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TACAMINE, THE FIRST EXAMPLE OF A NEW CLASS OF INDOLE ALKALOIDS

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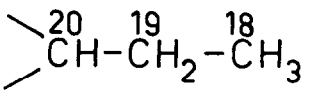
Summary: From the leaves of *Tabernaemontana eglandulosa* a new alkaloid was isolated, which was assigned structure 1 on the basis of spectroscopic evidence.

From the leaves of *Tabernaemontana eglandulosa* Stapf (Apocynaceae) 50 mg of a new alkaloid has been isolated, which was named tacamine. With ceric sulphate it gave a yellow colour which slowly changed to orange. The colour with ferric chloride perchloric acid was greenish-black upon heating. The UV spectrum showed maxima at 227, 277 and 282 nm with a shoulder at 290 nm. This is due to an indole-chromophore. The MS gave a M^+ at m/z 354 with major fragments at m/z 339 ($M^+ -CH_3$), m/z 295 ($M^+ -COOCH_3$), m/z 293, m/z 292, m/z 252 and m/z 223. In the ^{1}H-NMR, the most characteristic signals were a methoxy- or a carbomethoxy group at 3.83 ppm, 4 aromatic protons and a triplet (3H) at 0.86 ppm. No NH could be observed. This last fact, together with the MS data (fragment at m/z 252), suggests the presence of an alkaloid of the vincamine type. This was confirmed by the ^{13}C-NMR (table 1).

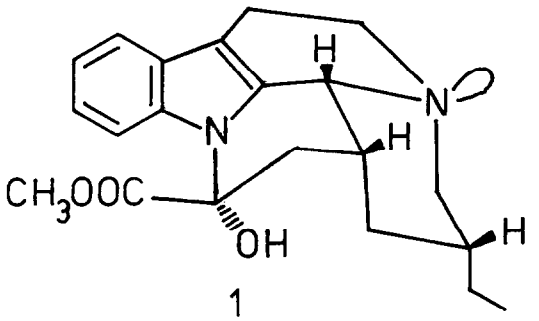
The shifts for the aromatic carbons were almost identical to the ones published for vincamine[1]. The aliphatic carbon shifts except for C_5 and C_6 were, however, quite different, suggesting a change in this part of the molecule. The shifts of C_{18} and C_{19} are more characteristic for the iboga type of alkaloids, for comparison: vincamine C_{19}: 29.0 ppm, C_{18}: 7.6 ppm[1] and coronaridine C_{19}: 27.0 ppm, C_{18}: 11.6 ppm[2].

The fact that in the ^{1}H-NMR the H_{19} protons gave a doublet-quartet pattern with coupling constants 7.3 and 7.2 Hz, gave additional evidence for the fact that the following group must be present:

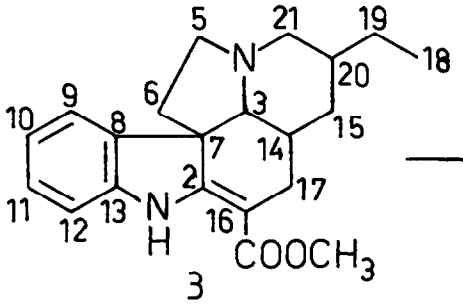


The only biosynthetically reasonable explanation for these data is structure 2, which could be formed from the pandoline type of alkaloids 3, in the same manner as the vincamine type 4 are probably derived from the tabersonine type 5.

The ^{13}C-NMR data (table 1) and the MS data (table 2) are in agreement with a skeleton of the type 2. The structures of the fragments at m/z 292 and m/z 223, which are characteristic for tacamine, are given (structures 6 and 7).



1



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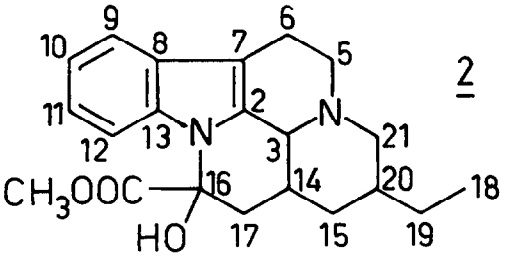

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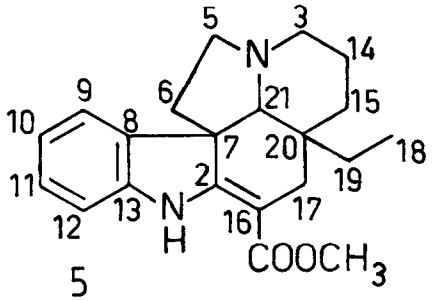

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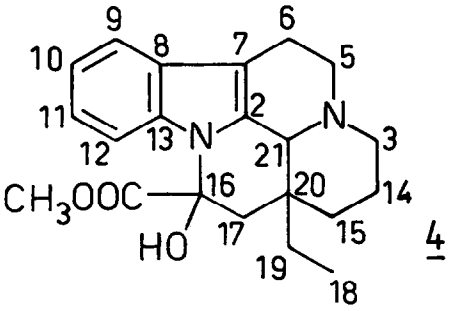

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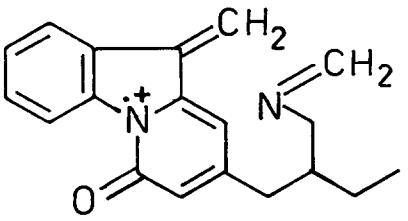
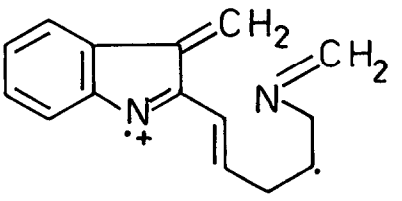


6 m/z 292



7 m/z 223

Table 1: ^{13}C-NMR data tacamine ($CDCl_3$, 25.2 MHz, TMS = 0 ppm)
δ:11.5 (q, C-18), 17.0 (t, C_6), 26.9 (t, C_{19}), 31.1 (t, C_{15}), 32.1 (d, C_{14}), 38.3 (d, C_{20}), 40.2 (t, C_{17}), 50.5 (t, C_{21}), 50.7 (t, C_5), 54.2 (q, $COOCH_3$), 54.2 (d, C_3), 81.8 (s, C_{16}), 106.1 (s, C_7), 110.4 (d, C_{12}), 118.4 (d, C_9), 120.2 (d, C_{11}), 121.6 (d, C_{10}), 128.8 (s, C_8), 130.9 (s, C_2), 134.4 (s, C_{13}), 174.3 (s, $\underline{C}OOCH_3$).

Table 2: MS data (electron-impact, 70 eV)
vincamine: 100 °C (m/z, rel. int.): 355 (M+1, 25), 354 (M^+, 100), 353 (M-1, 40), 339 (M-15, 2), 325 (M-29, 2), 307 (M-29-18, 12), 295 (M-59, 34), 294 (M-60, 9), 293 (M-60-1, 6), 284 (M-70, 11), 267 (M-59-28, 48), 266 (M-70-18, 17), 265 (M-60-29, 10), 252 (M-102, 86), 237 (M-60-29-28, 14), 224 (M-60-70, 23)
tacamine: 50 °C (m/z, rel. int.): 355 (M+1, 31), 354 (M^+, 100), 353 (M-1, 89), 339 (M-15, 22), 336 (M-18, 3), 295 (M-59, 23), 294 (M-60, 10), 293 (M-60-1, 37), 292 (M-60-2, 35), 267 (M-59-28, 4), 265 (M-60-29, 3), 252 (M-102, 62), 238 (5), 237 (5), 223 (M-102-29, 42), 196 (M-60-98, 13)

To determine the stereochemistry of the C_3, C_{14}, C_{20} and the N_4 nitrogen a detailed high resolution ^{1}H-NMR study of tacamine was performed.

By means of homonuclear decoupling experiments it was possible to assign all the protons and to determine all the coupling constants except for the aromatic protons. The results are presented in table 3.

Table 3: ^{1}H-NMR data tacamine ($CDCl_3$, 300 MHz, TMS = 0 ppm)

H nr	δ	coupling constants (Hz)
H3	4.35	J 3-6α: 2.3; J 3-6β: 1.9; J 3-14: 5.8; J 3-15β: <0.5
H5α	3.34	J 5α-5β: 14.0; J 5α-6α: 6.5; J 5α-6β: 0.6
H5β	3.43	J 5α-5β: 14.0; J 5β-6α: 11.2; J 5β-6β: 5.5
H6α	3.00	J 3-6α: 2.3; J 5α-6α: 6.5; J 5β-6α: 11.2; J 6α-6β: 16.3
H6β	2.59	J 3-6β: 1.9; J 5α-6β:0.6; J 5β-6β: 5.5; J 6α-6β: 16.3
H9	7.12	multiplet
H10	7.12	multiplet
H11	7.12	multiplet
H12	7.48	multiplet
H14	2.40	J 3-14:5.8; J 14-15α: 12.7; J 14-15β: 4.0; J 14-17α: 4.2; J 14-17β: 3.1
H15α	1.14	J 14-15α: 12.7; J 15α-15β: 13.2; J 15α-20: 12.6
H15β	1.67	J 3-15β: <0.5; J 14-15β: 4.0; J 15α-15β: 13.2; J 15β-20: 3.0; J 15β-21β: 1.6
H17α	2.62	J 14-17α: 4.2; J 17α-17β: 14.3
H17β	2.19	J 14-17β: 3.1; J 17α-17β: 14.3
H18	0.86	J 18-19: 7.3
H19	1.20	J 18-19: 7.3; J 19-20: 7.2
H20	1.48	J 15α-20: 12.6; J 15β-20: 3.0; J 19-20: 7.2; J 20-21α: 10.7; J 20-21β: 3.5
H21α	2.15	J 20-21α: 10.7; J 21α-21β: 10.9
H21β	2.66	J 15β-21β: 1.6; J 20-21β: 3.5; J 21α-21β: 10.9
HO	not observable*	
$COOCH_3$	3.83	singlet

*At 500 MHz a very broad singlet at 4.55 ppm was observed.

From the proton chemical shifts and coupling constants of the H_3, H_5 and H_6 and also the carbon-13 chemical shifts (see table 1) of C_3, C_5 and C_6 it can be concluded that tacamine has a similar relative configuration at C_3 and N_4 as vincamine[1] or the pseudo hetero yohimbine alkaloids (example: 3-iso 19-epi ajmalicine)[3,4]. From the maximum at 250 nm in the CD spectrum of tacamine (table 4) it can be concluded that H_3 has the β-configuration[5] (vide infra). Because of the relatively small coupling constant of 5.8 Hz between H_3 and H_{14}, H_{14} must also have the β configuration.

C_{20} has an equatorial ethyl group (H 20β) because H_{20} has coupling constants of 10.7 and 3.5 Hz with $H_{21}\alpha$ and β and 12.6 and 3.0 Hz with $H_{15}\alpha$ and β. The only carbon whose stereochemistry remains to be determined is C_{16}. Bombardelli suggested that the chemical shift difference between $H_{17}\alpha$ and β can be of use in determining the C_{16} stereochemistry of alkaloids of the vincamine type[1]. However, due to the absence of the ethyl group this is of no use in the tacamine type of alkaloids.

Blaha *et al.* have made an extensive ORD study of the vincamine type of alkaloids. They found that the ORD curve in the 220nm-280nm region was determined by the stereochemistry of C_{16} and C_{21}, the influence of C_{20} being of minor importance, because of its relatively large distance from the indole chromophore. In this region the CD spectrum of tacamine is almost superimposable with the CD of the enantiomer of (+) vincamine, see table 4:

Table 4: CD data (MeOH)

(-) vincamine: (λ, Δε): 311, +0.7; 302, 0.0; 270, -2.4; 253, -0.2; 237, -4.3; 233, 0.0; 222, +16.6; 204, 0.0
tacamine: (λ, Δε): 272, -5.0; 250, -3.9; 238, -6.3; 234, 0.0; 227, +14.8; 212, 0.0

Although no CD spectrum of the enantiomer of (-)16-epi vincamine is known to the authors, it can be concluded from the ORD data presented by Blaha *et al.* that in the CD spectrum the Δε value at 230nm of this compound must be of opposite sign to the Δε value of the enantiomer of (+) vincamine at this wavelength. This is due to the third Cotton effect, which is influenced most by the C_{16} stereochemistry. From all other spectrometric data it has been concluded, that tacamine possesses the conformation and the same configuration at C_3 as the enantiomer of (+) vincamine. Therefore tacamine must possess the same configuration at C_{16} as the enantiomer of (+) vincamine, *viz.* a β-$COOCH_3$ and an α-OH. From the above data it can be concluded that tacamine has the absolute configuration as presented in structure 1.

The enantiomer of tacamine has already been prepared from catharanthine by Le Men *et al.*[6] However, the low resolution of the ^{1}H-NMR spectra and the lack of ^{13}C-NMR and CD-data precludes a positive correlation with tacamine.

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