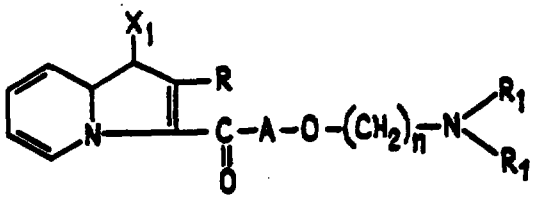
SPECIFICATION

Indolizine derivatives and their manufacture

This invention relates to indolizine derivatives having pharmacological activity and to the manufacture of said derivatives.

The indolizine derivatives with which the present invention is concerned are the compounds represented by the general formula:

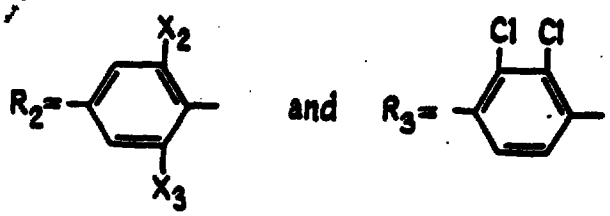


I

and the pharmaceutically aceptable acid addition salts thereof, for example the oxalate or hydrochloride, wherein: R represents a branched- or straight-chain alkyl group having from 1 to 8 carbon atoms, an unsubstituted phenyl group, or a phenyl group having one or two substituents, which may be the same or different, selected from halogen atoms, for example fluorine, chlorine and bromine, and lower alkyl and alkoxy groups, for example methyl and methoxy;

X_1 represents hydrogen, chlorine, bromine, iodine, methyl or methoxy;

A represents a group selected from;



in which X_2 represents hydrogen, chlorine, bromine, iodine, methyl or methoxy, and X_3 represents hydrogen, chlorine, bromine, iodine or methyl;

R_1 represents a methyl, ethyl, n-propyl or n-butyl group; and

n represents an integer in the range from 2 to 6; with the proviso that at least one of X_1, X_2 and X_3 is other than hydrogen and when X_1 is hydrogen, X_2 and X_3 are not both methyl.

The terms "lower alkyl" and "lower alkoxy" are used herein as meaning respectively alkyl and alkoxy groups containing from 1 to 4 carbon atoms.

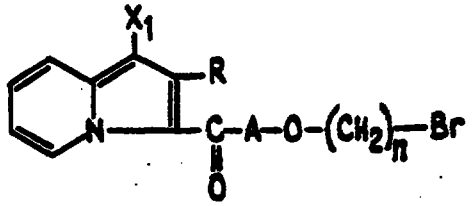
In the aforesaid general formula I, R represents, preferably, a branched- or straight-chain alkyl group having from 1 to 8 carbon atoms, a phenyl group, a mono-fluoro-, mono-chloro-, mono-bromo-, mono-methyl- or mono-methoxy-phenyl group, a di-fluoro-, di-chloro- or di-bromo-phenyl group, or a tolyl radical substituted in the aromatic ring by an atom of fluorine, chlorine or bromine.

The indolizine derivatives of the invention have been found to possess useful pharmacological properties capable of rendering them of considerable value in the treatment of certain pathological syndromes of the heart, more particularly in the treatment of angina pectoris and auricular and ventricular cardiac arrhythmias of various origins.

Thus the present invention is also concerned with pharmaceutical and veterinary compositions containing, as an essential active ingredient, an indolizine derivative of formula I or a pharmaceutically acceptable acid addition salt thereof, in association with a pharmaceutical carrier or excipient therefor.

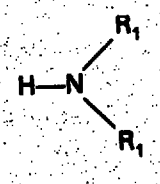
Daily dosages will preferably be from 100 to 300 mg of active ingredient by oral route and preferably from 1 to 3 mg of active ingredient by parenteral route to a subject weighing 60 kgs.

The compounds of formula I can be prepared, in accordance with the invention, by condensing, in an inert solvent such as, for example, benzene or toluene, a bromoalkoxy-benzoyl-indolizine of the general formula:



II

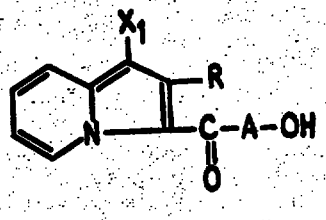
wherein X_1, R, A and n have the same meaning as in formula I, with a secondary amine of the general formula:



III

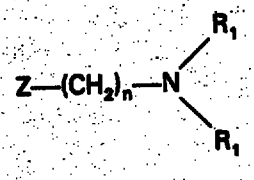
in which R_1 has the same meaning as in formula I, to form the required indolizine derivative of formula I which, if desired, is reacted with an appropriate organic or inorganic acid to provide a pharmaceutically acceptable acid addition salt thereof.

The compounds of formula I may alternatively be prepared by condensing, advantageously in an aprotic solvent such as, for example, acetone, methyl ethyl ketone or toluene, an alkali metal salt, preferably the potassium or sodium salt of an appropriately substituted indolizine derivative represented by the general formula:



IV

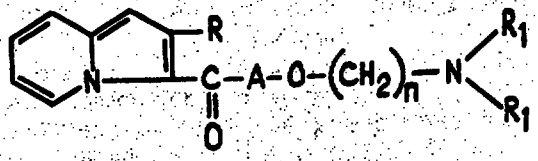
in which R, A and X_1 have the same meaning as in formula I, with an alkylamino derivative of the general formula:



V

or an acid addition salt thereof, in which Z represents a halogen atom such as chlorine or bromine or a p-toluenesulphonyloxy group and n and R_1 have the same meaning as in formula I to give the required indolizine derivate which, if desired, is reacted with an appropriate organic or inorganic acid to provide a pharmaceutically aceptable acid addition salt thereof.

In accordance with a further aspect of the invention, the indolizine derivatives of formula I in which X_1 represents chlorine, bromine or iodine and A represents the group R_3 or a group R_2 in which X_2 represents chlorine, bromine, iodine, methyl or methoxy and X_3 represents chlorine, bromine, iodine or methyl can also be prepared by reacting an indolizine derivative of general formula:



VI

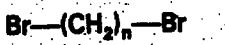
in which R, R_1 and n have the same meaning as in formula I and A represents the group R_3 or a group R_2 in which X_2 represents chlorine, bromine, iodine, methyl or methoxy and X_3 represents chlorine, bromine iodine or methyl:

a) *either* with N-chlorosuccinimide, the reaction taking place in a suitable medium such as dichlorethane and between 0°C and room-temperature, to obtain the required compound of formula I in which X_1 represents chlorine, in free base form,

b) *or* with bromine or iodine, the reaction taking place at room-temperature in a suitable solvent such as dioxan and in the presence of an alkali metal acetate, for instance sodium acetate, to obtain the required compound of formula I in which X_1 represents bromine or iodine, in free base form,

the free base so obtained being then reacted, if desired, with an organic or inorganic acid, to provide a pharmaceutically acceptable acid addition salt thereof.

The compounds of formula II can be obtained by condensing, advantageously in an inert medium such as for example acetone or methyl ethyl ketone, an alkali metal salt, preferably the potassium or sodium salt, of a compound of formula IV hereabove, with a dibromoalkane of the general formula:



VII

in which n has the same meaning as in formula I to obtain the required compound of formula II.

The compounds of formula IV in which A represents the group R_2 are either compounds described in our copending British patent application No. 80 21964 (Serial No. 2051812) or compounds which

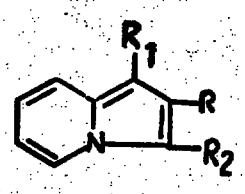
can be prepared in accordance with methods described in the aforesaid British patent application.

The other compounds of formula IV, i.e. those in which A represents the group R_3 can be obtained by reacting the appropriate 2-substituted-indolizine with 2,3-dichloro-4-acetyloxy or 4 tosyloxy-benzoyl chloride. This benzoly chloride derivative is itself prepared by acetylating 1,2-dichloro-anisole in accordance with the conditions of the FRIEDEL and CRAFTS reaction oxydating the acetyl derivative so obtained with sodium hypochlorite to form the corresponding benzoic acid derivative, demethylating with hydriodic acid in acetic acid to obtain 2,3-dichloro-4-hydroxy-benzoic acid. This last-cited compound is then reacted with acetyl chloride or tosyl chloride to form the required 2,3-dichloro-4-acetyloxy or 4-tosyloxy-benzoic acid and the corresponding acyl chloride is subsequently formed in accordance with known procedures, for instance by reaction with thionyl chloride.

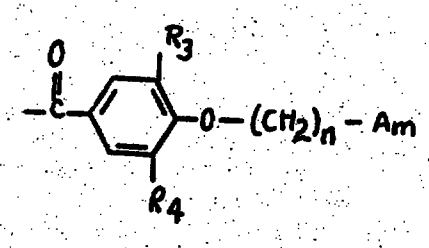
With respect to the compounds of formula II, these are compounds falling within the scope of formula I above.

Indolizine derivatives are already known which have pharmacoligical effects capable of rendering them useful in the treatment of angina pectoris and cardiac arrhythmias.

In this connection, British Patent Specification No. 1,518,443 discloses indolizine derivatives represented by the general formula:



wherein R represents a branched- or straight-chain alkyl radical having from 1 to 5 carbon atoms, a phenyl radical, a mono-fluoro-, mono-chloro, or mono-bromo-phenyl radical, a di-fluoro, di-chloro or di-bromo-phenyl radical, a methoxy-phenyl radical or a methyl-phenyl radical optionally substituted on the aromatic moiety by an atom of fluorine, chlorine or bromine and R_1 and R_2, which are different, each represent a hydrogen atom or a group of the formula:



wherein R_3 and R_4, which are identical, each represent a hydrogen atom or a methyl radical, Am represents a dimethylamino, diethylamino, di-n-propylamino, di-n-butylamino, morpholino, piperidino, pyrrolidino or 4-methyl-piperazino group and n is an integer in the range of from 2 to 6 inclusive.

More particularly this specification discloses the compound 2-ethyl-3-[4-(3-di-n-butylaminopropyl)-oxybenzoyl]-indolizine, known under the non-proprietary name of butoprozine.

In the British patent specification in question, antianginal properties are attributed to compounds described therein since they produce the following cardiovascular effects:

— bradycardia
— decrease in arterial pressure
— α-antiadrenergic effect
— β-antiadrenergic effect
— coronarodilating effect.

The increase of the blood-flow to the myocardium provoked by these compound is, in fact, only slight because theire action does not last long: it is exerted for only a few minutes after an intravenous injection.

Furthermore, the compounds described in the aforesaid British patent specification only possess a weak β-adrenergic antagonist action. This action is only slight at the minimum dose at which the other four cardiovascular effects cited above manifest themselves to a significant degree.

It has now been found quite surprisingly that by substituting R_1, R_3 or R_4 in an appropriate manner with one or more methyl or methoxy groups or halogen atoms for example chlorine, bromine or iodine, dialkylamino-alkyloxy-benzoyl indolizine derivatives, compounds are obtained which present a much broader spectrum of cardiovascular properties then the derivatives of British Specification No. 1,518,443 while showing less toxicity.

Thus, it has been possible to demonstrate that the indolizine derivatives of the invention can be regarded as powerful coronarodilators since they are capable of increasing the blood-flow to the myocardium to a marked degree and for a longer period of time than butoprozine. Compounds of the invention were also found to reduce cardiac frequency and arterial pressure in the animal.

Furthermore, the indolizine derivatives present a β-antiadrenergic effect which is much more powerful than that of the derivatives of the aforesaid British patent specification. At the minimum dose required to produce bradycardia, a reduction in arterial pressure, α-antiadrenergic and coronarodilatory effects to a significant degree, the β-antiadrenergic effect is, in fact, only slight in the case of the derivatives of the British patent specification in question whereas it is much stronger with the indolizine derivatives of the invention.

Moreover, the compounds of the invention reduce the comsumption of oxygen by the myocardium calculated by multiplying the difference between the arterial and venous blood in oxygen by the coronary blood-flow. Thus, the compounds of the invention cause a considerable reduction in the arterio-venous difference which induces a decrease in the comsumption of oxygen in spite of the increase of the coronary blood-flow.

Furthermore, unlike butoprozine, these beneficial effects on the consumption of oxygen are obtained with the compounds of the invention without any decrease in the contractility of the myocardium.

It has been further demonstrated that the derivatives of the invention are less toxic than the compounds of British patent No. 1,518,443. Acute toxicity tests carried out by intravenous and oral routes in the animal have shown that the lethal doses are higher in the case of compounds of the invention than in the case of derivatives of the British patent in question.

Furthermore, higher blood levels can be obtained with compounds of the invention than with butoprozine.

Thus, it has been shown that the same oral dose of 1-bromo-2-methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine and of butoprozine administered to the dog induces a blood level which is three times higher with the compound of the invention than with butoprozine. Likewise, the compounds of the invention, when administered in long-term treatment per os in the dog have shown no cardial toxicity as represented by ventricular arrhythmia which is not the case with butoprozine. Finally, the indolizine derivatives of the invention exert a milder depressant action on the contractility of the myocardium than does butoprozine.

In man, an attack of angina pectoris is the painful consequence of a deficiency between the supply and the requirement of oxygen of the myocardium.

A compound can thus be active in the treatment of angina pectoris either by increasing the supply of oxygen or by decreasing the need for oxygen. Amongst the products commonly used in humans for treating angina pectoris, can be cited dipyrodamole amongst the coronarodilators and amiodarone amongst the compounds which decrease the consumption of oxygen by the myocardium.

Comparative tests have, however, shown that the compounds of the invention are very superior to dipyridamole and amiodarone from several points of view.

In particular, it has been shown that dipyrodamole does not decrease the consumption of oxygen by the myocardium and that amiodarone cannot be regarded as a coronarodilator.

The derivatives of the present invention exert their effect through both of these factors. Thus, they decrease the consumption of oxygen by the myocardium through their metabolic effects and also increase the coronary blood-flow in a long-lasting manner. Moreover, they are capable of preventing or curing not only arrhythmias induced by ischemia of the myocardium but also the auricular and ventricular arrhythmias of widely varying origins.

Thus, it appears that the halogenating, methoxylating or methylating of indolizine derivatives of British patent No. 1,518,443 gives rise to compounds possessing a novel spectrum of pharmacological properties valuable in the treatment of cardiac deficiencies.

For instance:

— the sites of the myocardium which are insufficiently irrigated can be nourished by means of the coronarodilating effect which can induce the development of an additional collateral circulation. This effect is valuable for the treatment of both anginal pain and the disturbances of rhythm consequent upon ischemia of the myocardium.

— the antidrenergic effect is also valuable for the treatment of both angina pectoris and cardiac arrhythmia in view of the important role played by hyperactivity of the sympathetic system in the etiology of these two cardiac diseases.

Since the physiological mediator of the sympathetic system is epinephrine, a compound which inhibits all the effects of epinephrine will probably be more active than a compound which only inhibits a part of these effects. For this reason, the compounds of the present invention which inhibit both α and β effects of epinephrine present an advantage over the derivatives of the British patent No. 1,518,443 which practically only inhibit the α effects at the minimum dose at which the other pharmacological cardiovascular effects occur.

Amongst the compounds of the invention which have shown the most outstanding anti-anginal potentialities, the following may be cited:

1-Bromo-2-methyl-3-[4-3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine

2-n-Butyl-3-[4-3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine

2-Ethyl-3-[4-3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine

2-n-Butyl-3-[4-3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine

2-Isopropyl-3-[4-3-di-n-butylaminopropyl)-oxy-3-,5-dichloro-benzoyl]-indolizine
1-Bromo-2-phenyl-3-[4-3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine
1-Chloro-2-ethyl-3-[4-3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine
1-Chloro-2-n-butyl-3-[4-3-di-n-butylaminopropyl)-oxy-benzoyl]-indolizine
1-Bromo-2-(4-chloro-phenyl)-3-[4-3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine
these compounds being in the form of the free base or of a pharmaceutically acceptable acid addition salt such as, for example, the hydrochloride or acid oxalate.

The results of pharmacological tests carried out in order to determine the cardiovascular properties of the compounds of the invention are given hereunder.

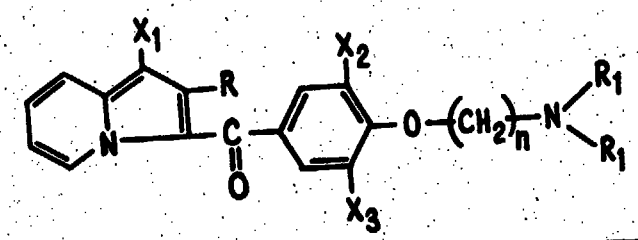
I. Antianginal properties

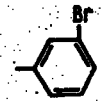
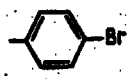
1) Effect of blood-flow to the myocardium.

This test was carried out in accordance with the techniques described by R. CHARLIER & J. BAUTHIER in Arzneimittel—Forschung "Drug Research" *23* n° 19, 1305—1311 (1973).

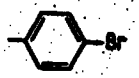
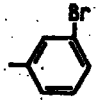
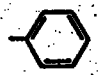
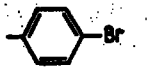
It was undertaken on anaesthetized dogs which received the substance under study by intravenous route. The intensity of the maximum effect on blood-flow to the myocardium was expressed in percentage of the corresponding value before injection. The time required for the maximum effect to decrease by 50% represented the duration of the effect. This time was measured in minutes.

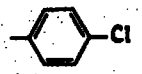
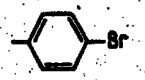
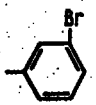
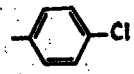
The following results were registered:



X_1	X_2	X_3	R	R_1	n	Dose (mg/kg)	Max. increase (%)	Time required to decrease to 50%
Br	Br	H	C_2H_5	n-C_4H_9	3	10	60	90
Br	Br	H	CH_3	n-C_4H_9	3	10	125	40
Br	Br	H	n-C_4H_9	n-C_3H_7	3	10	100	20
Br	Br	H	n-C_3H_7	n-C_3H_7	3	10	90	20
Br	Br	H		n-C_3H_7	3	10	100	20
Br	Br	H		n-C_4H_9	3	10	150	100
H	Br	H		n-C_4H_9	3	10	90	25
Br	Br	H	CH_3	n-C_4H_9	3	10	77	45
H	Br	H	n-C_3H_7	n-C_4H_9	3	2	120	25
H	Br	H	n-C_4H_9	n-C_4H_9	3	5	70	60
Br	Cl	H	iso-C_3H_7	n-C_4H_9	3	5	133	20
Cl	H	H	n-C_4H_9	n-C_4H_9	3	10	60	30

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X_1	X_2	X_3	R	R_1	n	Dose (mg/kg)	Max. increase (%)	Time required to decrease to 50%
H	Cl	Cl	iso-C_3H_7	n-C_4H_9	3	10	30	75
H	Cl	Cl		n-C_4H_9	3	10	45	15
H	Cl	Cl	iso-C_3H_7	n-C_4H_9	3	10	30	75
H	Cl	H		n-C_4H_9	3	10	30	45
H	Cl	H		n-C_3H_7	3	8	45	25
H	Cl	H	iso-C_3H_7	n-C_3H_7	3	5	80	90
Br	Cl	H		n-C_4H_9	3	10	90	90
Br	Cl	H	n-C_4H_9	n-C_3H_7	3	10	40	90
Br	Cl	H		n-C_3H_7	3	10	50	50
H	Cl	H	n-C_4H_9	n-C_4H_9	3	5	75	30
H	Cl	H	C_2H_5	n-C_4H_9	3	6	70	45

X_1	X_2	X_3	R	R_1	n	Dose (mg/kg)	Max. increase (%)	Time required to decrease to 50%
Br	Cl	H		$n\text{-}C_3H_7$	3	10	63	45
H	Cl	H		$n\text{-}C_4H_9$	3	10	60	25
Br	Cl	H	$n\text{-}C_3H_7$	$n\text{-}C_4H_9$	3	2.5	50	60
Cl	Cl	H		$n\text{-}C_3H_7$	3	8	70	90
Cl	Cl	H	C_2H_5	$n\text{-}C_4H_9$	3	1	40	15
Cl	Cl	H	C_2H_5	$n\text{-}C_3H_7$	3	3.3	60	25
Cl	H	H		$n\text{-}C_3H_7$	3	5	50	40
Butoprozine						10	120	4
Amiodarone						10	36	7

These results clearly show that the compounds of the invention are more valuable than butoprozine and amiodarone as regards the effects on bloodflow to the myocardium.

2. Antiadrenergic effects

The purpose of this test was to determine the capacity of the compounds under study to reduce epinephrine-increased blood-pressure (anti-α effect) and epinephrine-accelerated heart rate (anti-β effect) in the dog previously anaesthetized with pentobarbital and atropinized.

— Anti-α effect

For each dog, the dose of ephinephrine was first determined which provoked a reproductible increase by about 100 mm. Hg in the arterial pressure (between 5 and 10 μg/kg).

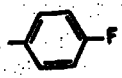
After that the dose of epinephrine so determined was administered followed by a dose by intravenous route of the compound to be studied. The percentage of reduction of the hypertension provoked by the compound under study in comparison with the hypertension previously obtained (about 100 mm.Hg) was then registered.

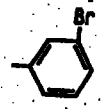
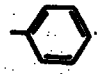
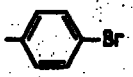
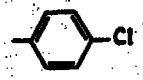
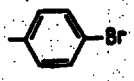
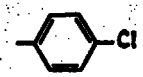
— Anti-β effect

During the same test as that described above, the epinephrine provoked a reproductible increase in the heart-rate of about 70 beats/min. The percentage of reduction of the epinephrine-induced acceleration of heart-rate produced by the compound under study in comparison with the tachycardia previously measured (about 70 beats) was then registered. In both cases, the results were expressed as follows:

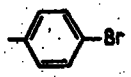
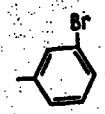
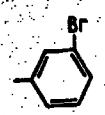
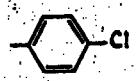
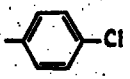
\+ for a $< 50\%$-reduction of the increase in pressure or cardiac frequency
\++ for a $\geqslant 50\%$-reduction of the increase in pressure or cardiac frequency
\+++ for a subtotal reduction of the increase in pressure or cardiac frequency

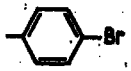
The following results were registered:

X_1	X_2	X_3	R	R_1	n	Dose (mg/kg)	Anti-α effect	Anti-β effect
Br	Br	H	C_2H_5	n-C_4H_9	3	10	+++	+++
Br	H	H	C_2H_5	n-C_4H_9	3	6	+++	+++
Br	Br	H		n-C_4H_9	3	10	+++	++
Br	Br	Br	n-C_3H_7	n-C_3H_7	3	10	+++	+++
H	Br	H		n-C_4H_9	3	10	+++	++
H	Br	H	C_2H_5	n-C_4H_9	3	7.5	+++	++
H	Br	H	n-C_4H_9	n-C_4H_9	3	5	+++	++
H	Br	H	n-C_4H_9	n-C_3H_7	3	5	+++	++
H	Br	H	CH_3	n-C_4H_9	3	5 10	+++ +++	++ +++
H	Br	H	n-C_4H_9	n-C_4H_9	3	5 10	+++ +++	+++ +++
H	Br	H	iso-C_3H_7	n-C_4H_9	3	6	+++	++
Cl	H	H	n-C_4H_9	n-C_4H_9	3	10	+++	++
Cl	H	H	n-C_3H_7	n-C_4H_9	3	7.5	+++	+++
H	Cl	H	n-C_4H_9	n-C_4H_9	3	10	+++	++
H	Cl	H	C_2H_5	n-C_3H_7	3	10	++	++

X_1	X_2	X_3	R	R_1	n	Dose (mg/kg)	Anti-α effect	Anti-β effect
H	Cl	H	C_2H_5	n-C_4H_9	3	6	+++	++
H	Cl	Cl	iso-C_3H_7	n-C_4H_9	3	10	++	++
H	Cl	H		n-C_4H_9	3	10	++	++
H	Cl	H	iso-C_3H_7	n-C_3H_7	3	10	++	++
Br	Cl	H		n-C_4H_9	3	10	++	+++
Br	Cl	H	C_2H_5	n-C_3H_7	3	7.8	++	++
Br	Cl	H		n-C_3H_7	3	10	++	++
Br	Cl	H	n-C_4H_9	n-C_3H_7	3	10	++	+
Br	Cl	H		n-C_4H_9	3	10	++	++
Br	Cl	H		n-C_3H_7	3	10	++	++
Br	Cl	H	C_2H_5	n-C_4H_9	3	10	+++	+++
Br	Cl	H		n-C_3H_7	3	10	+++	++

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X_1	X_2	X_3	R	R_1	n	Dose (mg/kg)	Anti-α effect	Anti-β effect
H	Cl	H		$n\text{-}C_4H_9$	3	10	++	+
Br	Cl	H		$n\text{-}C_3H_7$	3	10	+++	+++
Br	Cl	H	$n\text{-}C_3H_7$	$n\text{-}C_4H_9$	3	10	+++	+++
Cl	Cl	H		$n\text{-}C_3H_7$	3	8	+++	++
Cl	Cl	H	C_2H_5	$n\text{-}C_4H_9$	3	0.5	+++	+
Cl	Cl	H	C_2H_5	$n\text{-}C_3H_7$	3	3.3	+++	+++
Cl	H	H		$n\text{-}C_4H_9$	3	10	+++	++
Cl	H	H		$n\text{-}C_3H_7$	3	5	++	+
Cl	H	H		$n\text{-}C_4H_9$	3	5	+++	+++
H	Br	H	iso-C_3H_7	$n\text{-}C_3H_7$	3	7.5	+++	++
Br	OCH_3	H	CH_3	$n\text{-}C_3H_7$	3	7.5	++	++

X_1	X_2	X_3	R	R_1	n	Dose (mg/kg)	Anti-α effect	Anti-β effect
Cl	Cl	Cl	C_2H_5	n-C_3H_7	3	10	++	++
Cl	Cl	Cl		n-C_4H_9	3	10	+++	++
Cl	Br	H	C_2H_5	n-C_4H_9	3	10	+++	+++
Cl	Br	Br		n-C_3H_7	3	10	+	+
Br	Cl	Cl		n-C_3H_7	3	10	++	++
Br	Cl	Cl		n-C_4H_9	3	10	++	++
Br	CH_3	CH_3	CH_3	n-C_4H_9	3	10	+++	++
H	Br	Br		n-C_3H_7	3	10	+++	+++
H	Br	Br		n-C_4H_9	3	10	++	++

X_1	X_2	X_3	R	R_2	n	Dose (mg/kg)	Anti-α effect	Anti-β effect
OCH_3	Cl	H		$n\text{-}C_3H_7$	3	10	+++	+++
OCH_3	OCH_3	H		$n\text{-}C_3H_7$	3	10	++	++
H	OCH_3	H	C_2H_5	$n\text{-}C_4H_9$	3	10	+++	+++
Br	OCH_3	H	C_2H_5	$n\text{-}C_4H_9$	3	5	++	++
Br	OCH_3	H	CH_3	$b\text{-}C_4H_9$	3	7	++	++
Br	OCH_3	H	CH_3	$n\text{-}C_3H_7$	3	7.5	++	++
Butoprozine						5	++	+
Amiodarone						10	++	++

These results again show that the compounds of the invention are more valuable than those of the prior art.

II. *Anti-arrhythmic properties.*

These properties were demonstrated after administration of the compound under study by intragastric route to mice using the LAWSON test (J. Pharmac. Exp. Therap. 1968, *160* (1) p. 22—31).

The arrhythmia was provoked by making the animals inhale chloroform to total asphyxia and by later observing the ventricular rhythm.

The dose of compound protecting 50% of the animals against ventricular fibrillation i.e. the AD_{50} was then recorded. The following results were registered:

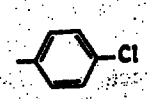
X_1	X_2	X_3	R	R_1	n	AD_{50} (mg/kg)
Br	Br	H	CH_3	$n\text{-}C_4H_9$	3	180
H	Br	H	$n\text{-}C_4H_9$	$n\text{-}C_4H_9$	3	170
Butoprozine						270

III *Toxicity*

Acute toxicity

Acute toxicity tests were carried out on rats and mice. The following results were registered in comparison with butoprozine. The compounds of the invention were used in oxalate acid form except those marked (*) which were tested in hydrochloride form.

a) By intravenous route to rats

X_1	X_2	X_3	R	R_1	n	LD_{50} (mg/kg)
(*) Br	Br	H	CH_3	$n\text{-}C_4H_9$	3	70
H	Br	H	$n\text{-}C_4H_9$	$n\text{-}C_4H_9$	3	60
(*) H	Cl	H	C_2H_5	$n\text{-}C_4H_9$	3	65
H	Cl	Cl	$iso\text{-}C_3H_7$	$n\text{-}C_4H_9$	3	>100
(*) Br	Cl	H		$n\text{-}C_4H_9$	3	>100
(*) H	Cl	H	$n\text{-}C_4H_9$	$n\text{-}C_4H_9$	3	>50 (LD_0 >50 mg/kg)
Cl	Cl	H	C_2H_5	$n\text{-}C_4H_9$	3	50
Cl	H	H	$n\text{-}C_4H_9$	$n\text{-}C_4H_9$	3	50
Br	Cl	H		$n\text{-}C_4H_9$	3	>100 (LD_0 >100 mg/kg)
Butoprozine						22

b) By intravenous route to mice

(*) Br	Br	H	CH_3	$n\text{-}C_4H_9$	3	50
Butoprozine						2.5

c) By intragastric route to mice

(*) Br	Br	H	CH_3	$n\text{-}C_4H_9$	3	>5000 (LD_0 >5000 mg/kg)
Butroprozine						1600

These results show that the compounds of the invention are far less toxic than butoprozine.

— Cardiac tolerance and general toxicity in long-term toxicity tests.

1-Bromo-2-methyl-3-[4-3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine hydrochloride, 2-n-butyl-3-[4-3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine hydrochloride and 2-n-butyl-3-[4-3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine hydrochloride provoked neither ventricular arrhythmia nor mortality at the dose of 200 mg/kg/day by oral route in the dog.

As against this, butoprozine was found to provok ventricular arrhythmia with a dose as low as 50 mg/kg/day by oral route in the dog, the lethal dose of this compound being between 50 and 100 mg/kg/day.

It will be appreciated that for therapeutic use the compound of the invention will normally be administered in the form of a pharmaceutical or veterinary composition, which may be in a dosage unit form appropriate to the desired mode of administration.

Thus the pharmaceutical or veterinary composition may be in a dosage unit form suitable for oral administration, for example a coated or uncoated tablet, a hard- or soft-gelatin capsule, a packaged powder, or a discrete amount of a suspension, or a syrup. The composition may alternatively take the form of a suppository for rectal administration, or of a solution or suspension for parenteral administration.

When in dosage unit form, the composition may contain for example from 15% to 50% by weight of the active ingredient per dosage unit for oral administration, from 3% to 15% of the active ingredient

per dosage unit for rectal administration and from 3% to 5% of the active ingredient per dosage unit for parenteral administration.

Irrespective of the form which the composition takes, the pharmaceutical or veterinary composition of the invention will normally be prepared by associating at least one of the compounds of formula I or a pharmaceutically acceptable acid addition salt thereof with an appropriate pharmaceutical carrier or excipient therefor, for example one or more of the following substances: milk sugar, starches, talc, magnesium stearate, polyvinylpyrrolidone, alginic acid, colloidal silica, distilled water, benzyl alcohol or flavouring agents.

The following Examples illustrate the invention:

EXAMPLE 1

1-Bromo-2-ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine and its acid oxalate.

a) 1-Bromo-2-ethyl-3-[4-(3-bromopropyl)-oxy-benzoyl]-indolizine

A mixture of 7.7 g (0.018 mol) of 1-bromo-3-(3-bromo-4-hydroxy-benzoyl)-indolizine, 5 g (0.036 mol) of anhydrous potassium carbonate and 50 ml of methyl ethyl ketone was stirred in a flask for 30 minutes. To this reaction medium 14.4 g (0.072 mol) of 1,3-dibromo-propane were then added and the mixture was refluxed for 20 hours. After cooling, the mineral salts were filtered out and washed with acetone. The solvents were avaporated off together with the 1,3-dibromo-propane in excess. In this manner, 13.2 g of a product were obtained which were purified by elution chromatography on silica using benzene as elution agent. A first fraction of an unkown product was obtained and then a second fraction of 8 g of the desired product.

In this manner, 1-bromo-2-ethyl-3-[4-(3-bromopropyl)-oxo-benzoyl]-indolizine was obtained in a yield of 83.6%.
M.P.: 105—106°C.

b) 1-Bromo-2-ethyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine

A mixture of 2.2 g (0.004 mol) of 1-bromo-2-ethyl-3-[4-(3-bromopropyl)-oxy-benzoyl]-indolizine, 1.2 g (0.012 mol) of di-n-propylamine and 25 ml of toluene were refluxed in a flask for 20 hours. After cooling, the reaction medium was washed twice with 10 ml of water and the solvent was evaporated off under vacuum. Thus, 2.5 g of a residue were obtained which were purified by elution chromatography on silica using ethyl acetate as eluent. By this method, 2.4 g of 1-bromo-2-ethyl-3-[4-3-di-n-propylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine in free base form were obtained.

c) 1-Bromo-2-ethyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate.

The base previously obtained was dissolved in 30 ml of ethyl ether and then reacted with 0.55 g of oxalic acid in 70 ml of ethyl ether to give 2.4 g of the desired salt in crude form. From this quantity, 2.0 g of pure 1-bromo-2-ethyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate were obtained by recristallization from 75 ml of isopropanol.
Yield: 75%
M.P.: 139—140°C.

EXAMPLE 2

1-Bromo-2-methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine and salts thereof.

Into a 1-l flask, a mixture of 180 ml of water, 180 ml of toluene, 73 g (0.178 mol) of 1-bromo-2-methyl-3-(3-bromo-4-hydroxy-benzoyl)-indolizine, 42.7 g (0.21 mol) of 1-di-n-butylamino-3-chloro-propane and 34.5 g of potassium carbonate was introduced while stirring. The reaction medium was heated under reflux for 20 hours. After cooling to room-temperature, the aqueous phase was decanted and the toluene layer was washed three times, each time with 200 ml of water. The toluene solution was transferred to a flask and, under atmospheric pressure, toluene was distilled off to dryness and the residue so obtained was cooled.

In this manner, crude 1-bromo-2-methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine was obtained in free base form.
The following salts of this compound were then prepared:

a) hydrochloride

To the free base previously obtained, a solution of 8 g of hydrochloric acid in 61 ml of ethyl acetate was added. The precipitate so formed, i.e. 104 g, was suction-filtered, washed with ethyl acetate and recrystallized from 500 ml of isopropanol. In this manner, 93 g of 1-bromo-2-methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine hydrochloride was obtained.
Yield: 84.7%
M.P.: 172°C.

b) acid oxalate

To an ethereal solution of the base previously obtained, an equimolecular solution of oxalic acid in ethyl ether was added. The salts so obtained was recrystallized from isopropanol.

In this manner, 1-bromo-2-methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate was obtained.
M.P.: 89—90°C.

EXAMPLE 3

2-Methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate.

Into a 250 ml-flask, a mixture of 4 g (0.01 mol) of 2-methyl-3-(3,5-dibromo-4-hydroxy-benzoyl)-indolizine and 150 ml of acetone was introduced. After the indolizine dissolved, there were added 4 g of anhydrous potassium carbonate and 2.2 g of di-n-butylaminopropyl chloride.

While stirring, the reaction mixture was refluxed for 16 hours. After cooling to room-temperature, the mineral salts were filtered out and washed with acetone on the filter. The acetone was then distilled off under reduced pressure using a rotatory evaporator and the oily residue was dissolved in about 100 ml of ethyl acetate. The medium was filtered on a filter and 1.5 g of anhydrous oxalic acid was added to the filtrate. The reaction medium was allowed to stand and the oxalate which crystallized was filtered out, washed on the filter with ethyl acetate and dried under vacuum.

In this manner, 6.2 g of 2-methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate were obtained.
Yield: 92.7%
M.P.: 96°C.

EXAMPLE 4

1-Bromo-2-ethyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate.

Into a 250 ml-flask were introduced 2.8 g (0.005 mol) of 2-ethyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate and 80 ml of dioxan. The reaction mixture was stirred and after the indolizine had dissolved, 0.8 g of anhydrous sodium acetate was added. Through a dropping-funnel was added, dropwise and under vigorous stirring, a solution of 0.8 g of bromine in 20 ml of dioxan. The temperature was maintained at about 20°C during the introduction of the bromine.

After the medium had been stirred for 2 hours at room-temperature, the dioxan was distilled off under vacuum with a rotatory evaporator. The solid residue was dissoved in water, made alkaline with a sodium hydroxide solution and extracted with chloroform. The chloroformic solution was washed three times with water and the chloroform was distilled off under reduced pressure. The oily residue so obtained was taken up in dry ethyl ether and after filtration on a filter the acid oxalate was formed.

In this manner, 1.8 g of 1-bromo-2-ethyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate was obtained after recrystallization from ethyl acetate.
Yield: 55.8%
M.P.: 135°C.

Using the appropriate starting-products, the following compounds were prepared by utilizing the various processes described in the foregoing Examples.

Compounds	*M.P. °C*
1-Bromo-2-ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-benzoyl]-indolizine acid oxalate	107—108 (isopropanol)
1-Bromo-2-(4-bromo-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-benzoyl]-indolizine acid oxalate	92—94 (isopropanol)
1-Chloro-2-methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-benzoyl]-indolizine acid oxalate	92—93 (isopropanol)
1-Chloro-2-ethyl-3-[4-(3-di-n-propylaminopropyl)-oxy-benzoyl]-indolizine acid oxalate	162 (isopropanol)
1-Chloro-2-n-propyl-3-[4-(3-di-n-butylaminopropyl)-oxy-benzoyl]-indolizine acid oxalate	111—112 (isopropanol)
1-Chloro-2-n-butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-benzoyl]-indolizine acid oxalate	106—108 (isopropanol)

Compounds	M.P. °C
1-Chloro-2-phenyl-3-[4-(3-di-n-propylaminopropyl)-oxy-benzoyl]-indolizine acid oxalate	161—162 (isopropanol)
1-Chloro-2-(4-chloro-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-benzoyl]-indolizine acid oxalate	158—159 (methanol)
1-Chloro-2-phenyl-3-[4-(3-di-n-butylaminopropyl)-oxy-benzoyl]-indolizine acid oxalate	160—161 (methanol)
1-Chloro-2-n-butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-benzoyl]-indolizine acid oxalate	80—82 (benzene)
2-Methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	141—143 (10/1 ethyl acetate/isopropanol)
2-Ethyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	163 (isopropanol)
2-Ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	98—99 (isopropanol)
2-n-Propyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	145 (isopropanol)
2-n-Propyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	113—115 (isopropanol)
2-Isopropyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	105—107 (benzene)
2-n-Butyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	136—137 (isopropanol)
2-n-Butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	86—87 (isopropanol)
2-Phenyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	148—149 (isopropanol)
2-Phenyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	129—130 (isopropanol)
2-(4-Fluoro-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	110 (isopropanol)

Compounds	M.P. °C
2-(4-Chloro-phenyl)-3-[4-(3-di-n-propylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	163—164 (methanol)
2-(4-Chloro-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	139—140 (isopropanol)
2-(3-Bromo-phenyl)-3-[4-(3-di-n-propylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	142—143 (isopropanol)
2-(4-Bromo-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	147—148.5 (methanol)
2-(4-Methoxy-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	169 (isopropanol)
2-Isopropyl-3-[4-(5-di-n-butylaminopentyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	80—82 (benzene)
2-Isopropyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	179 (isopropanol)
2-Methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	141—143 (isopropanol)
2-Ethyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	161—162 (methanol)
2-Ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	116—117 (isopropanol)
2-Isopropyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	115—117 (isopropanol)
2-Isopropyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	168—169 (methanol)
2-n-Butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	84—85 and 107—109 (isopropanol)
2-n-Butyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	130—131 (isopropanol)
2-Phenyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	121—122 (isopropanol)
2-Phenyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	157—159 (methanol)

Compounds	*M.P. °C*
2-(4-Methyl-phenyl)-3-[4-(3-di-n-propylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	134—135 (isopropanol)
2-(4-Bromo-phenyl)-3-[4-(3-di-n-propylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	154—155 (methanol)
2-(4-Bromo-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	134—135 (isopropanol)
2-(3-Bromo-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	92—93 (isopropanol)
2-(3-Bromo-phenyl)-3-[4-(3-di-n-propylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	148—150 (isopropanol)
2-(4-Chloro-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	116—118 (isopropanol)
2-(4-Chloro-phenyl)-3-[4-(3-di-n-propylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	159—160 (methanol)
1-Bromo-2-methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	89—90 (isopropanol)
1-Bromo-2-methyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	164—165 (isopropanol/methanol)
1-Bromo-2-ethyl-3-[4-(2-dimethylaminoethyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	164—165 (dichlorethane)
1-Bromo-2-ethyl-3-[4-(3-dimethylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	150—151 (dichlorethane)
1-Bromo-2-ethyl-3-[4-(3-diethylaminoethyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	168—169 (dichlorethane)
1-Bromo-2-ethyl-3-[4-(3-diethylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	140—141.5 (isopropanol)
1-Bromo-2-ethyl-3-[4-(2-di-n-propylaminoethyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	163—164 (isopropanol)
1-Bromo-2-ethyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	139—140 (isopropanol)
1-Bromo-2-ethyl-3-[4-(2-di-n-butylaminoethyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	164—165 (isopropanol)

Compounds	*M.P. °C*
1-Bromo-2-ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	101—101.5 (isopropanol)
1-Bromo-2-n-propyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	92 (benzene)
1-Bromo-2-n-propyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	132—136 (isopropanol)
1-Bromo-2-n-butyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	151—152 (2/1 isopropanol/methanol)
1-Bromo-2-n-butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	101—103 (isopropanol)
1-Bromo-2-phenyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	169—170 (1/1 methanol/isopropanol)
1-Bromo-2-phenyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	167—169 (isopropanol)
1-Bromo-2-(4-methoxy-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	178—179 (methanol)
1-Bromo-2-(4-methyl-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	169—170.5 (1/1 isopropanol/methanol)
1-Bromo-2-(4-fluoro-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	170—171 (methanol)
1-Bromo-2-(3-bromo-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	172—173 (methanol)
1-Bromo-2-n-butyl-3-[4-(4-di-n-butylaminobutyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	118—120 (isopropanol)
1-Chloro-2-ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	115—117 (isopropanol)
1-Chloro-2-ethyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	137—138 (isopropanol)
1-Chloro-2-(3-bromo-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	171—172 (methanol)
1-Chloro-2-(3-bromo-phenyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	194—195 (methanol)

Compounds	*M.P. °C*
1-Chloro-2-ethyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate	141 (ethyl acetate)
1-Chloro-2-ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dichloro-benzyl]-indolizine acid oxalate	129 (ethyl acetate)
1-Chloro-2-phenyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate	156 (isopropanol)
1-Chloro-2-phenyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate	136 (isopropanol/heptane)
1-Bromo-2-methyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	110—112 (isopropanol)
1-Bromo-2-methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	108—110 (isopropanol)
1-Bromo-2-ethyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	136.5—138 (isopropanol)
1-Bromo-2-ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	103—105 (isopropanol)
1-Bromo-2-n-propyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	95—96 (isopropanol)
1-Bromo-2-isopropyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	116 (isopropanol)
1-Bromo-2-n-butyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	159—160 (methanol)
1-Bromo-2-n-butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	101—103 (isopropanol)
1-Bromo-2-phenyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	167.5—169 (methanol)
1-Bromo-2-phenyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	169—170 (methanol)
1-Bromo-2-(4-chloro-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	160—161 (isopropanol)
1-Bromo-2-(4-chloro-phenyl)-3-[4-(3-di-n-propylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	184—185 (methanol)

Compound	M.P. °C
1-Bromo-2-(4-bromo-phenyl)-3-[4-(3-di-n-propylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	176—177 (methanol)
1-Bromo-2-(4-bromo-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	168—169 (isopropanol)
1-Bromo-2-(3-bromo-phenyl)-3-[4-(3-di-n-propylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	200—201 (methanol)
1-Bromo-2-(3-bromo-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	170.5—172 (methanol)
1-Chloro-2-ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	104—105 (isopropanol)
1-Chloro-2-ethyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	157 (isopropanol)
1-Chloro-2-ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	140 (isopropanol)
1-Chloro-2-phenyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	172 (isopropanol)
1-Chloro-2-phenyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	146 (isopropanol)
2-Methyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine sesqui oxalate	136 (ethyl acetate)
2-Ethyl-3-[4-(3-dimethylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	148 (ethyl acetate)
2-Ethyl-3-[4-(2-diethylaminoethyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	171 (ethanol)
2-Ethyl-3-[4-(3-diethylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine hydrochloride	191 (50/50 ethyl acetate/acetone)
2-Ethyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine hydrochloride	166 (ethyl acetate)
2-Ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine hydrochloride	157 (ethyl acetate)
2-n-Propyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine hydrochloride	145 (ethyl acetate)

Compounds	M.P. °C
2-n-Propyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	107 (ethyl acetate)
2-Isopropyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	126 (ethyl acetate/ethanol)
2-Isopropyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	86 (ethyl acetate/ethyl ether)
2-n-Butyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	146 (ethyl acetate)
2-n-Butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	110 (ethyl acetate)
2-Phenyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	142 (ethyl acetate/ethanol)
2-Phenyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	86 (ethyl acetate)
2-(4-Fluoro-phenyl)-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	166 (ethyl acetate/ethanol)
2-(4-Fluoro-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	152 (isopropanol)
2-(4-Chloro-phenyl)-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	190 (ethyl acetate)
2-(4-Chloro-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	88 (ethyl acetate)
2-(3,4-Dichloro-phenyl)-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine sesquioxalate	114 (ethyl acetate/isopropanol)
2-(3,4-Dichloro-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	95 (ethyl acetate/isopropanol)
2-(3-Bromo-phenyl)-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	136 (ethanol)
2-(3-Bromo-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid fumarate	122 (ethyl acetate)
2-(4-Methyl-phenyl)-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	126 (ethyl acetate/isopropanol)

Compounds	M.P. °C
2-(4-Methyl-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	90 (ethyl acetate)
2-(4-Methoxy-phenyl)-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	167 (acetone)
2-(4-Methoxy-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	pasty at about 70°C (ethanol/ethyl ether)
2-Methyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate	145 (ethyl acetate/ethanol)
2-Methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate	95 (ethyl acetate/ethyl ether)
2-Ethyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate	100 (pasty)(ethyl acetate)
2-Ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate	95 (ethyl acetate)
2-n-Propyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate	142 (isopropanol)
2-n-Propyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate	114 (isopropanol)
2-Isopropyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate	86 (ethyl acetate)
2-Isopropyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate	90 (ethyl acetate)
2-Phenyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate	146 (ethanol)
2-Phenyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate	pasty at about 90°C (ethyl acetate)
2-(4-Bromo-phenyl)-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate	174 (ethyl acetate)
2-(4-Bromo-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate	133 (ethyl acetate)
1-Bromo-2-methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	141—143 (isopropanol)

Compounds	*M.P. °C*
1-Bromo-2-n-propyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	138—139 (isopropanol)
1-Bromo-2-ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	131—132.5 (isopropanol)
1-Bromo-2-phenyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	160—161 (isopropanol)
1-Bromo-2-(4-methyl-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	105—106 (isopropanol)
1-Bromo-2-(4-bromo-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	148—149 (isopropanol)
1-Bromo-2-(3,4-dichloro-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	196—197 (isopropanol)
1-Bromo-2-(3-chloro-4-methyl-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine acid oxalate	168—169 (isopropanol)
1-Bromo-2-ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate	134 (isopropanol)
1-Bromo-2-phenyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate	145 (ethyl acetate)
1-Bromo-2-phenyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine acid oxalate	106 (ethyl acetate)
2-n-Butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine hydrochloride	113—113.5 (ethyl acetate)
2-n-Propyl-3-[4-(3-diethyl-aminopropyl)-oxy-3,5-dibromo-benzoyl]-indolizine hydrochloride	154 (80/20 ethyl acetate/acetone)
2-Ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine hydrochloride	132—133 (ethyl acetate/isopropanol)
2-n-Butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine hydrochloride	104 (ethyl acetate)
1-Bromo-2-phenyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine hydrochloride	156—157
1-Chloro-2-(4-chloro-phenyl)-3-[4-(3-di-n-propylaminopropyl)-oxy-benzoyl]-indolizine acid oxalate	168—169 (methanol)

Compounds	M.P. °C
1-Methoxy-2-phenyl-3-[4-(3-di-n-propylaminopropyl)-oxy-benzoyl]-indolizine acid oxalate	117 (ethyl acetate)
1-Methoxy-2-phenyl-3-[4-(3-di-n-butylaminopropyl)-oxy-benzoyl]-indolizine acid oxalate	80 (ethyl acetate)
1-Methoxy-2-phenyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	172 (ethyl acetate)
1-Methoxy-2-phenyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine acid oxalate	120 (ethyl acetate)
1-Methoxy-2-phenyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	160 (ethyl acetate)
1-Methoxy-2-phenyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	78 (ethyl acetate)
1-Methoxy-2-phenyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-methoxy-benzoyl]-indolizine acid oxalate	148 (ethyl acetate)
1-Methoxy-2-phenyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-methoxy-benzoyl]-indolizine acid oxalate	78 (ethyl acetate)
1-Methoxy-2-(4-fluoro-phenyl)-3-[4-(3-di-n-propylaminopropyl)-oxy-3-methoxy-benzoyl]-indolizine acid oxalate	79 (ethyl acetate)
2-Methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-methoxy-benzoyl]-indolizine acid oxalate	159 (isopropanol)
2-Methyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-methoxy-benzoyl]-indolizine acid oxalate	171 (methanol)
2-Ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-methoxy-benzoyl]-indolizine acid oxalate	88 (ethyl acetate)
2-Ethyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-methoxy-benzoyl]-indolizine acid oxalate	121—122 (ethyl acetate)
1-Bromo-2-methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-methoxy-benzoyl]-indolizine acid oxalate	87—90 (benzene)
1-Bromo-2-methyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-methoxy-benzoyl]-indolizine acid oxalate	139—141 (isopropanol)
1-Bromo-2-ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-methoxy-benzoyl]-indolizine acid oxalate	11 (benzene)

Compounds	M.P. °C
1-Bromo-2-ethyl-3-[4-(3-di-n-propylaminopropyl)-oxy-3-methoxy-benzoyl]-indolizine acid oxalate	149 (isopropanol)
2-(4-Fluoro-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3-methoxy-benzoyl]-indolizine acid oxalate	85 (ethyl acetate)
2-Methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-methyl-benzoyl]-indolizine acid oxalate	149 (isopropanol)
2-Ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-methyl-benzoyl]-indolizine acid oxalate	133 (ethyl acetate)
1-Methyl-2-n-propyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	127 (ethyl acetate)
2-Isopropyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-methyl-benzoyl]-indolizine acid oxalate	91 (isopropanol)
2-n-Butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-methyl-benzoyl]-indolizine acid oxalate	89 (isopropanol)
1-Methyl-2-n-butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	99 (ethyl acetate)
1-Methyl-2-ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine acid oxalate	117 (ethyl acetate)
1-Bromo-2-methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dimethyl-benzoyl]-indolizine acid oxalate	120—122 (isopropanol)
1-Iodo-2-ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dimethyl-benzoyl]-indolizine acid oxalate	115 (ethyl acetate)
2-Ethyl-3-[2,3-dichloro-4-(3-di-n-propylaminopropyl)-oxy-benzoyl]-indolizine	117 (heptane)
2-Ethyl-3-[2,3-dichloro-4-(3-di-n-butylaminopropyl-oxy-benzoyl]-indolizine	95 (heptane)
2-Phenyl-3-[2,3-dichloro-4-(3-di-n-propylaminopropyl-oxy-benzoyl]-indolizine	99 (heptane)
2-Phenyl-3-[2,3-dichloro-4-(3-di-n-butylaminopropyl-oxy-benzoyl]-indolizine	87 (heptane)
2-(4-Fluoro-phenyl)-3-[2,3-dichloro-4-(3-di-n-propylaminopropyl-oxy-benzoyl]-indolizine	119 (heptane)

Compounds	*M.P. °C*
2-(4-Fluoro-phenyl)-3-[2,3-dichloro-4-(3-di-n-butylaminopropyl-oxy-benzoyl]-indolizine	95—96 (heptane)
1-Bromo-2-ethyl-3-[2,3-dichloro-4-(3-di-n-butylaminopropyl-oxy-benzoyl]-indolizine acid oxalate	164 (isopropanol)
1-Bromo-2-phenyl-3-[2,3-dichloro-4-(3-di-n-propylaminopropyl-oxy-benzoyl]-indolizine acid oxalate	171 (isopropanol)
1-Chloro-2-phenyl-3-[2,3-dichloro-4-(3-di-n-propylaminopropyl-oxy-benzoyl]-indolizine	136 (heptane)
2-n-Butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-iodo-benzoyl]-indolizine acid oxalate	90—92 (ethyl acetate)

EXAMPLE 5

In accordance with known pharmaceutical techniques soft-gelatin capsules containing the following ingredients, were prepared:

Ingredient	*mg*
2-n-Butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo/or 3-chloro-benzoyl]-indolizine hydrochloride	100
Starches	99.5
Colloidal silica	0.5
	200.0

EXAMPLE 6

In accordance with known pharmaceutical techniques, injectable solutions containing the following ingredients, were prepared:

Ingredient	*mg*
2-n-Butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo/or 3-chloro-benzoyl]-indolizine hydrochloride	150
Polysorbate 80	150
Benzyl alcohol	75
Water to 3 ml	

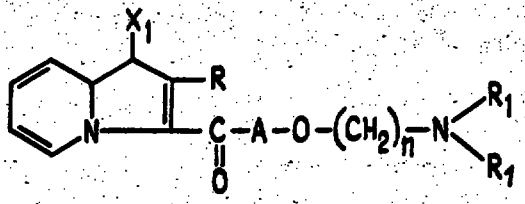
EXAMPLE 7

In accordance with known pharmaceutical techniques, suppositories containing the following ingredients, were prepared:

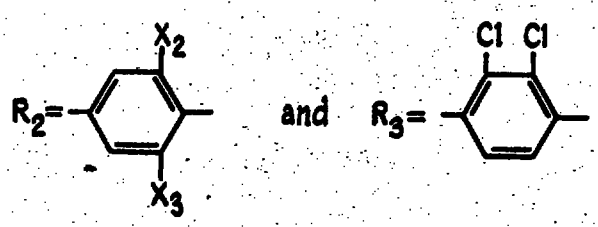
Ingredient	*mg*
2-n-Butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo/or 3-chloro-benzoyl]-indolizine hydrochloride	100
Mixture of mono- and di-glycerides of saturated acids (C_{12} to C_{18})	1400
	1500

CLAIMS:

1. Indolizine derivatives being the free bases represented by the general formula:



and the pharmaceutically acceptable acid addition salts thereof, wherein:
R represents a branched- or straight-chain alkyl group having from 1 to 8 carbon atoms, an unsubstituted phenyl group, or a phenyl group having one or two substituents, which may be the same or different, selected from halogen atoms and lower alkyl and alkoxy groups;
X_1 represents hydrogen, chlorine, bromine, iodine, methyl or methoxy;
A represents a group selected from;



in which X_2 represents hydrogen, chlorine, bromine, iodine, methyl or methoxy, and X_3 represents hydrogen, chlorine, bromine, iodine or methyl;
R_1 represents a methyl, ethyl, n-propyl or n-butyl group; and
n represents an integer in the range from 2 to 6; with the proviso that at least one of X_1, X_2 and X_3 is other than hydrogen and when X_1 is hydrogen, X_2 and X_3 are not both methyl.

2. Indolizine derivatives as claimed in Claim 1, wherein R represents a branched- or straight-chain alkyl group having from 1 to 8 carbon atoms, a phenyl group, a mono-fluoro-, mono-chloro-, mono-bromo-, mono-methyl- or mono-methoxy-phenyl group, a di-fluoro-, di-chloro- or di-bromo-phenyl group, or a tolyl radical substituted in the aromatic ring by an atom of fluorine, chlorine or bromine.

3. 1-Bromo-2-methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine and pharmaceutically acceptable acid addition salts thereof.

4. 2-n-Butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine and pharmaceutically acceptable acid addition salts thereof.

5. 2-Ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine and pharmaceutically acceptable acid addition salts thereof.

6. 2-n-Butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine and pharmaceutically acceptable acid addition salts thereof.

7. 2-Isopropyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine and pharmaceutically acceptable acid addition salts thereof.

8. 1-Bromo-2-phenyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine and pharmaceutically acceptable acid addition salts thereof.

9. 1-Chloro-2-ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine and pharmaceutically acceptable acid addition salts thereof.

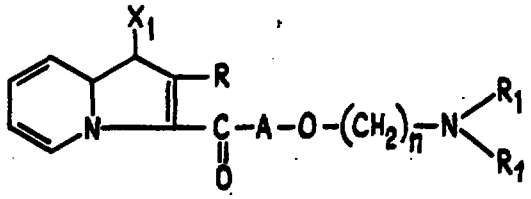
10. 1-Chloro-2-n-butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-benzoyl]-indolizine and pharmaceutically acceptable acid addition salts thereof.

11. 1-Bromo-2-(4-chloro-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine and pharmaceutically acceptable acid addition salts thereof.

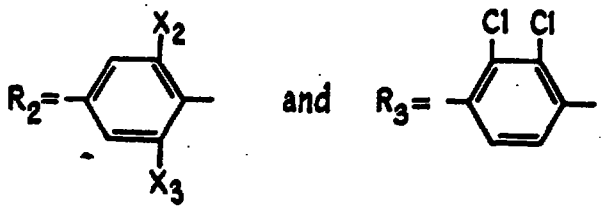
Ingredient	*mg*
2-n-Butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo/or 3-chloro-benzoyl]-indolizine hydrochloride	100
Mixture of mono- and di-glycerides of saturated acids (C_{12} to C_{18})	1400
	1500

CLAIMS:

1. Indolizine derivatives being the free bases represented by the general formula:



and the pharmaceutically acceptable acid addition salts thereof, wherein:
R represents a branched- or straight-chain alkyl group having from 1 to 8 carbon atoms, an unsubstituted phenyl group, or a phenyl group having one or two substituents, which may be the same or different, selected from halogen atoms and lower alkyl and alkoxy groups;
X_1 represents hydrogen, chlorine, bromine, iodine, methyl or methoxy;
A represents a group selected from;



in which X_2 represents hydrogen, chlorine, bromine, iodine, methyl or methoxy, and X_3 represents hydrogen, chlorine, bromine, iodine or methyl;
R_1 represents a methyl, ethyl, n-propyl or n-butyl group; and
n represents an integer in the range from 2 to 6; with the proviso that at least one of X_1, X_2 and X_3 is other than hydrogen and when X_1 is hydrogen, X_2 and X_3 are not both methyl.

2. Indolizine derivatives as claimed in Claim 1, wherein R represents a branched- or straight-chain alkyl group having from 1 to 8 carbon atoms, a phenyl group, a mono-fluoro-, mono-chloro-, mono-bromo-, mono-methyl- or mono-methoxy-phenyl group, a di-fluoro-, di-chloro- or di-bromo-phenyl group, or a tolyl radical substituted in the aromatic ring by an atom of fluorine, chlorine or bromine.

3. 1-Bromo-2-methyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine and pharmaceutically acceptable acid addition salts thereof.

4. 2-n-Butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-bromo-benzoyl]-indolizine and pharmaceutically acceptable acid addition salts thereof.

5. 2-Ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine and pharmaceutically acceptable acid addition salts thereof.

6. 2-n-Butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine and pharmaceutically acceptable acid addition salts thereof.

7. 2-Isopropyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3,5-dichloro-benzoyl]-indolizine and pharmaceutically acceptable acid addition salts thereof.

8. 1-Bromo-2-phenyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine and pharmaceutically acceptable acid addition salts thereof.

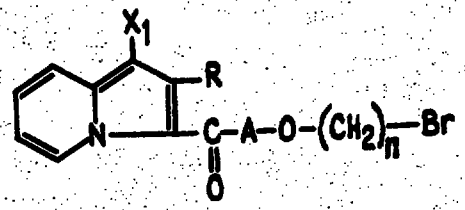
9. 1-Chloro-2-ethyl-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine and pharmaceutically acceptable acid addition salts thereof.

10. 1-Chloro-2-n-butyl-3-[4-(3-di-n-butylaminopropyl)-oxy-benzoyl]-indolizine and pharmaceutically acceptable acid addition salts thereof.

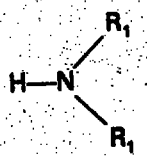
11. 1-Bromo-2-(4-chloro-phenyl)-3-[4-(3-di-n-butylaminopropyl)-oxy-3-chloro-benzoyl]-indolizine and pharmaceutically acceptable acid addition salts thereof.

12. Indolizine derivatives as claimed in any one of Claims 1 to 11, wherein the pharmaceutically acceptable acid addition salts are the hydrochlorides or the acid oxalates.

13. A process for preparing an indolizine derivative represented by the general formula defined in Claim 1 or a pharmaceutically acceptable acid addition salt thereof, which process comprises condensing in an inert solvent a bromoalkoxy-benzoyl-indolizine of the general formula:



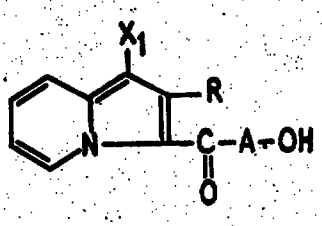
wherein X_1, R, A and n have the same meaning as in Claim 1, with a secondary amine of the general formula:



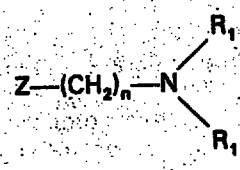
in which R_1 has the same meaning as in Claim 1, to form the required indolizine derivative which, if desired, is reacted with an appropriate organic or inorganic acid to provide a pharmaceutically acceptable acid addition salt thereof.

14. A process according to Claim 13, wherein the inert solvent is benzene or toluene.

15. A process for preparing an indolizine derivative represented by the general formula defined in Claim 1 or a pharmaceutically acceptable acid addition salt thereof, which process comprises condensing in an aprotic solvent an alkali metal salt of an indolizine derivative represented by the general formula:



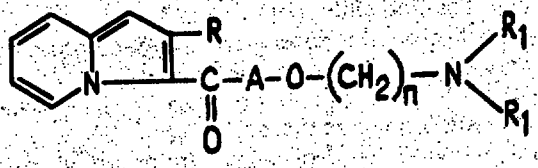
in which R, A and X_1 have the same meaning as in Claim 1, with an alkylamino derivative of the general formula:



or an acid addition salt thereof, in which Z represents a halogen atom or a p-toluenesulphonyloxy group and n and R_1 have the same meaning as in Claim 1, to form the required indolizine derivative which, if desired, is reacted with an appropriate organic or inorganic acid to provide a pharmaceutically acceptable acid addition salt thereof.

16. A process according to Claim 15, wherein the aprotic solvent is acetone, methyl ethyl ketone or toluene, the alkali metal salt is the potassium or sodium salt, and Z represents chlorine or bromine.

17. A process for preparing an indolizine derivative represented by the general formula defined in Claim 1 in which X_1 represents chlorine, bromine or iodine, and A represents the group R_3 or a group R_2 in which X_2 represents chlorine, bromine, iodine, methyl or methoxy and X_3 represents chlorine, bromine, iodine or methyl, which process comprises reacting an indolizine derivative of the general formula:



in which R, A, n and R_1 have the same meanings as given above,

either (a) with N-chlorosuccinimide, the reaction taking place in a suitable medium and between 0°C and room-temperature, to obtain the required indolizine derivative, in which X_1 represents chlorine, in free base form, or b) with bromine or iodine, the reaction taking place at room-temperature in a suitable solvent and in the presence of an alkali metal acetate, to obtain the required indolizine derivative, in which X_1 represents bromine or iodine, in free base form, the free base so obtained then being reacted, if desired, with an organic or inorganic acid to provide a pharmaceutically acceptable acid addition salt thereof.

18. A process according to Claim 17, wherein the medium is dichloroethane, the solvent is dioxan, and the alkali metal acetate is sodium acetate.

19. A pharmaceutical or veterinary composition comprising as an essential active ingredient an indolizine derivative as claimed in Claim 1, in the form of a free base or a pharmaceutically acceptable acid addition salt thereof, in association with a pharmaceutical carrier or excipient therefor.

20. A pharmaceutical or veterinary composition comprising as an essential active ingredient an indolizine derivative as claimed in Claim 2, in the form of a free base or a pharmaceutically acceptable acid addition salt thereof, in association with a pharmaceutical carrier or excipient therefor.

21. A process for preparing an indolizine derivative as claimed in Claim 1, substantially as described in any one of the foregoing Examples 1 to 4.

22. A pharmaceutical composition substantially as described in any one of the foregoing Examples 5 to 7.

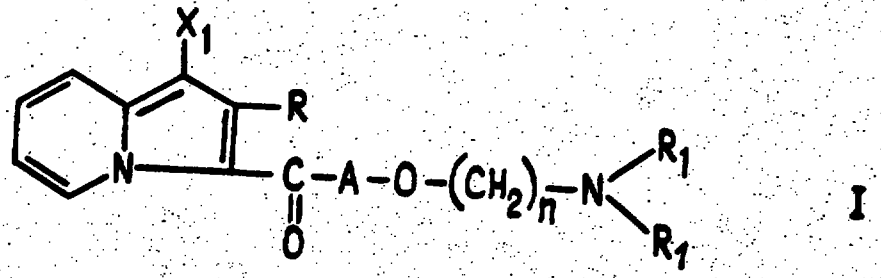
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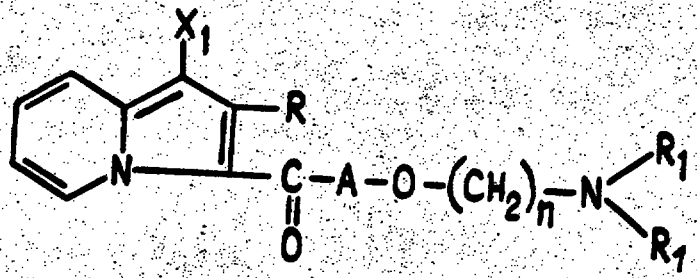
The following corrections were allowed under Section 117 on 5 January 1984:

Page 1, line 7, *delete* whole line *insert*



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Page 31, line 10, *delete* whole line *insert*



THE PATENT OFFICE
10 February 1984