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PROCESS FOR PREPARING PENTACYCLIC ALKALOIDS

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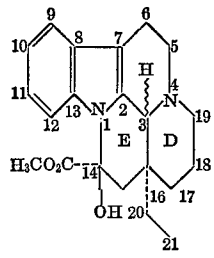
ABSTRACT OF THE DISCLOSURE

Process for preparing pentacyclic alkaloids of general formula:



(I)

BACKGROUND OF THE INVENTION

This invention relates to a process for preparing pentacyclic alkaloids of general Formula I.

This invention has as an object a process for preparing pentacyclic alkaloids of the eburnamonine-vincamine group and in particular, racemic and optically active vincamine.

The compound of general Formula I, for which the junction of the cycles D and E is cis, that is to say where hydrogen at position 3 and the ethyl radical at position 16 are cis with respect to one another, corresponds to dl-vincamine.

The compound of general Formula I, where the junction of the cycles D and E is trans, corresponds to dl-iso-vincamine.

It is known that (+) vincamine has been isolated from several species of the vinca kind, particularly *Vinca minor L.* As for dl-vincamine, it would have been found in the *Tabernaemontana rigida* species.

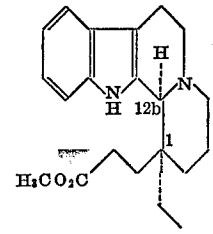
It is also well known that vincamine possesses very interesting therapeutic properties thanks to a double action.

It improves the oxygenation of the cerebral tissue which contributes to maintaining the nervous tissue in good functioning condition. In addition it manifests a vasodilatory action more particularly on the cerebral capillary system which permits re-establishment or maintenance of normal blood flow.

Vincamine is used especially in vascular cerebral complaints, in cerebrosclerosis, loss of conscience due to cranial traumatisms or due to the after-effects of acute cerebral insufficiency.

This invention has principally as object to allow one to obtain a pure vincamine by a synthetic route which does not necessitate a starting material of vegetable origin, the provision of which is often expensive and risky.

Syntheses of dl-vincamine have certainly already been described. Thus Kuehne, by treating the tetracyclic compound Formula IIa:



(IIa)

with p-nitrosodimethylaniline and triphenylmethyl sodium then with hydrochloric acid, obtains a mixture of dl-vincamine and dl-epivincamine from which dl-vincamine can only be isolated with a very low yield [J. Am. Chem. Soc. 86, 2946 (1964)]. In addition, conversion of dl-homo-eburnamonine into dl-vincamine, by a process in five stages, has recently been described, the starting material being itself accessible by quite a long process starting with tryptamine and 2-ethoxy carbonyl 2-ethyl cyclopentanone [K. H. Gibson et al., Col. Chem. Comm. (1969), 799 and 1490].

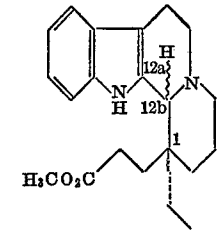
These processes of preparation have various disadvantages and lead to a mixture of isomers and low yields.

In addition, the publication of K. H. Gibson (Chem. Comm. 1969, p. 1490) indicates the impossibility of obtaining 14,15-dioxo E-homo-eburnane starting with homo-eburnamenine, either because the intermediately formed ketol cannot be oxidized, or even because the ketol is reduced, even under oxidizing conditions. This impossibility of arriving at a supplementary oxidation degree has forced authors to have recourse to an indirect route and to the subsequent use of a very particular oxidation agent. The purity of the vincamine obtained under these conditions remains to be proved.

The process of this invention allows precisely the avoidance of the disadvantages mentioned above.

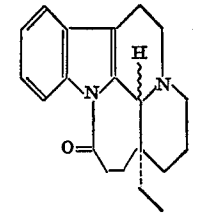
DETAILED DESCRIPTION OF THE INVENTION

The process of the present invention is essentially characterized in that one treats the tetracyclic compound of general Formula II:



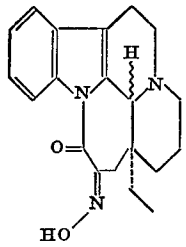
(II)

with a basic agent to obtain the lactamic compound of general Formula III:



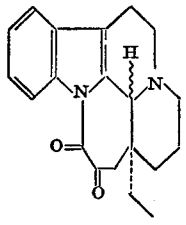
(III)

on which one causes a nitrosation reagent to react to obtain the hydroxyimino compound of general Formula IV:



(IV)

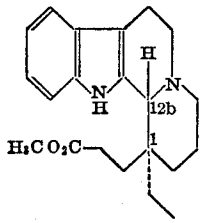
treats the said compound with a reagent for regeneration of a ketone starting from oxime to obtain the di-oxo compound of general Formua V:



(V)

which one subjects to the action of an alkali-metal methylate.

With this process, one thus obtains, starting with the Compound IIa, where the hydrogen atom at position 12*b* and the ethyl at position 1 are cis, dl-vincamine, and starting with the Compound IIb:



where the hydrogen atom at position 12*b* and the ethyl at position 1 are trans, dl-isovincamine.

In the present application, the derivatives of indolo-(2,3-a) quinolizine, whose substituents 12*b*-H and 1-ethyl are at cis position with respect to one another, are called cis indolo-(2,3-a) quinolizine.

In an analogous way, the derivatives of indolo-(2,3-a) quinolizine, whose substituents 12*b*-H and 1-ethyl are at trans position with respect to one another, are called trans indolo-(2,3-a) quinolizine.

The derivatives of eburnane or E-homo-eburnane at junction D/E cis are called cis-eburnane or cis E-homo-eburnane.

In an analogous way, the derivatives of eburnane or E-homo-eburnane at junction D/E trans eburnane or trans E-homo-eburnane.

The conversion of the tetracyclic compound, II, into lactam, III, is effected in the presence of a basic agent, specifically a strong alkaline base. This can for example be an alkali-metal hydride, amide or alcoholate. Thus one uses preferably an alkali-metal tertiary alcoholate such as sodium t-amylate to convert the compound, IIa, into the corresponding lactam, 14-oxo E-homo-eburnane, of the D/E cis series.

The following stage, conversion of the lactam, III, into the hydroxyimino derivative, IV, is one of the more characteristic phases of the process of the invention.

It has in fact been found that the methylene group at α of the lactamic carbonyl could be nitroso. This result is unexpected, given the very slight tendency of lactams to appear in enolic form. It can be obtained by the action of a classic nitrosation reagent, specifically by the action of an alkyl nitrite (containing from 1 to 5 carbon atoms),

the reaction being carried out in the presence of a basic agent. As nitrite, one can use n-propyl nitrite, butyl nitrite, such as t-butyl nitrite or isoamyl nitrite. As basic agent, one generally uses a strong alkaline base, such as an alkali-metal hydride or tertiary alcoholate, such as sodium hydride, sodium t-butylate or t-amylate.

Under these conditions, one obtains in D/E cis series starting with 14-oxo E-home-eburnane, 14-oxo 15-hydroxyimino E-homo-eburnane.

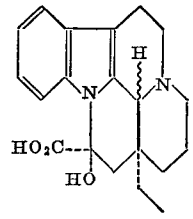
Passage of the hydroxyimino derivative, IV, to the corresponding dioxo compound, V, is accomplished by the classic methods for regenerating a ketone function starting from an oxime. In order to do this, one operates specifically by displacement while treating the Compound IV with an aldehydic or ketonic reagent, such as benzaldehyde, formaldehyde, pyruvic acid, glyoxylic acid or levulic acid, the reaction preferably being carried out in the presence of an acid, for example hydrochloric acid or sulphuric acid.

14-oxo 15-hydroxyimino E-homo-eburnane thus leads to 14,15-dioxo E-homo-eburnane.

Conversion of the dioxo compound, V, into the final product I can be accomplished in the following way:

It has in fact been found that the treatment of the compound, V, with an alkali-metal methylate, such as sodium or potassium methylate, gave rise to the conversion of the E-homo cycle into an E cycle with six groups containing, at position 14, the OH and CO_2CH_3 function desired with stereochemistry corresponding to that of natural vincamine, in the case where one operates in D/E cis series, or to that of iso-vincamine when one operates in D/E trans series. Formation at this stage, in an exclusive or preponderant manner, of a single isomer is of great advantage avoiding long and laborious purifications.

It has also been found that one could, according to a variant of the preceding method, treat the compound V with an acid agent or a basic agent producing hydroxyl $OH^{\ominus}$ ions, such as an alkali-metal or alkaline-earth hydroxide, such as caustic potash or baryte, and obtain the acid compound of general Formula VI:



(VI)

which can then be esterified according to the usual methods for example by the action of diazomethane, to give the methyl ester I.

Passage of the Compound V to the product I, either directly or by the intermediate of the Compound VI, also constitutes one of the most characteristic stages of the process of the invention. One can imagine that this reaction of reduction of a cycle having 7 groups into a cycle having 6 groups proceeds by breaking the lactamic bond

then formation of a new bond between the indolic nitrogen and the carbon of the ketonic function, or else by a re-arrangement of the benzilic type. It goes without saying however that these mechanical considerations in no way limit the scope of the invention.

Application of the process of the invention to optically active compounds allows one to obtain optically active final products and specifically (+) vincamine, identical to the natural product isolated, for example, from

Vinca minor L. This process also enables one to prepare (—) vincamine, optical antipode of the above.

Thus, application of the process of the invention to an enantiomer of cis 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethyl indolo (2,3-a) quinolizine (IIa) allows the preparation of an optically active vincamine. One obtains, according to the enantiomer chosen, either (+) vincamine starting with the 12bα-H 1α-ethyl enantiomer, or (−) vincamine starting with the 12bβ-H 1β-ethyl enantiomer.

The present invention has as object a process for preparing an optically active vincamine, characterized in that one treats an enantiomer of cis 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethyl indo (2,3-a) quinolizine with a basic agent to obtain the corresponding enantiomer of cis 14-oxo E-homo-eburnane (D/E cis junction), causes a nitrosation reagent to react on this latter to form the corresponding enantiomer of cis 14-oxo 15-hydroxy-imino E-homo-eburnane, treats this with a reagent for regeneration of ketones starting from oximes, to obtain the corresponding enantiomer of cis 14,15-dioxo E-homo eburnane which one subjects to the action of an alkali-metal methylate, and obtains, according to the starting enantiomer chosen, either (+) vincamine or (−) vincamine.

The process of the invention, for the preparation of (+) vincamine, is characterized in that one treats 1,2,3,4,6,7,12,12b-octahydro 1α-ethyl 1β-carbomethoxyethyl 12bα-indolo (2,3-a) quinolizine with a basic agent to obtain 14-oxo 3α,16α(20)-E-homo eburnane, causes this latter to react with a nitrosation reagent to form 14-oxo 15-hydroxyimino 3α,16α(20)-E-homo eburnane, treats this with a reagent for regenerating a ketone starting from oxime, to obtain 14,15-dioxo 3α,16α(20)-E-homo eburnane which one subjects to the action of an alkali-metal methylate.

This process is carried out in a manner identical to that specified above for the use of a basic agent of the nitrosation reagent and of the reagent for regenerating a ketone starting from the corresponding oxime.

The present application has likewise as object a variant of the above process, in which the final reaction is effected in two stages.

This variant is characterized in that one treats one of the enantiomers of cis 14,15-dioxo E-homo eburnane with an acid agent or with a basic agent giving rise to hydroxyl ions, obtains the corresponding enantiomer of cis 14-hydroxy 14-carboxy-eburnane, and causes this latter to react with a reagent for forming methyl esters to obtain an optically active vincamine.

In particular, to obtain according to this variant (+) vincamine, one treats 14,15-dioxo 3α,16α(20)-E-homo eburnane with an acid agent or with a basic agent giving rise to hydroxyl ions to form vincaminic acid, and causes this latter to react with a reagent for forming methyl esters.

In this variant of the process, the basic agent giving rise to hydroxyl ions is preferably an alkali-metal or alkaline-earth hydroxide, for example caustic potash or baryte. Conversion of the acid obtained into methyl ester is effected according to the usual methods, such as for example by the action of diazomethane.

The enantiomers of cis-1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethyl indolo (2,3-a) quinolizine, used as starting products in the above process can be prepared as follows:

The cis and trans epimers of 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carboxyethyl 4-oxo indolo (2,3-a) quinolizine are obtained by saponification of the mixture of epimers of 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethyl 4-oxo indolo (2,3-a) quinolizine and can be separated by physical methods, and particularly by simple fractionated crystallization.

It is possible to effect at this stage the resolution of the cis isomer by the formation of a salt with an optically active base, separation of the diasteroisomeric salts by the usual methods specifically by fractionated crystallization, and isolation of each of the two optical antipodes of cis 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carboxyethyl 4-oxo indolo (2,3-a) quinolizine by acid treatment of the corresponding salt.

Comparison of the curves of circular dichroism of the two enantiomers obtained, with the curves of circular dichromism of (+) vincamine of natural origin has enabled one to identify, at this stage, the enantiomer which has the same configuration as (+) vincamine. This enantiomer (levorotatory in dimethylformamide) leads to (+) vincamine during the synthesis.

As the absolute configuration of (+) vincamine is known (see K. Blaha et al., Chem. and Ind., 1965, page 1261), one can deduce therefrom that this levorotatory isomer is 1,2,3,4,6,7,12,12b-octahydro 1α-ethyl 1β-carboxyethyl 4-oxo 12bα-indolo (2,3-a) quinolizine.

The other enantiomer, dextrorotatory in dimethylformamide, is the corresponding 1β-ethyl 12bβ-H derivative, and leads, during the syntheses, to (−) vincamine.

This separation of the cis and trans isomers, and this resolution of the cis isomer, at an early stage of the synthesis, allow of advantageously preparing optically active vincamine. For that, one converts optically active cis 1,2,3,4,6,7,12,12b-octa-hydro 1-ethyl 1-carboxyethyl 4-oxo indolo (2,3-a) quinolizine, according to a method analogous to that described for racemic products by Kuehne (cited article), into optically active cis 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethyl indolo (2,3-a) quinolizine. Application of the process of the invention to this latter compound leads to optically active vincamine.

The application has likewise as object a process for preparing (+) vincamine or (−) vincamine according to the process or variant above, and in which the starting product is obtained by saponification of 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1 - carbomethoxyethyl 4-oxo indolo (2,3-a) quinolizine, separation of the cis and trans isomers of 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carboxyethyl 4-oxo indolo (2,3-a) quinolizine, resolution of cis 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carboxyethyl 4-oxo indolo (2,3-a) quinolizine into its optical antipodes by means of an optically active base, esterification of an enantiomer of cis 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carboxyethyl 4-oxo indolo (2,3-a) quinolizine into an enantiomer of cis 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethyl 4-oxo indolo (2,3-a) quinolizine, reaction of this latter with phosphorus pentasulphide to obtain the corresponding enantiomer of cis 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethyl 4-thioxo indolo (2,3-a) quinolizine and desulphidation of this into an enantiomer of cis 1,2,3,4,6,7,12,12b-octahydro 1 - ethyl 1-carbomethoxyethyl indolo (2,3-a) quinolizine.

In particular the 1,2,3,4,6,7,12,12b-octahydro 1α-ethyl 1β-carbomethoxyethyl 12bα-indolo (2,3-a) quinolizine used as starting product for preparing (+) vincamine, is obtained by saponification of 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethyl 4-oxo indolo (2,3-a) quinolizine, separation of the cis and trans isomers of 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carboxyethyl 4-oxo indolo (2,3-a) quinolizine, resolution of the cis isomer into its optical antipodes by means of an optically active base, isolation of the enantiometer 1,2,3,4,6,7,12,12b-octahydro 1α-ethyl 1β-carboxyethyl 4-oxo 12bα-indolo (2,3-a) quinolizine, esterification of this latter into 1,2,3,4,6,7,12,12b-octahydro 1α-ethyl 1β-carbomethoxyethyl 4-oxo 12bα-indolo (2,3-a) quinolizine, reaction of this with phosphorus pentasulphide to form 1,2,3,4,6,7,12,12b-actahydro 1α-ethyl 1β-carbomethoxyethyl 4-thioxo 12bα-indolo (2,3-a) quinolizine, and treatment of this latter with a desulphidation agent.

The process which has just been mentioned is effected preferably according to the following methods of performance:

(a) Saponification is effected according to the usual methods, by the action of an alkali-metal hydroxide, for example caustic soda or caustic potash.

(b) Separation of the cis and trans epimers is effected according to the usual physical methods, for example by simple fractionated crystallization. This separation can conveniently be carried out on the mixture of alkaline salts obtained by saponification, before liberation of the carboxyl group by acid treatment.

If one uses for example caustic soda as saponification agent, the epimeric sodium salts obtained can be separated by crystallization of one of the epimers in ethanol or in a mixture of ethanol and water, such as 95% ethanol.

(c) The optically active base is for example 1-ephedrine, d-ephidrine, quinine, (d) α-phenyl ethylamine, cinchonine, D(−) or L(+) threo 1-p-nitrophenyl 2-N,N-dimethylamino propane 1,3-diol, L(+) threo 1-p-nitrophenylamino propane-1,3-diol or L(−) threo 5-amino 6-phenyl 1,3-dioxan.

(d) Esterification of the optically active acid obtained is effected with methanol in the presence of a mineral acid, such as hydrochloric or sulphuric acid as catalyst. This esterification can likewise be effected with diazomethane.

(e) The desulphidation reaction is effected by means of Raney nickel.

The following examples illustrate the invention without giving it any limitative character.

PREPARATION I: 1,2,3,4,6,7,12,12B-OCTAHYDRO 1-ETHYL 1-CARBOMETHOXYETHYLINDOLO (2,3-A) QUINOLIZINE

Stage A: 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethyl 4-oxo indolo (2,3-a) quinolizine

One takes to reflux a mixture of 231.5 g. of tryptamine, 371 g. of dimethyl 4-ethyl 4-formyl pimelate obtained according to the process described in [J. Am. Chem. Soc. 86 (1964), 2946] and 1160 cc. of benzene; one maintains reflux for one hour while eliminating the water formed by azeotropy and distills the solution to dryness in vacuo at 50° C.; one takes up the residue with 463 cc. of acetic acid, heats at reflux for one hour thirty minutes and distills to dryness; one pours the residue into a mixture of 3000 cc. of water-ice and 231 cc. of soda lye; one extracts with methylene chloride, washes the organic phases with water, reextracts the mother washing waters with methylene chloride, dries the combined organic phases on magnesium sulphate, filters and distills to dryness; one takes up the residue with ethyl acetate, ice-cools for one night, suction-filters, washes with iced ethyl acetate and dries; one obtains 366.2 g. of 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethyl 4-oxo indolo (2,3-a) quinolizine. M.P.=135–140° C. Solvation: 5.3‰.

One evaporates the mother liquors of ethyl acetate to dryness, takes up the residue with 200 cc. of acetic acid, heats at reflux for two hours, evaporates to dryness and pours the residue into a mixture of 2000 cc. of water-ice and 50 cc. of soda lye; one extracts with methylene chloride, washes the organic phases with water, dries on magnesium sulphate and distills to dryness; one takes up the residue with ethyl acetate, ice-cools for four hours, suction-filters, washes with iced ethyl acetate and dries; one obtains a 2nd yield of 85.4 g.

Stage B: 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethylindolo (2,3-a) quinolizine

One puts in suspensions, under agitation and under nitrogen, 250 g. of 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethyl 4-oxo indolo (2,3-a) quinolizine in 2500 cc. of tetrahydrofuran, adds 172.5 g. of phosphorus pentasulphide and continues agitation for four hours at 25–27° C.; one filters, rinses the filter with tetrahydrofuran. One thus obtains solution A.

One washes 1.250 kg. of Raney nickel with tetrahydrofuran, to eliminate the water, by pasting under agitation: one leaves to decant and eliminates the supernatant liquid. To the suspension of Raney nickel thus prepared one adds the preceding tetrahydrofuranic solution A under agitation and under nitrogen, keeping the temperature at 25° C.; one leaves in contact for one hour thirty minutes, decants the tetrahydrofuranic phase, washes the nickel with tetrahydrofuran, distills the combined organic phases in vacuo and dries the residue at 60° C.; one collects 181 g. of a mixture of 2 isomers. One recrystallizes 176.5 g. of this mixture in 3150 cc. of boiling methanol, filters, cools to 20° C. under agitation and leaves the mixture for five hours at 20° C. One suction-filters and dries; one obtains 68 g. of trans derivative of 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethylindolo (2,3-a) quinolizine, melting at 149° C., which will be used in the preparation of isovincamine.

One concentrates the mother liquors and cools to 20° C., leaves for two hours at this temperature, suction-filters, recrystallizes the precipitate in 600 cc. of boiling methanol, returns to ambient temperature, suction-filters and dries at 40° C.; one obtains 45.8 g. of cis derivative 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethylindolo (2,3-a) quinolizine, melting at 140° C., which will be used for the preparation of vincamine.

For analysis, one recrystallizes the 2 products in cyclohexane and desolvates with boiling water.

The trans derivative of 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethylindolo (2,3-a) quinolizine is in the form of a solid colourless product, melting at 149° C.

Analysis.—$C_{21}H_{28}O_2N_2$=340.45. Calculated (percent): C, 74.08; H, 8.28; N, 8.23. Found (percent): C, 73.9; H, 8.3; N, 8.4.

I.R. spectrum

Presence of C=O at 1718 and 1740 cm.$^{-1}$ and NH (complex) at 3495, 3436 and 3355 cm.$^{-1}$.

The cis derivative of 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethylindolo (2,3-a) quinolizine is also in the form of a solid product, melting at 140° C.

Analysis.—$C_{21}H_{28}O_2N_2$=340.45. Calculated (percent): C, 74.08; H, 8.28; N, 8.23. Found (percent): C, 74.3; H, 8.4; N, 8.5.

I.R. spectrum

Presence of C=O at 1727 and 1736 cm.$^{-1}$ and NH at 3498 cm.$^{-1}$.

PREPARATION II: 1,2,3,4,6,7,12,12B-OCTAHYDRO 1α-ETHYL 1β-CARBOMETHOXYETHYL 12Bα-INDOLO (2,3-A) QUINOLIZINE

Stage A: 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carboxyethyl 4-oxo indolo (2,3-a) quinolizine—separation of the cis and trans isomers

One heats at reflux for one hour, while agitating, a mixture of 700 g. of 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethyl 4-oxo indolo (2,3-a) quinolizine (obtained according to the process described in Stage A of Preparation I), 158 g. of caustic soda (pastilles) and 2.8 litres of 95% ethanol. One filters the boiling suspension, and washes the precipitate twice with 350 cc. of boiling 95% ethanol.

Treatment of the filtrate—Obtaining the cis isomer

One eliminates the solvent by distillation. One adds 2.8 litres of water to the oily residue obtained. One distills about 300 cc. of the mixture to eliminate the ethanol totally.

The solution obtained is cooled to 20° C. One adds 1.975 litres of 2 N hydrochloric acid. One agitates for two hours at about 20–24° C.

One separates the precipitate by filtration, washes it with water and dries it.

By recrystallization in methanol, one obtains cis 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carboxyethyl 4-oxo indolo (2,3-a) quinolizine, with a yield of about 45%, being 90% with respect to the cis isomer contained in the starting product. M.P.=264° C.

Analysis.—$C_{20}H_{24}N_2O_3$=340.41. Calculated (percent): C, 70.56; H, 7.10; N, 8.23. Found (percent): C, 70.6; H, 7.2; N, 8.3.

Treatment of the precipitate—Obtaining the trans isomer

The precipitate is taken up with water and acidified with N hydrochloric acid until pH=1. One isolates, by filtration and recrystallization in methanol, trans 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carboxyethyl 4-oxo indolo (2,3-a) quinolizine. M.P.=254° C.

Analysis.—$C_{20}H_{24}N_2O_3$=340.41. Calculated (percent): C, 70.56; H, 7.10; N, 8.23. Found (percent): C, 70.6; H, 7.2; N, 8.4.

Stage B: Resolution of cis 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carboxyethyl 4-oxo indolo (2,3-a) quinolizine

One prepares a solution containing 263 g. of 1-ephedrine in 1.45 litres of dichlorethane. One adds 525 g. of the cis isomer obtained in the preceding stage, then 380 cc. of dichlorethane. One takes to reflux while agitating and distills about 380 cc. of dichlorethane. One cools to about 25° C., starts crystallization by scraping, and leaves for twenty hours at 20° C.

The precipitate obtained is separated by filtration.

Treatment of the precipitate

The precipitate is a dextrorotatory salt

$$[\alpha]_D^{20}=+137°\pm3°$$

(c.=1%, dimethylformamide) which, by treatment with a hydrochloric solution, leads to the corresponding dextrorotatory acid; $[\alpha]_D^{20}=+235°\pm3°$ (c.=1%, dimethylformamide); M.P.=about 293° C.

Treatment of the filtrate

One adds to the filtrate 390 cc. of an aqueous solution containing 130 cc. of concentrated hydrochloric acid. The mixture is agitated for two and a half hours at a temperature in the region of 20° C. one separates by filtration the precipitate thus formed and obtains 157 g. of a levorotatory acid which is (−)cis 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carboxyethyl 4-oxo indolo (2,3-a) quinolizine. M.P.=about 293° C. (differential thermal analysis) $[\alpha]_D^{20}=-235°$ (c.=1%, dimethylformamide).

Comparison of the curves of circular dichroism with those of (+) vincamine (optically active vincamine of natural origin) has allowed of concluding that this levorotatory isomer possesses a configuration analogous to that of (+) vincamine.

The levorotatory isomer obtained above is thus 1,2,3,4,6,7,12,12b-octahydro 1α-ethyl 1β-carboxyethyl 4-oxo 12bα-indolo (2,3-a) quinolizine, and the dextrorotatory isomer ($[\alpha]_D=+235°$) is thus 1,2,3,4,6,7,12,12b-octahydro 1β-ethyl 1α-carboxyethyl 4-oxo 12bβ-indolo (2,3-a) quinolizine.

The mother liquors of filtration of the levorotatory isomer are evaporated to dryness. The residue recrystallized in ethanol is constituted of 159 g. of starting racemic acid which one can again resolve.

The rotatory power of the 1-ephedrine salt of 1,2,3,4,6,7,12,12b-octahydro 1α-ethyl 1β-carboxyethyl 4-oxo 12α-indolo (2,3-a) quinolizine, is characterized by:

$$[\alpha]_D^{20}=-154°$$

(c.=1%, dimethylformamide).

If one effects resolution with d-ephedrine instead of 1-ephedrine, the least soluble salt is this time the levorotatory acid salt, that is to say the d-ephedrine salt of 1,2,3,4,6,7,12,12b-octahydro 1α-ethyl 1β-carboxyethyl 4-oxo 12bα-indolo (2,3-a) quinolizine, characterized by its rotatory power $[\alpha]_D^{20}=-137°\pm3°$ (c.=1%, dimethylformamide).

The treatment of this salt with a hydrochloric solution leads to 1,2,3,4,6,7,12,12b-octahydro 1α-ethyl 1β-carboxyethyl 4-oxo 12bα-indolo (2,3-a) quinolizine, identical to the product obtained above.

As far as is known, these compounds are not described in the literature.

Stage C: 1,2,3,4,6,7,12,12b-octahydro 1α-ethyl 1β-carbomethoxyethyl 4-oxo 12bα-indolo (2,3-a) quinolizine

One introduces 32.4 g. of levorotatory isomer obtained in the preceding stage in 130 cc. of methanol containing 4 g./litres of sulphuric acid. One heats at reflux while agitating under an atmosphere of nitrogen for two hours. One cools to 25° C. and neutralizes by the addition of 1.2 cc. of pyridine.

One slowly adds, while agitating, 1300 cc. of water. The precipitate is separated by filtration, washed with water and dried.

One obtains 33.35 g. of 1,2,3,4,6,7,12,12b-octahydro 1α-ethyl 1β-carbomethoxyethyl 4-oxo 12bα-indolo (2,3-a) quinolizine. $[\alpha]_D^{20}=-205°\pm3.5°$ (c.=0.5%, ethanol), $[\alpha]_D^{20}=-212°\pm1.5°$ (c.=1%, dimethylformamide) M.P.=152° then 161° C. (Kofler).

Analysis.—$C_{21}H_{26}N_2O_3$=354.44. Calculated (percent): C, 71.17; H, 7.39; N, 7.90. Found (percent): C, 71.1; H, 7.4; N, 7.9.

As far as is known, these compounds are not described in the literature.

Stage D: 1,2,3,4,6,7,12,12b-octahydro 1α-ethyl 1β-carbomethoxyethyl 12bα-indolo (2,3-a) quinolizine

200 g. of the product obtained in the preceding stage are put in suspension in 2 litres of tetrahydrofuran. One adds 138 g. of phosphorus pentasulphide. One agitates for 4 hours under an atmosphere of nitrogen, while keeping the temperature in the region of 25° C.

One filters and rinses the filter with tetrahydrofuran.

The filtrate obtained is a solution of 1,2,3,4,6,7,12,12b-octahydro 1α-ethyl 1β-carbomethoxyethyl 4-thioxo 12bα-indolo (2,3-a) quinolizine; $[\alpha]_D^{20}=-204°$ (c.=1%, dimethylformamide). Saponification index=157 mg. KOH/g. (theory: 151). Sulphur content=8.75% (theory 8.65%).

This product is characterized in fine-zone chromatography by R_f=0.7.

As far as is known, this compound is not described in the literature.

The filtrate is added slowly to 1 kg. of Raney nickel (previously washed with tetrahydrofuran), while agitating under an atmosphere of nitrogen, at about 25° C. One leaves in contact for one and a half hours after the end of the addition of the filtrate. One separates the nickel by filtration. The filtrate is evaporated to dryness in vacuo. One obtains 173 g. of 1,2,3,4,6,7,12b-octahydro 1α-ethyl 1β-carbomethoxyethyl 12bα-indolo (2,3-a) quinolizine.

This product is characterized in fine-zone chromatography by $R_f\simeq0.39$.

As far as is known, this compound is not described in the literature.

PREPARATION III: 1,2,3,4,6,7,12,12B-OCTAHYDRO 1β-ETHYL 1α-CARBOMETHOXYETHYL 12Bβ-INDOLO (2,3-A) QUINOLIZINE

Starting with 1,2,3,4,6,7,12,12b-octahydro 1β-ethyl 1α-carboxyethyl 4-oxo 12bβ-indolo (2,3-a) quinolizine (obtained in stage B of Preparation II), by applying the process described in stages C and D of Preparation II, one obtains successively:

1,2,3,4,6,7,12,12b-octahydro 1β-ethyl 1α-carbomethoxyethyl 4-oxo 12bβ-indolo (2,3-a) quinolizine

1,2,3,4,6,7,12,12b-octahydro 1β-ethyl 1α-carbomethyethyl 4-thioxo 12bβ-indolo (2,3-a) quinolizine

1,2,3,4,6,7,12,12b-octahydro 1β-ethyl 1α-carbomethoxyethyl 12bβ-indolo (2,3-a) quinolizine.

As far as is known, these compounds are not described in the literature.

EXAMPLE I: dl-VINCAMINE

Stage A: 14-oxo E-homo-eburnane, dl, cis isomer

One dissolves 10 g. of the cis derivative of 1,2,3,4,6,7, 12,12b - octahydro 1 - ethyl 1-carbomethoxyethylindolo (2,3-a) quinolizine (obtained according to the process described in stage B of Preparation I) in 140 cc. of a solution of sodium t-amylate in toluene titrating 1.45 g. of sodium per 100 cc., under agitation and under nitrogen; one agitates for ten minutes at 21–22° C., pours in a solution of 10 g. of ammonium chloride in 300 cc. of water, extracts with toluene, washes the organic phases with water, dries on sodium sulphate and distills to dryness; one takes up the residue with 30 cc. of ether, suction-filters, washes with ether and dries; one obtains 6.43 g. of 14-oxo E-homo-eburnane, dl, cis isomer, in the form of a solid colourless product, melting at 164° C. (yield: 71%).

Analysis.—$C_{20}H_{24}ON_2$=308.4. Calculated (percent): C, 77.88; H, 7.84; N, 9.08. Found (percent): C, 77.7; H, 7.8; N, 9.0.

I.R. spectrum

Presence of C=O

U.V. spectrum, ethanol

Max. at 242 mμ $E^{1\%}_{1cm.}$=538

Max. at 268–269 mμ $E^{1\%}_{1cm.}$=351

Infl. at about 273 mμ $E^{1\%}_{1cm.}$=337

Max. at 292 mμ $E^{1\%}_{1cm.}$=163

Max. at 301 mμ $E^{1\%}_{1cm.}$=153

As far as is known, this compound is not described in the literature.

Stage B: 14-oxo 15-hydroximino E-homo-eburnane, dl, cis isomer

One mixes 12.2 g. of 14-oxo E-homo-eburnane, dl, cis isomer, 80.5 cc. of toluene and 36.6 cc. of t-butyl nitrite, adds 80.5 cc. of a solution of sodium t-amylate in toluene titrating 1.7 g. of sodium per 100 cc. and leaves in contact for one hour, at 24–26° C., under nitrogen; one pours the reaction mixture into a solution of 25 g. of ammonium chloride in 300 cc. of water; one extracts with toluene, washes the organic phases with water, dries on sodium sulphate and distills to dryness in vacuo; one pastes the residue with ether, suction-filters, washes with ether and dries; one obtains 7.8 g. of 14-oxo 15-hydroxyimino E-homo-eburnane, dl, cis isomer. By evaporation of the mother liquors and recrystallization in ether, one obtains a second crop of 0.375 g. of the compound.

This compound is in the form of a solid colourless product, melting at 260° C.

Analysis.—$C_{20}H_{23}O_3N_3$=337.4. Calculated (percent): C, 71.19; H, 6.87; N, 12.44. Found (percent): C, 71.1; H, 6.8; N, 12.8.

U.V. spectrum

(1) Ethanol

Max. at 217 mμ $E^{1\%}_{1cm.}$=507

Max. at 259 mμ $E^{1\%}_{1cm.}$=556

Max. at 307 mμ $E^{1\%}_{1cm.}$=133

(2) Ethanol—HCl N/10

Max. at 216 mμ $E^{1\%}_{1cm.}$=551

Infl. at about 200 mμ $E^{1\%}_{1cm.}$=509

Max. at 254 mμ $E^{1\%}_{1cm.}$=588

Max. at 307 mμ $E^{1\%}_{1cm.}$=165

As far as is known, this compound is not described in the literature.

Stage C: 14,15-dioxo E-homo-eburnane, dl, cis isomer

One dissolves 6.78 g. of 14-oxo 15-hydroximino E-homo-eburnane dl, cis isomer, in 34 cc. of 40% formic aldehyde, 17 cc. of water and 17 cc. of hydrochloric acid, heats the solution at 75° C. for fifteen minutes and cools; one alkalizes by the addition of ammonia, extracts with methylene chloride, washes the organic phases with water, dries on sodium sulphate and distills to dryness; one purifies by chromatography and recrystallization in ether; one obtains 1.38 g. of 14,15-dioxo E-homo-eburnane, dl, cis isomer, in the form of a solid yellow product, melting at 158° C.

Analysis.—$C_{20}H_{22}O_2N_2$=322.50. Calculated (percent): C, 74.50; H, 6.87; N, 8.69. Found (percent): C, 74.3; H, 7.1; N, 8.5.

U.V. spectrum, ethanol

Infl. at about 224 mμ $E^{1\%}_{1cm.}$=343

Max. at 255 mμ $E^{1\%}_{1cm.}$=459

Max. at 305 mμ $E^{1\%}_{1cm.}$=123

I.R. spectrum

Absence of OH.

Presence of C=O at 1728 and 1690 cm.$^{-1}$.

As far as is known, this compound is not described in the literature.

Stage D: dl-vincamine

One dissolves 0.25 g. of sodium in 50 cc. of methanol, brings the solution back to 25° C. and adds 0.50 g. of 14,15 - dioxo E-homo-eburnane, dl, cis isomer, under nitrogen; one leaves in contact for one hour at ambient temperature, neutralizes by the addition of 0.65 cc. of acetic acid, distills the methanol in vacuo and takes up the residue with water; one suction-filters, washes with water and dries at 60° C.; one obtains 0.471 g. of dl-vincamine in the form of a solid colourless product, melting at 265° (Koffler block) and at 239.5° C. by differential thermal analysis.

Analysis.—$C_{21}H_{26}O_3N_2$=354.44. Calculated (percent): C, 71.15; H, 6.39; N, 7.90. Found (percent): C, 70.9; H, 7.4; N, 7.9.

N.M.R. spectrum

Triplet of the ethyl at 46, 53 and 61 Hz.

$COOCH_3$ at 229.5 Hz.

Angular proton at 234 Hz.

OH at 275 Hz.

Aromatic at 426, 429 and 449 Hz.

The mass spectrum as well as the I.R. spectrum agree with those of natural vincamine.

EXAMPLE II: DL-ISO-VINCAMINE

Stage A: 14-oxo E-homo-eburnane, dl, trans isomer

One puts in suspension in 200 cc. of tetrahydrofuran 4.2 g. of sodium hydride (50%) in mineral oil and agitates for ten minutes at ambient temperature; one adds 20 g. of trans derivative of 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethylindolo (2,3-a) quinolizine obtained according to the process described in Stage B of Preparation I, and 400 cc. of tetrahydrofuran and agitates for fifteen minutes at 25° C.; one obtains a solution of 14-oxo E-homo-eburnane, trans isomer, which one uses it is in the following stage.

In order to isolate the product, one pours the solution obtained above into an aqueous 40‰ solution of ammonium chloride, evaporates the tetrahydrofuran in vacuo, extracts with methylene chloride, dries the organic phases on sodium sulphate and distills to dryness; one takes up the residue with 50 cc. of methanol, evaporates to dryness, pastes the residue with 60 cc. of methanol, leaves in contact for two hours, suction-filters and dries at 60° C.; one purifies the product by dissolution in methylene chloride and precipitation by the addition of methanol; after drying at 40° C., one obtains 13.4 g. of 14-oxo E-

homo-eburnane, dl, trans isomer, in the form of a colourless product, melting at 132° C.

Analysis.—$C_{20}H_{24}ON_2$=308.4. Calculated (percent): C, 77.88; H, 7.84; N, 9.08. Found (percent): C, 77.6; H, 7.8; N, 9.1.

U.V. spectrum

(1) Ethanol

Max. at 242 $E^{1\%}_{1cm.}$=563

Max. at 267 mμ $E^{1\%}_{1cm.}$=351

Infl. at about 273 mμ $E^{1\%}_{1cm.}$=327

Max. at 293 mμ $E^{1\%}_{1cm.}$=154

Max. at 301 mμ $E^{1\%}_{1cm.}$=150

(2) Ethanol HCl N/10

Max. at 240–241 mμ $E^{1\%}_{1cm.}$=565

Max. at 264 mμ $E^{1\%}_{1cm.}$=349

Infl. at about 269–270 mμ $E^{1\%}_{1cm.}$=323

Max. at 290 mμ $E^{1\%}_{1cm.}$=182

Max. at 299 mμ $E^{1\%}_{1cm.}$=181

As far as is known, this compound is not described in the literature.

Stage B: 14-oxo 15-hydroximino E-homo-eburnane, dl, trans isomer

To the tetrahydrofuranic solution of 14-oxo E-homo-eburnane, dl, trans isomer, obtained in Stage A, one adds 60 cc. of t-butyl nitrite and leaves in contact for one hour fifteen minutes, under nitrogen and at 25° C.; one pours the reaction mixture in a solution of 40 g. of ammonium chloride in 1500 cc. of water, agitates for several minutes and evaporates the tetrahydrofuran in vacuo; one extracts with methylene chloride, washes the organic phases with water, dries on magnesium sulphate and distills to dryness in vacuo; one takes up the residue with 50 cc. of methanol, evaporates to dryness, pastes the residue with 100 cc. of methanol, leaves for 2 days in a refrigerator, suction-filters, washes with cold methanol and dries; one collects 10.45 g. of crude product which one purifies by recrystallization in ethanol at 24° C.; after drying, one obtains 14-oxo 15-hydroximino E-homo-eburnane, dl, trans isomer, with a yield of crystallization of 57%.

The compound is in the form of a solid yellow product, melting at 226° C.

Analysis.—$C_{20}H_{23}O_2N_3$=337.4. Calculated (percent): C, 71.19; H, 6.87; N, 12.44. Found (percent): C, 70.9; H, 6.8; N, 12.4.

As far as is known, this compound is not described in the literature.

Stage C: 14,15-dioxo E-homo-eburnane, dl, trans isomer

One heats to 85° C. a mixture of 2 g. of 14-oxo 15-hydroximino E-homo-eburnane, dl, trans isomer, 10 cc. of 5 N hydrochloric acid and 10 cc. of 40% formic aldehyde for fifteen minutes; one pours the reaction mixture onto ice, brings to pH=10 by the addition of ammonia and extracts with methylene chloride; one filters, dries the organic phases on magnesium sulphate and evaporates to dryness; one chromatographs the residue on silica gel, elutes with a methylene chloride-acetone mixture (10–2) and evaporates to dryness; one obtains 1.15 g. of 14,15-dioxo E-homo-eburnane, dl, trans isomer, in the form of a solid yellow product, melting at 143° C.

U.V. spectrum

(1) Ethanol HCl N/10

Infl. at about 214 mμ $E^{1\%}_{1cm.}$=361

Max. at 249 mμ $E^{1\%}_{1cm.}$=354

Infl. at about 263 mμ $E^{1\%}_{1cm.}$=266

Max. at 289 mμ $E^{1\%}_{1cm.}$=125

Max. at 302 mμ $E^{1\%}_{1cm.}$=124

(2) Ethanol NaOH N/10

Max. at 229 mμ $E^{1\%}_{1cm.}$=811

Infl. at about 277 mμ $E^{1\%}_{1cm.}$=194

Max. at 282 mμ $E^{1\%}_{1cm.}$=199

Infl. at about 290 mμ $E^{1\%}_{1cm.}$=164

Max. at 335 mμ $E^{1\%}_{1cm.}$=15

As far as is known, this compound is not described in the literature.

Stage D: dl 3-iso vincaminic acid

One takes to reflux for eight hours under nitrogen 1.1 g. of 14,15-dioxo E-homo-eburnane, dl, trans isomer, 100 cc. of 95% alcohol and 10 g. of caustic potash in pastilles; one evaporates to dryness in vacuo, adds 60 g. of ice to the residue, neutralizes by the addition of 12 cc. of hydrochloric acid and 0.4 cc. of acetic acid and leaves at rest for two hours; one suction-filters, washes the residue with water and dries in an oven at 40° C.; one obtains 0.61 g. of dl, 3-iso vincaminic acid in the form of a solid colourless product, melting at 247° C.

I.R. spectrum, Nujol

OH/NH absorption—acid OH absorption—present of C=O at 1630 cm.$^{-1}$.

As far as is known, this compound is not described in the literature.

Stage E: dl-iso vincamine

To 2 cc. of a solution of diazomethane in methylene chloride one adds 3 mg. of dl 3-iso vincaminic acid and leaves in contact for fifteen minutes at ambient temperature; one destroys the excess diazomethane by the addition of acetic acid, evaporates to dryness in vacuo and obtains dl 3-iso vincamine in the form of a solid colourless product.

I.R. spectrum

Presence of C=O at 1730 and 1755 cm.$^{-1}$, C=C at 1638 cm.$^{-1}$, OH and —N< dl.-iso vincamine can again be obtained in the following way:

One heats at 85° C. for 15 minutes under nitrogen 0.50 g. of 14-oxo 15-hydroximino E-homo-eburnane, dl, trans isomer, 2.5 cc. of 5 N hydrochloric acid and 2.5 cc. of 40% formic aldehyde; one cools, adds ice and brings to pH=10 by the addition of ammonia; one extracts with methylene chloride, filters, dries the organic phases on magnesium sulphate, and distills to dryness; one takes up the residue with 25 cc. of a solution of sodium methylate in methanol titrating 5 g. of sodium per 100 cc. and leaves in contact for one hour under nitrogen at 25–27° C.; one destroys the excess sodium methylate by the addition of acetic acid, suction-filters, washes the residue with water and dries at 80° C.; one obtains 0.21 g. of dl-iso vincamine melting at 229° C.

Analysis.—$C_{21}H_{26}O_3N_2$=354.44. Calculated (percent): C, 71.15; H, 7.39; N, 7.90. Found (percent): C, 70.5; H, 7.2; N, 7.9.

I.R. spectrum

OH band, carbonyl, C=C, tertiary amine

EXAMPLE III: (+) vincamine

Stage A: 14-oxo-3α,16α(20)-E-homo-eburnane

One adds to 173 g. of 1,2,3,4,6,7,12,12b-octahydro 1α-ethyl 1β-carbomethoxyethyl 12bα-indolo (2,3-a) quinolizine (obtained according to the process described in stage D of Preparation II) 1025 cc. of a solution of sodium t-amylate in toluene titrating 19 g. of sodium per litre. One agitates the solution for fifteen minutes at 24–25° C. under an atmosphere of nitrogen. One then pours the solution into 1 litre of water containing 200 g. of ammonium chloride. One separates the organic phase and extracts the aqueous phase with toluene. One combines the organic phases, washes them with water until neutral, dries

them on magnesium sulphate and distills them to dryness in vacuo.

The residue is recrystallized in ethyl ether. One obtains 89.4 g. of optically active E-homo-eburnamonine, corresponding to the 14-oxo 3α,16α(20)-E-homo eburnane isomer.

The mother liquors are evaporated to dryness and undergo another treatment with sodium t-amylate. One thus obtains a second crop (23.25 g.) of 14-oxo 3α,16α(20)-E-homo eburnane, identical to the product of the first yield. M.P.=151° C.; $[\alpha]_D^{20}$: +17.5°±1° (c.=1%, dimethylformamide).

As far as is known, this compound is not described in the literature.

Stage B: 14-oxo 15-hydroxyimino 3α,16α(20)-E-homo-eburnane

One mixes 110 g. of 14-oxo 3α,16α(20)-E-homo-eburnane, 660 cc. of toluene and 440 cc. of t-butyl nitrite. One adds to the suspension obtained 670 cc. of a solution of sodium t-amylate in toluene titrating 19 g. of sodium per litre. One leaves in contact for one hour at 21–22° C., then pours the mixture into 5.5 litres of water containing 138 g. of ammonium chloride. One agitates for fifteen minutes, separates the toluene phase and extracts the aqueous phase with toluene. One combines the organic phases, washes them with water until neutral, dries them on magnesium sulphate and distills to drynes in vacuo. One obtains 14-oxo 15-hydroxyimino 3α,16α(20)-E-homo eburnane.

This product is characterized in fine-zone chromatography by R_f: 0.22. Kieselgel support (F 254), eluting: methylene chloride-acetone (5–1). For the purified product: $[\alpha]_D^{20}$: +55° (c.=1%, dimethylformamide).

I.R. spectrum

Presence of C=O
Presence of OH
Presence of C=C aromatic

U.V. spectrum (ethanol, HCl N/10)

Infl. at about 220 mμ $E_{1\,cm.}^{1\%}$=447
Max. 253.5 mμ $E_{1\,cm.}^{1\%}$=470
Max. 307 mμ $E_{1\,cm.}^{1\%}$=139

Circular dichroism

Δε 294: −3.8
Δε 260–262: +7.7
Δε 222–220: +6.2

As far as is known, this compound is not described in the literature.

Stage C: 14,15-dioxo 3α,16α(20)-E-homo-eburnane

One mixes the product obtained in the preceding stage with 600 cc. of 40% formol, 300 cc. of water and 300 cc. of hydrochloric acid. One heats at 75° C. under an atmosphere of nitrogen; while agitating for twenty minutes. The solution is then poured onto 2 kg. of ice. One neutralizes by the slow addition of 300 g. of sodium bicarbonate. One adds 500 cc. of methylene chloride, then 100 g. of sodium bicarbonate, agitates for fifteen minutes, and extracts with methylene chloride.

The organic phases are washed with water, and evaporated to dryness.

The residue is chromatographed on magnesium silicate and eluted with methylene chloride.

One obtains 30.8 g. of 14,15-dioxo 3α,16α(20)-E-homo eburnane. By elution with acetone, one then recovers 21.8 g. of starting product.

14,15-dioxo 3α,16α(20)-E-homo-eburnane has the following characteristics:

M.P.=118° C.

I.R. spectrum

Presence of C=O

U.V. spectrum (ethanol, HCl N/10)

Max. 244 mμ $E_{1\,cm.}^{1\%}$=477
Max. 262 mμ $E_{1\,cm.}^{1\%}$=324
Max. 293–294 mμ $E_{1\,cm.}^{1\%}$=163
Max. 301–302 mμ $E_{1\,cm.}^{1\%}$=170

Circular dichroism

Δε 302: +1.5
Δε 278: −0.9 (±20%)
Δε 255: +2.9 (±10%)
Δε 200–208: +4.1 (±30%)

As far as is known, this compound is not described in the literature.

Stage D: (+) vincamine

The product obtained in the preceding stage is put in suspension in 100 cc. of methanol, and the mixture is poured into a solution of 15 g. of sodium in 2.5 litres of methanol.

One agitates for one hour at about 25° C., under an atmosphere of nitrogen.

One decomposes the excess reagents by the addition of 37 cc. of acetic acid, concentrates by distillation until about 300 cc.

One cools to 25° C. and leaves in contact for thirty minutes at this temperature.

The precipitate thus formed is filtered, washed and dried. The crude vincamine obtained is purified by the formation of acetate then decomposition of acetate with triethylamine.

One obtains 22.8 g. of (+) vincamine. M.P. (instantaneous) =272° C. $[\alpha]_D^{20}$ =+41° (c.=1%, pyridine).

Analysis.—$C_{21}H_{26}N_2O_3$=354.44. Calculated (percent): C, 71.15; H, 7.39; N, 7.90. Found (percent): C, 70.9; H, 7.1; N, 7.9.

U.V. spectrum

Max. 220 mμ $E_{1\,cm.}^{1\%}$=893
Max. 268 mμ $E_{1\,cm.}^{1\%}$=242

This compound is identical to the vincamine extracted from Vinca Minor.

(+) Vincamine can also be obtained in the following way:

One treats 14,15-dioxo 3α,16α(20)-E-homo eburnane with a mixture of caustic potash and 95% ethyl alcohol. After seven hours of reflux, the mixture is evaporated to dryness, taken up with water, and neutralized at 0° C. by the addition of hydrochloric acid. One leaves to rest for several hours then separates by filtration the precipitate of 14β-hydroxy 14α-carboxy 3α,16α(20)- eburnane, or vincaminic acid, washes it with water and dries it. The vincaminic acid is then esterified with diazomethane, and one obtains (+) vincamine, identical to the product obtained above.

EXAMPLE IV:(−) VINCAMINE

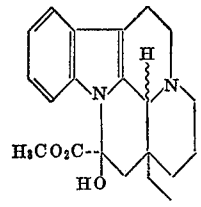
Starting with 1,2,3,4,6,7,12,12b-octahydro 1β-ethyl 1α-carbomethoxyethyl 12bβ-indolo (2,3-a) quinolizine (obtained in Preparation III), by applying the process described in Stages A—B—C—D of Example III, one obtains successively:

14-oxo 3β,16β(20)-E-homo-eburnane
14-oxo 15-hydroxyimino 3β,16β(20)-E-homo-eburnane
14,15-dioxo 3β,16β(20)-E-homo-eburnane
(−) vincamine.

As far as is known, the E-homo eburnanes above are not described in the literature.

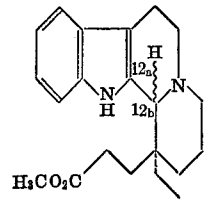
What is claimed is:

1. A process for preparing the pentacyclic compounds of general Formula I:



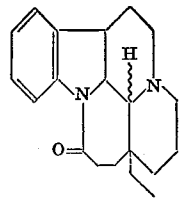
(I)

wherein one treats the tetracyclic compound of general Formula II:



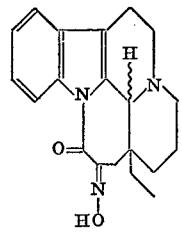
(II)

with a basic agent to obtain the lactamic compound of general Formula III:



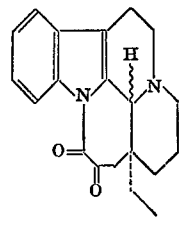
(III)

on which one causes a nitrosation reagent to react to obtain the hydroxyimino compound of general Formula IV:



(IV)

treats the said compound with a reagent for regeneration of a ketone starting from an oxime to obtain the di-oxo compound of general Formula V:



(V)

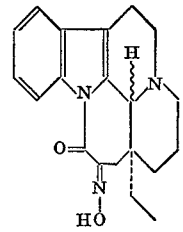
which one subjects to the action of an alkali-metal methylate.

2. The process of claim 1, for the preparation of dl-vincamine or an optically active vincamine, wherein one treats racemic or optically active cis 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethyl indolo (2,3-a) quinolizine with a basic agent to obtain the corresponding cis 14-oxo E-homo eburnane, causes a nitrosation reagent to react on this latter to form the corresponding cis 14-oxo 15-hydroxyimino E-homo eburnane, treats this with a reagent for regeneration of ketones starting from oximes, to obtain the corresponding cis 14,15-dioxo E-homo eburnane which one subjects to the action of an alkali-metal methylate.

3. The process of claim 1, for the preparation of dl-vincamine, wherein one treats racemic cis 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethyl indolo (2,3-a) quinolizine with a basic agent to obtain the corresponding cis 14-oxo E-homo eburane, causes a nitrosation reagent to react on this latter to form the corresponding cis 14-oxo 15 hydroxyimino E-homo eburnane, treats this with a reagent for regenerating ketones starting from oximes, to obtain the corresponding cis 14, 15-dioxo E-homo eburnane which one subjects to the action of an alkali-metal methylate.

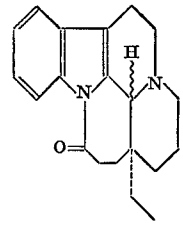
4. The process of claim 1, for the preparation of (+) vincamine, wherein one treats 1,2,3,4,6,7,12,12b-octahydro 1α-ethyl 1β-carbomethoxyethyl 12bα-indolo (2,3-a) quinolizine with a basic agent to obtain 14-oxo 3α,16α (20)-E-homo eburnane, causes this latter to react with a nitrosation reagent to form 14-oxo 15-hydroxyimino 3α, 16α(20)-E-homo eburnane, treats this with a reagent for regeneration of a ketone starting from an oxime, to obtain 14,15-dioxo 3α,16α(20)-E-homo eburnane which one subjects to the action of an alkali-metal methylate.

5. A process for preparing the hydroxyimino compounds of general Formula IV:



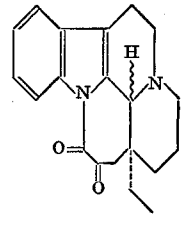
(IV)

wherein one causes a nitrosation reagent selected from the group consisting of an alkyl nitrite containing from 1 to 5 carbon atoms to react on the lactamic compound of general Formula III:



(III)

6. A process for preparing the pentacyclic compounds, I, wherein one treats the di-oxo compound of general Formula V:



(V)

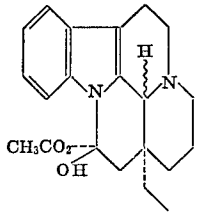
with an alkali-metal methylate.

7. In a process for the preparation of an optically active vincamine, the improvement wherein the starting product, an optically active cis 1,2,3,4,6,7,12,12b-octahydro 1 - ethyl 1 - carboxyethyl 4 - oxo indolo (2,3-a) quinolizine, is obtained by saponification of 1,2,3,4,6,7, 12,12b-octahydro 1 - ethyl 1 - carbomethoxyethyl 4-oxo indolo (2,3-a) quinolizine, separation of the cis and trans isomers of 1,2,3,4,6,7,12,12b - octahydro 1-ethyl 1 - carboxyethyl 4 - oxo indolo (2,3 - a) quinolizine, resolution of cis 1,2,3,4,6,7,12,12b-octahydro 1 - ethyl 1 - carboxyethyl 4 - oxo indolo (2,3-a) quinolizine into its optical antipodes by means of an optically active base, esterification of an enantiomer of cis 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carboxyethyl 4-oxo indolo (2,3-a) quinolizine into an enantiomer of cis 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethyl

4-oxo indolo (2,3-a) quinolizine, reaction of this latter with phosphorus pentasulphide to obtain the corresponding enantiomer of cis 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethyl 4-thioxo indolo (2,3-a) quinolizine, and desulphidation of this into a desired enantiomer of cis 1,2,3,4,6,7,12,12b-octahydro 1-ethyl 1-carbomethoxyethyl indolo (2,3-a) quinolizine.

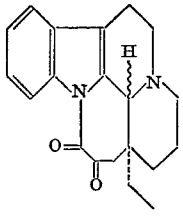
8. An E-homo-eburnane selected from the group consisting of 14-oxo E-homo-eburnane, 14-oxo 15-hydroxyimino E-homo-eburnane and 14,15-dioxo E-homo-eburnane.

9. A process for preparing a pentacyclic compound of general Formula I



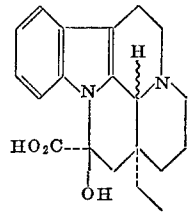
(I)

wherein one treats a di-oxo compound of general Formula V



V

with an acid agent or with a basic agent giving rise to hydroxyl ions to obtain an acid compound of general Formula VI:



VI

on which one causes to react a reagent for forming methyl esters.

10. The optically active enantiomer of the E-homo-eburnane of claim **9** wherein the junction of the D and E rings is cis.

References Cited

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HENRY R. JILES, Primary Examiner

G. T. TODD, Assistant Examiner

U.S. Cl. X.R.

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