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MYRTINE AND EPIMYRTINE, QUINOLIZIDINE ALKALOIDS FROM *VACCINIUM MYRTILLUS*

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Abstract—The structures (including conformation and absolute configuration) of myrtine and epimyrtine, quinolizidine alkaloids from *Vaccinium myrtillus*, are reported. The two bases are obtainable from pelletierine by Mannich condensation with acetaldehyde, or can be derived stereospecifically by 1,4-nucleophilic addition to enaminones. They have been resolved with tartaric acid. The isomerization of myrtine is discussed.

In a preliminary communication[1] we reported the isolation from *Vaccinium myrtillus* (Ericaceae) of the new quinolizidine alkaloid myrtine. Myrtine was assigned the structure **1** (absolute configuration) on the basis of chemical and spectroscopic evidence. More recently, epimyrtine **2** (relative configuration) was also isolated from the same species. A stereospecific synthesis of the racemic bases **1** and **2** has been achieved.[2] In this paper, we present a full report of our chemical investigations.

The crude alkaloids were obtained from the aerial parts of *Vaccinium myrtillus* by a mild extraction procedure and separated by counter-current distribution. Myrtine $[\alpha]_D^{20} + 3.1°$ (c = 2.1 chloroform), and epimyrtine $[\alpha]_D^{20} - 2.5°$ (c = 1.2, chloroform) were isolated as homogeneous (TLC, GLC) colourless oils (20 and 5 ppm respectively from the fresh plant). These compounds have low optical purities.

Structure of myrtine and epimyrtine

The empirical formula $C_{10}H_{17}NO$ was established for myrtine **1** by high resolution mass spectrometry. On the mass spectrum, the base peak appeared at *m/z* 152 and corresponds to the loss of a methyl radical from the molecular ion.

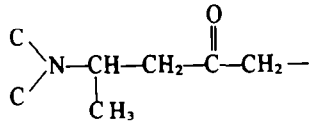
The IR spectrum (CCl_4) of **1** indicated the absence of OH and NH functions but displayed a strong band at 1715 cm^{-1} attributed to the ketone carbonyl group of a six-membered (or larger) ring. Reduction of the base with $NaBH_4$ in methanol led to a mixture of epimeric alcohols ($M^{+\cdot}$ at *m/z* 169 shifted to *m/z* 211 upon acetylation).

Deuterium exchange in alkaline D_2O at room temperature resulted in the uptake of four deuterium atoms in **1** (tetradeuteriomyrtine: $M^{+\cdot}$ at *m/z* 171). As there is no $COCH_3$ in myrtine (PMR) this result indicates that the carbonyl group is flanked by two methylene groups.

The PMR spectrum of myrtine established that the tertiary nitrogen atom did not carry a simple alkyl group. It showed a 3H doublet (J = 6.75 Hz) at 0.97 ppm (shifted to 1.30 ppm upon addition of trifluoroacetic acid) attributed to a secondary methyl group β to the nitrogen atom.[3] Double irradiation experiments established that the secondary methyl group was coupled with a methine proton appearing at 3.4 ppm. This proton was also coupled with two methylenic protons (J = 6.75 and 2.6 Hz) adjacent to the carbonyl function: it appeared in the spectrum of myrtine as a double quintet and as a quartet in the spectrum of tetradeuteriomyrtine (J = 6.75 Hz).

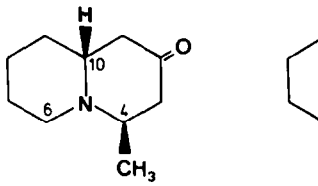
†Research Associate of the National Fund for Scientific Research (Belgium).

The structural unit **A** is therefore present in myrtine and

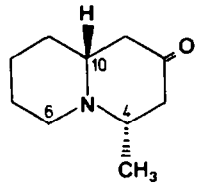


A

4-methylquinolizidin-2-one was retained as the most probable structure for this alkaloid. That our assignment was in fact correct was demonstrated by synthesis. Mannich condensation of *dl*-pelletierine **3** with acetaldehyde in acetic acid (*vide infra*) yielded a mixture, the two main constituents of which were *dl*-myrtine (hydrochloride: m.p. 196–198°C (dec) and *dl*-epimyrtine (hydrochloride: m.p. 200–201°C (dec) identical (MS, IR, PMR, GLC) with the natural compounds.



1



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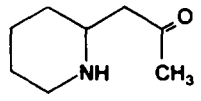

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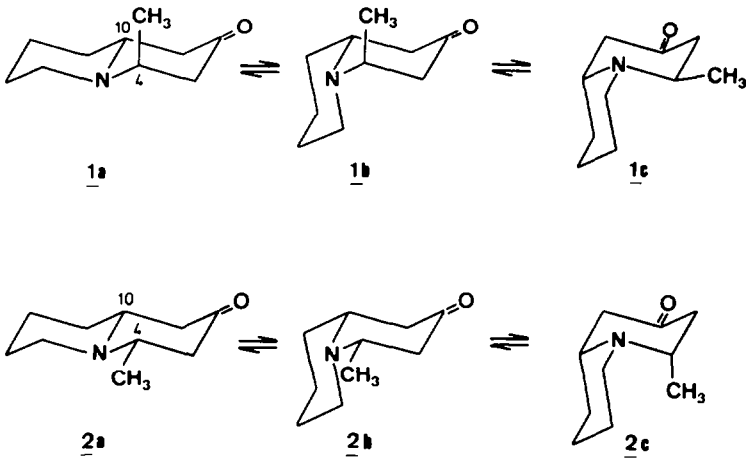
The second alkaloid isolated from *V. myrtillus* appeared to be epimyrtine **2**. The mass spectra of **1** and **2** were virtually identical. The IR spectrum (CCl_4) of epimyrtine exhibited intense Bohlmann bands[4] at 2790 and 2745 cm^{-1} and a carbonyl absorption at 1720 cm^{-1}. A mixture of epimeric alcohols ($M^{+\cdot}$ at *m/z* 169) was obtained upon treatment of epimyrtine with $NaBH_4$ in methanol. As in the case of myrtine, four deuterium atoms were incorporated in **2** by exchange in alkaline D_2O at room temperature. In the PMR spectrum of epimyrtine, a poorly resolved doublet appeared at 1.18 ppm and was shifted to 1.55 ppm upon addition of trifluoroacetic acid.

Being β-aminoketones, myrtine and epimyrtine are epimerized (and therefore interconverted) in a variety of



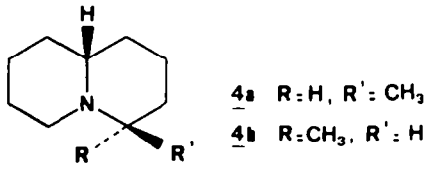
Scheme 1.

conditions. Prolonged reflux of *dl*-myrtine or *dl*-epimyrtine in basic medium (K_2CO_3, H_2O, dioxane) led to the same 3:7 mixture (PMR) of **1** and **2**. Similarly, a 2:8 mixture of **1** and **2** was obtained from *dl*-myrtine or *dl*-epimyrtine in refluxing 0.1 N HCl. Epimyrtine is therefore the thermodynamically more stable epimer.

Trans-4,10-H-4-methylquinolizidin-2-one **1** and *cis*-4,10-H-4-methylquinolizidin-2-one **2** each have three interconvertible chair conformations as illustrated in Scheme 1.

For the *cis*-4,10-H-4-methylquinolizidin-2-one, the equilibrium between the conformers must be strongly shifted towards conformer **2a** which has a *trans*-fused ring conformation and an equatorial methyl group. It is clear therefore that **2** must be thermodynamically more stable than **1** whatever the favoured conformation of the latter may be. Myrtine is therefore **1** and epimyrtine **2**.

It is likely that myrtine exists in the *trans*-fused ring conformation **1a** rather in the *cis*-fused ring conformation **1c** (conformation **1b** can be ignored owing to the presence of a *cis*-ring fusion and an axial substituent). *Trans*-4,10-H-4-methylquinolizidine **4a** was shown to exist at room temperature in a predominently *trans*-fused ring conformation with an axial methyl group.[5] In the case of myrtine, conformation **1a** is favoured besides (relative to **4a**) because one of the 1,3-diaxial CH_3–H interactions present in **4a** is missing (3-alkylketone effect[6]).



4a R=H, R'= CH_3

4b R=CH_3, R'= H

Epimyrtine displays strong Bohlmann bands at 2790 and 2745 cm^{-1} indicative of a *trans*-conformation. The IR spectrum of **1** is devoid of such absorptions (weak shoulder at 2765 cm^{-1}) but exhibited a band at 2810 cm^{-1}. A similar absorption is observed for **4a** and is probably a trans band.[7,8]

The above conclusions regarding the relative configuration and the favoured conformation of **1** and **2** are substantiated by the nmr properties of the two bases. At 270 MHz, most of the protons of myrtine appeared as separate signals which could be assigned by selective decoupling and simulation experiments[10], δ and J values are given in Table 1. On the other hand, the spectrum of epimyrtine did not allow comparable selective decoupling experiments but showed a sharp doublet for the methyl group; an isolated multiplet at 3.32 ppm is attributed to H_{6eq}. The methyl group of **1** appears at higher field and exhibits a larger splitting than that of **2** (**1**; 0.97 ppm, J = 6.75 Hz; **2**; 1.18 ppm, J = 5.7 Hz) as generally observed for a given pair of axial and equa-

Table 1. Chemical shifts and coupling constants in myrtine

Proton	Chemical shift (ppm)	Coupling constant (Hz)	
H_{1ax}	2.23	1ax,1eq	-13.9
H_{1eq}	2.27	1eq,3eq	2.8
		1eq,10ax	3.8
H_{3ax}	2.85	1ax,10ax	10.8
H_{3eq}	2.20	1ax,3ax	1.2
H_{4eq}	3.39	3ax,3eq	-13.1
		3ax,4eq	6.75
H_{6ax}	2.48	3eq,4eq	2.6
H_{10ax}	2.65	9ax,10ax	9.6
		9eq,10ax	2.4

Table 2. ^{13}C chemical shifts and splittings of myrtine and epimyrtine

Carbon	Myrtine 1	Epimyrtine 2
1	48.0_9 (t)	48.8_0 (t)
2	209.5_8 (s)	208.3_5 (s)
3	48.7_4 (t)	49.8_5 (t)
4	57.1_9 (d)	59.3_6 (d)
6	51.5_0 (t)	51.0_9 (t)
7	25.9_2 (t)	26.0_4 (t)
8	23.4_6 (t)	24.0_4 (t)
9	34.3_1 (t)	34.3_1 (t)
10	53.5_5 (d)	62.1_1 (d)
CH_3	11.0_8 (q)	20.8_2 (q)

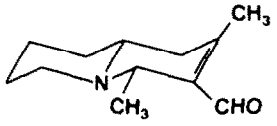
torial epimers.[7,9] The coupling constants between H_{4eq} and the adjacent methylenic protons in **1** (6.75 and 2.6 Hz) indicate that the substituted cycle is a slightly distorted chair; the deformation may be ascribed to a C-10H:CH_3 interaction leading to an increase of the dihedral angle H_4–C–C–H_{3eq} and a concomitant decrease of the dihedral angle H_4–C–C–H_{32x}. The other coupling constants of Table 1 are in agreement with this view.

The ^{13}C chemical shifts of myrtine and epimyrtine are shown in Table 2. The off-resonance proton decoupled spectra of **1** and **2** showed one quartet, six triplets, two doublets and one singlet. The singlet and the quartet of each spectrum obviously resulted from C-2 and CH_3 respectively. C-7, C-8 and C-9 were assigned by direct comparison with the corresponding carbon atoms in model compounds e.g. quinolizidine.[11] Single frequency decoupling experiments allowed the assignment of C-1, C-3, C-4, C-6 and C-10 in the spectrum of **1** and C-6 in the spectrum of **2**; C-3 and C-4 in **2** were assigned by comparison with the spectra of epimyrtine-3-d_1 (reduced intensity of the 49.8 ppm signal) and epimyrtine-4-d_1 (disappearance of the 59.3 ppm signal). In myrtine, the C-3, C-4, C-10 and CH_3 resonances are shifted upfield (1.1, 2.1, 8.5 and 9.7 ppm respectively) from their position in epimyrtine as expected from the substitution of an equatorial by an axial methyl group. The magnitude of the shielding of C-10 and CH_3 is consistent with that observed on the model compounds **4a** and **4b**,[12] supporting conformation **1a** for myrtine.

The pelletierine condensation with acetaldehyde; resolution and absolute configuration of myrtine and epimyrtine

The Mannich condensation of pelletierine **3** with acetaldehyde was carried out in basic and in acidic media. Condensation in 1.5 N NaOH at room temperature yielded a complex mixture. Repeated column chromatography afforded a mixture of **1** and **2** (13:1 by GLC; yield 9%) and compound **5** (oil, yield 13%) identified on the basis of its spectral properties. The ratio of 13:1 observed for **1**:**2** in this experiment implies that myrtine is the kinetic product of the condensation. In the same way, *trans*-4,10-H-4-arylquinolizidin-2-ones are formed more rapidly than the thermodynamically more stable *cis* derivatives in the condensation of **3** with benzaldehyde or substituted benzaldehydes.[13–15]

On the other hand, condensation of pelletierine hydrochloride with acetaldehyde in acetic acid at 90°C afforded a mixture from which myrtine **1** (15%), epimyrtine **2** (20%) and compound **6** (oil, yield 16%) were isolated. In this synthesis, the quantity of epimyrtine resulting from the epimerization of myrtine must be small because the latter reaction was found to be slow in these conditions (see Table 3).



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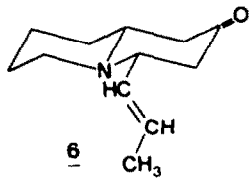
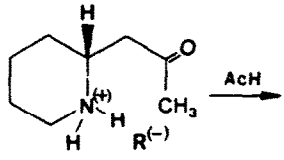


6

Mannich condensation of (*R*)-pelletierine hydrogen (*R*)-6,6'-dinitrobiphenyl-2,2'-dicarboxylate[16] **7** with acetaldehyde in acetic acid afforded(+)-myrtine $[\alpha]_D^{20}$ + 5.1° (c = 7, chloroform) and (+)-epimyrtine $[\alpha]_D^{20}$ + 10.2° (c = 5.7, chloroform). (+)-Myrtine is therefore (4*R*, 10*R*)-4-methylquinolizidin-2-one **1** and (+)-epimyrtine (4*S*, 10*R*)-4-methylquinolizidin-2-one **2**. As the above quoted rotation values are lower than the rotations of optically pure **1** and **2** (*vide infra*), some racemization must have occurred in the conditions of the condensation.



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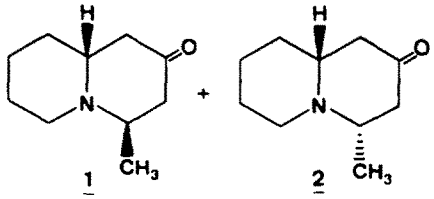
R = Hydrogen R-6,6'-dinitrobiphenyl-2,2'-dicarboxylate



1 **2**

Optically pure myrtine and epimyrtine were obtained by resolution of the racemic bases with tartaric acid. With (−)-tartaric acid the salts of dextrorotatory myrtine and laevorotatory epimyrtine separated first from acetone; they were purified by repeated crystallizations from the same solvent and gave (+)-myrtine $[\alpha]_D^{23}$ + 11.3° (c = 2.7, chloroform), m.p. 41–43°C and (−)-epimyrtine $[\alpha]_D^{23}$ − 18° (c = 5.4, chloroform).

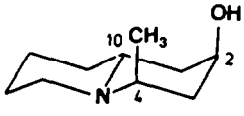
Table 3. Isomerization of myrtine

Medium	T(°C)	Time (hours)	1:2[a]
2N NH_4OH	20	48	ca 100:0
2N NaOH	20	40	92:8
0.1N HCl	20	48	ca 100:0
Methanol	Reflux	24	84:16
Methanol	Reflux	160	58:42
0.1N HCl	Reflux	24	33:67
0.1N HCl	Reflux	48	23:77
0.1N HCl	Reflux	96	20:80
0.5M K_2CO_3	Reflux	52	27:73
Acetic acid	90	24	50:50
Acetic acid[b]	90	24	68:32
Acetic acid[c]	80	22	73:27
Neat	90	24	90:10

[a]The 1:2 ratios were determined by gc.
[b]Myrtine hydrochloride and [c]myrtine hydrogen 6,6'-dinitrobiphenyl-2,2'-dicarboxylate were used in these experiments.

(−)-Epimyrtine gave a positive Cotton effect (in isooctane) confirming the absolute configuration (4*R*, 10*S*).

The absolute configuration 1 deduced above for (+)-myrtine was confirmed by another method. Reduction of optically pure 1 with potassium trisiamyl borohydride in tetrahydrofuran yielded the axial alcohol 8 (m.p. 91–92°C). The attribution of a *trans* fused-ring conformation with axial methyl and hydroxy groups to 8 rests on spectroscopic evidence, i.a. the appearance of the CHOH proton as a narrow quintet (J = 5 Hz) at 3.99 ppm on the PMR spectrum. Application of Horeau's method[17] led to the isolation of dextrorotatory 2-phenylbutanoic acid (optical yield 15%) implying the absolute configuration (2*S*, 4*R*, 10*R*) depicted for 8.



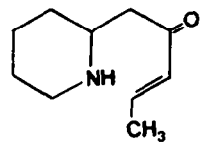
8

The two bases isolated from *Vaccinium myrtillus*, (+)-myrtine and (−)-epimyrtine have low optical purities (*ca* 25 and 15% respectively) and possess opposite configurations at C-10. This could be attributed to a partial isomerization occurring during the extraction procedure. This is not the case however, because it was checked that 1 did not isomerize in conditions similar to those employed for the isolation of the alkaloids from the vegetal material.

Isomerization of myrtine

Isomerization of myrtine occurred in a variety of acidic, neutral and basic conditions, as shown in Table 3. In all cases, the reaction was slow. It was found to be very slow at room temperature, whatever the solvent may be. Prolonged heating in aqueous 0.1 N HCl or 0.5 M K_2CO_3 was required to reach the equilibrium.

The most reasonable mechanisms for the isomerization of myrtine involve either a retro-Michael or a retro-Mannich reaction followed by recyclisation of the intermediates **9**, **9a**, **10** or **10a** with inversion at C-4 or at C-10.



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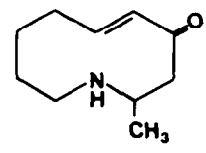
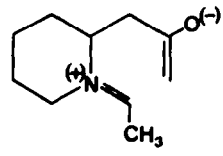


9a



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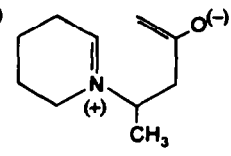


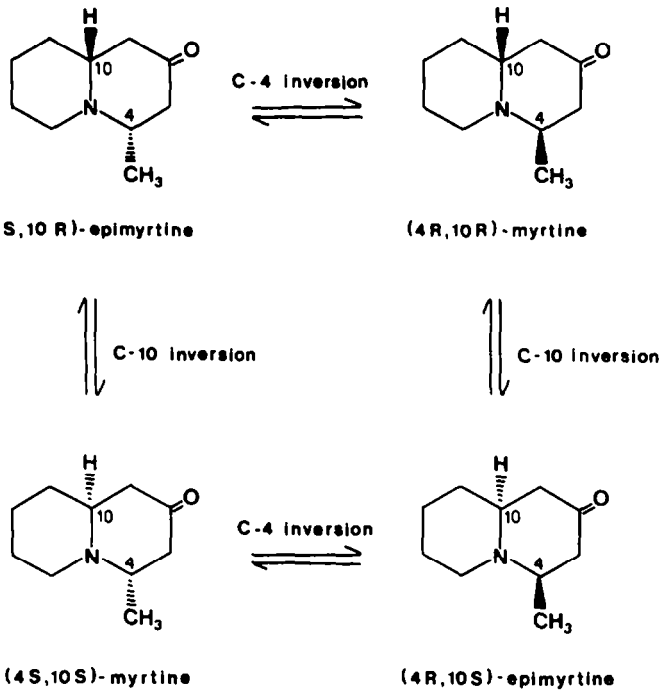
10a

The stereochemical consequences of the inversion at C-4 and at C-10 are represented in Scheme 2.

The simultaneous occurrence of the two processes must lead, from one enantiomer of myrtine, to epimerization together with racemization. This is observed in basic medium: refluxing optically active 1 in 0.1 N NaOH yielded a mixture of racemic myrtine and epimyrtine. On the other hand, inversion at C-4 or at C-10 will give a mixture of 1 and 2 whose optical purities will equal that of the starting material. Epimerization without racemization is observed in acidic medium: refluxing optically pure (−)-myrtine (4*S*, 10*S*) in 0.1 N HCl furnished (−)-myrtine and (+)-epimyrtine (4*S*, 10*R*). In this case, isomerization thus occurred exclusively through inversion at C-10.

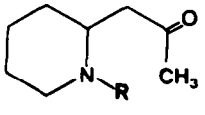
Stereospecific synthesis of myrtine and epimyrtine by nucleophilic additions to enaminones

Enaminones are occasional precursors of β-aminoketones.[18] The enaminone 12 was recently obtained[19] in the course of a study directed toward the synthesis of a cernuine derivative and required only reduction of the carbon–carbon double bond to be converted to 4-methylquinolizidin-2-one.

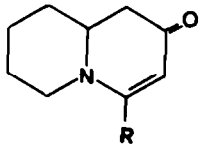


Scheme 2.

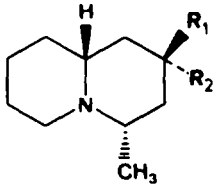
N-Acetylation of pelletierine 3 yielded 11 which was cyclised into 12 in the presence of aluminum t-butoxide by the procedure described.[19] Reduction of 12 with $LiAlH_4$ (5 equiv.) in tetrahydrofuran at 0°C furnished epimyrtine 2 (yield 50%) and a 9:1 mixture (PMR) of the secondary alcohols 13 and 14 (yield 37%). The same alcohols had been obtained previously from the reduction of epimyrtine with $NaBH_4$ in methanol (13:14 ratio of 5:1 by GLC). Epimyrtine-4-d_1, alluded to before, was obtained by reduction of 12 with $LiAlD_4$.



3 R = H
11 R = CH_3CO
15 R = CHO



12 R = CH_3
16 R = H



13 R_1 = H, R_2 = OH
14 R_1 = OH, R_2 = H

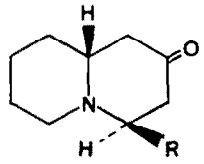
From the above results it appeared that the 1,4-reduction of the enaminone 12 is stereospecific and that there is a *cis*-relationship between the entering nucleophile and the hydrogen atom at C-10. On this basis, it was expected that entering a methyl group as the nucleophile on the enaminone 16 should lead to myrtine.

Formylation of pelletierine 3 with acetic-formic anhydride in pyridine yielded quantitatively N-formylpelletierine 15. Cyclisation of 15 in refluxing toluene in the presence of aluminum t-butoxide furnished the enaminone 16 (m.p. 69–70°C, yield 50%). Addition of methylmagnesium iodide to 16 in benzene proceeded stereospecifically by axial introduction of the methyl group, affording *dl*-myrtine in 73% yield. Epimyrtine was not detected in the reaction mixture (GLC).

In the same way, *trans*-4,10-H-4-ethylquinolizidin-2-one 17 (hydrochloride m.p. 156–159°C) and *trans*-4,10-H-4-phenylquinolizidin-2-one 18 were obtained by addition of ethylmagnesium iodide and phenylmagnesium bromide respectively on the enaminone 16. From the CMR spectrum and by analogy with 1, 17 exists in the predominently *trans*-fused ring conformation with an axial ethyl group. 18 is known to exist in a *cis*-fused ring conformation.[13,14]

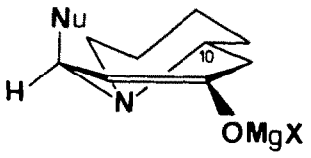
The stereospecificity observed for the addition of nucleophiles to the enaminones 12 and 16 may be rationalized by considering the intermediates 19 and 20. Introduction of the nucleophile from the upper side (i.e. *cis* to the hydrogen at C-10) leads to a pseudo-chair form 19 favoured relative to the strained pseudo-boat form 20 which would result from an attack on the α-side of the molecule. Grignard additions on cyclohexenones have been rationalized on the same grounds.[20]

1,4-Additions to 3,4-dehydroquinolizidin-2-ones thus represent an attractive method for the stereochemically controlled synthesis of 4-substituted quinolizidin-2-ones.



17 R = CH_2-CH_3

18 R = C_6H_5



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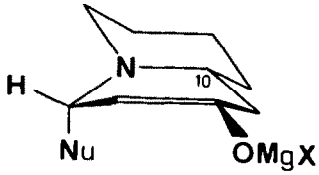

20

EXPERIMENTAL

M.ps were determined on a Kofler microscope and are uncorrected. The IR spectra were determined on Perkin–Elmer 125 and 237 spectrometers. Unless otherwise stated, nuclear magnetic resonance spectra were recorded in $CDCl_3$ with TMS as internal standard (PMR: Jeol JNM-MH-100 and Bruker HDX-270; CMR: Bruker WP 60). Mass spectral data were obtained on Hitachi Perkin–Elmer RMU-6D and Micromass 7070F spectrometers. Optical rotations were measured on a Perkin–Elmer 141 polarimeter. Vapor phase chromatography was performed on a Hewlett–Packard 402 chromatograph equiped with six feet columns. The counter-current distributions were analyzed by measuring the optical density at 420 nm of the $CHCl_3$ phase of each tube after basification, drying and addition of picric acid.

Isolation an separation of the bases of Vaccinium myrtillus

Fresh plants (aerial parts) of *V. myrtillus* (4 Kg) were cut in small fragments and extracted at room temperature with methanol (30 L). The methanolic solution was concentrated under reduced pressure at 25°C to give a tar which was triturated four times with 2% aqueous HCl (800 mL). The combined aqueous extracts were filtered on celite, rendered alkaline with NH_4OH and the crude basic fraction (1 g) obtained by $CHCl_3$ extraction. The crude bases were filtered on a short column of alumina (eluent: AcOEt) and distributed between a stationary $CHCl_3$ phase and McIlvaine buffer (pH 5.8) in a 23-tube counter-current apparatus.

Tubes 2–12 gave myrtine (oil, 70 mg); $[\alpha]_D^{20}+3.1°$ (c = 2.1, $CHCl_3$); IR (CCl_4): 2810 and 2765 (w) cm^{-1}, 1715 cm^{-1}; PMR: δ 0.97(3H, d, J = 6.75 Hz), 3.38(1H, d quintet, J = 6.75 and 2.6 Hz); MS: 167(36%; $C_{10}H_{17}NO$, found: 167.1309, Calc.: 167.1306), 152 (100%; $C_9H_{14}NO$, found: 152.1072, calc.: 152.1072, 124(36%; $C_8H_{14}N$, found: 124.1126, calc.: 124.1123), 110(86%; $C_7H_{12}N$, found: 110.0971, calc.: 110.0967), 96(7%; $C_6H_{10}N$, found: 96.0812, calc.: 96.0811), 83(53%; C_5H_9N, found: 83.0731, calc.: 83.0733), 82(17%), 69(20%); GLC (125°C, 3% OV3 on Chromosorb W AW 80/100) retention time: 6 min.

Tubes 13–20 gave epimyrtine (oil, 17 mg); $[\alpha]_D^{20}-2.5°$ (c = 1.2, $CHCl_3$; IR (CCl_4): 2790 and 2745 cm^{-1}, 1720 cm^{-1}; PMR (270 MHz): δ 1.18(d, J = 5.7 Hz), 3.32(m); MS: 167(29%), 152(100), 124(39), 110(84), 96(7), 83(53), 82(20), 69(21); glc (125°C, 3% OV3 on Chromosorb W AW 80/100) retention time: 5.1 min.

Deuterium exchange experiments

15 mg of the base (1 or 2) were dissolved in anhydrous dioxane (2 mL); D_2O (2 mL) and anhydrous K_2CO_3 (150 mg) were added and the mixture was left at room temperature for three days and extracted with $CHCl_3$. Tetradeuteriomyrtine: $M^{+\cdot}$ at *m/z* 171, characteristic fragmentation ions at *m/z* 156, 126, 112, 83; PMR: δ 3.38(q, J = 6.75 Hz). Tetradeuterioepimyrtine: $M^{+\cdot}$ at *m/z* 171.

Isomerization of myrtine and epimyrtine: typical experiments

Basic conditions (a) 42 mg of *dl*-myrtine were refluxed for 48 h in H_2O:dioxane (1:1, 4 mL) in the presence of K_2CO_3 (150 mg). Extraction with $CHCl_3$ and filtration on a short column of alumina yielded 40 mg of a 3:7 mixture (PMR) of 1 and 2. The same 3:7 mixture was obtained when *dl*-epimyrtine was treated in the same conditions. (b) 50 mg of myrtine $[\alpha]_D^{20}+9°$ (c = 3, $CHCl_3$; 80% optical purity) were refluxed for 45 h in 3 mL of 0.1 N NaOH. Extraction with $CHCl_3$ and filtration on alumina yielded 31 mg of a 3:7 mixture (PMR) of myrtine and epimyrtine $[\alpha]_D^{20}$ 0° (c = 3. $CHCl_3$).

Acidic conditions 215 mg of myrtine $[\alpha]_D^{20}-11.4°$ (c = 4, $CHCl_3$) were refluxed for 112 h in 40 mL of 0.1 N HCl. The solution was basified with NH_4OH and extracted with $CHCl_3$. Fractionation by two successive counter-current distributions ($CHCl_3$/McIlvaine buffer pH 5.8) yielded, after filtration on alumina 34 mg of myrtine (PMR) $[\alpha]_D^{20}-11.3°$ (c = 1.3, $CHCl_3$) and 133 mg of epimyrtine (PMR) $[\alpha]_D^{20}+17.9°$ (c = 6.1, $CHCl_3$).

Plant extraction conditions 22 mg of myrtine $[\alpha]_D^{20}+9°$ (c = 3, $CHCl_3$) were dissolved in methanol (200 mL) and the solution was left at room temperature for three days and then at 30°C for another three days period. After evaporation of the solvent, the residue was dissolved in 2% aqueous HCl (50 mL). After 24 hr at room temperature the solution was rendered alkaline (NH_4OH) and extracted with $CHCl_3$. Evaporation of the solvent and filtration on alumina yielded myrtine (19 mg; PMR) $[\alpha]_D^{20}+8.8°$ (c = 1.9, $CHCl_3$).

The pelletierine condensation with acetaldehyde in basic medium

541 mg of pelletierine hydrochloride were dissolved in 50 mL of 1.5 N NaOH. Four 2.5 mL portions of a 13 M aqueous acetaldehyde solution were added at intervals of 15 min. After one hour, the reaction mixture was extracted with $CHCl_3$; 620 mg of a brown oil were obtained after evaporation of the solvent. Repeated column chromatography on alumina (eluent: AcOEt) yielded 74 mg (13%) of 5 and 47 mg (9%) of a 13:1 mixture (glc) of 1 and 2. 5 (oil): ms: 193($M^{+\cdot}$, 3%), 178(100), 148(13), 134(13), 85(12), 83(14); IR (film): strong Bohlmann bands at 2795 and 2750 cm^{-1}, 1675 and 1655 (sh) cm^{-1} (C=C–C=O); PMR δ 10.05(1H, s, CHO), 2.17(3H, s, CH_3), 1.23(3H, d, J = 6.2 Hz, CH_3).

The pelletierine condensation with acetaldehyde in acetic acid

(a) *Synthesis of racemic* 1 *and* 2. Pelletierine hydrochloride (535 mg; 3 mmol), acetaldehyde (300 mg; 7 mmol) and acetic acid (30 mL) were heated at 90°C (water bath) in a sealed flask for 14 h. After evaporation of the solvent, water, NH_4OH and $CHCl_3$ were added to the residue. Evaporation of the $CHCl_3$ yielded 480 mg of a brown oil. Repeated column chromatography on alumina (eluent: AcOEt) yielded 47 mg (16%) of 6 and a mixture from which myrtine (75 mg; 15%) and epimyrtine (100 mg; 20%) were isolated after two successive counter-current distributions ($CHCl_3$/McIlvaine buffer pH 5.9).

dl-Myrtine 1 (oil; hydrochloride mp 196–198°C (dec) from 2-butanone) identical (MS, PMR, IR, GLC; *vide supra*) with the natural compound. The 270 MHz PMR spectrum and the CMR spectrum were described above.

dl-Epimyrtine **2** (oil; hydrochloride mp 200–201°C (dec) from 2-butanone) identical (MS, PMR, IR, GLC: *vide supra*) with the natural compound. The CMR spectrum was described above.

6 (oil): MS: 193($M^{+\cdot}$, 4%), 150(24), 136(41), 122(11), 110(100); IR (film): strong Bohlmann bands at 2790 and 2750 cm^{-1}, 1720 (C=O), 965 (*trans*-substituted double bond); PMR: δ 1.7 (d, J = 5 Hz, CH_3), 5.5(m, two vinylic protons).

(b) *Synthesis of optically active* **1** *and* **2**. Condensation of (*R*)-pelletierine hydrogen (*R*)-6,6'-dinitrobiphenyl-2,2'-dicarboxylate[16] $[\alpha]_D^{20}$ + 156° (c = 3, pyridine) (4.1 g) with acetaldehyde (5.2 g) in acetic acid (85 mL) as described under (a) yielded myrtine $[\alpha]_D^{20}$ + 5.1° (c = 7, $CHCl_3$) and epimyrtine $[\alpha]_D^{20}$ + 10.2° (c = 5.7, $CHCl_3$).

Resolution of dl-*myrtine*

308 mg of *dl*-myrtine (1.84 mmol) and 278 mg of (−)-tartaric acid (1.84 mmol) were dissolved under warming in acetone (25 mL) and the solution was allowed to stand at room temperature for three days. The precipitate was collected by filtration, washed with acetone and crystallized three times from the same solvent. The salt (m.p. 165–168°C, $[\alpha]_{579}^{23}$ − 20.3° (c = 2.6, CH_3OH) was dissolved in water, the solution was basified with aqueous ammonia and extracted with $CHCl_3$. After filtration through a short column of alumina, the solvent was evaporated, yielding 77 mg of crystalline myrtine m.p. 41–43°C, $[\alpha]_D^{23}$ + 11.3° (c = 2.7, $CHCl_3$) $[\alpha]_D^{23}$ + 20° (c = 3, isooctane).

Resolution of dl-*epimyrtine*

dl-Epimyrtine (1.78 g) and (−)-tartaric acid (1.62 g) were dissolved in hot acetone (200 mL) and the solution was allowed to stand at room temperature for two days. Five successive crystallizations of the precipitate from acetone yielded 835 mg of salt m.p. 162–165 (dec) from which (−)-epimyrtine (404 mg) $[\alpha]_D^{23}$ − 18° (c = 5.2, $CHCl_3$) was obtained after the usual work up (hydrochloride, m.p. 211–213°C (dec) from 2-butanone); $[\alpha]_D^{23}$ − 31.7°, $[\alpha]_{576}^{23}$ − 33.1°, $[\alpha]_{546}^{23}$ − 36.7°, $[\alpha]_{436}^{23}$ − 50.4°, $[\alpha]_{407}^{23}$ − 47.8°, $[\alpha]_{366}^{23}$ − 25.6°, $[\alpha]_{334}^{23}$ + 127°, $[\alpha]_{313}^{23}$ + 337°, $[\alpha]_{302}^{23}$ − 91°, $[\alpha]_{297}^{23}$ − 319°, $[\alpha]_{290}^{23}$ − 756°, $[\alpha]_{280}^{23}$ − 1140° (*c* = 5, isooctane).

Reduction of myrtine with potassium trisiamylborane

(+)-Myrtine (110 mg) in THF (15 mL) was allowed to react at − 78°C with 5 mL of a 0.5 M THF solution of potassium trisiamylborane for 2 hr. Water (2 mL) and methanol (20 mL) were added. After evaporation of the solvents, the residue was dissolved in 10 mL of 1 N HCl. The solution was extracted twice with $CHCl_3$, basified (NH_4OH) and extracted again with $CHCl_3$. The organic phase, after washing and drying, yielded 100 mg of the crude alcohol. Two crystallizations from pentane afforded **8**, m.p. 91–92°C, $[\alpha]_D^{22}$ − 3.5° (c = 1.7, $CHCl_3$); MS: 169(M^+), 154(100%), 136, 124, 110; IR (CCl_4): 3625 cm^{-1}, 2810(m), 2760(w); PMR: δ 3.99 (quintet, J = 5 Hz, CHOH), 1.14(d, J = 7 Hz, CH_3); CMR: 65.8$_1$ (C-2), 51.5$_0$, 51.1$_5$ and 50.2$_1$(C-4, C-6, C-10), 41.0$_0$ (C-1 and C-3), 30.5$_6$ (C-9), 25.2$_2$ (C-7), 23.2$_8$ (C-8), 16.0$_7$ (CH_3).

Absolute configuration of **8** *by Horeau's method*

The alcohol **8** (33 mg) was allowed to react with α-phenylbutyric anhydride (121 mg) in pyridine (1 mL) for 16 hr at room temperature. Some drops of water were added and the mixture was neutralized with 0.1 N NaOH and extracted with $CHCl_3$. The basic aqueous phase was acidified with 0.1 N HCl and extracted with $CHCl_3$. Evaporation of the solvent yielded α-phenylbutyric acid (91 mg) $[\alpha]_D^{20}$ + 14° (c = 2, benzene); optical yield 15%.

Sodium borohydride reduction of epimyrtine

dl-Epimyrtine (120 mg) was allowed to react at 20°C for 15 min with $NaBH_4$ (120 mg) in methanol (10 mL). The solvent was removed and the residue was dissolved in water and extracted with $CHCl_3$. Removal of the solvent furnished 120 mg of a mixture of **13** and **14** (5:1 by GLC, 190°C, 10% Carbowax 20 M on Chromosorb W AW 80/100, retention times: **13**: 10.7 min, **14**: 9.8 min). The mixture was acetylated (acetic anhydride: pyridine 1:1) and the acetyl derivatives were separated by repeated column chromatography on alumina; hydrolysis with 0.2 N NaOH gave the alcohols **13** and **14**.

14 (m.p. 96–97°C from pentane); ms: 169($M^{+\cdot}$, 12%), 168(8) 154(100), 152(10), 136(12), 124(8), 110(26), 84(12), 83(16); IR(CCl_4): 3620 cm^{-1}, 2790, 2750; PMR: δ 1.07(d, J = 6 Hz, CH_3), 3.25(m, H_{6eq}), 4.05(quintet, J = 3 Hz, CHOH).

13 (picrate m.p. 159–161°C from benzene); MS: 169($M^{+\cdot}$, 9%), 168(7), 154(100), 152(7), 136(11), 124(11), 110(37), 85(15), 84(16), 83(23); IR(CCl_4): 3620 cm^{-1}, 2790, 2750; PMR: δ 1.1(d, J = 6 Hz, CH_3), 3.23(m, H_{6eq}), 3.6(tr t, J = 11 and 4.7 Hz, CHOH); CMR: 67.9$_8$(d, C-2), 60.9$_4$(d, C-10), 57.3$_0$(d, C-4), 51.4$_4$(t, C-6), 44.3$_4$(t, C-3), 43.1$_7$(t, C-1), 33.6$_6$(t, C-9), 26.1$_6$(t, C-7), 24.5$_1$(t, C-8), 20.4$_7$(q, CH_3).

3,4-Dehydro-4-methylquinolizidin-2-one **12**

The method of Ban[19] for the preparation of **12** from pelletierine was used, affording the enaminone in 55% yield. CMR: 191.5$_1$(s, C-2), 163.0$_7$(s, C-4), 101.9$_4$(d, C-3), 58.7$_1$(d, C-10), 48.1$_5$(t, C-6), 42.9$_9$(t, C-1), 31.4$_9$(t, C-9), 25.8$_0$(t, C-7), 23.7$_5$(t, C-8), 21.1$_7$(q, CH_3)

Lithium aluminum reduction of **12**

(a) To a stirred suspension of 50 mg of $LiAlH_4$ in 7 mL of THF at 0°C were added 173 mg of **12** in 10 mL of THF. After the addition had been completed, the reaction mixture was left at 0°C for 10 min, decomposed with aqueous THF and filtered on celite. After evaporation of the solvent, the residue was dissolved in water and the solution extracted with $CHCl_3$. Fractionation by chromatography on alumina afforded 87 mg of epimyrtine (50%), 4 mg of **12** and 63 mg (37%) of a mixture of **13** and **14** (9:1 by GLC).

(b) Reduction of **12** (113 mg) with $LiAlD_4$ (30 mg) in the same conditions yielded epimyrtine-4-d_1 (57 mg) and a mixture of the corresponding deuteriated alcohols. Epimyrtine-4-d_1: MS: 168($M^{+\cdot}$), 153(100%), 125, 111, 83; PMR: δ 1.19(s), 3.32(m); CMR: 208.4$_7$(C-2), 62.0$_6$(C-10), 51.0$_3$(C-6), 49.7$_8$(C-3), 48.7$_4$(C-1), 34.2$_5$(C-9), 25.9$_8$(C-7), 23.9$_9$(C-8), 20.6$_4$(CH_3).

(c) 416 mg of **12** were allowed to react with $LiAlH_4$ (110 mg) as described under (a). Decomposition of the reaction mixture with THF:D_2O afforded a mixture (223 mg) of epimyrtine and epimyrtine-3-d_1 (MS). The CMR spectrum is identical to that of **2** except for the reduced intensity of the signal at 49.8$_5$ ppm.

N-Formylpelletierine **15**

To a stirred solution of pelletierine hydrochloride (2.65 g) in 15 mL of pyridine at 0°C were added dropwise 15 mL of acetic-formic anhydride. After the addition had been completed, the mixture was poured onto ice and water and extracted with $CHCl_3$. Evaporation of the solvent yielded **15** as a colourless oil; MS: 169($M^{+\cdot}$, 27%), 152(6), 140(18), 126(59), 112(89), 98(35), 84(100); PMR (C_2Cl_4): δ 1.96 and 2.0 (2s, CH_3), 7.76 and 7.88(2s(40:60), CHO; coalescence at 85°C).

3,4-Dehydroquinolizidin-2-one **16**

N-Formylpelletierine (813 mg) in xylene (60 mL) was refluxed with aluminum t-butoxide (1.2 g) for 18 hr. After evaporation of the solvent, the residue was treated with H_2O and extracted with $CHCl_3$. Chromatography on alumina (eluent: AcOEt) afforded, after crystallization from ether:petroleum ether 360 mg (50%) of **16** m.p. 69–70°C; MS: 151($M^{+\cdot}$, 100%), 122(80), 98(60), 95(60), 81(67); IR(KBr): 1625 and 1580 cm^{-1}; λ_{max}^{EtOH} 320 nm (ϵ = 15,600); PMR: 4.92(d, J = 8 Hz, H_3), 6.84(d, J = 8 Hz, H_4); CMR: 192.1$_6$(s, C-2), 154.9$_1$(d, C-4), 99.2$_4$(d, C-3), 57.1$_9$(d, C-10), 53.0$_2$(t, C-6), 43.2$_8$(t, C-1), 31.6$_7$(t, C-9), 25.6$_3$(t, C-7), 23.1$_5$(t, C-8).

Myrtine from 3,4-*dehydroquinolizidin-2-one*

Methylmagnesium iodide was prepared from CH_3I (3.4 g) and magnesium turnings (500 mg) in ether (10 mL). Benzene (15 mL) was added and the solution was heated until 20 mL of solvent were eliminated. After cooling, **16** (522 mg) in benzene (8 mL) was added dropwise. After the addition had been completed, the solution was left at room temperature for one hour, decomposed with ice and water and extracted with $CHCl_3$. Myrtine (420 mg, 73%) was isolated by counter-current distribution.

Trans-4,10-H-4-ethylquinolizidin-2-one **17**

A solution of **16** (240 mg) in benzene (9 mL) was added dropwise to a solution of ethylmagnesium iodide in benzene prepared

from magnesium turnings (250 mg) and ethyl iodide (1.7 g) as described above for CH_3MgI. The mixture was stirred for one hour, decomposed with ice and water and extracted with $CHCl_3$. After evaporation of the solvent, the residue was subjected to two successive counter-current distributions ($CHCl_3$/McIlvaine buffer pH 5.2, 23 transfers). Tubes 4–14 afforded homogeneous **17** (150 mg, 53%; hydrochloride m.p. 156–159°C from 2-butanone): MS: 181($M^{+\cdot}$, 10%), 152(100), 138(5), 124(7), 110(62), 83(8); IR(CCl_4): 2810 cm^{-1}, 2750(w), 1715; CMR: 209.7$_5$(s, C-2), 64.2$_8$(d, C-4), 53.9$_0$(d, C-10), 50.7$_9$(t, C-6), 47.2$_7$(t, C-1), 44.5$_2$(t, C-3), 34.0$_2$(t, C-9), 25.9$_8$(t, C-7), 23.0$_5$(t, C-8), 18.3$_0$(t, $\underline{C}H_2$–CH_3), 11.4$_3$(q, CH_3).

Trans-4-10-H-4-*phenylquinolizidin*-2-*one* **18**

A solution of **16** (224 mg) in benzene (10 mL) was added dropwise to a solution of phenylmagnesium bromide in benzene, prepared from magnesium turnings (250 mg) and phenyl bromide (1.6 g) as previously described for CH_3MgI. The mixture was stirred for one hour after the addition had been completed. The usual work up yielded a residue which was subjected to a counter-current distribution ($CHCl_3$/McIlvaine buffer pH 3.0, 23 transfers). Tubes 6–16 afforded homogeneous **18** (174 mg, 48%) identified on the basis of its spectral properties (MS, PMR, IR).[15]

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REFERENCES

[1]P. Slosse and C. Hootelé, *Tetrahedron Lett.* 397 (1978).
[2]P. Slosse and C. Hootelé, *Ibid.* 4587 (1979).
[3]G. Slomp and J. G. Lindberg, *Analyt. Chem.* **39**, 60 (1967).
[4]F. Bohlmann, *Chem. Ber.* **91**, 2157 (1958).
[5]C. D. Johnson, R. A. Y. Jones, A. R. Katritzky, C. R. Palmer, K. Schofield and R. J. Wells, *J. Chem. Soc.* 6797 (1965).
[6]E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis* Interscience, New York. (1962).
[7]T. M. Moynehan, K. Schofield, R. A. Y. Jones and A. R. Katritzky, *J. Chem. Soc.* 2637 (1962).
[8]T. A. Crabb, R. F. Newton and D. Jackson, *Chem. Revs.* **71**, 109 (1971).
[9]L. M. Jackman and S. Sternhell, *Applications of NMR spectroscopy in Organic Chemistry*. Pergamon Press, Oxford (1969).
[10]G. Van Binst and D. Tourwé, *Org. Magn. Reson.* **6**, 590 (1974).
[11]R. T. Lalonde and T. N. Donvito, *Can. J. Chem.* **52**, 3778 (1974).
[12]M. Sugiura and Y. Sasaki, *Chem. Pharm. Bull.* **24**, 2988 (1976).
[13]M. Hanaoka, N. Ogawa, K. Shimizu and Y. Arata, *Ibid.* **23**, 1573 (1975).
[14]J. T. Wrobel and W. Golebiewski, *Bull. Acad. Pol. Sci., Ser. Chim.* **23**, 593 (1975).
[15]J. Quick and C. Meltz, *J. Org. Chem.* **44**, 573 (1979).
[16]H. C. Beyerman and L. Maat, *Rec. Trav. Chim.* **84**, 385 (1965).
[17]A. Horeau, In *Stereochemistry, Fundamentals and Methods* (Edited by H. B. Kagan), Vol. 3, Georg Thieme, Stuttgart (1977).
[18]J. V. Greenhill, *Chem. Soc. Rev.* **6**, 277 (1977).
[19]Y. Ban, M. Kimura and T. Oishi, *Chem. Pharm. Bull.* **24**, 1490 (1976).
[20]N. L. Allinger and C. K. Riew, *Tetrahedron Lett.* 1269 (1966).