Tetrahedron Vol. 41, No. 23, pp. 5553 to 5561, 1985
Printed in Great Britain.

0040-4020/85 $3.00+.00

SYNTHESIS AND ^{1}H NMR STUDY OF 3,4-DIETHYL-1,2,3,3A,4,5-HEXAHYDRO-CANTHINONE-6

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(*Received in UK* 27 *June* 1985)

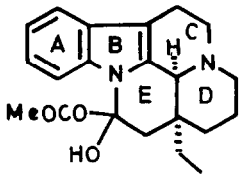
ABSTRACT

The racemic mixtures of the two epimers of 3,4-diethyl-1,2,3,3a,4,5-hexahydro-canthinone-6 (3,4-diethyl-2,3,3a,4,5,6-hexahydro-6-oxo-1H-indolo- (3,2,1,de)(1,5)naphtyridine) have been prepared. They were separated by crystallization of one of the synthesis intermediates. Identification of the configuration was possible by ^{1}H NMR spectroscopy after running a 2D J- resolved spectrum of the "cis"-isomer.

INTRODUCTION

The therapeutic qualities of vicamine (1), vincamone (2) and vincamate methyl ester (3) are well recognized[1].

This knowledge inspired us to prepare new compounds with a similar structure, in order to check their possible pharmaceutic properties. Thus we found that 3,4-diethyl-1,2,3,3a,4,5-hexahydro-canthinone-6 (4)[2], a structure close to vincamone (2) but without the D-ring, showed interesting properties concerning hemodynamic action and cerebral metabolism. In the present study we describe the synthesis of this compound, the separation into two racemic mixtures, as well as the identification of the cis and trans modifications by ^{1}H NMR spectroscopy. Throughout this study cis and trans refer to the disposition of the protons at H-3a and H-4.



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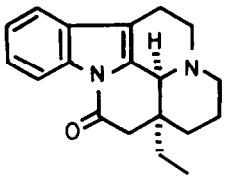

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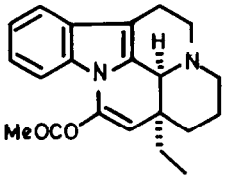

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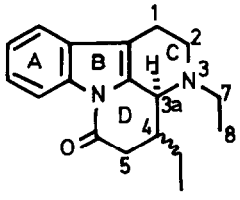

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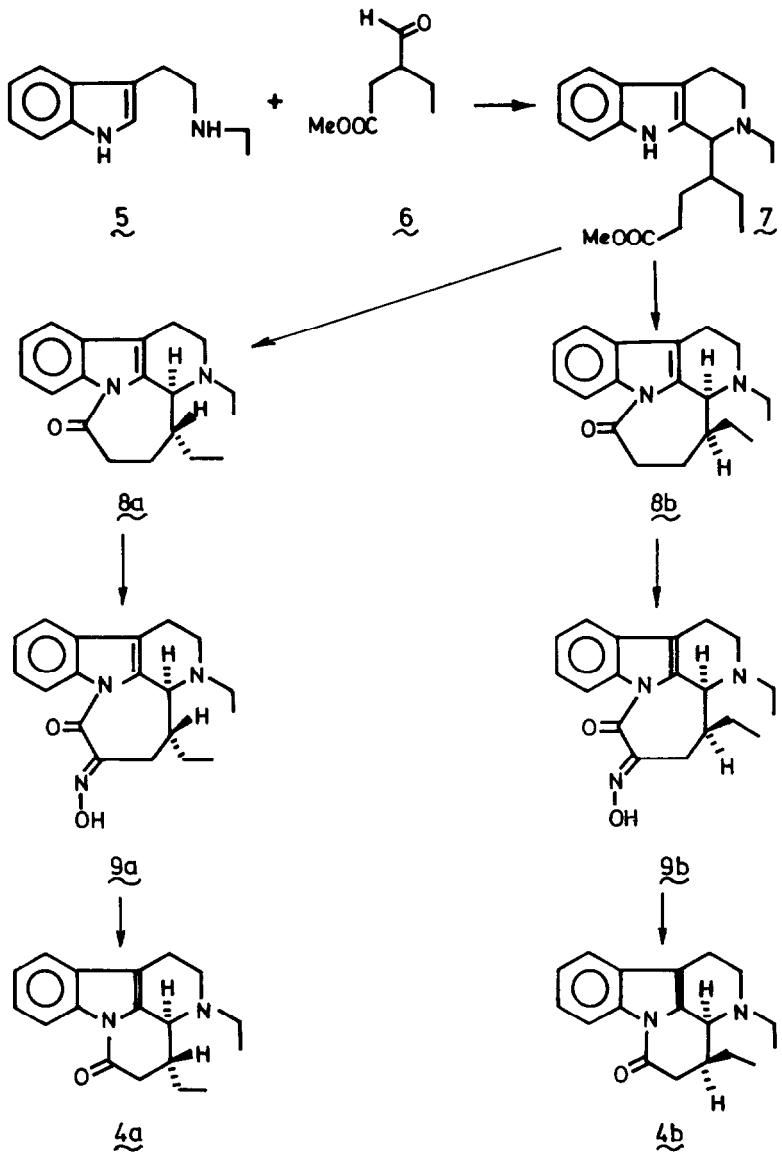
RESULTS AND DISCUSSION

SYNTHESIS

Many efforts have been undertaken in order to prepare the E ring in vincamine (1) and related derivatives. The progress in that work can be followed in the Specialist Periodical Reports "The Alkaloids"[3]. For the present study the work of Le Men et al.[4] is specifically interesting. They obtained eburnamonine [(-)vincamine] from the ring contraction of (-) homovincamone after a Beckmann rearrangment of the derived α-oxime compound[5]. Le Men and his coworkers synthesized compounds analogueous to vincamone, but without the D ring[6].

In the present study we have modified the procedure of Le Men et al. in order to obtain the present compounds. The successive reactions are represented in Scheme 1. First the tricyclic 2-ethyl-1-[(2-methoxycarbonyl-ethyl)-propyl]-1,2,3,4-tetrahydro-ß-carboline (7) was prepared from a reaction of ethyltryptamine (5) and 4-formyl-hexanoate methylester(6). The latter could be prepared from the condensation of 1-pyrrolidino-butene and methyl acrylate. The enamine was prepared by reaction between pyrrolidine and butyral. During the cyclisation to (7) a second chiral center is introduced. In a following step the fourth ring was introduced as a lactam between the ester group and the nitrogen of the indole system. In the scheme only one of the enantiomers is proposed. In fact two racemic mixtures (cis and trans) of D-homo-diethyl-hexahydro-canthinone are obtained. If 8a is the racemic mixture of the trans enantiomers then 8b is that of the corresponding cis enantiomers. On this phase of the reaction the two racemic mixtures could be separated by crystallization. Dissolved in ether the racemic mixture of the trans derivatives crystallizes readily. The racemic mixture of the cis-derivatives was recovered from the mother liquor. From this point on parallel reactions are applied on both the racemic mixtures . In the presence of tert.butylnitrite, oximation occurs in the position of the carbonyl function in 8a and 8b, yielding respectively the trans and cis modifications of D-homo-hydroxyiminodiethyl-hexahydro-canthinone 9a and 9b[7].



Scheme 1

Now a Beckmann rearrangement occurs[7], followed by a rearrangement causing the ringcontraction. Then 9a or 9b is first treated by ethoxyethanol, then the reaction mixture is treated with sodium hydroxyde and finally it is treated with 3 N HCl in order to yield the two racemic mixtures of trans and cis 3,4-diethyl-1,2,3,3a,4,5-hexahydro-canthinone-6 (4a and 4b respec-tively).

^{1}H NMR study

The relative configuration of the protons on C-3a and C-4 was assigned by ^{1}H NMR spectroscopy. The ^{1}H NMR data of both racemic mixtures are gathered in Table 1.Because of the complexity of the ^{1}H NMR spectrum of the cis isomer, a 2D J-resolved spectrum was run[8], which allowed to assign all the resonances in the region δ 2.20-3.00. In the F2

TABLE 1 : 3,4-Diethyl-1,2,3,3a,4,5-hexahydrocanthinone-6 (4a and 4b)

Chemical shifts ($CDCl_3$, TMS)

	H-1A	H-1B	H-2A	H-2B	H-3A	H-4	H-5A	H-5B	H-7A	H-7B	H-8	H-9A	H-9B	H-10
4a	2.76	2.42	3.53	3.08	3.83	2.14	2.92	2.39	2.51	2.38	1.17	1.98	1.31	1.02
											or 1.02			or 1.17
4b	2.80	2.64	3.29	2.52	3.55	2.32	2.88	2.72	2.94	2.42	1.16	2.09	0.86	0.89
											or 0.89			or 1.17

Coupling constants

	$^3J(1A,2A)$	$^3J(1A,2B)$	$^2J(1A,1B)$	$^3J(1B,2A)$	$^3J(1B,2B)$	$^2J(2A,2B)$	$^3J(3A,4)$
4a	4.2	10.8	16.4	1.6	5.0	14.4	11.6
4b	5.2	11.6	16.8	0.8	4.0	11.6	4.4
	$^5J(3A,1B)$	$^5J(3A,1A)$	$^3J(4,5A)$	$^3J(4,5B)$	$^2J(5A,5B)$	$^3J(4,9A)$	$^3J(4,9B)$
4a	2.0	2.8	3.6	12.4	16.4	2.8	9.2
4b	2.4	3.2	3.0	4.4	17.2	2.8	10.8
	$^2J(9A,9B)$	$^3J(9A,10)$	$^3J(9B,10)$	$^4J(5B,9A)$	$^2J(7A,7B)$	$^3J(7A,8)$	$^3J(7B,8)$
4a	14.4	7.6	7.6	1.2	12.4	7.2	7.2
4b	14.0	7.6	7.6	-	12.4	7.2	7.2

dimension the chemical shifts could be determined, while the coupling constants could be measured from the patterns in the F1 dimension (see Fig. 1). These data, together with the data from the less complex spectrum of the racemic mixture of the trans isomer provided the necessary information for discrimination between both compounds.

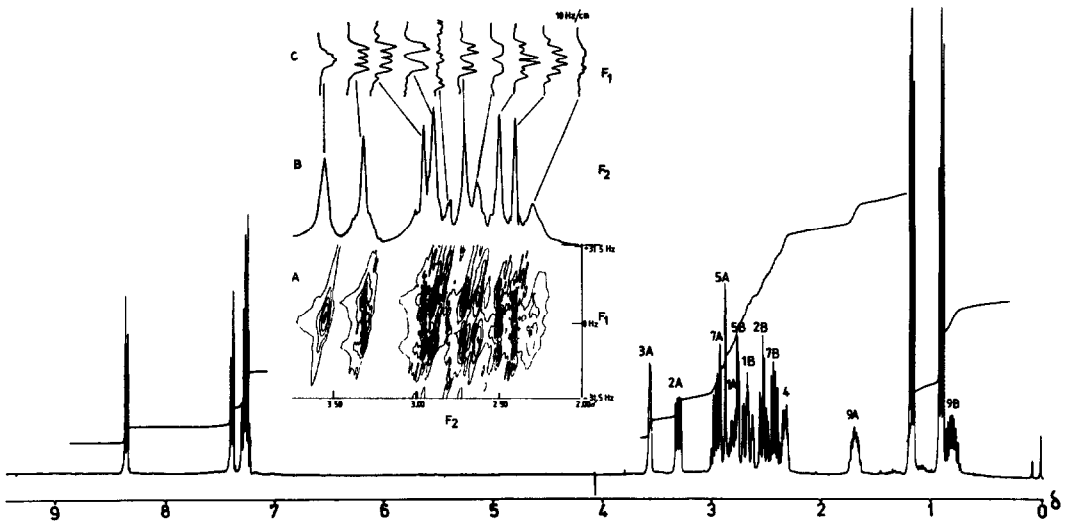


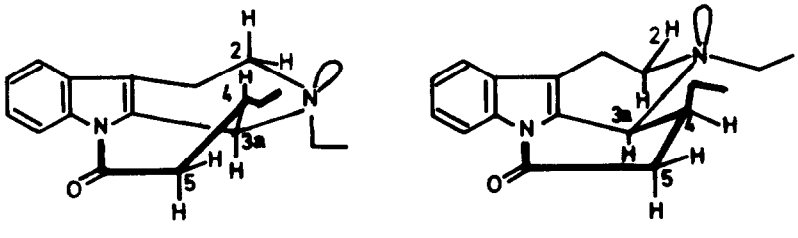
Fig. 1 : ^1H NMR Spectrum of cis-3,4-diethyl-1,2,3,3a,4,5-hexahydrocanthinone-6 in $CDCl_3$ solution
Inserts : 2 D J-resolved NMR spectroscopy.
A : The contour plot. B : The projection of the resonances in the F2 direction (region δ 2.00-δ4.00). C : The corresponding multiplets as found in the F1 direction (10Hz/cm).

From the geminal coupling constants it is possible to discriminate between the resonances of the protons on C-1 and C-5 on one hand and those on C-2 on the other. The Barfield-Grant effect [9] presumes that the coupling constant between the geminal protons in position of a system should be more negative than in a corresponding system without double bond ([16.2/17.4] Hz versus [12/13] Hz). The vicinal couplings of these resonances - those on C-5 belong to an ABX subspin system and those on C-1 to an ABXY subspin system - allow a certain discrimination between the protons on C-1 and C-5. Because of its implantation on the rigid system of the rings A and B and containing moreover a further sp^2 carbon (from the carbonyl group), the D ring in the tetracyclic ringsystem shows little flexibility. For the D ring a half chair conformation is highly probable. Here C-4 is outside the plane formed by the other 5 carbons. In this case the ethyl group on C-4 can only be in a pseudo-axial or pseudo-equatorial position. These are the only cases to be considered, because epimerization on C-3a gives an enantiomer of one of the cases under consideration. The rigid conformation of ring D allows the identification of the two isomers. Indeed from the coupling constants between H-4 and H-5, no doubt is left concerning the puckering.

In the case of 4b the vicinal coupling constant between H-4 and the two protons on C-5 are respectively 3.0 aand 4.4 Hz. That means that the projection of the bond C(4)-H(4) almost bisects the angle H(5A)-C(5)-H(5B), thus showing two times a dihydral angle of about 60°. As in this case the ethyl group on C-4 is pseudo-axial, an angle of about 60° must occur between H-3a and H-4, corresponding indeed with a value of 4.4 Hz. In this case it is evident that H-3a and H-4 are in a cis disposition.

For the other compound (4a) the ethyl group must be in a pseudo equatorial position. Here H-4 and H-5B are in a quasi-antiperiplanar disposition and therefore a value of 12.4 Hz is possible for the corresponding vicinal coupling. As the dihedral angle between H-4 and H-5a is 60° a coupling constant of 3.6 Hz is expected. In the rigid structure H-3a and H-4 must be antiperiplanar. A value of 11.6 Hz for the mutual coupling constant is expected. In 8a, H-3a and H-4 are trans.

The two structures 4a and 4b are shown in Fig. 2, illustrating the relative position of H-3a and H-4.



4a 4b

Fig. 2

Our proposal agrees with Le Men et al.[6]. In the corresponding 2 chano vincamines, where a cis-relationship is obtained between the protons on C-3a and C-4, they find 2-4 Hz.

More interesting features can be derived from the Table with the ^1H NMR data. The difference in values for $^2J(2A,2B)$ is striking.

If the proposed staggered configuration for the D ring is accepted, in the cis modification (4b) the ethyl group can take the equatorial position on the nitrogen of the C-ring. In this case the electron lobe of the nitrogen is parallel with one of the protons of C-2. A value of ~11 Hz[10] is expected for the geminal coupling constants between the protons on a neighbouring carbon. The coupling constants between H-4 and H-5 agree with a flattened conformation of the D ring, thus avoiding the parallelism between the electron lobe of the nitrogen on the C ring and the ethyl group on the D ring. However, in the trans modification this leads to the unfavorable synaxial disposition between the ethylgroup on C-4 and the ethyl group on the nitrogen of the C ring. Because of the staggered situation of the D-ring, the tension between the two ethyl groups can be avoided if the C ring accepts another conformation. In this case the parallelility between the electron lobe of the nitrogen and one of the protons of C-2 is lost, leading to coupling constant of ~14 Hz if the electron lobe of the nitrogen bisects the projection of the two protons on C-2[10], as in the conformation proposed in fig. 2.

Taking into consideration the syn upfield rule (which holds if compounds with the same conformations are compared, thus for the present compounds only for the D ring valuable conclusions can be drawn) the same conclusions can be drawn concerning the cis and trans modifications. From the vicinal coupling cosntants it can be concluded that in both compounds, the H-5 at the lowest field must be the pseudo-equatorial proton. In the cis modification now H-3A is syn to the ethylgroup, thus expected at a higher field than in the trans modification. In the trans modification H-5B is syn to the ethyl group, thus there H-5B is expected to be found at a higher field than in the cis modification.

EXPERIMENTAL

Melting points were determined on a Mettler FP 5 and are uncorrected. The UV spectra were run on a Perkin-Elmer Coleman 575 apparatus, the IR spectra on a Perkin-Elmer 197, the mass spectra on a VARIAN MAT 311 A apparatus. Except for the spectra of 4a and 4b, the ^1H NMR data were obtained from a Varian T60 apparatus.

The ^1H NMR spectra of 4a and 4b were run on a BRUKER WH360 apparatus, at 18°C, for 2 % solutions in $CDCl_3$ (F.T. mode, pulse width of 2 μsec, quadrature detection, resolution 0.208 Hz/point). The 2D J-resolved NMR experiment was performed with the Bruker FTNMR 2D program version 810515. Acquisition size in the F2 dimension : 2K points, in the F1 dimension : 14 points. We used zero-filling up to 4 K points in the F2 dimension and to 32 points in the F1 dimension. Blocks of 8 scans were accumulated. The 2D J resolved spectrum was plotted from 214.4 Hz to 917.6 Hz on the t2 axis and ± 31.5 Hz on the t1 axis. For this experiment the π pulse was explicitely measured to be 18.6 µsec.

1-pyrrolidino-butene

A mixture of 213 g (3 moles) pyrrolidine and 213 g (1,5 mole) potassium carbonate are shaken at 0°C under nitrogen. 108 g (1,5 mole) freshly distilled butyraldehyde is added

dropwise. After one night shaking at room temperature, the reaction mixture is diluted with 300 ml benzene and filtered. Vacuum destillation of the residue gave pure 1-pyrrolidine-butene (b.p. 88-94°, 70 mm Hg). Yield : 110 g (59 %).
NMR (CCl_4) : δ 6.00 (d, 1H), δ 4.00 (q, 1H), δ 1.00 (t, 3H).

4-formyl hexanoate methyl ester (6)
(6) is obtained from the condensation of 1-pyrrolidino-butene with methyl acrylate. A mixture of 31 g 1-pyrrolidino-butene and 150 ml acetonitrile is stirred at 0°C under nitrogen. A solution of 27 ml methyl acrylate in 50 mL acetonitrile is added dropwise. The stirring is continued during 6 hours at room temperature and then during 40 hours under refluxing. Then 15 ml acetic acid in 100 ml water is added in small portions. The refluxing is continued for another 8 hours. The mixture is allowed to cool and saturated with sodium chloride. The water phase is isolated and extracted with ether. The organic phases are gathered and distilled in vacuo. 4-formyl hexanoate methyl ester passes at 85°-90° C at 10 mm Hg. Yield : 54 %.
NMR (CCl_4) : δ 9.6 (s, 1H), δ 3.6 (s, 3H), δ 1.0 (t, 3H).

2-ethyl-1-(2-methoxycarbonyl-ethyl)-propyl-1,2,3,4-tetrahydro-ß-carboline (7)
50.7 g (0.27 mole) ethyltryptamine (5) and 38.78 g (0.245 mole) 4-formyl-hexanoate methylester (6) are added to a mixture of 500 ml benzene and 50 ml acetic acid. This solution is heated to reflux temperature in a Dean-Stark apparatus during 16 hours. The reaction mixture is allowed to cool and extracted with 2 % aqueous sulfuric acid. The acidic aqueous phase is made alkaline with ammonia and is extracted with methylene chloride. The methylene chloride phase is washed with water, dried and evaporated. The dry residue is again dissolved in a small quantity of methylene chloride and chromatographed on a column of 200 g Al_2O_3 (eluent : methylene chloride). Thus a fraction of 64 g (0.194 mole) of 7 is obtained (64 g; 79.4 %).
UV (λ nm, log ε) : 225 (4,54); 280 (3,9); 190 (3,81).
MS (m/z, %) : 328 (M^+, 100).
NMR (CCl_4) : δ 8.1 (broad s, 1H); δ 7.0-7.5 (m, 4H), δ 3.7 (s, 3H), δ 0.8-1.2 (m, 6H).
El. Anal. for $C_{20}H_{28}O_2N_2$, calc. (%) : C, 73.15; H, 8.59; N, 8.52. Found : C, 73.24; H, 8.56; N, 8.60.

Cis- and trans-D-homo-diethyl-hexahydro-canthinone (8a,8b)
50 g (0.56 mole) t.amyl alcohol is dissolved in 600 ml dry toluene. 22,4 g (0.56 mole) sodium hydride (dispersed in oil, 55-60 %) is added and the mixture is heated under reflux during 2 hours. The reaction mixture is cooled to room temperature and added to 55 g (0.185 mol) of 7. After 15 minutes this reaction mixture is poured in water. The organic phase is washed with water, dried and evaporated.
58,3 g white crystals are obtained. This is a mixture of cis and trans compounds. When dissolving these 58,3 g in 250 ml ether and shaking at roomtemperature, white crystals are obtained. 11 g of what shall be proved the be the cis modification (8b) could be isolated. The mother liquor is evaporated to dryness, and the residue is dissolved in a minimum quantity of methanol and more methanol saturated with gaseous hydrogenchloride is added to a pH < 7. 21 g of the trans isomer (8a) are obtained after crystallization.
Data for 8a (trans) :
IR ($CHCl_3$) : 2950; 1690; 1610; 1450; 1360; 1330; 1140.
UV (λ nm, log ε)(methanol) : 343 (4.28); 266 (4.06); 293 (3.74); 301 (3.74).
MS (m/z, %) : 296 (M^+, 100), 240, 198, 197, 183.
NMR (CCL_4) : δ 8.5 (1H); δ 7.2-7.3 (3H); δ 0.9-1.3 (6H).
El. Anal. for $C_{19}H_{24}O_1N_2$. Calc. (%) : C, 76.98; H, 8.16; N 9.44. Found : C, 76.88; H, 8.26; N, 9.50.
Data for 8b (cis)
IR ($CHCl_3$) : 2930, 1685, 1615, 1360.
UV (λ nm, log ε) (methanol) : 243 (4.27); 266 (4.02); 293 (3.63); 301 (3.62).
MS (m/z) : 296 (M^+); 281; 267; 240; 199; 198; 194; 184; 183; 169.
NMR (CCl_4) δ 8.6 (1H); δ 7.2-7.5 (3H); δ 3.9 (1H); δ 1.1 (3H); δ 0.8 (3H).
El. Anal. for $C_{19}H_{24}O_1N_2$. Calc. (%) : C, 76.98; H, 8.16; N 9.44. Found : C, 77;10; H, 8.22; N 9.48.

trans-3,4-diethyl-1,2,3,3a,4,5,6,7-octahydro-7-oxo-6-oxyimino-azepino(1,2,3,lm)-β-carboline (9a)

13,5 g (0,045 mole) of 8a is dissolved in 200 ml toluene. Successively 59,4 g (0,499 mole) tert butylnitrite and a suspension of 0,073 mole sodium tert.amylate in 150 ml toluene are added. The reaction mixture is stirred at room temperature during two hours and then poured in 550 ml of a 10 % aqueous ammoniumchloride solution. The organic phase is separated, washed with water and evaporated. 14.6 g of 9a is obtained (98 %). The chlorohydrate of this compound is obtained by dissolving 9a in a minimal quantity of acetone followed by the addition of ether saturated with hydrogenchloride, until pH < 7 is reached. 10.5 g of white crystals are obtained.

M.p. 264-265°C.

IR (film) : 3400; 2960; 1680; 1610; 1450; 1380; 1330; 1020; 750; 730.

UV (for hydrochloride, C = 5.33 x 10^5 mole/L, CH_3OH (λ max, log ε) : 258 (4.16), 3.13 (3.7).

MS (m/z) : 325 (M^+); 398, 396, 282, 268, 251, 226, 199, 198, 197, 169.

NMR (base, $CDCl_3$) : δ 8.4 (m, 1H), δ 7.0-7.4 (m, 3H), δ 3.5 (d, 1H).

$^3J(3a,4)$ = 11 Hz); 0.9-1.3 (m, 6H).

El. Anal. for $C_{19}H_{23}O_2N_3$. Calc. (%) : C, 70.12; H, 7.01; N, 13.03. Found : C, 70.21; H, 7.06; N, 13.11.

Cis-3,4-diethyl-1,2,3,3a,4,5,6,7-octahydro-7-oxo-6-oxyimino-azepino(1,2,3,lm)-β-carboline (9b)

The reaction is carried out under the same circumstances as for the trans derivative. 16 g of 9b is obtained and 11 g of the corresponding hydrochloride.

M.p. : 236°C.

IR (for base, film) : 3400, 2970; 1685; 1610; 1450; 1370; 1330; 910; 730.

UV (for hydrochloride, C = 2.73 x 10^{-5} mole/L, CH_3OH)(λ max, logε) : 257 (4.26), 308 (369).

MS (m/z) : 325 (M^+), 308, 296, 283, 268, 252, 239, 226, 214, 199, 198, 180, 167.

NMR (for base) ($CDCl_3$) : δ 8.4 (1H), δ 7.0-7.4 (m, 3H), δ 3.9 (d, 1H), J(3a,4) = 5 Hz), δ 0.8-1.3 (m, 6H).

El. Anal. for $C_{19}H_{23}O_2N_3$. Calc. (%) : C, 70.12; H, 7.01, N, 13.03. Found : C, 70.14; H, 7.08; N 13.14.

cis-3,4-diethyl-2,3,3a,4,5,6-hexahydro-6-oxo-1H-indolo(3,2,1,de)(1,5)naphtyridine (or cis-2,4-diethyl-1,2,3,3a,4,5-hexahydro-canthinone-6) 4b.

9,56 g (0.02461 mole) of 9b is mixed with 40 ml of ethoxyethanol (as a suspension). 3,17 (0.07925 mole) NaOH is added and the reaction mixture is stirred for 1 hour at roomtemperature and then refluxed for 18 hours. The reaction mixture is evaporated to dryness. The residue is dissolved in 50 ml 3 N HCl and further refluxed for 1 hour. The solution is cooled, made alkaline and extracted with CH_2Cl_2. The separated organic phase is stirred for 15 minutes in the presence of 100 g Al_2O_3. After filtration of the alumina, the filtrate is washed with water, dried and concentrated to dryness. 5,9 g (0.0208 mole) of a solid residue is obtained. It is dissolved in acetone in order to prepare the corresponding hydrochloride by stepwise addition of HCl saturated ether. Filtration yields 4.17 g of white crystals.

M.p. (hydrochloride) = 240-241°C.

IR (base)(film) : 2960, 1700, 1635, 1450, 1380, 1320, 1150, 910, 750 cm^{-1}.

UV (hydrochloride) (C = 3.13.10^{-5} mole/L, CH_3OH) (λ max, log ε) : 242 (4.30), 265 (4.00), 298-303 (3.59) nm.

MS (m/z) 282 (M^+), 281, 267, 253, 239, 225, 198, 197, 196, 167.

NMR : see Table 1.

El. Anal. for $C_{18}H_{22}O_1N_2$. Calcd (%) : C, 76.56; H, 7.85; N, 9.92. Found : C, 76.64; H, 7.96; N, 10.01.

trans-3,4-diethyl-2,3,3a,4,5,6-hexahydro-6-oxo-1H-indolo(3,2,1,de)(1,5)-naphtyridine (4a)

The same reactions are used as for 4b, but with 9.4((29 mmole) 9a and yielding 4 g of white crystals of the hydrochloride of 4a.

M.p. (hydrochloride) : 240-241°C.

IR (base)(film) : 2960, 1700, 1635, 1450, 1380, 1320, 1150, 910, 750.

UV (hydrochloride) (C = $3.14.10^{-5}$ mole/L, CH_3OH) (λ max, log ε) : 242 (4.29), 265 (3.99), 298-303 (3.59).
MS (m/z) : 282, 281, 267, 253, 225, 198, 197, 196, 182, 167, 154, 142.
NMR (base) ($CDCl_3$) : see Table 1.
El. Anal. for $C_{18}H_{22}O_1N_2$. Calc. (%) : C,76.56; H, 7.85; N, 9.92. Found : C, 76.67; H, 7.81; N, 9.96.

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