine Doppelbindung zwischen Kohlenstoffatomen darstellt, R^1 die in Anspruch 1 angegebene Bedeutung hat, das in 2-Stellung des Indolringsystems gebundene Symbol R^2 eine gerad- oder verzweigt-kettige Alkylgruppe mit 7 bis 24 Kohlenstoffatomen darstellt, das in 3-Stellung gebundene Symbol R^2 ein Wasserstoffatom darstellt und R^3 ein Wasserstoffatom bedeutet, welches die katalytische Hydrierung einer Verbindung der allgemeinen Formel



25 (worin R^1 und $R^{2''}$ die in Anspruch 1 bzw. Anspruch 4 angegebene Bedeutung haben) und anschließende Cyclisierung des so erhaltenen Amin-Zwischenprodukts umfaßt.

9. Verfahren zur Herstellung einer Indolverbindung der in Anspruch 1 dargestellten allgemeinen Formel, worin --- eine Doppelbindung zwischen Kohlenstoffatomen darstellt, R^1 angegebene Bedeutung hat, das in 3-Stellung des Indolringsystems gebundene Symbol R^2 eine gerad/ oder verzweigt-kettige Alkylgruppe mit 7 bis 24 Kohlenstoffatomen darstellt, das in 2-Stellung gebundene Symbol R^2 ein Wasserstoffatom darstellt und R^3 die in Anspruch 1 angegebene Bedeutung hat, welches die Decarboxylierung durch Erhitzen eines 2-Alkoxycarbonylindolderivats der allgemeinen Formel:



40 worin R^1 und R^3 die in Anspruch 1 angegebene Bedeutung haben und $R^{2''}$ und R^4 die in Anspruch 4 bzw. Anspruch 5 angegebene Bedeutung haben, umfaßt.

10. Verfahren zur Herstellung eines Indol- oder Indolinderivats der in Anspruch 1 dargestellten allgemeinen Formel, worin R^1 ein Wasserstoffatom darstellt und R^2 und R^3 die in Anspruch 1 angegebene Bedeutung haben, welches die Hydrolyse eines entsprechenden Esters in Anspruch 1 angegebenen allgemeinen Formel, in welcher R^2 und R^3 die in Anspruch 1 angegebene Bedeutung haben und R^1 eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, gegebenenfalls substituiert wie in Anspruch 1 angegeben, darstellt, umfaßt.

11. Verfahren zur Herstellung eines Esters eines Indol- oder Indolinderivats der in Anspruch 1 dargestellten allgemeinen Formel, worin R^1 eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen (welche durch einen oder mehrere gleichartige Substituenten, ausgewählt aus der Hydroxygruppe, Alkenylgruppen mit 2 bis 5 Kohlenstoffatomen und Alkanoyloxygruppen mit 2 bis 7 Kohlenstoffatomen substituiert sein kann) darstellt, welches die Veresterung einer entsprechenden Carbonsäure, worin R^1 in der in Anspruch 1 dargestellten allgemeinen Formel ein Wasserstoffatom darstellt, und R^2 und R^3 die in Anspruch 1 angegebene Bedeutung haben, umfaßt.

12. Verfahren zur Herstellung eines Indol- oder Indolinderivats der in Anspruch 1 dargestellten allgemeinen Formel, worin R^3 eine gerad- oder verzweigt-kettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen darstellt und R^1 und R^2 die in Anspruch 1 angegebene Bedeutung haben, welches die N-(C_1 — C_6)Alkylierung einer entsprechenden Verbindung der in Anspruch 1 dargestellten allgemeinen Formel, worin R^3 ein Wasserstoffatom darstellt, umfaßt.

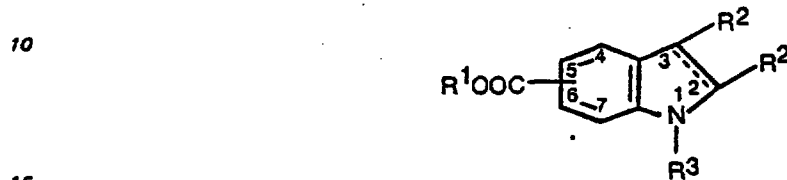
13. Verfahren nach einem der vorhergehenden Ansprüche mit der anschließenden Stufe der Über-



führung einer so erhaltenen Indol- oder Indolinverbindung der in Anspruch 1 dargestellten Formel — wenn zutreffend — in ein pharmazeutisch zulässiges Salz.

5 Revendications pour les Etats contractants: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Dérivés de l'indole et de l'indoline de formule générale:



dans laquelle le symbole ——— représente soit une double, soit une simple liaison entre les atomes de carbone, R¹ représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone (qui peut être substitué par un ou plusieurs substituants du même type, choisis parmi les radicaux hydroxy, alcényle, contenant 2 à 5 atomes) de carbone et alcanoyloxy, contenant 2 à 7 atomes de carbone ou un atome d'hydrogène et l'un des symboles R² représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 24 atomes de carbone et l'autre symbole R² représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 24 atomes de carbone ou un atome d'hydrogène et R³ représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone ou un atome d'hydrogène, ainsi que leurs sels pharmaceutiquement acceptables.

2. Composés selon la revendication 1 dans lesquels le radical R¹OOC— est attaché en position 5 ou 6 du cycle indole ou indoline.

3. Composés selon la revendication 1 ou 2 dans lesquels R¹ représente un atome d'hydrogène.

4. Composés selon la revendication 1, 2 ou 3, dans lesquels l'un des symboles R² représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 20 atomes de carbone et l'autre symbole R² représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 24 atomes de carbone ou un atome d'hydrogène.

5. Composés selon l'une des revendications 1 à 4 dans lesquels le second symbole R² représente un atome d'hydrogène.

6. Composés selon la revendication 4 dans lesquels le second symbole R² représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone.

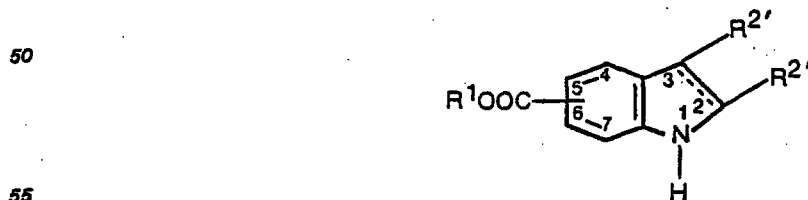
7. Composés selon l'une quelconque des revendications précédentes dans lesquels l'un des symboles R² représente un atome d'hydrogène ou un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone et dans lesquels ce symbole particulier est attaché en position 3 du cycle indole ou indoline.

8. Composés selon la revendication 7 dans lesquels le symbole R² attaché en position 3 du cycle indole ou indoline représente le radical méthyle.

9. Composés selon l'une quelconque des revendications 1, 2 et 4 à 8 dans lesquels R¹ représente un radical méthyle, éthyle, butyle, dihydroxy-2,3 propyle-1, allyle ou pivaloyloxyméthyle.

10. Composés selon l'une quelconque des revendications précédentes dans laquelle le symbole R³ dans la formule générale (I) de la revendication 1 représente un atome d'hydrogène.

11. Dérivés de l'indole et de l'indoline selon la revendication 1 de formule générale:



dans laquelle le symbole ——— représente soit une double, soit une simple liaison entre les atomes de carbone, le radical R¹ OOC— est attaché en position 5 ou 6 du cycle indole ou indoline, R¹ représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone ou un atome d'hydrogène et l'un des symboles R²' représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 24 atomes de carbone et l'autre symbole R²' représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 24 atomes de carbone ainsi que leurs sels pharmaceutiquement acceptables.

12. Composés selon la revendication 11 dans laquelle R¹ représente un atome d'hydrogène.

13. Composés selon la revendication 11 ou 12 dans lesquels l'un des symboles R²' représente un



78

radical alcoyle en chaîne droite ou ramifiée contenant 7 à 20 atomes de carbone et l'autre symbole R^2 représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 24 atomes de carbone.

14. Composés selon la revendication 11, 12 ou 13 dans lesquels le second symbole R^2 représente un radical alcoyle contenant 1 à 6 atomes de carbone et dans lesquels ce symbole est attaché en position 3 du cycle indole ou indoline.

15. Dérivés de l'indole ou de l'indoline selon la revendication 1 de formule générale: dans laquelle le symbole --- représente soit une double, soit une simple liaison entre les atomes de carbone, le radical $R^1 \text{OOC---}$ est attaché en position 5 ou 6 du cycle indole ou indoline, R^1 représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone ou un atome d'hydrogène et R^2 représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 24 atomes de carbone ainsi que leurs sels pharmaceutiquement acceptables.

16. Composés selon la revendication 15 dans lesquels R^1 représente un atome d'hydrogène.

17. Composés selon la revendication 15 ou 16 dans lesquels R^2 représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 20 atomes de carbone.

18. Composés selon la revendication 11, 13, 14 ou 15 dans lesquels R^1 représente un radical méthyle, éthyle ou butyle.

19. Composés selon la revendication 1 qui est l'acide n-octadécyl-2 indolecarboxylique-5 et ses sels pharmaceutiquement acceptables.

20. Composés selon la revendication 1 qui est l'acide n-octadécyl-2 indolecarboxylique-6 et ses sels pharmaceutiquement acceptables.

21. Composés selon la revendication 1 qui est l'acide n-pentadécyl-2 indolecarboxylique-5 et ses sels pharmaceutiquement acceptables.

22. Composés selon la revendication 1 qui est l'acide n-undécyl-2 indolecarboxylique-5 et ses sels pharmaceutiquement acceptables.

23. Composés selon la revendication 1 qui est l'acide n-pentadécyl-2 indolecarboxylique-6 et ses sels pharmaceutiquement acceptables.

24. Composés selon la revendication 1 qui est l'acide (méthyl-1 décyl)-2 indolecarboxylique-6 et ses sels pharmaceutiquement acceptables.

25. Composés selon la revendication 1 qui est l'acide n-undécyl-2 indolinecarboxylique-5 et ses sels pharmaceutiquement acceptables.

26. Composés selon la revendication 1 qui est l'acide n-décyl-2 indolinecarboxylique-5 et ses sels pharmaceutiquement acceptables.

27. Composés selon la revendication 1 qui est l'acide n-undécyl-2 indolinecarboxylique-6 et ses sels pharmaceutiquement acceptables.

28. Composés selon la revendication 1 qui est l'acide n-undécyl-2 méthyl-3 indolinecarboxylique-6 et ses sels pharmaceutiquement acceptables.

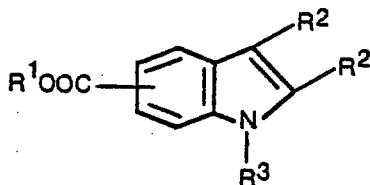
29. Composés selon la revendication 1 qui est l'acide n-heptadécyl-2 indolecarboxylique-5 et ses sels pharmaceutiquement acceptables.

30. Composés selon la revendication 1 qui est l'acide n-octyl-2 indolecarboxylique-6 et ses sels pharmaceutiquement acceptables.

31. Composés selon la revendication 1 qui est l'acide n-dodécyl-2 indolecarboxylique-6 et ses sels pharmaceutiquement acceptables.

32. Composés selon la revendication 1 qui est l'acide n-hexadécyl-2 indolecarboxylique-5 et ses sels pharmaceutiquement acceptables.

33. Procédé pour la préparation d'un composé de l'indoline selon la revendication 1 dans la formule duquel le symbole --- représente une liaison simple entre les atomes de carbone et R^1 , R^2 et R^3 sont définis comme dans la revendication 1, qui comprend la réduction d'une double liaison entre les carbones C_2 et C_3 du composé de l'indole correspondant de formule générale:



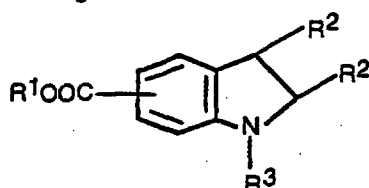
V

dans laquelle les symboles R^1 , R^2 et R^3 sont définis comme la revendication 1, par hydrogénation catalytique.

34. Procédé pour la préparation d'un composé de l'indole selon la revendication 1 dans la formule duquel le symbole --- représente une double liaison entre les atomes de carbone et R^1 , R^2 et R^3 sont



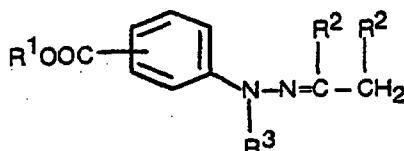
définis comme à la revendication 1, qui comprend la déhydrogénation catalytique d'un composé de l'indoline correspondant de formule générale:



IV

dans laquelle R¹, R² et R³ sont définis comme à la revendication 1.

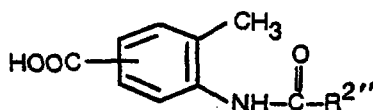
35. Procédé pour la préparation d'un composé de l'indole selon la revendication 1 dans la formule duquel le symbole $\equiv$ représente une double liaison entre les atomes de carbone et R¹, R² et R³ sont définis comme à la revendication 1, qui comprend la cyclisation d'un composé de formule générale:



VI

dans laquelle R¹, R² et R³ sont définis comme à la revendication 1, par réaction avec un acide minéral ou tout autre acide de Lewis, à température élevée, éventuellement en présence d'un solvant organique inerte.

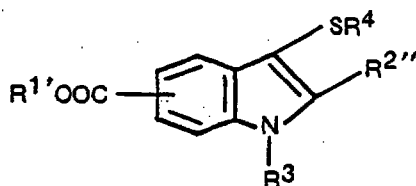
36. Procédé pour la préparation d'un composé de l'indole selon la revendication 1 dans la formule duquel le symbole $\equiv$ représente une double liaison entre les atomes de carbone, le symbole R² attaché en partie 2 du cycle indole représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 24 atomes de carbone, le symbole R¹ attaché en position 3 représente un atome d'hydrogène et R¹ et R³ représentent un atome d'hydrogène, qui comprend la cyclisation d'un composé de formule générale:



VII

dans laquelle R²'' représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 24 atomes de carbone en présence d'une base à température élevée avec ou sous solvant organique inerte.

37. Procédé pour la préparation d'un composé de l'indole selon la revendication 1 dans la formule duquel $\equiv$ représente une double liaison entre les atomes de carbone, R¹ représente un radical alcoyle éventuellement substitué défini comme à la revendication 1, le symbole R² attaché en position 2 du cycle indole représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 24 atomes de carbone, le symbole R² attaché en position 3 représente un atome d'hydrogène et R³ est défini comme à la revendication 1, qui comprend l'action d'un dérivé de l'alcoylthio-3 indole de formule générale:



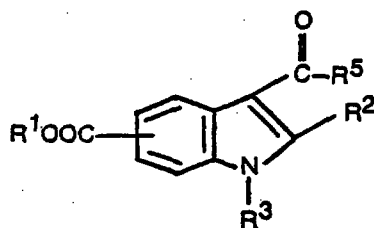
VIII

dans laquelle R²'' et R³ sont définis respectivement comme aux revendications 36 et 1, R¹' représente un radical alcoyle éventuellement substitué défini comme R¹ à la revendication 1, et R⁴ représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone, avec du nickel Raney en présence d'un solvant organique inerte pour remplacer le substituant alcoylthio-3 par un atome d'hydrogène.

38. Procédé pour la préparation d'un composé de l'indole ou de l'indoline selon la revendication 1 dans la formule duquel le symbole R² en position 3 du cycle indole ou indoline représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 24 atomes de carbone, le symbole R² attaché en position 2 représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 24 atomes de carbone, ou un atome d'hydrogène ou un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone quand R² en position 3 représente un radical alcoyle contenant 7 à 24 atomes de



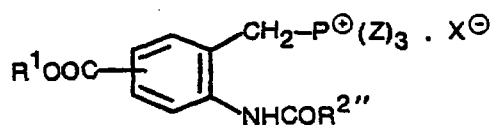
carbone, et R^1 et R^3 sont définis comme à la revendication 1, qui comprend la réduction du radical carbonyle d'un composé de formule générale:



IX

dans laquelle R^1 et R^3 sont définis comme à la revendication 1, R^5 représente un atome d'hydrogène ou un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 23 atomes de carbone, et R^2 représente un atome d'hydrogène ou un radical alcoyle choisi convenablement pour répondre à la formule générale (I) telle que définie à la revendication 1, en un radical méthylène, en utilisant le borane lorsqu'on désire obtenir un produit de l'indole selon la revendication 1 dans la formule duquel le symbole $\equiv$ représente une double liaison entre les atomes de carbone, ou par hydrogénation catalytique lorsqu'on désire obtenir un produit de l'indoline selon la revendication 1 dans la formule duquel le symbole $-$ représente une liaison simple entre les atomes de carbone.

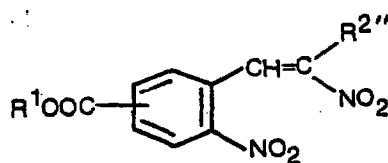
39. Procédé pour la préparation d'un composé de l'indole selon la revendication 1 dans la formule duquel le symbole $\equiv$ représente une double liaison entre les atomes de carbone, R^1 est défini comme à la revendication 1, le symbole R^2 attaché en position 2 du cycle indole représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 24 atomes de carbone, le symbole R^2 attaché en position 3 représente un atome d'hydrogène, et R^3 représente un atome d'hydrogène, qui comprend la cyclisation d'un composé de formule générale:



X

dans laquelle $X^\ominus$ représente un anion, Z représente un radical phényle éventuellement substitué et R^1 et $R^{2''}$ sont définis respectivement comme aux revendications 1 et 36, dans un solvant organique inerte en présence d'une base, de préférence à température élevée.

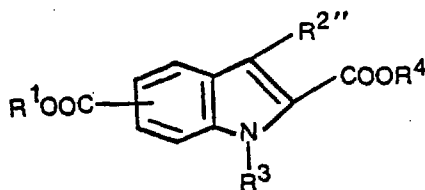
40. Procédé pour la préparation d'un composé de l'indole selon la revendication 1 dans la formule duquel le symbole $\equiv$ représente une double liaison entre les atomes de carbone, R^1 est défini comme à la revendication 1, le symbole R^2 attaché en position 2 du cycle indole représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 24 atomes de carbone, le symbole R^2 attaché en position 3 représente un atome d'hydrogène et R^3 représente un atome d'hydrogène, qui comprend l'hydrogénation catalytique d'un composé de formule générale:



XI

dans laquelle R^1 et $R^{2''}$ sont définis respectivement comme aux revendications 1 et 36, suivie d'une cyclisation de l'amine intermédiaire obtenue.

41. Procédé pour la préparation d'un composé de l'indole selon la revendication 1 dans la formule duquel le symbole $\equiv$ représente une double liaison entre les atomes de carbone, R^1 est défini comme à la revendication 1, le symbole R^2 attaché en position 3 du cycle indole représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 24 atomes de carbone, le symbole R^2 attaché en position 2 représente un atome d'hydrogène et R^3 est défini comme à la revendication 1, qui comprend la décarboxylation par chauffage d'un dérivé de l'alcoyloxy-carbonyl-2 indole de formule générale:



XII



dans laquelle R¹ et R³ sont définis comme à la revendication 1, et R^{2''} et R⁴ sont définis respectivement comme aux revendications 36 et 37.

42. Procédé pour la préparation d'un dérivé de l'indole ou de l'indoline selon la revendication 1, dans la formule duquel R₁ représente un atome d'hydrogène et R² et R³ sont définis comme à la revendication 1, qui comprend l'hydrolyse de l'ester correspondant de formule générale (I) dans laquelle R² et R³ sont définis comme à la revendication 1 et R¹ représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone éventuellement substitué comme décrit à la revendication 1.

43. Procédé pour la préparation d'un ester d'un dérivé de l'indole ou de l'indoline selon la revendication 1 dans la formule duquel R¹ représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone (éventuellement substitué par un ou plusieurs substituants du même type choisis parmi les radicaux hydroxy, alcényle contenant 2 à 5 atomes de carbone et alcanoyloxy contenant 2 à 7 atomes de carbone), qui comprend l'estérification de l'acide carboxylique correspondant dans la formule duquel le symbole R₁ de la formule générale (I) représente un atome d'hydrogène et R² et R³ sont définis comme à la revendication 1.

44. Procédé pour la préparation d'un dérivé de l'indole ou de l'indoline selon la revendication 1 dans la formule duquel R³ représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone et R¹ et R² sont définis comme à la revendication 1, qui comprend la N-alcoylation (C₁—C₈) d'un composé correspondant selon la revendication 1 dans lequel R³ représente un atome d'hydrogène.

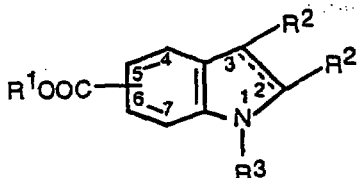
45. Procédé selon l'une quelconque des revendications 33 à 44 suivi d'une étape consistant à convertir le composé de l'indole ou de l'indoline selon la revendication 1 ainsi obtenue en un sel pharmaceutiquement acceptable, lorsqu'il existe.

46. Compositions pharmaceutiques qui comprennent comme ingrédient actif au moins l'un des dérivés de l'indole ou de l'indoline selon la revendication 1 dans la formule duquel le symbole — et les symboles R¹, R² et R³ sont définis comme dans la revendication 1 ou, lorsqu'il existe, un de ses sels pharmaceutiquement acceptables, en association avec un adjuvant ou un enrobage pharmaceutiquement acceptable.

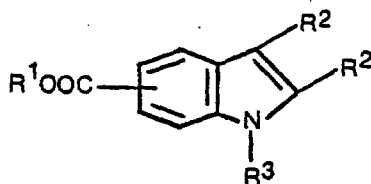
47. Dérivés de l'indole ou de l'indoline selon la revendication 1 dans la formule duquel les symboles —, R¹, R² et R³ sont définis comme à la revendication 1 et, lorsqu'ils existent, leurs sels pharmaceutiquement acceptables, pour l'usage dans la prévention ou le traitement du diabète sucré, des états hyperlipoprotéiniques de l'artériosclérose, et de l'angine de poitrine, de l'infarctus du myocarde, de l'occlusion vasculaire cérébrale, de l'anévrisme artériel, des maladies vasculaires périphériques, des pancréatites périodiques et des xanthomes.

Revendications pour l'Etat contractant: AT

1. Procédé pour la préparation d'un composé de l'indoline de formule générale:

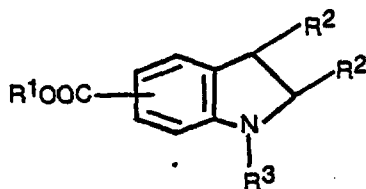


dans laquelle le symbole — représente une simple liaison entre les atomes de carbone, R¹ représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone (qui peut être substitué par un ou plusieurs substituants du même type, choisis parmi les radicaux hydroxy, alcényle, contenant 2 à 5 atomes de carbone et alcanoyloxy, contenant 2 à 7 atomes de carbone) ou un atome d'hydrogène et l'un des symboles R² représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 24 atomes de carbone et l'autre symboles R² représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 24 atomes de carbone ou un atome d'hydrogène et R³ représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone ou un atome d'hydrogène, qui comprend la réduction d'une double liaison entre les carbones C₂ et C₃ du composé de l'indole correspondant de formule générale:



dans laquelle les symboles R_1 , R_2 et R_3 sont définis comme la revendication 1, par hydrogénation catalytique.

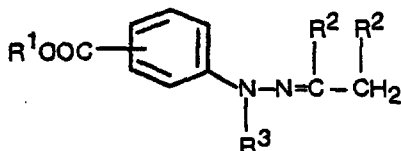
2. Procédé pour la préparation d'un composé de l'indole selon la formule décrite dans la revendication 1 dans laquelle le symbole $\equiv$ représente une double liaison entre les atomes de carbone et R^1 , R^2 et R^3 sont définis comme à la revendication 1, qui comprend la déhydrogénation catalytique d'un composé de l'indoline correspondant de formule générale:



IV

dans laquelle R^1 , R^2 et R^3 sont définis comme à la revendication 1.

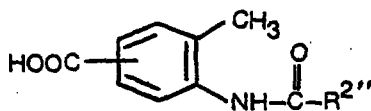
3. Procédé pour la préparation d'un composé de l'indole selon la formule décrite dans la revendication 1 dans laquelle le symbole $\equiv$ représente une double liaison entre les atomes de carbone et R^1 , R^2 et R^3 sont définis comme à la revendication 1, qui comprend la cyclisation d'un composé de formule générale:



VI

dans laquelle R^1 , R^2 et R^3 sont définis comme à la revendication 1, par réaction avec un acide minéral ou tout autre acide de Lewis, à température élevée, éventuellement en présence d'un solvant organique inerte.

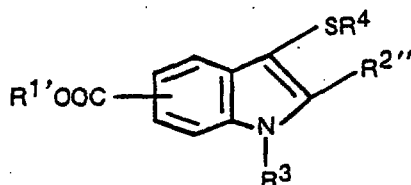
4. Procédé pour la préparation d'un composé de l'indole selon la formule décrite dans la revendication 1 dans laquelle le symbole $\equiv$ représente une double liaison entre les atomes de carbone, le symbole R^2 attaché en partie 2 du cycle indole représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 24 atomes de carbone, le symbole R^2 attaché en position 3 représente un atome d'hydrogène et R^1 et R^3 représentent un atome d'hydrogène, qui comprend la cyclisation d'un composé de formule générale:



VII

dans laquelle $R^{2''}$ représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 24 atomes de carbone en présence d'une base à température élevée avec ou sous solvant organique inerte.

5. Procédé pour la préparation d'un composé de l'indole selon la formule décrite dans la revendication 1 dans laquelle $\equiv$ représente une double liaison entre les atomes de carbone, R^1 représente un radical alcoyle éventuellement substitué défini comme à la revendication 1, le symbole R^2 attaché en position 2 du cycle indole représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 24 atomes de carbone, le symbole R^2 attaché en position 3 représente un atome d'hydrogène et R^3 est défini comme à la revendication 1, qui comprend l'action d'un dérivé de l'alcoylthio-3 indole de formule générale:

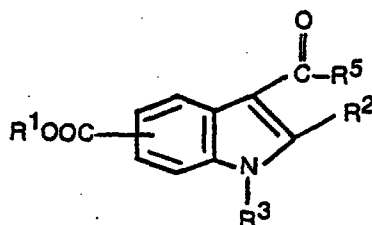


VIII

dans laquelle $R^{2''}$ et R^3 sont définis respectivement comme aux revendications 4 et 1, R^1 représente un radical alcoyle éventuellement substitué défini comme R^1 à la revendication 1, et R^4 représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone, avec du nickel Raney en présence d'un solvant organique inerte pour remplacer le substituant alcoylthio-3 par un atome d'hydrogène.



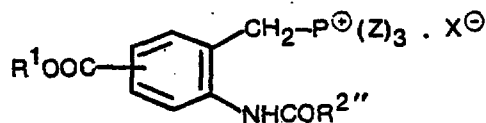
6. Procédé pour la préparation d'un composé de l'indole ou de l'indoline selon formule décrite dans la revendication 1 dans laquelle le symbole R^2 en position 3 du cycle indole ou indoline représente un radical alcoyle en chaîne ou ramifiée contenant 1 à 24 atomes de carbone, le symbole R^2 attaché en position 2 représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 24 atomes de carbone, ou un atome d'hydrogène ou un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone quand R^2 en position 3 représente un radical alcoyle contenant 7 à 24 atomes de carbone, et R^1 et R^3 sont définis comme à la revendication 1, qui comprend la réduction du radical carbonyle d'un composé de formule générale:



IX

dans laquelle R^1 et R^3 sont définis comme à la revendication 1, R^5 représente un atome d'hydrogène ou un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 23 atomes de carbone, et R^2 représente un atome d'hydrogène ou un radical alcoyle choisi convenablement pour répondre à la formule générale décrite dans la revendication 1 en un radical méthylène, en utilisant le borane lorsqu'on désire obtenir un produit de l'indole selon la formule décrite dans la revendication 1 dans laquelle le symbole $==$ représente une double liaison entre les atomes de carbone, ou par hydrogénation catalytique lorsqu'on désire obtenir un produit de l'indoline selon la formule décrite dans la revendication 1 dans laquelle le symbole $---$ représente une liaison simple entre les atomes de carbone.

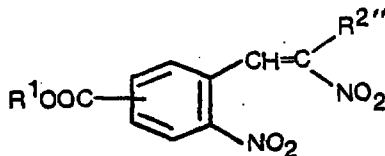
7. Procédé pour la préparation d'un composé de l'indole selon la formule décrite dans la revendication 1 dans laquelle le symbole $==$ représente une double liaison entre les atomes de carbone, R^1 est défini comme à la revendication 1, le symbole R^2 attaché en position 2 du cycle indole représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 24 atomes de carbone, le symbole R^2 attaché en position 3 représente un atome d'hydrogène, et R^3 représente un atome d'hydrogène, qui comprend la cyclisation d'un composé de formule générale:



X

dans laquelle X^- représente un anion, Z représente un radical phényle éventuellement substitué et R^1 et R^2'' sont définis respectivement comme aux revendications 1 et 4, dans un solvant organique inerte en présence d'une base, de préférence à température élevée.

8. Procédé pour la préparation d'un composé de l'indole selon la formule décrite dans la revendication 1 dans laquelle le symbole $==$ représente une double liaison entre les atomes de carbone, R^1 est défini comme à la revendication 1, le symbole R^2 attaché en position 2 du cycle indole représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 24 atomes de carbone, le symbole R^2 attaché en position 3 représente un atome d'hydrogène et R^3 représente un atome d'hydrogène, qui comprend l'hydrogénation catalytique d'un composé de formule générale:



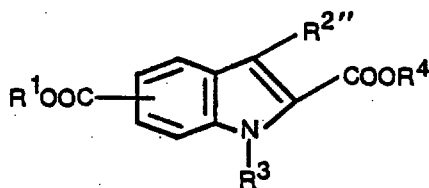
XI

dans laquelle R^1 et R^2'' sont définis respectivement comme aux revendications 1 et 4, suivie d'une cyclisation de l'amine intermédiaire obtenue.

9. Procédé pour la préparation d'un composé de l'indole selon la formule décrite dans la revendication 1 dans laquelle le symbole $==$ représente une double liaison entre les atomes de carbone, R^1 est défini comme à la revendication 1, le symbole R^2 attaché en position 3 du cycle indole représente un radical alcoyle en chaîne droite ou ramifiée contenant 7 à 24 atomes de carbone, le symbole R^2 attaché en position 2 représente un atome d'hydrogène et R^3 est défini comme à la revendication 1, qui



comprend la décarboxylation par chauffage d'un dérivé de l'alcoyloxycarbonyl-2 indole de formule générale:



XII

10.

dans laquelle R¹ et R³ sont définis comme à la revendication 1, et R²'' et R⁴ sont définis respectivement comme aux revendications 4 et 5.

10. Procédé pour la préparation d'un dérivé de l'indole ou de l'indoline selon la formule décrite dans la revendication 1 dans laquelle R¹ représente un atome d'hydrogène et R² et R³ sont définis
15 comme à la revendication 1, qui comprend l'hydrolyse de l'ester correspondant de formule générale décrite dans la revendication 1 dans laquelle R² et R³ sont définis comme à la revendication 1 et R¹ représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone éventuellement substitué comme décrit à la revendication 1.

11. Procédé pour la préparation d'un ester d'un dérivé de l'indole ou de l'indoline selon la formule
20 décrite dans la revendication 1 dans laquelle R¹ représente un radical alcoyle en chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone (éventuellement substitué par un ou plusieurs substituants du même type choisis parmi les radicaux hydroxy, alcényle contenant 2 à 5 atomes de carbone et alcanoyloxy contenant 2 à 7 atomes de carbone), qui comprend l'estérification de l'acide
25 carboxylique correspondant dans la formule duquel le symbole R¹ de la formule générale décrite dans la revendication 1 représente un atome d'hydrogène et R² et R³ sont définis comme à la revendication 1.

12. Procédé pour la préparation d'un dérivé de l'indole ou de l'indoline selon la formule décrite contenant 1 à 6 atomes de carbone et R¹ et R² sont définis comme à la revendication 1, qui comprend
la N-alcoylation (C₁—C₆) d'un composé correspondant selon la formule décrite dans la revendication 1
30 dans laquelle R³ représente un atome d'hydrogène.

13. Procédé selon l'une quelconque des revendications précédentes suivi d'une étape consistant à convertir le composé de l'indole ou de l'indoline selon la formule décrite à la revendication 1 ainsi obtenu en un sel pharmaceutiquement acceptable, lorsqu'il existe.

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