conformation **13**) can be expected to convert the usual C/D trans configuration of the *Aspidosperma* bases[21] to a *cis*-indolizidine system. The consequently new nonbonded interactions in conformation **14** of the alkaloids **10**, **11a**, and **11b** are sufficiently complex and all-pervasive to lead to the observed general shift changes.

Experimental Section

The ^{13}C NMR spectra were recorded on a Varian XL-100-15 spectrometer operating at 25.2 MHz in the Fourier transform mode. All samples were run in 0.05–0.5 M deuteriochloroform solutions. Except for substances **8a**, **8b**, and **11b**, all compounds were submitted to proton-noise decoupling, single-frequency off-resonance decoupling, and low-power, noise-modulated decoupling,[22] to establish carbon shifts and degrees of protonation. In select instances partially relaxed Fourier transform spectra, obtained by the 180°–τ–90° inversion recovery method, were recorded for verification of the latter. For the alkaloids examined by this technique τ intervals in the range of 0.070–0.080 s were found to distinguish qualitatively methine from methylene carbons by making the latter null. The shifts enumerated on formula **9** are in parts per million downfield from Me_4Si [$\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm]. The starred numbers indicate possible signal reversal.

Anhydrovobtusine (9). The following represents an improved method of preparation of **9**.[18,19] A solution of 1.0 g of vobtusine (**1a**) in a minimum of methylene chloride was added to a solution of 2 g of *p*-toluenesulfonic acid in 200 ml of anhydrous benzene in the presence of a Dean-Stark water separator and the mixture refluxed for 4 h. It then was poured into 200 ml of water, made basic to pH 10, and extracted with chloroform. The extract was washed with water, dried over sodium carbonate, and evaporated. Chromatography of the resin, 1 g, on Baker silica gel (activity I) and elution with methylene chloride–methanol yielded 700 mg of **9** and 100 mg of apovobtusine, identical in all respects with the reported compounds.[18]

Registry No.—**1a**, 19772-79-3; **1b**, 19772-81-7; **1c**, 19772-80-6; **1d**, 59803-47-3; **1e**, 59796-71-3; **1f**, 50924-04-4; **1g**, 50924-05-5; **3b**, 2447-58-7; **4a**, 32063-91-5; **4b**, 31947-67-8; **5a**, 33055-38-8; **5b**, 31947-66-7; **8a**, 59829-32-2; **8b**, 59829-33-3; **10**, 32340-00-4; **11a**, 31148-60-4; **11b**, 59796-72-4.

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Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. 48. Dimeric Quinolinic *Melodinus* Alkaloids[1]

Michel Daudon, M. Hachem Mehri, and Michel M. Plat

U. E. R. de Chimie Thérapeutic, Faculté de Pharmacie, 92290 Châtenay-Malabry, France

Edward W. Hagaman and Ernest Wenkert*

Department of Chemistry, Rice University, Houston, Texas 77001

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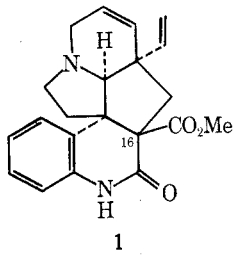
The *Melodinus* C_{41} alkaloids scandomelonine and episcandomelonine are shown by ^{13}C NMR spectroscopy to be 19 epimers of 10-(3′α-pachysiphinyl)meloscandonine. A similar study of the C_{42} *Melodinus* bases scandomeline and episcandomeline reveals them to be structurally related, 19-epimeric carbinolamines.

The New Caledonian plant *Melodinus scandens* Forst. has been shown to produce a large array of alkaloids containing inter alia the two unusual quinolones scandine (**1**) and meloscandonine (**2**).[2-7] Further fractionation of the plant extract now has yielded four "dimeric" alkaloids, scandomelonine,[6] episcandomelonine, scandomeline,[6] and episcandomeline. The present communication presents their structure analysis mostly by the use of ^{13}C NMR spectroscopy.

Scandomelonine and episcandomelonine are $C_{41}H_{42}O_5N_4$



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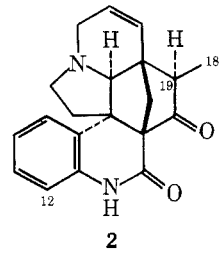

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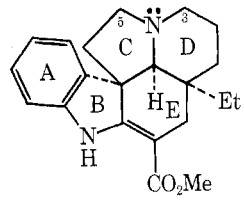
isomers whose common infrared bands at 3370, 1745, 1675, and 1610 cm^{-1} reveal the alkaloids to possess NH groups, two keto groups characteristic of meloscandonine (**2**), and a vinylogous amide unit reminiscent of vincadifformine (**3**), a congener of these alkaloids.[4,5] The ultraviolet absorption characteristics common to both compounds, λ_{max} 214 nm (log ϵ 4.40), 264 (4.08), 296 (4.03), 329 (4.18), $\lambda_{shoulder}$ 233 (4.11), can be interpreted to be a composite of the chromophores of meloscandonine (**2**) and vincadifformine (**3**). The exhibition of a peak of 456 mass units, corresponding to the loss of a $C_{13}H_{12}O_2N$ fragment represented by **4**, in the mass spectra



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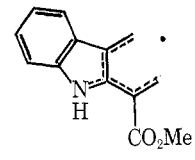

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of the alkaloids shows the latter to possess the ABE ring system of vincadifformine (**3**).[8] Finally, the methyl doublet (J = 7 Hz) at 1.21 and 0.93 ppm in the ^1H NMR spectra of scandomelonine and episcandomelonine, respectively, is identical with H(18) shifts and multiplicities of meloscandonine (**2**)[4] and its 19 isomer[9] and suggests the two new bases to be 19 epimers of each other.

The above data facilitated the interpretation of the ^{13}C NMR spectra of especially scandomelonine by suggesting an early comparison with the ^{13}C NMR spectra of meloscandonine (**2**).[7] Such comparison showed all carbons of the monomer represented in the spectra of the "dimer", the aromatic carbon shifts and multiplicities having been modified. The last fact indicates that the second alkaloid monomer unit is attached to the aromatic ring of meloscandonine (**2**). The interdependent problem of the center of attachment and aromatic methine shift allocation can be solved most readily by analysis of the coupling characteristics of the aromatic methines. Single-frequency off-resonance decoupled (sford) spectra can be run under conditions in which aromatic methine carbons display coupling only with ipso and meta hydrogens, i.e., one-bond and three-bond carbon–hydrogen interactions. These conditions are met when the $^1J_{CH}$ value is reduced to ca. one-half its normal size.[10] Since every methine carbon of an ortho-disubstituted benzene has a hydrogen meta oriented to it, the sford spectrum of such an aromatic substance reveals the methines as doublets of doublets. This behavior is common to all ring A unsubstituted indole alkaloids as well as to meloscandonine (**2**). Carbon 12 of the meloscandonine portion of the "dimer" is recognized easily in view of its ortho relationship to the quinolone nitrogen placing its signal at a high field position. In contrast to all aromatic methines it appears as a sharp doublet in the sford spectrum, thereby showing C(10) to be the site of the tie-up with the nonmeloscandonine monomer unit and the latter to be unsubstituted on ring A of its indolic nucleus.

All resonances of the trigonal carbon centers of rings A, B and E of vincadifformine (**3**)[11] appear unchanged in the ^{13}C NMR spectra of scandomelonine. The one-bond coupling constants of 142 ± 2, 156 ± 2, 178 ± 2, and 179 ± 2 Hz of the tetrahedral methine carbons of the vincadifformine-like portion of the alkaloid reveal these carbons to be attached to heteroatom centers[12] and those of $^1J_{CH}$ = ca. 180 Hz to be part of an epoxide moiety.[12,13] To be incorporated into a vincadifformine-like structure, the remaining methines must be aminomethines, thus limiting the second site of coupling of the two monomer alkaloid units to C(3) or C(5) of **3**. These facts invited comparison of the shift data of scandomelonine

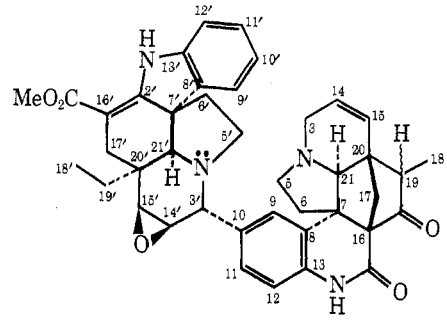
Table I. Carbon Shifts of Scandomelonine and Episcandomelonine[a]

	2[b]	5a	5b		5a	5b	3a[c]
C(3)	47.2	47.3	47.0	C(2′)	164.6	164.7	164.9
C(5)	54.8	54.7	54.9	C(3′)	57.4	57.6	49.4
C(6)	38.1	37.9	38.0	C(5′)	47.8	47.5	51.0
C(7)	54.8	54.7	56.7	C(6′)	42.1	42.3	43.9
C(8)	130.5	130.7	130.3	C(7′)	53.8	53.6	54.7
C(9)	123.5[d]	124.7	125.0	C(8′)	137.2	137.1	137.5
C(10)	123.4[d]	129.1	128.6	C(9′)	121.2	121.6	121.3
C(11)	127.6	127.1	126.8	C(10′)	120.8	121.1	120.3
C(12)	116.3	116.0	115.8	C(11′)	127.3	127.2	127.6
C(13)	136.5	136.3	136.3	C(12′)	108.9	108.7	109.2
C(14)	124.0	123.9	125.5	C(13′)	142.5	142.3	142.9
C(15)	127.4	127.7	128.0	C(14′)	56.2	56.2	52.0
C(16)	67.7	67.6	67.6	C(15′)	53.5	53.5	56.2
C(17)	36.0	36.0	40.0	C(16′)	90.2	90.1	90.4
C(18)	11.0	11.1	8.6	C(17′)	23.6	23.2	23.5
C(19)	50.7	50.8	52.6	C(18′)	7.3	7.27.1	
C(20)	44.3	44.5	45.4	C(19′)	26.6	26.3	26.5
C(21)	69.9	70.4	61.5	C(20′)	36.5	36.7	37.0
NC=O	169.0	169.0	168.7	C(21′)	61.5	61.5	70.9
C=O	210.0	209.8	208.4	C=O	168.4	168.4	168.6
				OMe	50.8	50.8	50.8

[a] In parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] From ref 7. [c] From ref 14. [d] Signals may be reversed.

with those of pachysiphine (14β,15β-oxido-**3**) (**3a**).[14] This comparison leads to the formulation of the "dimer" alkaloid as 10-(3′α-pachysiphinyl)meloscandonine (**5a**).[15] All its carbon shifts are listed in Table I.

Comparison of the ^{13}C NMR spectra of episcandomelonine with those of scandomelonine (**5a**) indicates that not only is



5a, 19α-H
b, 19β-H

the 3′α-pachysiphinyl moiety common to both alkaloids, but they also are very similar in the meloscandonine unit except within the vicinity of C(19). The shift changes at C(17), C(18), and C(21) provide conclusive evidence for the conversion of an *exo*-α-methylnorbornanone fragment to one of an *endo*-α-methyl structure.[16] Thus episcandomelonine proves to be 10-(3′α-pachysiphinyl)-19-epimeloscandonine (**5b**). Its chemical shifts are presented in Table I.

Scandomeline and episcandomeline are $C_{42}H_{46}O_6N_4$ isomers with common infrared absorptions at 3540, 3340, 1725, 1665, and 1610 cm^{-1}, characteristic of hydroxy and NH groups, an ester keto function, and a vinylogous amide moiety as that in vincadifformine (**3**). Their superimposable ultraviolet spectra, λ_{max} 214 nm (log ϵ 4.23), 257 (3.86), 300 (3.86), 325 (3.95), $\lambda_{shoulder}$ 233 (3.91), are a composite of the chromophores of vincadifformine (**3**) and *o*-toluidine. The mass spectra exhibit a peak at 488 mass units, representative of the loss of the $C_{13}H_{12}O_2N$ fragment **4**. Finally, the ^1H NMR spectra reveal the alkaloids to possess a carbomethoxy group

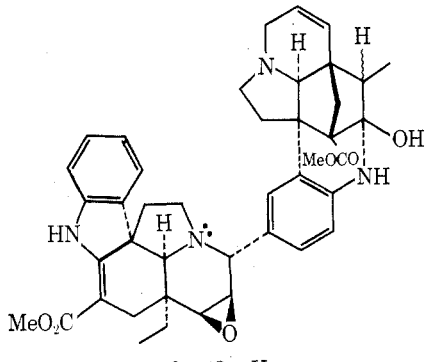
in view of the presence of a 3.68-ppm three-proton singlet and methyl doublets (J = 7 Hz) at different field positions, 1.18 ppm for scandomeline and 0.75 ppm for its isomer. These facts show that the third and fourth "dimeric" alkaloids differ from the other two by the replacement of the quinolone and cyclopentanone carbonyl groups by an ester function and nonacylated aniline system and, formally, by the addition of methanol.

The ^{13}C NMR spectra of scandomeline and episcandomeline indicate the alkaloids to possess a 3′α-pachysiphinyl unit attached to C(10) of the nonlactam equivalent of the quinolone unit. The aromatic shift modifications of the latter are reminiscent (in direction, albeit not in magnitude) of the shift differences of the aromatic oxindole and indoline carbons of gelsemine and its 2-deoxo-2,2,18,19-tetrahydro derivative.[17] The spectra reveal further the presence of a carbomethoxy function and the attachment of the remaining two heteroatoms to a single nonprotonated carbon site, i.e., a carbinolamine unit. Finally, the only difference between scandomeline and episcandomeline is their C-methyl orientation, ascertained by the shift differences between the compounds, as in the distinction between **5a** and **5b**. Interpretation of the combined physical data leads to structures **6a** and **6b** for scandomeline and episcandomeline, respectively. Their carbon shifts are listed in Table II.

Table II. Carbon Shifts of Scandomeline and Episcandomeline[a]

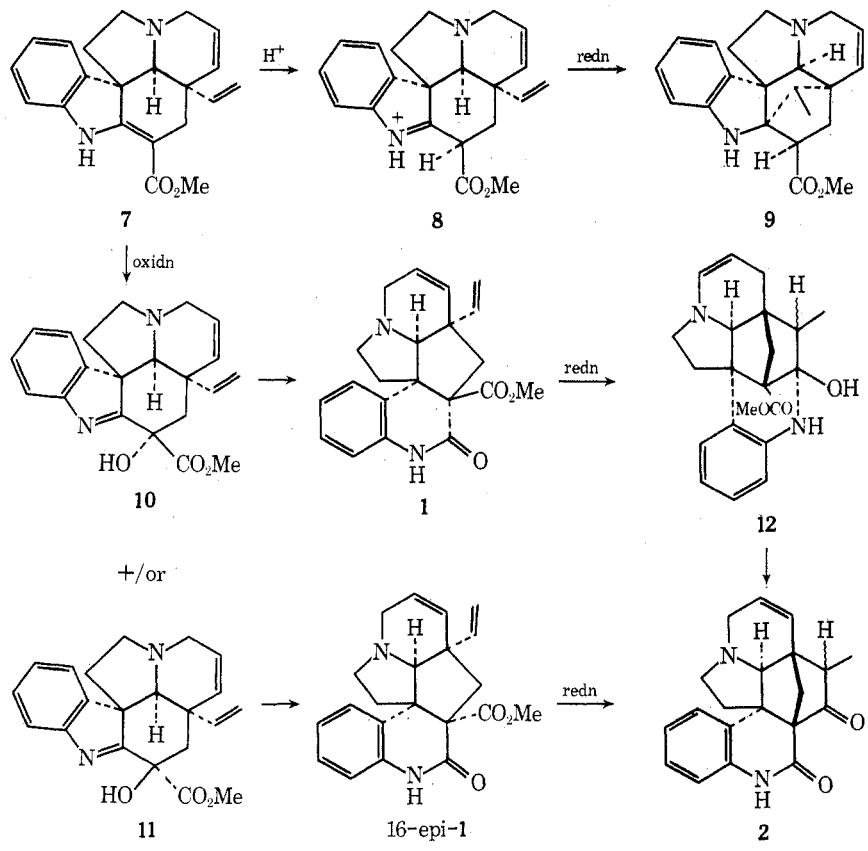
	6a[b]	6b		6a[b]	6b
C(3)	49.2	49.4	C(2′)	164.9	164.9
C(5)	52.7	52.9	C(3′)	58.2	58.2
C(6)	38.1	36.7	C(5′)	48.2	47.8
C(7)	50.9[c]	51.4	C(6′)	42.4	42.5
C(8)	124.5	124.6	C(7′)	54.1	53.8
C(9)	127.7[d]	127.4[e]	C(8′)	137.8	137.7
C(10)	123.5	123.2	C(9′)	121.6	121.2
C(11)	127.1[d]	127.3[e]	C(10′)	120.4	120.2
C(12)	114.6	112.8	C(11′)	127.4	127.3
C(13)	139.8	140.8	C(12′)	109.0	108.9
C(14)	125.8[d]	127.4	C(13′)	142.8	142.7
C(15)	129.4	129.9	C(14′)	56.4	56.3
C(16)	59.1	59.0	C(15′)	54.1	54.0
C(17)	40.3	41.9	C(16′)	90.6	90.5
C(18)	10.5	8.9	C(17′)	23.5	23.2
C(19)	49.8[c]	51.4	C(18′)	7.4	7.2
C(20)	46.5	47.6	C(19′)	26.9	26.7
C(21)	82.0	74.6	C(20′)	36.6	36.7
OCN	88.1	88.4	C(21′)	62.2	62.0
C=O	171.9	171.9	C=O	168.6	168.6
OMe	51.9	51.7	OMe	50.9	50.9

[a] In parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] Based solely on a proton-decoupled spectrum due to sample limitation. [c–e] Signals may be reversed.



6a, 19α-H
b, 19β-H

The relative stereochemistry of rings C and D of vincadifformine (**3**) and related *Aspidosperma* bases in solution has not been noted before. Models show that this indolizidine system remains unstrained in either cis or trans configuration. The association of the meloscandonine unit of **5a** and **5b** or its equivalent in **6a** or **6b** with the indolizidine part of pachysiphine offers some insight toward a choice between the



two configurations. The C(3′α) substituent of all four "dimeric" alkaloids shields both C(5′) and C(21′), a phenomenon possible only in a trans configuration.[18]

The *Melodinus* alkaloids are structurally unusual by incorporating a quinoline moiety within the framework of an *Aspidosperma* skeleton. The biogenetic origin of such structure pattern has been ascribed to an oxidative rearrangement of 18,19-dehydrotabersonine (**7**).[2] Analysis of this oxidation and semibenzilic acid rearrangement along stereochemical lines suggests that 16α-oxidation (via **10**) of **7** is conducive to forming scandine (**1**) and 16β-oxidation (via **11**) 16-episcandine (16-epi-**1**). In order to formulate the origin of the biogenetically exceedingly unusual structure of meloscandonine (**2**) or its equivalent in **6**, an analogy can be drawn with the derivation of vindolinine (**9**).[19] If it be assumed that the enzymic reduction of the vinyl group, normally proceeding toward tabersonine, involves a sterically well-disposed, neighboring positive carbon center, coupling would ensue causing **8**, **1**, and 16-epi-**1** to yield **9**, **12**, and **2**, respectively. Finallly, since the unraveling of the carbinolamine of **12**, yielding an aniline and norbornanone, followed by lactam formation, leading to **2**, is facile (see Experimental Section), alkaloids of both structure types **2** and **12** may be produced as a consequence of solely the sterically more favorable 16α-oxidation of **7**.

Experimental Section

The ^{13}C NMR spectra were recorded on a Varian XL-100-15 spectrometer operating at 25.20 MHz equipped to operate in the pulsed Fourier transform mode with Transform Technology Inc. computer and pulse hardware.

Chromatography of the crude alkaloid extract (59.76 g) from 5.80 kg of dry stems and leaves of *Melodinus scandens* Forst.[5] was chromatographed on Sephadex LH 20 (2 g of extract on 65 g of absorbent) and eluted with 7:3 methanol–chloroform. The eluates were monitored by TLC on Kieselgel H (50:1 ether–methanol). This procedure gave two fractions, 12.70 and 5.56 g, rich in "dimeric alkaloids". The first fraction was chromatographed on 400 g of Merck alumina (activity I) and eluted with ether up to 9:1 ether–methanol. This led to 536 mg of **6a**, 120 mg of **6b**, and 1.014 g of a mixture of **5a**, **5b**, **6a**, and **6b**. Chromatography of the second fraction on 180 g of Merck Kieselgel 60 (30–70 mesh) and elution with 20:1 ethyl acetate–methanol yielded 806 mg of a mixture of the four alkaloids, 682 mg of a mixture of **5a** and **5b**, and 1.435 g of **6a**, **6b**, and another alkaloid. Finally, preparative TLC on Merck Kieselgel G and elution with 9:1 ether–methanol led to the separation of **5a** and **5b** and preparative TLC on Merck alumina and elution with 20:1 ether–methanol separated **6a** and **6b**.

Scandomelonine (5a), crystallized from acetone: mp >300 °C dec; $[\alpha]_{578}^{22}$ −25° (*c* 1, $CHCl_3$); ir (KBr) NH 3370 (m), C=O 1745 (s), 1675 (s), C=C 1620 cm^{-1} (m); uv (EtOH) λ_{max} 264 nm (log ε 4.08), 296 (4.03), 329 (4.18), $\lambda_{shoulder}$ 235 (4.11); (EtOH–NaOH) λ_{max} 287 nm (log ε 4.21), 329 (4.19); ^1H NMR ($CDCl_3$) δ 0.84 (t, 3, *J* = 7 Hz, 19′-Me), 1.19 (d, 3, *J* = 7 Hz, 19-Me), 2.56 [s, 1, H(21′)], 3.80 (s, 3, OMe), 4.58 [s, 1, H(3′)], 5.98 (m, 2, olefinic H's), 6.18 [dd, 1, *J* = 7, 1.5 Hz, H(12)], 6.6–7.3 (m, 6, aromatic H's); MS *m/e* 670 (M^+, 5), 292 (72), 291 (42), 221 (43), 214 (base); accurate mass measurements[20] calcd for $C_{41}H_{42}O_5N_4$, 670.3155 (found, 670.3122); $C_{40}H_{41}O_4N_4$, 641.3128 (found, 641.3111); $C_{38}H_{30}O_3N_3$, 456.2287 (found, 456.2268); $C_{13}H_{12}O_2N$, 214.0868 (found, 214.0881).

Episcandomelonine (5b), amorphous: $[\alpha]_{578}^{22}$ +25° (*c* 1, $CHCl_3$); ir, uv, and ^1H NMR the same as those of **5a** except for 0.81 (d, 3, *J* = 7 Hz, 19-Me); MS *m/e* 670 (M^+, 11), 227 (45), 214 (base); accurate mass calcd for $C_{41}H_{42}O_5N_4$, 670.3155.

Scandomeline (6a), crystallized from acetone: mp >300 °C dec; $[\alpha]_{578}^{22}$ −170° (*c* 1, $CHCl_3$); ir (KBr) NH 3340 (w), C=O 1722 (s), 1660 (s), C=C 1610 (m), 1590 cm^{-1} (m); uv (EtOH) λ_{max} 259 nm (log ε 3.94), 302 (3.92), 3.28 (4.01), $\lambda_{shoulder}$ 232 (3.93); (EtOH–HCl) λ_{max} 270 nm (log ε 4.08), 296 (3.92), 327 (3.94), $\lambda_{shoulder}$ 234 (3.85); ^1H NMR ($CDCl_3$) δ 0.76 (t, 3, *J* = 7 Hz, 19′-Me), 1.16 (d, 3, *J* = 7 Hz, 19-Me), 3.63 (s, 3, saturated ester OMe), 3.76 (s, 3, unsaturated ester OMe), 4.51 [s, 1, H(3′)], 5.73 (m, 2, olefinic H's), 6.3–7.1 (m, 7, aromatic H's); *m/e* 702 (M^+, base), 673 (80), 606 (40), 392 (60); accurate mass calcd for $C_{42}H_{46}O_6N_4$, 702.8581 (found, 702.8563).

Episcandomeline (6b), crystallized from acetone: mp >300 °C dec; $[\alpha]_{578}^{22}$ −112° (*c* 0.5, $CHCl_3$); ir (KBr) OH 3540 (w), NH 3340 (w), C=O 1725 (s), 1655 (s), C=C 1600 cm^{-1} (m); uv and ^1H NMR the same as those of **6a** except for 0.77 (d, 3, *J* = 7 Hz, 19-Me); MS *m/e* 702 (M^+, 72), 685 (47), 684 (86), 673 (66), 655 (71), 626 (50), 588 (62), 488 (63), 470 (94), 392 (51), 375 (base); accurate mass calcd for $C_{42}H_{46}O_6N_4$, 702.8581.

Conversions of 6a and 6b into 5a and 5b, Respectively. A solution of 47 mg of scandomeline (**6a**) in 10 ml of acetic anhydride was heated at 100 °C for 6 h. Evaporation of the solvent under vacuum, preparative chromatography of the residue on Merck Kieselgel H, and elution with 12:1 ether–methanol yielded 3 mg of uninvestigated material, 12 mg of *N*-acetylscandomeline, and 7 mg (15%) of scandomelonine (**5a**), spectrally identical in all respects with **5a** above.

The same treatment of 200 mg of episcandomeline (**6b**) with 50 ml of acetic anhydride, preparative chromatography on Merck Kieselgel G, and elution with 13:1 ether–methanol yielded 62 mg of starting compound, 11 mg of *N*-acetylepiscandomeline, and 26 mg (13%) of episcandomelonine (**5b**), spectrally identical in all respects with **5b** above.

Registry No.—**5a**, 59813-31-9; **5b**, 59830-06-7; **6a**, 59813-32-0; **6b**, 59830-07-8.

References and Notes

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