

PATENT SPECIFICATION

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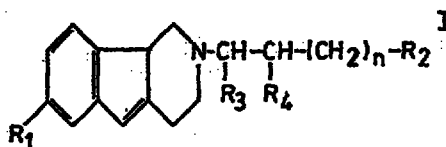
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(54) INDENOPYRIDINE DERIVATIVES

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4000 Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to acid addition salts of new indenopyridine derivatives of formula I,



in which

R_1 signifies hydrogen, a lower alkyl radical of from 1 to 4 carbon atoms, fluorine, bromine or chlorine,

R_2 signifies (i) the cyano radical, (ii) a COOR_5 radical, in which R_5 signifies hydrogen or a lower alkyl radical of from 1 to 6 carbon atoms, or (iii) a

$\text{CO}-\text{N} \begin{array}{l} \nearrow R_5 \\ \searrow R_6 \end{array}$ radical, in which R_5 has the above significance, and R_6 signifies

hydrogen or a lower alkyl radical of from 1 to 6 carbon atoms, or R_5 and R_6 together with the nitrogen atom form a heterocyclic ring system with a total of 5 to 7 ring members,

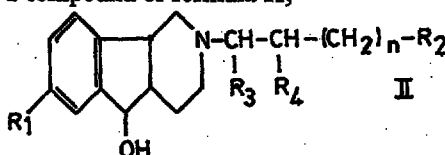
R_3 and R_4 signify hydrogen or a lower alkyl radical of from 1 to 4 carbon atoms, and

n signifies 0 to 3,

as well as processes for the production thereof.

The acid addition salts of the new indenopyridine derivatives of formula I are obtained in accordance with the invention by

a) removing water from a compound of formula II,



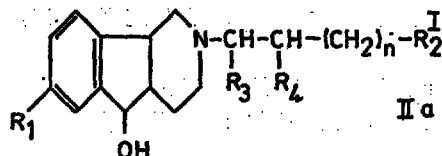
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in which R_1 , R_2 , R_3 , R_4 and n have the above significance, by treatment with a strong acid or the chloride, bromide or iodide of a strong acid, provided that when R_2 signifies COOH , a strong acid is employed for the removal of water, or

b) removing water from a compound of formula IIa,



in which

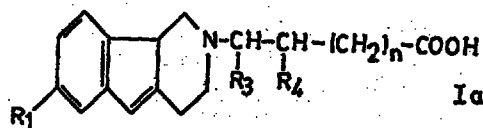
R_1 , R_3 , R_4 and n have the above significance, and

R_2^I signifies (i) the cyano radical, (ii) a COOR_5^I radical, in which R_5^I signifies a

lower alkyl radical of from 1 to 6 carbon atoms, or (iii) a $\text{CO}-\text{N} \begin{matrix} \nearrow R_5 \\ \searrow R_6 \end{matrix}$ radical,

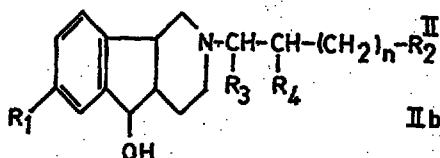
in which R_5 and R_6 have the above significance,

by treatment with a strong acid or the chloride, bromide or iodide of a strong acid, and simultaneously or subsequently hydrolyzing the substituent R_2^I to the carboxyl radical, to produce an acid addition salt of a compound of formula Ia,



in which R_1 , R_3 , R_4 and n have the above significance, or

c) removing water from a compound of formula IIb,



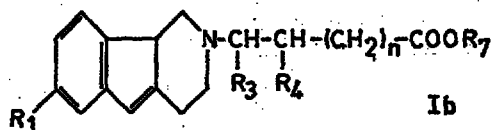
in which

R_1 , R_3 , R_4 and n have the above significance, and

R_2^{II} signifies (i) the cyano radical, (ii) the carboxyl radical, or (iii) a $\text{CO}-\text{N} \begin{matrix} \nearrow R_5 \\ \searrow R_6 \end{matrix}$

radical, in which R_5 and R_6 have the above significance,

by treatment with a strong acid or the chloride, bromide or iodide of a strong acid, and esterifying simultaneously or subsequently, to produce an acid addition salt of a compound of formula Ib,



in which

R_1 , R_3 , R_4 and n have the above significance, and

R_7 signifies a lower alkyl radical of from 1 to 6 carbon atoms.

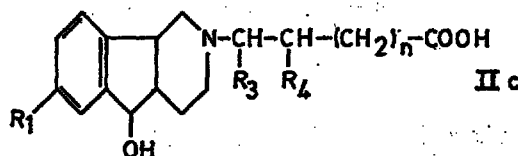
The compounds of formula I are stable in the form of their acid addition salts. In the form of free bases, however, a rearrangement occurs with a shifting of the double bond from the 4a,5 to the 4a,9b position. Therefore, it is preferred to effect the removal of water with strong acids which give crystalline salts with the compounds of formula I, or with chlorides, bromides or iodides of strong acids, the reaction products of which formed during the removal of water give crystalline salts with the compounds of formula I.

Chlorides, bromides or iodides of strong acids may only be used for the removal of water when R_2 signifies other than the COOH radical, since in this case the carboxyl radical is converted to the corresponding acid halide radical.

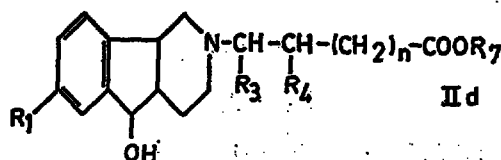
Examples of suitable strong acids for the removal of water are mineral acids (e.g. in aqueous or alcoholic solution) such as hydrochloric, hydrobromic, hydriodic or sulphuric acid, or organic acids, e.g. organic sulphonic acids such as methanesulphonic acid, benzenesulphonic acid or naphthalene-1,5-disulphonic acid. Thionyl chloride may, for example, be used as halide of a strong acid.

Water removal is effected by treating the hydroxy compounds of formula II, as free bases or in the form of their acid addition salts, e.g. as hydrochloride, during approximately one minute to 24 hours, preferably 15 minutes to 2 hours, at room temperature to the boiling temperature of the reaction mixture, optionally in a solvent which is inert under the reaction conditions, with strong acids or chlorides, bromides or iodides of strong acids. The reaction mixture is subsequently evaporated to dryness, and the resulting acid addition salts of the compounds of formula I are optionally purified in accordance with known methods.

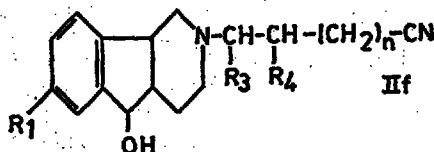
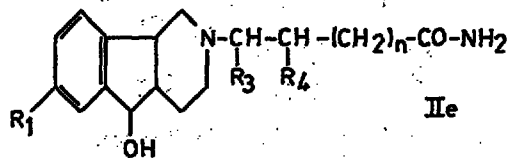
During the removal of water the substituent on the nitrogen atom may remain unchanged or likewise participate in a reaction, depending on the chosen reaction conditions. Thus, for example, compounds of formula Ia may not only be obtained from compounds of formula IIc,



in which R_1 , R_3 , R_4 and n have the above significance, but also from compounds of formula II d,



in which R_1 , R_3 , R_4 , R_7 and n have the above significance, or from compounds of formulae IIe and II f,



in which R_1 , R_3 , R_4 and n have the above significance.

When it is desired to obtain compounds of formula Ib as final products, then the removal of water is effected with acids or chlorides, bromides or iodides of strong acids, preferably in the absence of water, e.g. with hydrogen chloride gas in the corres-

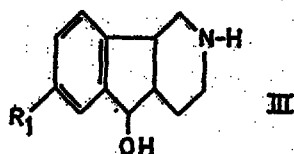
ponding anhydrous alcohol (R_1OH). In this case any amide or cyano group which may be present can first be hydrolyzed to the carboxyl radical and subsequently esterified. However, esterification of the amide, cyano or carboxyl radical may also be effected simultaneously with the removal of water.

The process of the invention may, for example, be effected as follows:

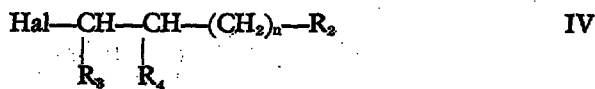
A hydroxy compound of formula II is heated to the boil under reflux for about half an hour with a strong acid or the chloride, bromide or iodide of a strong acid. The resulting acid addition salt of the compound of formula I usually already separates as a crystalline precipitate during heating or upon cooling the reaction mixture. If no precipitate results, the reaction solution is evaporated until crystallization commences or to dryness. The crude product can be purified in conventional manner.

The lower alkyl radicals represented by the symbols R_1 , R_2 and R_3 contain 1 to 4 carbon atoms and especially signify the methyl radical. The lower alkyl radicals represented by the symbols R_4 , R_5 , R_6 and R_7 contain 1 to 6, especially 1 to 3 carbon atoms.

The starting materials of formula II are new and may be obtained by a') reacting a compound of formula III,



in which R_1 has the above significance, with a compound of formula IV,



in which

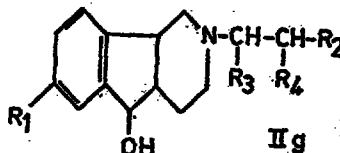
R_2 , R_3 , R_4 and n have the above significance, and

Hal signifies chlorine, bromine or iodine, in the presence of a basic condensation agent, or

b') reacting a compound of formula III with acrylic acid or with an acrylic acid derivative of formula V,



in which R_2 , R_3 and R_4 have the above significance, to produce compounds of formula IIg,



in which R_1 , R_2 , R_3 and R_4 have the above significance.

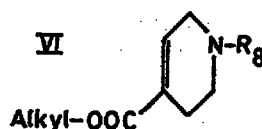
Process a') may, for example, be effected by reacting a compound of formula III in the presence of a basic condensation agent and in a solvent which is inert under the reaction conditions, e.g. a di(lower)alkyl-carboxylic acid amide such as dimethyl formamide, at an elevated temperature, e.g. 130°C , with a compound of formula IV, the reaction being complete after about 2 hours. An alkali metal carbonate such as sodium or potassium carbonate, or an excess of an equivalent of the compound of formula III may, for example, be used as basic condensation agent. The reaction product may be purified in accordance with known methods or may be worked up as such without further purification.

The reaction of a compound of formula III with a compound of formula V in accordance with process b') may, for example, be effected at an elevated temperature, preferably at the boiling temperature of the reaction mixture under reflux, optionally in a solvent which is inert under the reaction conditions, e.g. a lower alcohol such as

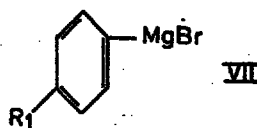
methanol or ethanol. The reaction has a duration of between about 2 and 16 hours. The resulting product may be isolated in accordance with known methods and purified, e.g. by crystallization, or may be worked up as such.

Some of the starting materials required for the production of compounds of formula II are known; they may be produced as follows:

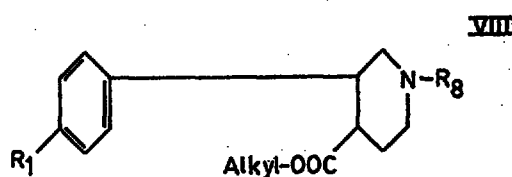
Compounds of formula III may be produced by reacting a tetrahydroisonicotinic acid ester of formula VI,



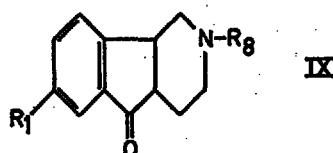
in which R₈ signifies the methyl or benzyl radical, with a magnesium compound of formula VII,



in which R₁ has the above significance; hydrolysis of the resulting products yields compounds of formula VIII,

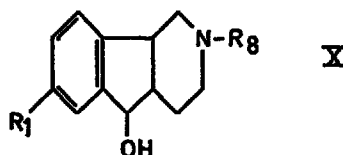


in which R₁ and R₈ have the above significance. These are converted into compounds of formula IX,



in which R₁ and R₈ have the above significance, either directly by heating with polyphosphoric acid, or by hydrolysis to the free carboxylic acids, production of the acid chloride, e.g. with thionyl chloride, and cyclization with Friedel-Crafts catalysts such as anhydrous aluminium chloride.

Compounds of formula X,



in which R₁ and R₈ have the above significance, may be obtained by selective reduction of the carbonyl radical of ketones of formula IX to the CHOH radical.

Compounds of formula III may be obtained in that the OH radical in a compound of formula X is protected by conversion into a readily cleavable ester or ether, the resulting compound is subsequently converted into the corresponding urethane by reaction with an ester of chloroformic acid, and the urethane radical is subjected to alkaline hydrolysis, the removal of the protective radical taking place simultaneously or being effected subsequently.

Pharmacologically tolerable acid addition salts of the compounds of formula I have interesting pharmacodynamic properties while their toxicity is low and are therefore indicated for use as medicaments.

The compounds exhibit an antiphlogistic effect, as shown by animal tests (traumatic edema in rats). The compounds are therefore indicated for use as antiphlogistic agents. The daily dose indicated is between about 5 and 30 mg. For oral administration partial doses contain between about 2 and 15 mg of the acid addition salts of the compounds of formula I aside from solid or liquid carrier materials.

The compounds furthermore possess ulcer-protective properties, as shown by results obtained in the phenylbutazone ulcer test in rats. The compounds are therefore indicated for use as ulcer-protective agents. The daily dose indicated for this use is between about 10 and 50 mg. For oral administration partial doses contain between about 3 and 25 mg of the acid addition salts of the compounds of formula I aside from solid or liquid carrier materials.

The compounds additionally exhibit a hypotensive effect as shown in blood circulation tests with narcotized dogs. The compounds are therefore indicated for use as hypotensive agents. The indicated daily dose for this use amounts to between about 3 and 10 mg. For oral administration the partial doses contain between about 1 and 25 mg of the acid addition salts of the compounds of formula I aside from solid or liquid carrier materials.

It is to be appreciated that precise doses depend on the activity of a particular compound, the mode of administration and particular condition to be treated. It is however to be observed that daily doses are generally administered in divided portions 2 to 3 times a day or in sustained release form.

Physiologically tolerable acid addition salts of the compounds of formula I may be used as medicaments on their own or in the form of appropriate medicinal preparations with conventional pharmacologically inert adjuvants.

Insofar as the production of the required starting materials is not described, these are known or may be produced in accordance with processes known *per se* or in a manner analogous to the processes described herein or to processes known *per se*.

In the follow non-limitative Examples all temperatures are indicated in degrees Centigrade and are uncorrected.

Example 1:

1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine propionic acid
methyl ester hydrochloride.

10 g of 1,3,4,4a,5,9b - hexahydro - 5 - hydroxy - 2(2H) - indeno - [1,2-c]pyridine propionic acid methyl ester are heated to the boil in 100 cc of methanol for 2 hours while passing hydrogen chloride through the solution. The solution is concentrated by evaporation in a vacuum and the residue is recrystallized from acetone/ether and then twice from methanol. The title compound has a M.P. of 183—185° (decomp.).

The following compound of formula I may be obtained in a manner analogous to that described in Example 1 (Example 2):

Ex.	R ₁	R ₂	R ₃	R ₄	n	Phys. chem. constants
2	H	COO·C ₂ H ₅	H	H	0	M.P. of the hydrochloride 176—178° (decomp.)

Example 3:

1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine propionamide hydrochloride. 10 cc of thionyl chloride are added dropwise to a solution of 17.9 g of 1,3,4,4a,5,9b - hexahydro - 5 - hydroxy - 2(2H) - indeno[1,2 - c] - pyridine propionamide in 350 cc of chloroform. The mixture is boiled at reflux for 30 minutes, whereby the initially resulting resin is dissolved, the solution is concentrated by evaporation in a vacuum and the residue is boiled with 150 cc of isopropanol. After cooling, the title compound is filtered off and recrystallized twice from methanol. M.P. 224—226° (decomp.).

Example 4:

1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine propionic acid hydrochloride. 10 g of 1,3,4,4a,5,9b-hexahydro-5-hydroxy-2(2H)-indeno-[1,2-c]pyridine propionic acid are boiled at reflux for 15 minutes with 100 cc of 2 N hydrochloric acid. The mixture is allowed to cool, the title compound is filtered off and recrystallized from water. M.P. 285—287° (decomp.).

Example 5:

1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine propionitrile hydrochloride. 10 g of 1,3,4,4a,5,9b - hexahydro - 5 - hydroxy - 2(2H) - indeno - [1,2 - c]pyridine propionitrile are boiled at reflux for 15 minutes with 100 cc of 2 N hydrochloric acid. The mixture is concentrated by evaporation in a vacuum, the residue is again evaporated with ethanol and the residue is recrystallized twice from ethanol. The title compound has a M.P. of 297—300° (decomp.).

Example 6:

1,3,4,9b-tetrahydro-N-methyl-2(2H)-indeno[1,2-c]pyridine propionamide hydrochloride. 12 g of 1,3,4,4a,5,9b - hexahydro - 5 - hydroxy - N - methyl - 2(2H) - indeno[1,2-c]pyridine propionamide are boiled at reflux for 15 minutes with 120 cc of 2 N hydrochloric acid. The mixture is cooled, is made alkaline with solid sodium carbonate and is shaken out several times with ethyl acetate. The extracts are washed with a saturated sodium chloride solution, are dried over magnesium sulphate and concentrated by evaporation. The residue is dissolved in acetone and the solution is acidified with hydrogen chloride in ether, whereupon the title compound crystallizes after some time. After recrystallization from acetone the compound has a M.P. of 186—188° (decomp.).

Example 7:

1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine
propionic acid hydrochloride.

20 g of crude 1,3,4,4a,5,9b-hexahydro-5-hydroxy-2(2H)-indeno[1,2-c]pyridine propionic acid methyl ester are boiled at reflux for 20 minutes with 200 cc of 2 N hydrochloric acid. The mixture is allowed to cool, the title compound is filtered off and is recrystallized from water. M.P. 285—287° (decomp.).

The following compounds of formula I may be obtained in a manner analogous to that described in Example 7 (Examples 8 to 16):

Ex.	R ₁	R ₂	R ₃	R ₄	n	Phys. chem. constants
8	H	COOH	H	H	3	M.P. of the hydrochloride 235—237° (decomp.)
9	Chlorine	COOH	H	H	0	M.P. of the hydrochloride 235—238° (decomp.)
10	Methyl	COOH	H	H	0	M.P. of the hydrochloride 234—236° (decomp.)
11	Ethyl	COOH	H	H	0	M.P. of the hydrochloride 243—246° (decomp.)
12	H	COOH	H	H	2	M.P. of the hydrochloride 185° (decomp.)
13	H	COOH	H	H	1	M.P. of the hydrochloride 255—258° (decomp.)
14	H	COOH	CH ₃	H	1	M.P. of the hydrochloride 150—180° (decomp.)
15	H	COOH	CH ₃	H	0	M.P. of the hydrochloride 190—192° (decomp.)
16	H	COOH	H	CH ₃	0	M.P. of the hydrochloride 225—227° (decomp.)

For the working up of the reaction mixture in Examples 15 and 16 the resulting solution is evaporated to dryness and the residue recrystallized.

Example 17:

1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine
propionic acid methyl ester hydrochloride.

A solution of 9.5 g of 1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine propionic acid hydrochloride (production see Example 4) in 150 cc of methanol is boiled at reflux for 2 hours while hydrogen chloride is passed through the solution. The solution is then concentrated to about 25 cc and after cooling the title compound is filtered off. After recrystallization from methanol it has a M.P. of 183—185° (decomp.).

The following compound of formula I may be obtained in a manner analogous to that described in Example 17 (Example 18):

Ex.	R ₁	R ₂	R ₃	R ₄	n	Phys. chem. constants
18	H	COO.C ₂ H ₅	H	H	0	M.P. of the hydrochloride 176—178° (decomp.)

Example 19:

1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine propionic acid
methyl ester hydrochloride.

The title compound may be obtained in a manner analogous to that described in Example 17, except that 1,3,4,4a,5,9b-hexahydro-5-hydroxy-2(2H)-indeno[1,2-c]pyridine propionic acid is used in place of 1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine propionic acid hydrochloride. The hydrochloride has a M.P. of 183—185° (decomp.).

Example 20:

1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine
propionic acid hydrochloride.

The title compound may be obtained by boiling 1,3,4,4a,5,9b-hexahydro-5-hydroxy-2(2H)-indeno[1,2-c]pyridine propionitrile or 1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine propionitrile hydrochloride (production see Example 5) with 2 N hydrochloric acid for 2 1/2 hours and working up the reaction mixture in a manner analogous to that described in Example 7. The hydrochloride has a M.P. of 285—287° (decomp.).

The following compounds of formula I may be obtained in a manner analogous to that described in Example 1, using the corresponding 1,3,4,4a,5,9b-hexahydro-5-hydroxy-2(2H)-indeno[1,2-c]pyridine nitriles as starting materials (Examples 21 to 23):

Ex.	R ₁	R ₂	R ₃	R ₄	n	Phys. chem. constants
21	H	COOH	H	H	1	M.P. of the hydrochloride 255—258° (decomp.)
22	H	COOH	Methyl	H	0	M.P. of the hydrochloride 190—192° (decomp.)
23	H	COOH	H	Methyl	0	M.P. of the hydrochloride 225—227° (decomp.)

Example 24:

1,3,4,9b-tetrahydro-2(2H)-indeno-[1,2-c]pyridine
propionic acid hydrochloride.

The title compound may be obtained in a manner analogous to that described in Example 20, using 1,3,4,4a,5,9b-hexahydro-5-hydroxy-2(2H)-indeno[1,2-c]pyridine propionamide or 1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine propionamide hydrochloride as starting material. The hydrochloride has a M.P. of 285—287° (decomp.). The compounds required as starting materials may be obtained as follows:

Example 25:

1,3,4,4a,5,9b-hexahydro-5-hydroxy-2(2H)-indeno[1,2-c]pyridine
propionic acid methyl ester (for Examples 1 and 7)

40 g of 1,3,4,4a,5,9b-hexahydro-5(2H)-indeno[1,2-c]pyridinol, 36 g of acrylic acid methyl ester and 400 cc of methanol are boiled at reflux for 16 hours. The mixture is then concentrated by evaporation in a vacuum, the residue is dissolved in ether and the solution is shaken out thrice with a sodium carbonate solution. After drying over magnesium sulphate the ether phase is concentrated by evaporation. The resulting residue is crude 1,3,4,4a,5,9b-hexahydro-5-hydroxy-2(2H)-indeno[1,2-c]pyridine propionic acid methyl ester in the form of a brown-coloured oil. It is sufficiently pure for working up further.

The following compounds of formula II may be obtained in a manner analogous to that described in Example 25 (Examples 26 to 37):

Ex.	R ₁	R ₂	R ₃	R ₄	n	Phys. chem. constants	for Ex.
26	H	COOH	H	H	0	M.P. 215—218° (decomp.)	4 and 19
27	H	CO.NH.CH ₃	H	H	0	M.P. 127—129° (decomp.)	6
28	H	CN	H	H	0	M.P. 84—86° (decomp.)	5 and 20
29	H	COO.C ₂ H ₅	H	H	0	Further worked up without purification	2
30	H	CO.NH ₂	H	H	0	M.P. 146—148° (decomp.)	3 and 24
31	Cl	COO.CH ₃	H	H	0	Further worked up without purification	9
32	CH ₃	COO.CH ₃	H	H	0	Further worked up without purification	10
33	C ₂ H ₅	COO.CH ₃	H	H	0	Further worked up without purification	11
34	H	COO.C ₂ H ₅	CH ₃	H	0	Further worked up without purification	15
35	H	COO.C ₂ H ₅	H	CH ₃	0	Further worked up without purification	16
36	H	CN	CH ₃	H	0	Further worked up without purification	22
37	H	CN	H	CH ₃	0	Further worked up without purification	23

Example 38:

1,3,4,4a,5,9b-hexahydro-5-hydroxy-2(2H)-indeno[1,2-c]pyridine caproic acid methyl ester (for Example 8)

16.8 g of sodium carbonate are added to a solution of 15 g of 1,3,4,4a,5,9b-hexahydro-5(2H)-indeno[1,2-c]pyridinol in 290 cc of dimethyl formamide, a solution of 16.6 g of 6-bromocaproic acid methyl ester is then added dropwise and the mixture is subsequently heated to 130° for 2 hours. The reaction mixture is cooled, is poured on 1000 cc of ice water, is extracted thrice with methylene chloride, the combined extracts are dried over magnesium sulphate and concentrated by evaporation. The residue is recrystallized twice from isopropanol/pentane. 1,3,4,4a,5,9b-hexahydro-5-hydroxy-2(2H)-indeno[1,2-c]pyridine caproic acid methyl ester has a M.P. of 84-86°.

The following compounds of formula II may be obtained in a manner analogous to that described in Example 38 (Examples 39 to 42):

Ex.	R ₁	R ₂	R ₃	R ₄	n	Phys. chem. constants	for Ex.
39	H	COO.C ₂ H ₅	CH ₃	H	1	Further worked up without purification	14
40	H	COO.C ₂ H ₅	H	H	2	Further worked up without purification	12
41	H	COO.C ₂ H ₅	H	H	1	Further worked up without purification	13
42	H	CN	H	H	1	Further worked up without purification	21

Example 43:

7-chloro-1,3,4,4a,5,9b-hexahydro-5(2H)-indeno[1,2-c]pyridinol (for Example 31)

23.5 g of acetic anhydride are added dropwise to a solution of 40 g of 7-chloro-1,3,4,4a,5,9b-hexahydro-2-methyl-5(2H)-indeno[1,2-c]pyridinol in 200 cc of pyridine, and the solution is allowed to stand at room temperature for 15 hours. The solution is then concentrated by evaporation in a vacuum, the residue is taken up in water and extracted thrice with methylene chloride. After drying over magnesium sulphate the solution is concentrated by evaporation and the resulting crude, resinous 5-acetoxy-7-chloro-1,3,4,4a,5,9b-hexahydro-2-methyl-2H-indeno[1,2-c]pyridine is dissolved in 300 cc of benzene. 70 g of chloroformic acid ethyl ester are added dropwise to this solution

while stirring, the solution is subsequently boiled at reflux for 3 hours, a small amount of precipitate is then filtered off, the filtrate is shaken out first with water, then with N hydrochloric acid and finally with a saturated sodium chloride solution, the benzene layer is dried over magnesium sulphate and concentrated by evaporation. The resulting

35 g of 5-acetoxy-2-ethoxycarbonyl-7-chloro-1,3,4,4a,5,9b-hexahydro-2H-indeno[1,2-c]pyridine is a viscous oil which slowly crystallizes upon standing.

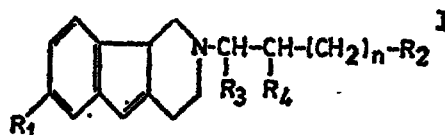
35 g of 5-acetoxy-2-ethoxycarbonyl-7-chloro-1,3,4,4a,5,9b-hexahydro-2H-indeno[1,2-c]pyridine are boiled at reflux for 9 hours with a solution of 35 g of potassium hydroxide in 350 cc of butanol. After cooling the mixture is poured on 500 cc of a saturated sodium chloride solution and is shaken out thrice with chloroform. After drying over magnesium sulphate the reaction mixture is concentrated by evaporation and the resulting 7-chloro-1,3,4,4a,5,9b-hexahydro-5(2H)-indeno[1,2-c]pyridinol is recrystallized from isopropanol. M.P. 197—199°.

The following compounds of formula III may be obtained in a manner analogous to that described in Example 43 (Examples 44 and 45):

Ex.	R ₁	Phys. chem. constants	for Ex.
44	Methyl	M.P. 168-170°	32
45	Ethyl	M.P. (isomer A) 128—130°	33

WHAT WE CLAIM IS:—

1. A process for the production of an acid addition salt of an indenopyridine derivative of formula I,



in which

R₁ signifies hydrogen, a lower alkyl radical of from 1 to 4 carbon atoms, fluorine, bromine or chlorine,

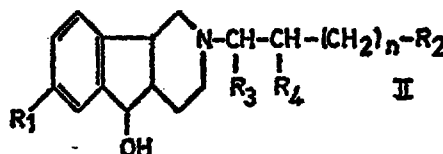
R₂ signifies (i) the cyano radical, (ii) a COOR₅ radical, in which R₅ signifies hydrogen or a lower alkyl radical of from 1 to 6 carbon atoms, or (iii) a

CO—N^{R₅} radical, in which R₅ has the above significance, and R₆ signifies hydrogen or a lower alkyl radical of from 1 to 6 carbon atoms, or R₅ and R₆ together with the nitrogen atom form a heterocyclic ring system with a total of 5 to 7 ring members,

R₃ and R₄ signify hydrogen or a lower alkyl radical of from 1 to 4 carbon atoms, and n signifies 0 to 3,

which comprises

a) removing water from a compound of formula II,



in which R₁, R₂, R₃, R₄ and n have the above significance, by treatment with a strong acid or the chloride, bromide or iodide of a strong acid, provided that when R₂ signifies COOH, a strong acid is employed for the removal of water, or

b) removing water from a compound of formula IIa,

while stirring, the solution is subsequently boiled at reflux for 3 hours, a small amount of precipitate is then filtered off, the filtrate is shaken out first with water, then with N hydrochloric acid and finally with a saturated sodium chloride solution, the benzene layer is dried over magnesium sulphate and concentrated by evaporation. The resulting

35 g of 5-acetoxy-2-ethoxycarbonyl-7-chloro-1,3,4,4a,5,9b-hexahydro-2H-indeno-

[1,2-c]pyridine is a viscous oil which slowly crystallizes upon standing. 35 g of 5-acetoxy-2-ethoxycarbonyl-7-chloro-1,3,4,4a,5,9b-hexahydro-2H-indeno-

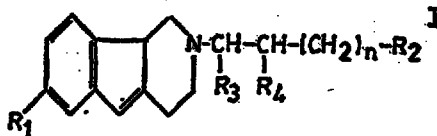
[1,2-c]pyridine are boiled at reflux for 9 hours with a solution of 35 g of potassium hydroxide in 350 cc of butanol. After cooling the mixture is poured on 500 cc of a saturated sodium chloride solution and is shaken out thrice with chloroform. After drying over magnesium sulphate the reaction mixture is concentrated by evaporation and the resulting 7-chloro-1,3,4,4a,5,9b-hexahydro-5(2H)-indeno[1,2-c]pyridinol is recrystallized from isopropanol. M.P. 197—199°.

The following compounds of formula III may be obtained in a manner analogous to that described in Example 43 (Examples 44 and 45):

Ex.	R ₁	Phys. chem. constants	for Ex.
44	Methyl	M.P. 168-170°	32
45	Ethyl	M.P. (isomer A) 128—130°	33

WHAT WE CLAIM IS:—

1. A process for the production of an acid addition salt of an indenopyridine derivative of formula I,



in which

R₁ signifies hydrogen, a lower alkyl radical of from 1 to 4 carbon atoms, fluorine, bromine or chlorine,

R₂ signifies (i) the cyano radical, (ii) a COOR_s radical, in which R_s signifies hydrogen or a lower alkyl radical of from 1 to 6 carbon atoms, or (iii) a

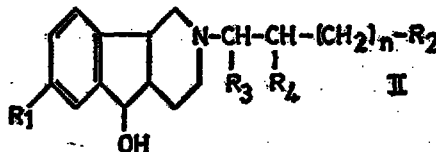
CO—N(R₅)—R₆ radical, in which R_s has the above significance, and R₆ signifies hydrogen or a lower alkyl radical of from 1 to 6 carbon atoms, or R₅ and R₆ together with the nitrogen atom form a heterocyclic ring system with a total of 5 to 7 ring members,

R₃ and R₄ signify hydrogen or a lower alkyl radical of from 1 to 4 carbon atoms, and

n signifies 0 to 3,

which comprises

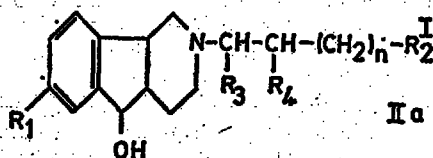
a) removing water from a compound of formula II,



in which R₁, R₂, R₃, R₄ and n have the above significance, by treatment with a strong acid or the chloride, bromide or iodide of a strong acid, provided that when R₂ signifies COOH, a strong acid is employed for the removal of water, or

b) removing water from a compound of formula IIa,





in which

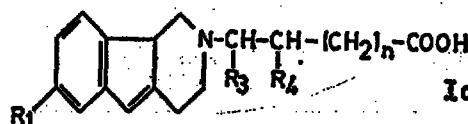
R_1 , R_3 , R_4 and n have the above significance, and

R_2^I signifies (i) the cyano radical, (ii) a COOR_5^I radical, in which R_5^I signifies a

lower alkyl radical of from 1 to 6 carbon atoms, or (iii) a $\text{CO}-\text{N}$ radical,

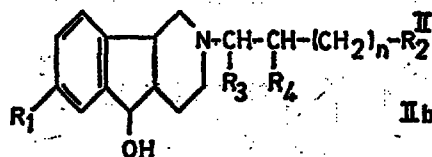
in which R_5 and R_6 have the above significance,

by treatment with a strong acid or the chloride, bromide or iodide of a strong acid, and simultaneously or subsequently hydrolyzing the substituent R_2^I to the carboxyl radical, to produce an acid addition salt of a compound of formula Ia,



in which R_1 , R_3 , R_4 and n have the above significance, or

c) removing water from a compound of formula IIb,



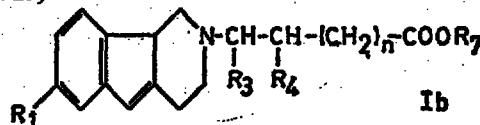
in which

R_1 , R_3 , R_4 and n have the above significance, and

R_2^{II} signifies (i) the cyano radical, (ii) the carboxyl radical, or (iii) a $\text{CO}-\text{N}$ radical,

radical, in which R_5 and R_6 have the above significance,

by treatment with a strong acid or the chloride, bromide or iodide of a strong acid, and esterifying simultaneously or subsequently, to produce an acid addition salt of a compound of formula Ib,



in which

R_1 , R_3 , R_4 and n have the above significance, and

R_7 signifies a lower alkyl radical.

2. A process according to Claim 1, in which the removal of water is effected under reflux.

3. A process according to Claim 1 or 2, in which the chloride, bromide or iodide of a strong acid is thionyl chloride.

4. A process for the production of an acid addition salt of an indenopyridine derivative of formula I, stated in Claim 1, substantially as herein described, with reference to any one of Examples 1 to 24.

5. An acid addition salt of an indenopyridine derivative of formula I, stated in Claim 1, whenever produced by the process of any one of the preceding Claims.

6. An acid addition salt of an indenopyridine derivative of formula I, stated in Claim 1.

7. An acid addition salt of 1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine propionic acid methyl ester.



8. An acid addition salt of 1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine propionic acid.
9. An acid addition salt of 1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine propionamide.
- 5 10. An acid addition salt of 1,3,4,9b-tetrahydro-N-methyl-2(2H)-indeno[1,2-c]-pyridine propionamide. 5
11. An acid addition salt of 1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine propionic acid ethyl ester.
12. An acid addition salt of 1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine propionitrile.
- 10 13. An acid addition salt of 1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine butyric acid. 10
14. An acid addition salt of 3-(1,3,4,9b-tetrahydro-2H-indeno[1,2-c]pyridin-2-yl)-butyric acid.
- 15 15. An acid addition salt of 3-(1,3,4,9b-tetrahydro-2H-indeno[1,2-c]pyridin-2-yl)-2-methyl propionic acid. 15
16. An acid addition salt of 4-(1,3,4,9b-tetrahydro-2H-indeno[1,2-c]pyridin-2-yl)-valerianic acid.
17. An acid addition salt of 1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine valerianic acid.
- 20 18. An acid addition salt of 1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine caproic acid. 20
19. An acid addition salt of 7-chloro-1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]pyridine propionic acid.
- 25 20. An acid addition salt of 7-methyl-1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]-pyridine propionic acid. 25
21. An acid addition salt of 7-ethyl-1,3,4,9b-tetrahydro-2(2H)-indeno[1,2-c]-pyridine propionic acid.
22. A pharmaceutical composition incorporating as active ingredient a compound of Claim 6, in association with a pharmaceutically acceptable carrier or diluent.
- 30 30

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