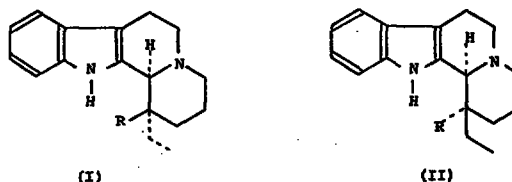


SPECIFICATION

Indolo (2,3-a) Quinolizidines, Preparation and Therapeutic Use

The invention relates to indolo (2,3-a)-quinolizidines, to methods for their preparation and to therapeutic compositions containing them.

5 The new indolo (2,3-a) quinolizidines according to the invention have the general formulae (I) and (II)



10 wherein R stands for $-\text{COOC}_2\text{H}_5$, $-\text{COOH}$, $-\text{CN}$, a primary or secondary aminomethyl group, an amidomethyl group or an amido group, or wherein R, together with the ring nitrogen of the indolo ring, represents one of the groupings $-\text{N}-\text{CO}-\text{NH}-\text{CH}_2-$ or $-\text{N}-\text{CO}-$; the latter derivatives are D

homo azaeburnamonines or D eburnamonines.

The invention also provides acid addition salts of the above compounds, when applicable.

15 R may be, for example, an N-alkoxycarbonyl-aminomethyl, N-aryloxycarbonyl-aminomethyl, N-alkanoyl-aminomethyl, N-alkyl-aminomethyl, substituted ureido-methyl, substituted piperazido, piperonyl-substituted amido group.

Preferred identities of R according to this invention are $-\text{COOH}$, $-\text{NH}_2$, N-ethoxycarbonyl-aminomethyl, N-(3,4,5-trimethoxybenzoyl)-aminomethyl, N-phenoxy carbonyl-aminomethyl, diethylaminoethyl-ureidomethyl, N-pentanoyl-aminomethyl, N-pentyl-aminomethyl and piperonyl-substituted piperazido.

20 The compounds according to this invention are especially interesting for their activity in the field of blood circulation in the brain. The invention accordingly provides therapeutic compositions comprising one or more such compounds in admixture with a therapeutically acceptable diluent or carrier.

25 The above compounds may be prepared according to the invention by condensing together 2-aminomethyl-3-indole and 1-chloro-4-(A)-4-chlorocarbonyl-hexane, wherein A stands for $-\text{COOC}_2\text{H}_5$ or $-\text{CN}$, to form the corresponding amide; subjecting the amide to strongly basic conditions to eliminate HCl and effect ring formation at the nitrogen atom on the 3-indole substituent; effecting quinolizidine ring formation of the product by treating it with a dehydrating agent followed by a perchlorate salt; hydrogenating the resulting quinolizidinium perchlorate to produce the corresponding indolo (2,3-a) quinolizidine isomer mixture and separating the isomers; the corresponding reaction schemes are represented hereafter under the heading "Initial Common Routes" and lead only to the compounds wherein R is $-\text{COOC}_2\text{H}_5$ or $-\text{CN}$ (2 isomer forms in each case, i.e., 4 compounds).

All the other derivatives derive from these compounds:—

35 either directly, e.g. the acids, from the esters, by saponification (see the schemes "Specific Routes" A= $-\text{COOC}_2\text{H}_5$), or the aminomethyl from the nitriles, by reduction with lithium aluminium hydride (see same schemes when A= $-\text{CN}$),

or from the acids or aminomethyl derivatives, by well known reactions.

In the following schemes:—

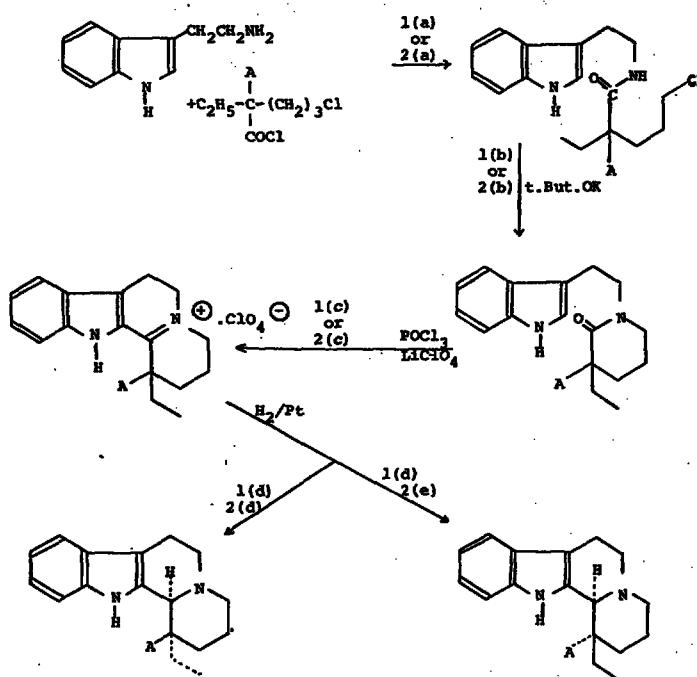
I is a reference to cis-isomers

40 II a reference to trans-isomers

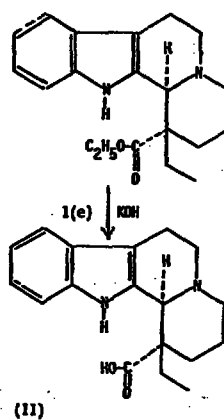
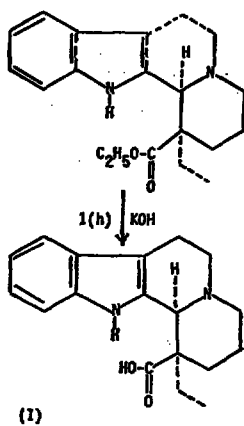
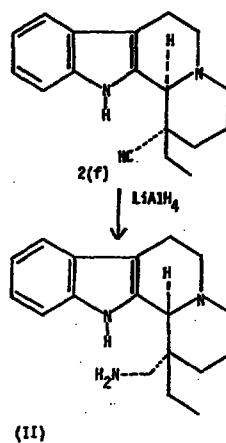
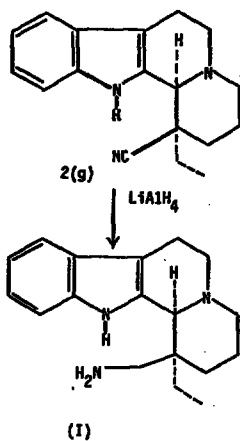
1(a) to 1(i), references of the various steps of Example 1 wherein the starting material is the 4-ethoxycarbonyl derivative and the final products, acids or derivatives thereof, and

2(a) to 2(g), references to the various steps of Example 2 wherein the starting material is the 4-cyano derivative and the final products aminomethyl compounds or derivatives thereof.

Initial Common Routes



Specific Routes

A = $-\text{COOC}_2\text{H}_5$ A = $-\text{CN}$ 

The compounds according to the invention in which R is a secondary amino or amido group, or E homo azaeburnamonines according to the invention, may be prepared from, the above products in which R is —COOH or —NH_2 by methods known *per se* for the interconversion of substituent groups.

- Typical reaction conditions for each reaction step sequence are as illustrated in the following Examples. Other conditions for effecting the same conversions will be readily apparent to those skilled in the art. 5

The invention is illustrated by the following Examples.

Example 1

(a) Preparation of 3-[2'-(2''-ethoxycarbonyl-2''-ethyl-5''-chloro-valeroylamino)-ethyl]-indole

- 10 To a suspension of 2.5 g (0.0184 mole) of 3-(2'-aminoethyl)-indole (tryptamine) in 50 ml dry chloroform containing 2 g (0.02 mole) of triethylamine cooled in an ice bath there were added drop by drop 4.7 g (0.0184 mole) of 2-ethyl-2-ethoxycarbonyl-5-chloro-valeroyl chloride. After stirring for 2 hours at room temperature, the solution was washed with diluted aqueous hydrochloric acid. After drying the organic phase and evaporating it under reduced pressure there was obtained 6.6 g of the 15 above product which, recrystallized from petroleum ether/isopropyl ether melted at 76°C and had a yield of 95%. The results of analysis were as follows: 15

- | | | | |
|----------|--|-----------------------------|----|
| IR (KBr) | 3350 and 3300 cm^{-1} | NH | |
| | 1735 cm^{-1} | CO ester | |
| | 1640 cm^{-1} | CO amide | |
| 20 | Calculated for $\text{C}_{20}\text{H}_{27}\text{N}_2\text{O}_3\text{Cl}$: | C=63.40%; H=7.18%; N=7.40% | 20 |
| | Found: | C=63.39%; H=7.05%; N=7.51%. | |

(b) Preparation of 1-[(2'-indol-3''-ylethyl)-3-ethyl-3-ethoxycarbonyl]-2-piperidone

- 25 To a suspension of 34.4 g (0.0908 mole) of the above compound in 150 ml of a 1:1 mixture of dry benzene and hexamethylphosphoric/triamide cooled in an ice bath there was added, in small quantities and in a nitrogen atmosphere, 10.6 g (0.0946 mole) of potassium t-butoxide. After stirring for 8 hours at room temperature, the solution was poured into a cold dilute aqueous solution of hydrochloric acid. The aqueous phase, after decantation, was extracted two times with benzene. The resulting organic phase was washed twice with water and dried. After evaporating under reduced pressure there was obtained 30 g of the desired product which, recrystallized from isopropyl ether, 30 melted at 84°F and had a yield of 96%, the results of analysis were as follows: 30

- | | | | |
|----------|---|-----------------------------|----|
| IR (KBr) | 3250 cm^{-1} | NH indole | |
| | 1730 cm^{-1} | CO ester | |
| | 1620 cm^{-1} | CO amide | |
| 35 | Calculated for $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_3$: | C=70.15%; H=7.65%; N=8.13% | 35 |
| | Found: | C=69.97%; H=7.65%; N=8.20%. | |

(c) Preparation of 1-ethyl-1-ethoxycarbonyl-5,12b-didehydro-indolo-(2,3-a) Quinolizidinum Perchlorate

- 40 Into a solution of 30 g (0.0876 mole) of the above compound in 480 ml of dry toluene there were poured 240 ml of distilled phosphoryl chloride. This solution was heated under reflux for 9 hours with a moisture guard. Excess phosphoryl chloride and toluene were then removed by evaporation under reduced pressure. The residue was taken up with methylene dichloride and the solution was washed with water, dried over sodium sulphate and evaporated under reduced pressure. A part of the solution was agitated with a 1M aqueous solution of lithium perchlorate. After decanting the aqueous phase, washing with water, drying over sodium sulphate and evaporating the solvent under reduced pressure 45 there was obtained a yellow powder which was recrystallized from ethanol. The resulting product melted at 191°F . The results of analysis were as follows: 45

IR (KBr)	3340 cm^{-1}	NH
	1740 cm^{-1}	CO ester
	1625 cm^{-1}	$\text{C}=\text{N}^{\oplus}$

- 50 (d) Preparation of 1-ethyl-1-ethoxycarbonyl-indolo (2,3-a)-quinolizidine (12b-H; 1- C_2H_5 Trans and 50 Cis Isomers)

- A solution of 6.25 g (0.0147 mole) of the above perchlorate salt in 80 mls ethanol was hydrogenated for 12 hours in the presence of 0.3 g of platinum oxide. After filtration, the ethanol was evaporated under reduced pressure and the residue taken up with methylene dichloride and agitated with 5% sodium hydroxide. The organic phase was decanted and washed with distilled water. 55

On chromatography of a solution of the product with methylene dichloride over 100 grams of silica, the elution with the same solvent, there was separated 1.12 g of a first fraction (yield 25%) which was the 12b-H; 1- C_2H_5 trans isomer of the product and melted at 112°C (recrystallized from petroleum ether/isopropyl ether). The results of analysis were as follows:

39

4

IR (KBr) 3410 cm^{-1}
2770, 2805, 2825 cm^{-1}
1710 cm^{-1}

NH
Bohlmann bands
CO ester

NMR (CDCl_3 , 90 MHz):

among other signals: 8.5 δ OH (s)
4.35 δ 2H (q)
3.85 δ 1H (s)
1.35 δ 3H (t)
0.75 δ 3H (t)

(NH indole)
(O— CH_2 — CH_3)
(H on C_{9a})
(CH_3 — CH_2 —O—)
(CH_3 — CH_2)

Calculated for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_2$:
Found:

C=73.59%; H=8.03%; N=8.58%
C=73.47%; H=8.12%; N=8.33%.

The later fractions of chromatography gave 1.8 g of an oil which was the 12b-H; 1- C_2H_5 cis isomers of the desired product.

The results of analysis were as follows:

IR (KBr) 3420 cm^{-1}
3750, 3800 cm^{-1}
1705 cm^{-1}

NH
Bohlmann bands
CO ester.

NMR (CCl_4 , 90 MHz):

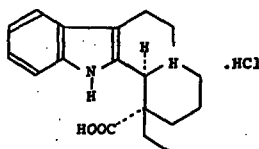
among other signals: 7.78 δ 1H (s)
4.15 δ 2H (q)
3.93 δ 1H (s)
1.09 δ 3H (t)
0.9 δ 3H (t)

(NH indole)
(— OCH_2 — CH_3)
(H on C_{9a})
(CH_3 — CH_2 —O)
(CH_3 — CH_2 —)

The hydrochloride, recrystallized from isopropanol, melted at above 260°C.

Calculated for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_2 \cdot \text{HCl} \cdot 1.5 \text{H}_2\text{O}$:
Found: C=61.57%; H=7.75%; N=7.18%
C=61.51%; H=7.33%; N=7.35%.

(e) Preparation of 1-ethyl-1-carboxy-indolo(2,3-a) Quinolizidine (12b-H; 1- C_2H_5 Trans Isomer), Hydrochloride



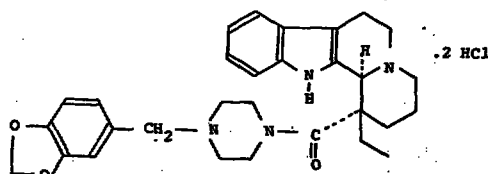
To a solution of 8.8 g of the ester obtained in step (d) above, in 100 ml of ethanol are added 8.8 g of KOH and the mixture is refluxed for 12 hours. The solvent is evacuated under reduced pressure and the residue retreated by iced water, acidified by concentrated hydrochloric acid until acid pH is reached; hydrochloride precipitates, is separated, washed and dried. Yield 9.5 g (100%) of the product crystallized with 1 mole of H_2O . M.P.: >260°C.

Analysis Formula $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2 \cdot \text{HCl} \cdot \text{H}_2\text{O}$ M.W.: 353.

	C	H	N
Calculated	61.01%	6.75%	7.72%
Found:	61.20%	7.08%	7.93%

IR (KBr) 3340 cm^{-1} NH
1705 cm^{-1} (—C—OH)
 $\text{O}=\text{C}$

(f) Preparation of 1-ethyl-1-piperonylpiperazidocarbonyl-indolo(2,3-a)-quinolizidine (12b-H; 1- C_2H_5 Trans Isomer) Dihydrochloride



6 g of hydrochloride of step (e) above are suspended in 50 ml of benzene and there are added, while cooling, 40 ml of oxalyle chloride. After stirring for 24 hours at 40°C, excess of oxalyle chloride is

- 5 evacuated by distillation under reduced pressure and the residue is retreated four times by dry benzene. The dry residue is thus suspended in 50 ml of methylene chloride and cooled at 0°C. A solution of 3.6 g of piperonylpiperazine and 3.4 g of triethylamine in 20 ml of methylene chloride are added and the mixture is stirred for 6 hours at room temperature. After filtration of the insolubles and evacuation of methylene chloride, the residue is treated on a silica gel column (eluent CH₂Cl₂). 4.9 g (yield: 60%) of an oily product are obtained. 5

IR (film) 3360 cm⁻¹ (NH); 1640 cm⁻¹ (CO).
NMR (COCl₂, internal TMS) δ in 10⁻⁶

- 10 9.2 1s (1H) NH indole
5.9 1s (2H) O—CH₂—O
4.05 1s (1H) H(C_{12b})
0.3 1t (3H) CH₃—CH₂

10

Dihydrochloride is obtained by treatment with aqueous HCl, in ethanol; crystallization with 3H₂O. Melting point 242°C.

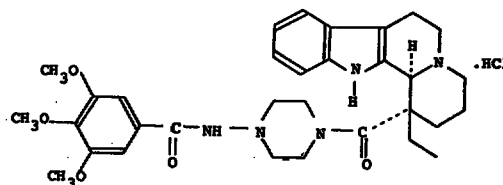
- 15 Analysis C₃₀H₃₆N₄O₃·2HCl·3H₂O M.W.:627.6

15

	C	H	N
Calculated	57.40	7.01	8.92
Found:	57.82	6.55	8.64

- 20 (g) Preparation of 1-ethyl-1[(trimethoxybenzamido-4)piperazinocarbonyl]indolo (2,3-a) Quinolizidine-(12b-H; 1-C₂H₅ Trans Isomer) Hydrochloride

20



- 25 5 g of hydrochloride of step (e) above are treated by oxalyle chloride as described in step (f) above. 5.3 g of dry residue are obtained, to which there are added 50 ml of methylene chloride and the mixture is cooled at 0°C. A solution of 3 g of triethylamine and 3 g of trimethoxy benzoyl-4-amino-1 piperazine in 20 ml of methylene chloride. The mixture is stirred for 24 hours at room temperature, then washed with a 10% aqueous soda solution, then with water, dried and the excess solvent is evacuated. 7.2 g of an oily product are obtained.

25

IR (film) 3380 cm⁻¹ and 3240 cm⁻¹ (NH)
1650 cm⁻¹ and 1620 cm⁻¹ (CO)

- 30 Hydrochloride is obtained by treatment with aqueous HCl, in ethanol.

30

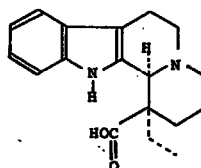
M.P.: 225°C.

Analysis C₃₂H₄₁N₅O₆·HCl M.W.:611

- 35 Calculated Found C H N
62.87 62.24 6.92 6.95 11.46 11.18

35

(h) Preparation of 1-ethyl-1-carboxy-indolo-(2,3-a)-quinolizidine (12b-H; 1-C₂H₅ Cis Isomer)

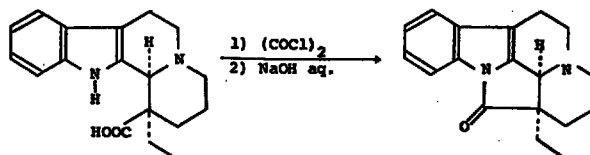


- 40 Into a solution of 6.8 g of 1-ethyl-1-ethoxycarbonyl-indolo(2,3-a) quinolizidine (12b-H; 1-C₂H₅ cis isomer) obtained in the preceding example (d), in 100 ml of ethanol at 95%, there are added 6.8 g of potassium hydroxide. The mixture is refluxed for 12 hours, the solvent evaporated under reduced pressure and the residue retreated with iced water and acidified with HCl up to pH=4.5. The product crystallizes, is separated, washed and dried. 4.1 g of acid are thus obtained.

40

Analysis $C_{18}H_{22}N_2O_2$ $M=298.37$

	C	H	N
Calculated	72.45	7.43	9.37
Found	72.61	7.49	9.20

5 IR 1620 cm^{-1} ν CO, OH associated. 5(i) Preparation of $\pm$ D Nor Eburnamonine

There are added, dropwise, to a suspension of 6 g (0.0179 mole) of 1-ethyl-1-carboxy-indolo(2,3-a) quinolizidine (12b-H; 1- C_2H_5 cis isomer) of previous step (h), in 60 ml of dry benzene, 30 ml of oxalyle chloride. The suspension is stirred for 2 hours at room temperature, then refluxed for 9 hours. The solvents are evacuated under reduced pressure and the residue retreated with methylene chloride, is stirred in the presence of diluted soda. The organic solution, washed with water, dried on sodium sulphate, evaporated under reduced vacuum, gives 4.25 g of the researched product. Yield 83%.

After washing on alumina column, 3.25 g of beige crystalline product are obtained. M.P.= 136°C (diisopropyl oxide).

IR (KBr): 2805, 2845, 1735, 1660 cm^{-1}
 $C_{18}H_{20}N_2O=280.96$.

Calculated %:	C 77.11	H=7.19	N 9.99
Found:	77.54	7.78	10.09

H_1 RMN ($COCl_2$) reference int. TMS $\delta_{TMS}=0$ 7.9—7.7 (m) aromatic; 7.5—7.05 (m) 3H aromatic; 4.3 (m) 1H; 1.1 (t) CH_3-CH_2

Hydrochloride

The necessary amount of aqueous HCl 7N is added to a solution of 3.25 g of base in 30 ml of absolute alcohol. The solvents are evaporated under reduced vacuum, at 30°C and the residue, retreated with acetone, gives 3.32 g of a white crystalline product. M.P.: 264°C .

IR (KBr): 3400, 2470, 2320, 1740, 1680 cm^{-1}
 C^{13} RMN (D_2O) reference dioxan δ ppm
 107.426 C=O; -13.712 CH; -82.162 CH_3

Example 2**(a) Preparation of 3-[2'-(2''-cyano-2''-ethyl-5''-chloro-valeroylamino)ethyl]-indole**

In a 1 litre flask there were placed 31 g (0.194 mole) of tryptamine 500 ml of dichloromethane and 20 g (0.198 mole) of triethylamine. The mixture was cooled to 0°C over ice and there were added 40 g (0.192 mole) of 2-cyano-2-ethyl-5-chloro-valeroyl chloride dissolved in 150 ml of methyl dichloride. After 2 hours at room temperature the mixture was washed with water, then with 10% hydrochloric acid, then with 10% sodium hydroxide. It was then dried and the solvent removed by evaporation. The product, recrystallized from isopropyl ether-petroleum ether, melted at 120°C (yield 40 g). The results of analysis are as follows:

IR (KBr) 3400 cm^{-1}	NH indole
3340 cm^{-1}	NH amide
2860 cm^{-1}	CN
1660 cm^{-1}	C—N
	$\parallel$
	O

Calculated for $C_{18}H_{22}N_3C10$
 Found:

C=65.0%; H=6.64%; N=12.65%
 C=64.03%; H=6.78%; N=12.60%.

(b) Preparation of 1-[(2'-indol-3''-yl-ethyl)-3-ethyl-3-cyano]-2-piperidone

In a 1 litre round-bottom flask there were placed 22 g (0.0665 mole) of the product of step (a) above, 200 ml of tetrahydrofuran, and 300 ml of *t*-butanol. the mixture was cooled to 0°C over ice and

- there were added, in small quantities, 8.5 g (0.076 mole) of potassium tert. butoxide. After 2 hours at room temperature, the mixture was reduced in volume and hydrolysed. The organic phase was extracted with methylene dichloride, washed with water, dried and the solvent removed by evaporation. The desired product, recrystallized from ethanol/ether 50/50 melted at 180°C (yield 15 g, 80%). The results of analysis are as follows:

IR 3400 cm^{-1} NH indole
 2260 cm^{-1} CN
 1635 cm^{-1} C—N
 ||
 O

- 10 Calculated for $\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}$: C=73.2%; H=7.1%; N=14.2%
 Found: C=72.46%; H=7.15%; N=14.01%.

(c) Preparation of 1-ethyl-1-cyano-5,12b-didehydro-indolo(2,3-a)-quinolizidium Perchlorate

- In a 1 litre flask there were placed, with stirring, 50 g (0.169 mole) of the product of step (b) above and 700 ml of phosphoryl chloride. After heating under reflux for 20 hours the reaction mixture was concentrated and extracted 2 or 3 times with 500 ml of methylene dichloride which was then removed by evaporation. The product was then taken up with 300 ml of methylene dichloride and cooled over ice, and 300 ml of a solution of lithium perchlorate (1 mole) was added with vigorous stirring. There was produced a yellow precipitate which, recrystallized from methanol melted at 260°C (yield 44 g, 70%). The results of analysis are as follows:

20 IR 3400 cm^{-1} NH indole
 2260 cm^{-1} C≡N
 1620 cm^{-1} C=N⁺

(d) Preparation of 1-ethyl-1-cyano-indolo(2,3-a)-quinolizidine (12b-H; 1-C₂H₅ Trans Isomer)

- In a 1-litre round-bottomed flask there were placed 200 ml methanol, 100 ml methylene dichloride and 13.5 g (0.036 mole) of the perchlorate product of step (c) above. The flask was cooled to about 5°C and 5 g of sodium borohydride were added in small quantities. The solution was then stirred for 2 hours at room temperature, concentrated, washed with water and extracted with methylene dichloride. After drying and removing the solvent, there were obtained 8 g of yellow crystals, recrystallized from isopropyl ether melting at 160°C (yield 80%). The results of analysis are as follows:

30 IR 3420 cm^{-1} }
 3440 cm^{-1} } NH and Bohlmann bands
 2760 cm^{-1} }
 2800 cm^{-1} }
 2250 cm^{-1} } CN

- 35 NMR (dimethylsulphoxide d_6 , 80 MHz)

0.86 δ , 3H (t) (CH_3)
 3.77 δ , 1H (s) (H at C_{9a})
 9.66 δ , 1H (s) (NH)

- 40 Calculated for $\text{C}_{18}\text{H}_{21}\text{N}_3$: C=77.7%; H=7.2%; N=15.2%
 Found: C=77.55%; H=7.32%; N=15.10%.

(e) Preparation of 1-ethyl-1-cyano-indolo(2,3-a)quinolizidine (12b-H; 1-C₂H₅ Cis Isomer)

- In a 1-litre flask there were placed 19 g of the perchlorate product of step (c) above, 300 cc of 95% ethanol and 40 g zinc powder. There was added in an ampoule 100 mls concentrated hydrochloric acid. Mild reflux could be observed during the addition of the acid. The mixture was allowed to stand at room temperature for 10 hours. It was then concentrated, washed with water and extracted with methylene dichloride. It was made alkaline with sodium hydroxide and filtered through Celite (Trade Mark). After decanting, drying and evaporating off the solvents there were obtained 6 g of a product, insoluble in ether, melting at 250°C. The results of analysis are as follows:

50 IR 3410 cm^{-1} (NH)
 2260 cm^{-1} (CN)

- Calculated for $\text{C}_{18}\text{H}_{21}\text{N}_3 \cdot 1/4\text{H}_2\text{O}$: C=76.5%; H=7.60%; N=14.85%
 Found: C=76.59%; H=7.80%; N=14.55%.

The ether extracts were concentrated to provide 4 g (total yield 71.5%) of the cis isomer of the same product as step (d) above.

NMR (dimethylsulphoxide d_6 , 80 MHz)

5	1.05 δ 3H (t) (CH_3)	5
	3.45 δ 1H (s) (H at C_{9a})	
	10.32 δ 1H (s) (NH)	

(f) Preparation of 1-ethyl-1-aminomethyl-indolo(2,3-a)quinolizidine (12b-H; 1- C_2H_5 Trans Isomer II)

- 10 In a 1-litre flask there were placed 4 g of lithium aluminium hydride and 400 ml of dry ether. The flask was cooled to from 0 to 5°C, and there were added, in small quantities, 8.9 g of the product of step (d) above. After leaving the flask to stand for 1 hour at room temperature; there were added 60 ml dry tetrahydrofuran. The mixture was heated for 2 hours under reflux. After cooling there were added, drop by drop, 40 ml water, followed by 200 ml of methylene dichloride. The mixture was stirred for 15 minutes. On filtering over celite, drying and concentrating the filtrate there was obtained 7.2 g of white crystals which, recrystallized from ether, melted at 175°C (80% yield).

The results of analysis are as follows:

IR 3280, 3190 cm^{-1} NH_2
3350 cm^{-1} NH indole

The CN peak at about 2250 cm^{-1} was absent.

20	Calculated for $C_{18}H_{25}N_3$:	C=76.4%; H=8.85%; N=14.8%	20
	Found:	C=75.85%; H=8.90%; N=15.52%.	

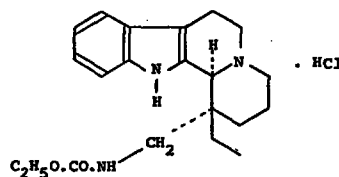
(g) Preparation of 1-ethyl-1-aminomethyl-indolo(2,3-a) Quinolizidine (12b-H; 1- C_2H_5 Cis Isomer I)

- 25 To a 500 ml flask there were added 3.4 g of lithium aluminium hydride, 200 ml of ether and 100 ml of tetrahydrofuran. While cooling over ice there were added, in small quantities, 6.9 g of the cis isomer of step (e) above. After allowing the mixture to stand for 15 hours at room temperature, the product was isolated as in step (f) above. On recrystallization from diethyl ether/petroleum ether 50/50 there was obtained 5 g of a product melting at 125°F (yield 71%).

30	Calculated for $C_{18}H_{25}N_3$:	C=76.4%; H=8.85%; N=14.8%	30
	Found:	C=76.25%; H=8.61%; N=14.43%.	

Example 3

1-ethoxycarbonylaminomethyl-1-ethyl-indolo(2,3-a) Quinolizidine Hydrochloride (12b-H; 1- C_2H_5 Trans Isomer II)



- 35 To a solution of 2 g (0.00705 mol) of the trans product II of Example 2(f) in 20 ml of dimethoxyethane, cooled to 0°C, there were alternately added, so as to maintain the pH basic, portions of:

800 mg of ethyl chloroformate in solution in 5 ml of dimethoxyethane; and
750 mg of sodium carbonate in solution in 5 ml of water.

- 40 After allowing the reaction mixture to stand for 3 hours at ambient temperature, the product was extracted with dichloromethane, the dichloromethane extract was washed with water, dried and evaporated to dryness. The product was recrystallized from ethanol.

Weight: 2 g Yield: 80%. M.P.: 140°C.

45	IR 3210 cm^{-1}	amide NH	45
	3400 cm^{-1}	indole NH	
	2760 and 2800 cm^{-1}	Bohlmann bands	
	1690 cm^{-1} carbamate C=O.		

The results of microanalysis are as follows:

Calculated for $C_{21}H_{29}N_3O_2$:

C=71.0%; H=8.17%; N=11.8%

Found:

C=70.94%; H=8.16%; N=11.54%.

The hydrochloride salt was formed from the above 2 g of product by adding 4N HCl in 20 ml of ethanol.

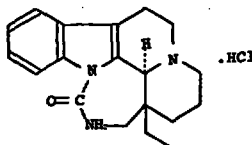
Weight: 2 g

Yield: 90%

M.P.: 260°C.

Example 4

E Homo Azaepieburnamonine Hydrochloride



First 1-phenoxycarbonylaminomethyl-1-ethyl-indolo (2,3-a) quinolizidine (12b-H; 1-C₂H₅ trans isomer) was prepared by repeating the procedure of Example 3, but replacing the ethyl chloroformate with phenyl chloroformate.

To a solution of 8 g (0.02 mol) of the product in 250 ml of tetrahydrofuran there were added 2 g of sodium hydride to 50%. After stirring for 90 minutes, the reaction product was extracted with diethyl ether, washed with water and dried. The diethyl ether was removed by evaporation to leave 5 g of an oil, analysis of which gave the following data:

IR 3200 cm⁻¹
1670 cm⁻¹

amide NH
amide C=O

NMR (CCl₄; internal TMS)

0.65 δ (3H, t, CH₃—CH₂)
1 to 3.2 δ (solid 15 protons)
3.3 δ (1H, s, angular proton 12b H)
7.2 δ (solid 3H aromatics)
8.1 δ (solid 1H aromatic)

The hydrochloride salt was prepared by treating the above oil with 4N hydrochloric acid in 20 ml of ethanol, followed by centrifuging. The yield was 60%, calculated on the starting amine (II). M.P.: 260°C. The product crystallized with 1/2 mol of water of crystallization.

The results of microanalysis are as follows:

Calculated for C₁₉H₂₃N₃O.HCl.0.5 H₂O

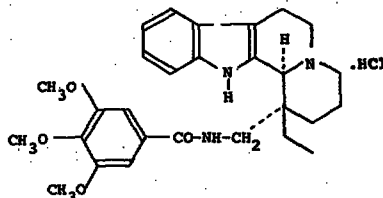
C=64.5%; H=7.05%; N=11.8%

Found:

C=64.38%; H=7.11%; N=11.62%.

Example 5

1-(3',4',5'-trimethoxybenzoylaminomethyl)-1-ethyl-indolo (2,3-a) Quinolizidine Hydrochloride (12b-H; 1-C₂H₅ Trans Isomer II)



Into a three-necked bottle of 250 ml capacity fitted with a stirrer, a CaCl₂ guard, a thermometer and a dropping funnel there were added 2.85 g of the trans product II of Example 2(f), 1.1 g of triethylamine and 50 ml of dichloromethane.

The mixture was stirred and cooled to 0.2°C. At this temperature there were slowly added 2.31 g of 3,4,5-trimethoxybenzoyl chloride in 15 ml of dichloromethane. The addition took place over a period of 15 to 20 minutes, after which time the reaction mixture was stirred for 1 hour at 0°C then for 15 hours at ambient temperature.

The reaction mixture was then washed several times with water, then with 10% aqueous sodium

hydroxide and then again with water. It was dried over sodium sulphate and concentrated to form a non-crystalline mass, having the texture of meringue and melting towards 100°C.

CCM:	90/10	8/10
IR	3230 cm ⁻¹	NH
	3190 cm ⁻¹	NH
	2750 and 2800 cm ⁻¹	Bohlmann bands
	1640 cm ⁻¹	C=O amide

5

dosage of the base with HClO₄: 97%

To prepare the hydrochloride salt, the above product was dissolved in a 1:1 mixture of di-isopropyl ether and isopropanol, and 4N hydrochloric acid was added. The hydrochloride salt crystallized when hot, and was filtered while hot and washed with ethanol to produce 4.5 g (88% yield) of the product.

10

CCM:	90/10	8/10
M.P.:	210°C	bond on the plate

15 dosage of hydrochloride: 100% (1 function).

15

Microanalysis gave the following results:

Calculated for C₂₆H₃₅N₃O₄·HCl:

C=65.45%; H=7.00%; N=8.18%

Found:

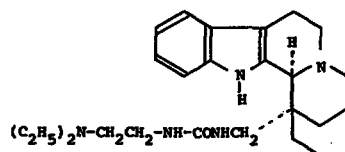
C=64.34%; H=7.17%; N=8.11%

C=64.15%; H=7.16%; N=7.96%.

20 Example 6

20

1-(N'[(diethylaminoethyl)-N-ureidomethyl-1-ethyl-indolo (2,3-a) Quinolizidine (12b-H; 1-C₂H₅ Trans Isomer II)



There was first prepared the corresponding 1-phenoxyaminomethyl-1-ethyl derivative, 7 g of the trans product II of Example 2(f) and 100 ml of tetrahydrofuran were placed in a three-necked flask of 500 ml capacity, having a stirrer and two dropping funnels. The flask was cooled to between 0°C and 5°C and at this temperature, there were simultaneously added 4.25 g of phenyl chloroformate in 50 ml of tetrahydrofuran and 2.9 g of sodium carbonate in 50 ml of water. The rates of addition were such as to maintain the pH at from 6 to 7. The flask was then allowed to warm to ambient temperature and stirring was continued for 3 hours. The reaction product was extracted with 100 ml of dichloromethane and the extract was washed several times with water before being dried with sodium sulphate, and concentrated by evaporation. There were obtained 11 g of the product, which was an oil.

25

30

IR 3270 cm ⁻¹	NH
1710 cm ⁻¹	C=O

The 1-ureidomethyl product was prepared as follows: into a 500 ml flask provided with a cooler, there were placed 11 g of the above oil 3.5 of dimethylaminoethyl amine and 180 ml of methanol. The amount of dimethylaminoethyl amine used corresponded to a 20% excess. The mixture was heated under reflux for 2.5 hours and then the methanol was removed by evaporation. The residue was taken up in dichloromethane and washed with 10% aqueous sodium hydroxide then with water. After drying over sodium sulphate it was concentrated to provide a yellowish crystalline product. The product was taken up in two stages in diethyl ether and centrifuged. The first stage yielded 4.6 g of crystalline product melting at 202°C, and the second stage yielded 0.8 g of crystalline product melting at 198°C. The combined products were then recrystallized from benzene to provide 4.65 g of the final product.

35

40

M.P.: 204°C.	Yield: 45% based on the amine (II).
CCM: 90/10	5/10

45

Dosage of the base with HClO₄: 100% (2 functions).

IR: 3360 cm ⁻¹	NH
3250 cm ⁻¹	NH
1620 cm ⁻¹	C=O urea.

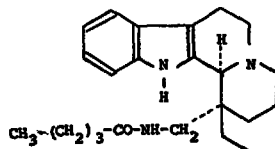
Microanalysis gave the following results:

Calculated for $C_{25}H_{39}N_5O$:
Found:

C=70.6%; H=9.17%; N=16.45%
C=70.58%; H=9.20%; N=16.67%.

Example 7

- 5 **1-pentanoylaminomethyl-1-ethyl-indolo (2,3-a)-quinolizidine (12b-H; 1-C₂H₅ Trans Isomer II)** 5



Using reaction conditions and techniques identical to those of Example 5, there were reacted a solution of 5.7 g of the trans product II of Example 2(f) and 2.1 g of triethylamine in 120 ml of dichloromethane and a solution of 2.45 g pentanoyl chloride in 20 ml of dichloromethane.

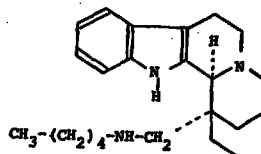
- 10 There were thus obtained 7.8 g of an oil containing a little residual triethylamine. 10

IR: 3180—3380 cm^{-1} NH
1630—1650 cm^{-1} C=O

From the oil it was possible to obtain crystals of the product, melting at 110°C.

Example 8

- 15 **1-pentylaminomethyl-1-ethyl-indolo (2,3-a)-quinolizidine (12b-H; 1-C₂H₅ Trans Isomer II)** 15



- 20 In a three-necked flask of 500 ml capacity having a stirrer, a condenser, a thermometer, and a dropping funnel there were placed 100 ml of anhydrous diethyl ether. When this had been cooled over an ice bath there added 4 g of lithium hydride, and the contents of the flask were stirred for 15 minutes. There was then added very slowly a solution of 7.4 g of the product of Example 7 in 50 ml of anhydrous diethyl ether. The mixture was then heated under reflux for 2 hours and stirred for a further 15 hours at ambient temperature. It was then cooled over an ice bath and there were added dropwise 20 ml of water followed by 150 ml of dichloromethane. The reaction mixture was then filtered over celite, dried over sodium sulphate and concentrated by evaporation. There were obtained 7 g of an oil 25 which could be crystallized to a product melting at 80°C. 25

Recrystallization from the minimum amount of isopropanol gave 4.3 g of a crystalline product melting at 97°C.

Dosage of the base with HClO_4 : 100% (2 functions).

Microanalysis gave the following results:

- 30 Calculated for $C_{23}H_{35}N_3$: C=78.20%; H=9.92%; N=11.90%
Found: C=78.18%; H=9.81%; N=12.00%. 30

IR basic: 3310 cm^{-1} NH
1620 cm^{-1} C=O

Dimaleate

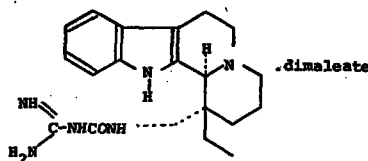
- 35 An acid addition salt with maleic acid was prepared, working in solution in a mixture of isopropanol and di-isopropyl ether. Initially the salt formed as an oil, but was recrystallized from ethyl acetate to give 6.7 g of the dimaleate, melting at 105°C. 35

Dosage of the dimaleate with HClO_4 : 99.6% (2 functions).

RF: 90/10 9/10.

Example 9

1-guanidinocarbonylaminomethyl-1-ethyl-indolo (2,3-a)-quinolizidine Dimaleate (12bH; 1-C₂H₅ Trans Isomer)



5 Into a 250 ml flask, 9 g of the compound prepared in Example 3, 2.2 g of base guanidine (liberated from 3 g of chlorohydrate by the couple ethylate-ethanol) are put into 120 ml of ethanol. The mixture is refluxed for 48 hours and the solvent evaporated to dryness. The residue is retreated by a water-methylene chloride mixture, filtered on celite and decanted, the organic phase washed again with water. The methylene chloride phase is then washed twice by a 5% acetic acid solution and the acid waters are alkalized with sodium bicarbonate in the presence of ether; the ethereal phases are dried and evaporated.

6.4 g of a porous mass are obtained and chromatographed on silica (60 g of silica: eluent CH₂Cl₂—MeOH 80—20).

After separating 0.7 g of a first product, a second one is isolated and crystallized in ether. Yield:

15 3.5 g. M.P.=150°C.

IR (KBr): 3200—3400 cm⁻¹ strong and broad bands (ν NH)
1600 cm⁻¹ broad band (ν C=O)

The dimaleate is prepared in isopropanol.

CCM (Merck plate MP 254: eluent acetone, CHCl₃, n butanol, NH₄OH 25%

20 30 30 30 10 20

R_f=0.4 1 spot

Microanalysis

C₂₀H₂₈N₆O + C₈H₈O₄M=600

Calculated %:

C 56.00

H 6.00

N 14.00

Found:

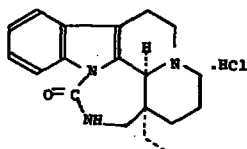
56.07

6.46

12.59

Example 10

E Homo 14 Azaeburnamonine (12b-H; 1-C₂H₅ Cis Isomer I)



Example 4 was repeated except that the cis product (I) of Example 2(g) was used in place of the trans product (II) of Example 2(f). There was obtained 5.7 g of product (yield 69%). M.P.: 190°C.

30 IR: 3620 cm⁻¹ NH
1690 cm⁻¹ C=O

Microanalysis gave the following results:

Calculated for C₁₉H₂₃N₃O:

C=73.8%; H=7.45%; N=13.6%

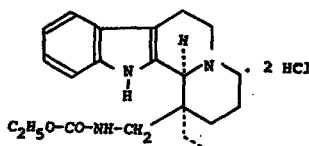
Found:

C=73.48%; H=7.35%; N=12.99%.

35 The hydrochloride was obtained by adding 4 N HCl to a solution of the base in a 1:1 mixture of ethanol and diethyl ether.

Example 11

1-Ethoxycarbonylaminomethyl-1-ethyl-indolo (2,3-a)-quinolizidine Hydrochloride (12b-H; 1-C₂H₅ Cis Isomer I)



40

40

The procedure of Example 3 was repeated except that the cis product (I) of Example 2(g) was used instead of the trans product (II) of Example 2(f). There was obtained 2.1 g of the free base (84% yield). M.P.: 210°C.

5 IR 3400 cm^{-1} indole NH
3210 cm^{-1} amide NH
2790 and 2810 cm^{-1} Bohlmann bands
1690 cm^{-1} carbamate C=O

Microanalysis gave the following results:

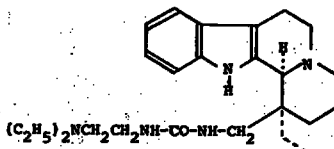
10 Calculated for $\text{C}_{21}\text{H}_{29}\text{N}_3\text{O}_2$: C=71.0%; H=8.17%; N=11.82%
Found: C=70.85%; H=8.22%; N=11.94%.

15 NMR (CDCl_3 ; internal TMS)
1.1 δ (6 H, t, CH_3 ethyl and ethyl ester)
1.5 to 3.5 δ (15H, solid)
3.9 δ (2H, q, CH_2O)
5.65 δ (1H, m, NH-amide)
7.25 δ (4H, solid, aromatics)
7.9 δ (1H, s, NH — indole)

The hydrochloride salt was prepared using 4N hydrochloric acid in acetone.

Yield: 90%. M.P.: 250°C.

20 **Example 12**
1-(N'-[diethylaminoethyl]-N-ureidomethyl)-1-ethyl-indolo (2,3-a)quinolizidine (12b-H, 1-C₂H₅ Cis Isomer I)



25 The first part of Example 6 was repeated using the cis product I of Example 2(g) instead of the trans product II of Example 2(f). The second part of Example 6 was then repeated on a smaller scale, using 3 g of the 1-phenoxy-carbonylaminomethyl derivative, 1.2 g of diethylaminoethyl amine and 50 ml of methanol. There was thus produced 2.8 g of the above product which was an oil.

30 The di-hydrochloride salt was obtained by treatment with 4N hydrochloric acid in acetone. The salt was isolated by concentrating the acetone solution and recrystallizing from a 1:1 mixture of ethyl acetate and ethanol.

There were obtained 1.8 g of product, melting at 250°C. Yield: 48.5% based on the weight of amine base.

IR 3300 cm^{-1}
1640 cm^{-1}

35 Microanalysis gave the following results assuming 1 mole of water of crystallization.

Calculated for $\text{C}_{25}\text{H}_{39}\text{N}_5\text{O} \cdot 2\text{HCl} \cdot \text{H}_2\text{O}$: C=58.30%; H=8.35%; N=13.74%
Found: C=58.56%; H=8.25%; N=13.60%.

Toxicity

40 LD 50 has been determined per os on mice. The compounds of the invention present a toxicity comparable to that of vincamine or a lower one. The more toxic (LD 50: 400 mg/kg; vincamine 450 mg/kg) are those of Examples 2(f), 3 and 4; the less toxic are those of Examples 5, 10 and 12 whereas the remaining compounds present an intermediate toxicity.

Pharmacology

45 The activity of the compounds of the invention has been researched in the field of femoral and vertebral flows, arterial pressure and cardiac rhythm. Comparison was made with vincamine and with compounds described in French Patent publications No. 2,285,377 and 2,292,475. The experimentation, conducted as known for vincamine, has shown that the compounds of the invention, and more particularly these of Examples 3 and 5:

- a) induce an increase of the femoral flow; French patent publications compounds present a similar action but vincamine reduces this flow;
 b) induce a strong increase of the vertebral flow; French patent publications compounds do not act at all or induce a moderate increase whereas vincamine reduces this flow;
 c) do not affect significantly arterial blood pressure whereas the comparison compounds lower it;
 d) induce a slight increase of cardiac rhythm whereas French patent publications compounds generally induce a more important increase and vacamine lowers this factor.

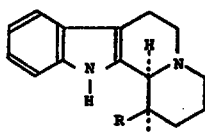
From these results the compounds of the invention appear to have a very favourable action in the field of cerebral irrigation, which was confirmed clinically.

10 Posology

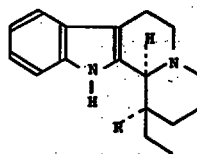
The compounds of the invention may be administered i.v. or *per os*, at doses comparable to those used for vincamine, (dosage units for 5 to 40 mg).

Claims

1. An indolo (2,3-*a*) quinolizidine of the general formulae (I) or (II)



(I)



(II)

wherein R stands for $-\text{COOC}_2\text{H}_5$, $-\text{COOH}$, $-\text{CN}$, a primary or secondary aminomethyl group, an amidomethyl group or an amido group, or wherein R, together with the ring nitrogen of the indolo ring, represents one of the groupings $-\text{N}-\text{CO}-\text{NH}-\text{CH}_2-$ or $-\text{N}-\text{CO}-$; or a therapeutically acceptable acid addition salt thereof.

2. A compound according to claim 1, substantially as disclosed in any of the Examples herein.
 3. A process for the preparation of a compound according to claim 1, comprising condensing together 2-aminoethyl-3-indole and 1-chloro-4-(A)-4-chlorocarbonyl-hexane, wherein A stands for $-\text{COOC}_2\text{H}_5$ or $-\text{CN}$, to form the corresponding amide; subjecting the amide to strongly basic conditions to eliminate HCl and effect ring formation at the nitrogen atom on the 3-indole substituent; effecting quinolizidine ring formation of the product by treating it with a dehydrating agent followed by a perchlorate salt; hydrogenating the resulting quinolizidinium perchlorate to produce the corresponding indolo (2,3-*a*) quinolizidine isomer mixture and separating the isomers.
 4. A process for the preparation of a compound according to claim 1, substantially as disclosed in any of the Examples herein.
 5. A therapeutic composition comprising one or more compounds according to claim 1 or claim 2 in admixture with a therapeutically acceptable diluent or carrier.



a) induce an increase of the femoral flow; French patent publications compounds present a similar action but vincamine reduces this flow;

b) induce a strong increase of the vertebral flow; French patent publications compounds do not act at all or induce a moderate increase whereas vincamine reduces this flow;

c) do not affect significantly arterial blood pressure whereas the comparison compounds lower it;

d) induce a slight increase of cardiac rhythm whereas French patent publications compounds generally induce a more important increase and vacamine lowers this factor.

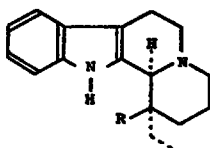
From these results the compounds of the invention appear to have a very favourable action in the field of cerebral irrigation, which was confirmed clinically.

10 Posology

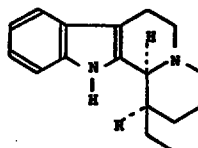
The compounds of the invention may be administered i.v. or *per os*, at doses comparable to those used for vincamine, (dosage units for 5 to 40 mg).

Claims

1. An indolo (2,3-*a*) quinolizidine of the general formulae (I) or (II)



(I)



(II)

wherein R stands for $-\text{COOC}_2\text{H}_5$, $-\text{COOH}$, $-\text{CN}$, a primary or secondary aminomethyl group, an amidomethyl group or an amido group, or wherein R, together with the ring nitrogen of the indolo ring, represents one of the groupings $-\text{N}-\text{CO}-\text{NH}-\text{CH}_2-$ or $-\text{N}-\text{CO}-$;

or a therapeutically acceptable acid addition salt thereof.

2. A compound according to claim 1, substantially as disclosed in any of the Examples herein.

3. A process for the preparation of a compound according to claim 1, comprising condensing together 2-aminoethyl-3-indole and 1-chloro-4-(A)-4-chlorocarbonyl-hexane, wherein A stands for $-\text{COOC}_2\text{H}_5$ or $-\text{CN}$, to form the corresponding amide; subjecting the amide to strongly basic conditions to eliminate HCl and effect ring formation at the nitrogen atom on the 3-indole substituent; effecting quinolizidine ring formation of the product by treating it with a dehydrating agent followed by a perchlorate salt; hydrogenating the resulting quinolizidinium perchlorate to produce the corresponding indolo (2,3-*a*) quinolizidine isomer mixture and separating the isomers.

4. A process for the preparation of a compound according to claim 1, substantially as disclosed in any of the Examples herein.

5. A therapeutic composition comprising one or more compounds according to claim 1 or claim 2 in admixture with a therapeutically acceptable diluent or carrier.