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PYRROLIZIDINE OXIMES: A NOVEL NEW CLASS OF DENDROBATID ALKALOIDS

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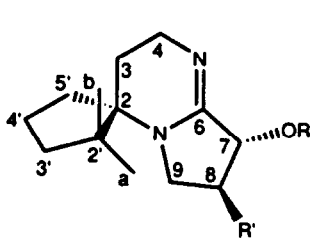
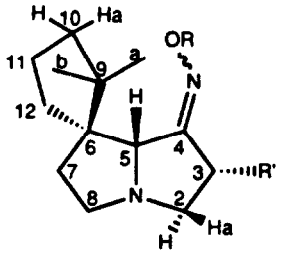
Abstract - Analysis of GC-FTIR spectra and reexamination of ^{1}H- and ^{13}C-NMR data led to revised structures for three closely related tricyclic alkaloids from a dendrobatid poison-frog *Dendrobates pumilio*. The simplest member, **222**, is a spiropentano-pyrrolizidine oxime, while **236** is the corresponding O-methyl oxime and **252**, a hydroxy-O-methyl oxime.

In 1987, tentative structures were proposed for three related minor alkaloids isolated from skin extracts of the Panamanian poison-frog *Dendrobates pumilio* (1). On the basis of NMR and mass spectrometry, tricyclic amidine structures, **1**-**3** (Fig. 1), were proposed for these alkaloids, **222**, **236** and **252** (1). However, GC-FTIR analysis of crude skin extracts and HPLC-purified materials has indicated that the strong IR absorption at 1660 cm^{-1}, previously found in a solution spectrum of **236** (2), was a result of contamination, since vapor phase spectra using a 30 m capillary column with **222**, **236** and **252** showed only the faintest absorption at ~1630 cm^{-1} (see Fig. 2) and not the intense absorption typical of amidines, such as exhibited (1675 cm^{-1}) by the model 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (3). The UV spectrum of **252** ($\lambda_{max}^{CH_3OH}$ 215 nm (ϵ 1950) sh 270-275 nm (ϵ 280)), likewise did not agree with published (4) spectral data, either for amidines or even imines.

These observations and further NMR studies raised serious doubts about the correctness of the originally proposed amidine structures and led us to reexamine our ^{1}H- and ^{13}C-NMR data and to augment these with long range ^{13}C-^{1}H correlation spectra and ^{1}H-NOESY studies. The amidine structures now are revised to the pyrrolizidine-4-oxime structures, **4**, **5** and **6** (Fig. 1), for alkaloids **222**, **236** and **252**, respectively (5).

Following is a brief summary of mass spectral data previously reported (1) for the three alkaloids: **222** (mass-measured molecular formula, $C_{13}H_{22}N_2O$, one exchangeable hydrogen, mass-measured base peak 112 ($C_5H_8N_2O$)); **236** ($C_{14}H_{24}N_2O$, no exchangeable hydrogen, base peak 126 ($C_6H_{10}N_2O$)), **252** ($C_{14}H_{24}N_2O_2$, one exchangeable hydrogen, base peak 142 ($C_6H_{10}N_2O_2$)).





1: 222 R = R' = H
2: 236 R = CH_3, R' = H
3: 252 R = CH_3, R' = OH

4: 222 R = R' = H
5: 236 R = CH_3, R' = H
6: 252 R = CH_3, R' = OH

Fig. 1. Structures **1**, **2**, **3** provisionally proposed (1) for alkaloids **222**, **236** and **252**; revised structures **4**, **5**, **6** for these three alkaloids

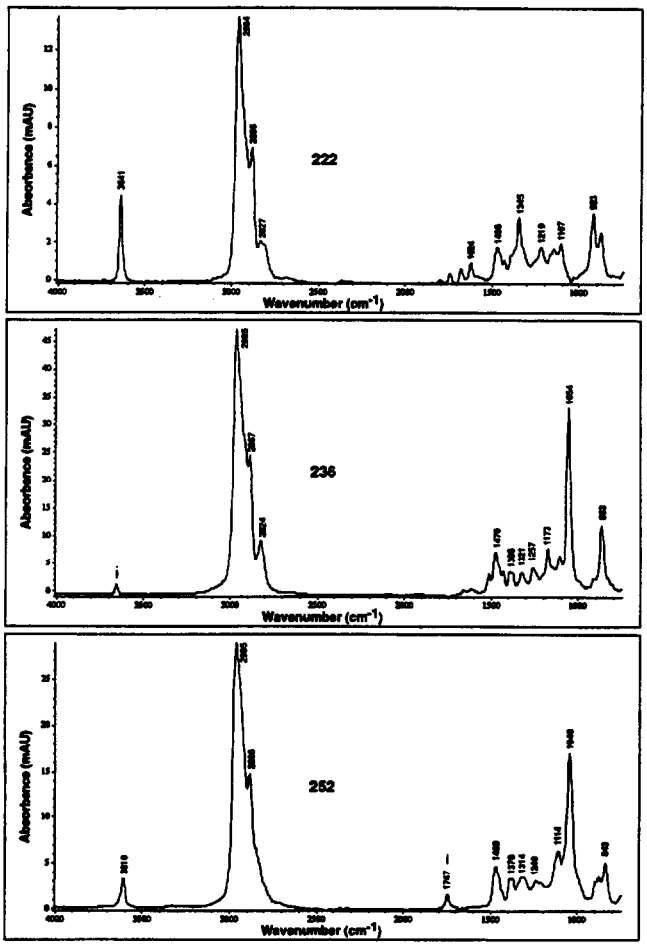


Fig. 2. GC-FTIR Spectra of Alkaloids **222**, **236** and **252** from *Dendrobates pumilio*. (see Experimental for conditions). i, impurity.

The ^{1}H-NMR spectra in C_6D_6 (Table 1) of the three alkaloids were very similar, including two well separated methyl singlets, which solution IR spectra showed were from a geminal dimethyl moiety (2), and a downfield singlet at δ3.8-4.0, originally assigned to a methine proton, H(7), adjacent to oxygen. We have now assigned this signal to H(5), a *CH* adjacent to nitrogen (6). Six other protons downfield from 2.4 ppm are common to **222** and **236** and are assigned to two pairs of geminal methylene protons adjacent to nitrogen with a third pair of protons in a different deshielded environment. Alkaloid **252** shares the former two pairs. The third pair of downfield protons mentioned above fits chemical shifts reported for hydrogens alpha to an oxime (9) or oxime ether (10).

These methylene protons adjacent to nitrogen show the significant δ_H difference between geminal protons as found in similar hydrogens in the pyrrolizidine alkaloids, due to nitrogen lone-pair anisotropy. Protons on the same face (a) as the lone-pair are deshielded. Inspection of Table 1 shows that with nearly every pair of geminal hydrogens, one (indicated with the "a" suffix) is significantly deshielded, either by N lone-pair anisotropy or another effect discussed below.

Table 1: ^{1}H-NMR Assignments (δ) for Pyrrolizidine Oximes[a]

Hydrogen Number	222 (C_6D_6)	236 (C_6D_6)	236 ($CDCl_3$)	252 (C_6D_6)	252 ($CDCl_3$)
2	2.46	2.50	2.48	2.80	2.79 (dd)
2a	2.93	2.88 (q)	3.10	3.23 (dd)	3.35 (dd)
3	2.47	2.43	2.70	--	--
3a	2.83	2.70 (ddd)	2.83	5.00 (dd)	5.04 (dd)
5	3.96 (s)	3.88 (s)	3.83 (s)	3.83 (s)	3.79 (s)
7	1.21 (dt)	1.25 (dt)	~1.55	1.39	~1.58
7a	1.80 (dt)	1.79 (dt)	1.95	1.73	1.97 (dt)
8	2.42	2.46	2.70	2.77	2.97
8a	2.88	2.85 (q)	3.05	2.86	
9-CH_3(a)	1.12	1.11	0.98	1.04	0.97
9-CH_3(b)	0.92	0.89	0.96	0.81	
10	1.39	1.40		1.40	1.48
10a	1.59	1.63	~1.4-1.7 (m)	1.57	~1.58
11	1.51	1.53		1.54	1.58
11a	1.67	1.65		1.69	1.67
12	1.07	1.12	1.25	1.40	1.35
12a	2.09	2.10	1.95	2.33	2.15 (ddd)
$NOCH_3$	---	3.81 (s)	3.87 (s)	3.57 (s)	3.90

[a]We have adopted the numbering system used by Meinwald *et al* (8) for nitropolyzonamine (7), even though that system differs from the conventional numbering of pyrrolizidines. The correspondence with the original amidine numbering (in parentheses) is as follows: 2 (9), 3 (8), 4 (6), 5 (7), 6 (2), 7 (3), 8 (4), 9 (2'), 10 (3'), 11 (4'), 12 (5'). To be consistent in nomenclature with "a" protons of a geminal pair being the more deshielded, we have reversed the original nomenclature for 2, 3, 7 and 8 protons. CH_3(a) in the original ^{1}H-NMR data (1) was incorrectly indicated in Table 7, but not the text, as the more shielded methyl in C_6D_6. The signals for H(2), H(2a) and H(3a) (originally H(9), H(9a) and H(8a), resp.) of **252** have been reversed from the original assignment. Note that CH_3(a) and CH_3(b) of all three alkaloids are well separated in C_6D_6 but overlap in $CDCl_3$.

The ^{13}C-NMR signals (Table 2) for **222**, **236** and **252** indicated one sp^2 carbon, C(4) (~164-5 ppm), requiring either a carbonyl or -C=N- group. The former is excluded by GC-FTIR. Two singlets at ~59 and 44 ppm are assigned to contiguous carbons, one, the spiro-, the other, the dimethyl substituted carbon. A CNOE experiment indicated only the sp^2 carbon, C(4), and the spiro carbon C(6) were affected by irradiation of H(5). CH long range correlation spectroscopy (see Experimental) with **222**, **236** and **252**, indicated C(5) to be within two bonds of the carbons (C(2), C(3) and C(8)) bearing downfield hydrogens, and led directly to a pyrrolizidine structure. Since one tertiary nitrogen is required here, the other nitrogen must be in a -C=N- bond, and from the absence of any significant IR absorption, most likely comprises an oxime group (11). The weak Bohlmann band (~2825 cm^{-1}) observed for **222**, **236** and **252** (Fig. 1) is typical of cis fused pyrrolizidines, e.g. methyl pyrrolizidine-1-carboxylate, 2807 cm^{-1} (vapor phase) (12). Computer molecular modelling indicated a dihedral angle of 138° for H(2) or H(8) with the nitrogen lone pair,

Table 2: ^{13}C-NMR Assignments (δ_C) for Pyrrolizidine Oximes[a]:

Carbon Number	**222** (C_6D_6)	**236** ($CDCl_3$)	**252** ($CDCl_3$)
2	50.4 (t)	50.4 (t)	57.7 (t)
3	26.4 (t)	26.8 (t)	70.4 (d)
4	163.9 (s)	164.0 (s)	165.0 (s)
5	67.8 (d)	67.9 (d)	67.9 (d)
6	58.6 (s)	58.4 (s)	58.9 (s)
7	35.6 (t)	35.5 (t)	35.3 (t)
8	52.7 (t)	52.7 (t)	53.0 (t)
9	43.5 (s)	43.3 (s)	43.7 (s)
10	39.3 (t)	39.1 (t)	39.0 (t)
11	20.0 (t)	19.9 (t)	20.1 (t)
12	34.3 (t)	34.2 (t)	36.0 (t)
9-CH_3(a)	25.9 (q)	25.6 (q)	25.8 (q)
9-CH_3(b)	23.8 (q)	23.8 (q)	23.8 (q)
N-OCH_3	--	61.5 (q)	62.2 (q)

[a]For correspondence with the original amidine numbering see legend to Table 1. Original assignments (1) for 2', 3', 4' and 5' have been revised.

much less than the 180° required for maximum Bohlmann bonds. In Table 1, note that the multiplicity (dt) observed for H(7) and H(7a) is that reported for similar hydrogens in the pyrrolizidines isoretronecanol and trachelanthamidine (13). The δ_H for H(8) and H(8a) of **236** ($CDCl_3$) also are similar to that of H(5) and H(5a) of isoretronecanol (2.64, 3.04 ppm) as are δ_c for C(2) and C(8) of **236** in comparison with reported values (54.8, 54.5 ppm) for the equivalent carbons of isoretronecanol (13).

The strong absorptions at ~1050 and 850-860 cm^{-1} (ν_{N-O}) seen in **236** and **252** have been reported in oxime O-methyl ethers (14), while the intense ν_{O-H} in the IR spectrum of **222** (3641 cm^{-1}) is typical of that absorption in oximes (15), but not alcohols (e.g. **252**) where it is much less intense.

Table 3. Interatomic Distances Calculated for **236** (**5**)[a] and Selected Measured Nuclear Overhauser Effects in C_6D_6 (1D-DIF)

Hydrogens	d (Å)[a]	NOE (%)[c]
H(2) - H(8)	1.7	
H(2a) - H(8a)	3.5	
H(2a) - H(5)	3.6	
H(3a) - H(5)	3.7	
H(5) - H(8a)	3.5	(1.5)
H(5) - H(7a)	3.3	(0.7)
H(5) - CH_3(a)	2.3	11 (4.8)
H(5) - CH_3(b)	2.3	6 (2.5)
H(7a) - H(10)	2.5	3 (4.2)
H(7a) - CH_3(b)	1.5	8 (7.4)
H(7a) - H(12)	2.4	
H(10) - CH_3(b)	2.2	5 (1.4)
H(10) - H(7a)	2.5	(4.2)
CH_3(a) - $NOCH_3$	~2.0[a,b]	(0.7)
CH_3(b) - $NOCH_3$		

[a]Chem 3D® program for the Macintosh computer.
[b]Greater than 4.3Å in anti stereoisomer.
[c]The steady state nuclear Overhauser effect observed upon irradiation of the first proton of the pair in "Hydrogens" column. Data in parentheses were obtained at 40°C. See Experimental for additional data.

The configuration of the spiro-fused cyclopentane ring is clearly indicated by NOE and ^{1}H-NOESY studies (see Experimental, Table 3). In particular, irradiation of H(5) in **236** caused an 11% NOE with the downfield methyl, CH_3(a), and a 6% NOE with the other methyl. In the case of **252**, irradiation of either CH_3(a) or CH_3(b) led to a 15% NOE at H(5). This establishes the dimethyl-substituted side of the spirocyclopentane ring closer to H(5). This ring is fused to C(6) of the pyrrolizidine to account for the H(5) singlet. The significantly downfield-shifted C(6) signal in the ^{13}C-NMR spectrum (-59 ppm), erroneously assumed to be adjacent to nitrogen in structures **1-3**, may be a consequence of steric congestion (*cf.* C(7) of bornylene, 56.6 ppm). One face (a) of the spiro-fused C_5 ring is deshielded relative to the other, evidently by the influence of the oxime or oxime ether anisotropy. NOE studies (see Experimental) establish the H(12a) hydrogen being close to the deshielded methyl CH_3(a) and H(7a) and H(10) being close to CH_3(b).

HOHAHA- correlations were detected at a long mixing time between H(5), H(3) and H(2) of alkaloid **236**. This probably reflects a small ^{4}J acting through a w-shaped linkage between H(5) and H(3) and also H(5) and H(2) in the same manner as CH_3(a) protons are coupled to CH_3(b) protons.

The hydroxyl group in **252** is clearly located at C(3) in view of the major downfield shift seen at C(3) and minor shift at C(2) in the ^{13}C-NMR spectrum of **252** compared to **236**. This also is reflected in the δ_H (Table 1) of H(3), which is shifted to 5.0 ppm and appears as a doublet of doublets. The adjacent hydrogens H(2) and H(2a) of **252** are shifted downfield relative to their positions in **236** and form an ABX pattern with H(3) ($J_{2,3} \cong 6.1$, $J_{2a,3} = 7.1$, $J_{2,2a} = 10.8$ Hz; 100 MHz, C_6D_6). The relative configuration of the

3-hydroxyl group in **252** is trans to H(5) on the basis of the following observations:

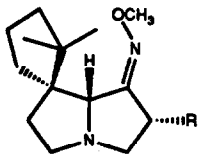
a) In comparing **236** and **252** (Table 1), it will be noted that H(7), H(8), H(12) and H(12a) of **252** all show downfield ($\Delta\ \delta$ = 0.14-0.31) shifts, but H(7a), H(8a) show little change, suggesting that the 3-OH group is deshielding protons on the molecular face opposite the nitrogen lone-pair.

b) NOE studies (1D-Diff.) detected a strong NOE between H(3) and H(2a) but only a weak NOE with H(3) and H(2). A 6% NOE is observed between H(3) and H(5). In $CHCl_3$, where CH_3(a) and CH_3(b) overlap, a 13% NOE is observed between them and H(2a). Computer molecular modelling studies indicate the H(3)-H(2a) and H(3)-H(2) dihedral angles are approximately equal and ca. 120°, in agreement with the observed multiplicity and vicinal couplings of 7.1 and 6.1 Hz, respectively. These alone do not permit an assignment of the 3-hydroxyl group configuration.

The configuration of the oxime group, while not as unambiguously established, is assigned as **Z** (syn) for **236** (**5a**) or **E** (substituent priority change) for **252** (**6a**), based on the following:

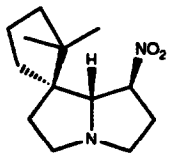
a) A steady state 1D-NOE experiment in C_6D_6 indicated a 1% enhancement of the $NOCH_3$ signal when CH_3(a) was irradiated.

b) The ^{1}H-NMR spectrum of 4-*t*-butylcyclohexane oxime shows δ2.05, 2.48 for axial and equatorial hydrogens for the α-methylene group on the anti side, roughly similar to H(3) and H(3a) of **236** (2.70, 2.83), while showing δ1.81(a), δ3.39(e) for the α-CH_2 group on the syn side (9). Oxime *O*-methyl ethers in CCl_4 have a similar, but smaller deshielding of the *syn* side relative to the *anti* side, but the difference is reversed in C_6D_6 (10). The observed deshielding of one face of the spiro cyclopentane ring (CH_3(a), 10a, 11a, 12a) in all three alkaloids most probably reflects the deshielding effect of the *syn* side of the oxime (16) or oxime ether.



5a: R = H

6a: R = OH

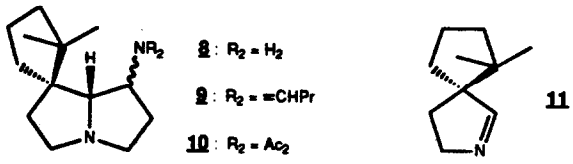


Z

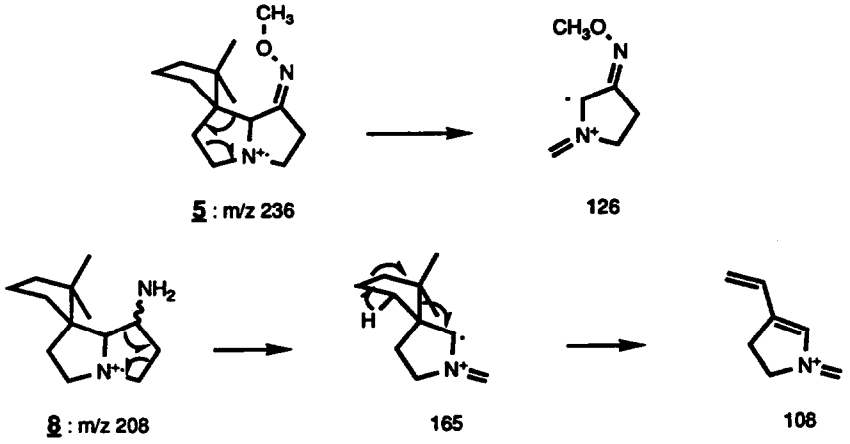
In the course of our structural investigation, we found a report on a closely related natural product, nitropolyzonamine (**7**), the defensive secretion of a small millipede, *Polyzonium rosalbum*, which had been determined by x-ray diffraction analysis and synthesis (17). Clearly related to our oximes, it may even have the same absolute configuration (*cf.* $[\alpha]_D$ nitropolyzonamine +12° (17); **236** +56° (1); **252** +18° (1)).

The meager amounts of **222**, **236** or **252** available to us have precluded significant chemical studies; however, we have reduced **236** with sodium in refluxing *n*-butanol to a

primary amine, 8, (m/z 208, 165, 108), isolated from the reaction as a butyraldehyde Schiff's base 9 (m/z 262, 165, 108). It was acetylated to a ~2:1 mixture of diastereomeric diacetates 10 (see Experimental).



The mass spectral fragmentation of 222, 236, 252 is nearly exclusively dominated by the cleavage of a 110 amu fragment from the molecular ion. This is illustrated in Scheme 1 for 5, along with proposed cleavages for the two major ions in the derived amine 8.



Scheme 1. Major E.I. Mass Spectral Fragmentations for Alkaloid 236 (5) and its Reduction Product (8).

Although oximes have been proposed as intermediates in the oxidative metabolism of amine compounds (NH_2 --> NH-OH --> -N=O -->=N-OH) (19), to our knowledge no naturally occurring oximes or oxime ethers have been reported. The biosynthesis of these alkaloids could involve as a precursor the terpenoid alkaloid, polyzonimine 11, (17) as has been hypothesized for nitropolyzonamine (8). However, neither polyzonimine nor nitropolyzonamine have been detected as yet in frogs or toads.

EXPERIMENTAL

Instrumentation: GC-FTIR spectra were obtained with a Hewlett-Packard 5890 gas chromatograph equipped with a bonded fused silica (30 m x 0.32 mm) HP-5 column (poly 5% phenylmethylsiloxane - 95% dimethylsiloxane) programmed 100-280° (10°/min) and interfaced with a Hewlett-Packard 5965A IR detector (narrow band 4000 - 750 cm^{-1}). The UV spectrum of **252** in CH_3OH was obtained with a Beckman DU-7 spectrophotometer and 1.0 cm cells. Mass spectra were measured with a Finnigan Model 800 ion trap mass detector interfaced with a Hitachi gas chromatograph equipped with a similar column as used for GC-FTIR. A Finnigan 4500 mass spectrometer with a 25 m x 0.25 mm OV-1 GC column was also used. An ND_3 bleed on this instrument permitted the determination of exchangeable hydrogens. ^1H- and ^{13}C-NMR spectra were measured in C_6D_6 or $CDCl_3$ with a JEOL FX 100 or GX 400 spectrometers. δ_H are in ppm downfield from internal TMS (δ = 0.0). IR solution spectra of **236** and **252** were measured in $CHCl_3$ with 0.5 mm cells and a JASCO Model A-100 instrument.

Sodium-Butanol Reduction Product (8) of 236:

MS (E.I.) 209 (40), 192 (5), 165 (68), 150 (14), 136 (5), 122 (27), 109 (47), 108 (100), 95 (53), 82 (38).

Butyraldehyde Schiff's Base (9) of Sodium-Butanol Reduction Product:

MS (Finnigan 4500): 262 (18), 233 (5), 165 (78), 150 (7), 136 (5), 122 (18), 108 (52), 95 (24), 82 (100). No exchangeable H.

GC-FTIR: 2960, 2892, 2800, 1619, 1469, 1381 broad, 1318, 1125 broad, 766 cm^{-1}.

A single sharp peak on GC (RT = 11.1 min).

N,N-Diacetyl Derivatives (10a, 10b) of Sodium-Butanol Reduction Product

MS (E.I.): m/z 251 (M^++1-42) (18), 208 (26), 192 (15), 166 (12) 152 (30).

GC-FTIR (10a, 10b): Two peaks at 20.1, 20.2 mins. with identical FTIR spectra: 2960, 2890 (shoulder), 1710 (estd.), 1678 (vs) 1485, 1412, 1370, 1319, 1240 cm^{-1}.

Summary of ^1H- and ^{13}C-NMR Correlation Experiments:

222: *HMBC* (C_6D_6) (intense cross peaks are underlined).*

2C: H3, 3a, 5, 8, 8a.
3C: H2, 2a, 5.
4C: H2, 2a, 3, 3a, 5.
5C: H2, 2a, 3, 7, 7a, 8, 8a, 12a.
6C: H5, 7, 7a, 8, 8a, 10, 10a, 11a, 12, 12a, CH_3(a), CH_3(b)
7C: H8, 8a, 12, 12a.
8C: H2, 2a, 5, 7, 7a.
9C: H5, 7, 7a, 10, 10a, 12, CH_3(a), CH_3(b).
10C: H7 (weak), 11, 11a, CH_3(a), CH_3(b).
11C: H10, 10a, 12, 12a.
12C: H5, 7, 7a, 10, 10a.
CH_3(a): H7, 10, 10a, CH_3(b).
CH_3(b): H10, CH_3(a).

*a proton-detected long range heteronuclear multiple quantum coherence experiment.

^1H- and ^{13}C-NMR Corr. Expts. (Cont.).

236: Long range CH-COSY (low pass J-filtered) (more intense cross peaks are underlined) (C_6D_6):

2C with H3a, 5, 8
3C with H2, 5
4C with H2a, 3, 5
5C with H2, 2a, 7
6C with H5, 7a, 8, 8a, 10a, 12a, CH_3(a), CH_3(b)
7C with 8, 8a, 12a
8C with H2, 2a, 5, 7a
9C with H5, 7a, CH_3(a), CH_3(b)
10C with CH_3(a), CH_3(b)
11C with H10a
12C with H5, 7, 7a, 11
CH_3(a) with CH_3(b)
CH_3(b) with CH_3(a)

Long range CH (J resolution). Signals enhanced with INEPT.

irradiation of H-	affects C- (J_{C-H} (Hz))
3a	5 (2.8)
5	2 (5.0), 3 (2.5), 6 (3.0), 8 (3.0), 9 (3.3), 12 (4.0)
7a	5 (1.8), 6 (3.3), 8 (3.8), 9 (3.6), 12 (5.1)
12a	5 (3.6), 6 (3.8), 9 (1.6)
CH_3(a)	6 (3.2), 9 (4.2), 10 (4.2)

236: 2D ^{13}C-^1H HOHAHA (320 ms mixing time) (C_6D_6).

			$^1J_{CH}$ (Hz)
Correlation of:	2C with H8/8a, 3/3a, 5 (weak)		143,134
	3C with H2/8, 2a/8a, 5		131
	5C with H2/8, H2a/H8a, 3/3a,		146
	7C with H2/8, 2a/8a		131
	8C with H2/8, 2a/8a, 7, 7a		143,131
	10C with H11, 12a, CH_3(a)		127
	11C with H10, 10a, 12, 12a		131,126
	12C with H10, 10a, 11		128
	CH_3(a) with CH_3(b)	$^1J_{CH_3}$(a)	125
	CH_3(b) with CH_3(a)	$^1J_{CH_3}$(b)	124
		$^1J_{OCH_3}$	143

252: Long range CH (J resolution) ($CDCl_3$). Signals enhanced with INEPT.

irradiation of H-	affects C- (J_{C-H} (Hz))
2	4 (-2.1), 5 (1.7)
2a	3 (-1.1), 8 (2.7)
3	2 (-1.0), 4 (2.3), 5 (2.2)
5	3 (2.6), 6 (3.0), 8 (2.2), 9 (3.6), 12 (3.5), OCH_3
7	5 (2.6), 6 (3.0), 8 (3.6), 9 (3.8)
8/8a	5 (4.3), 6 (3.6), 7 (2.3)
12	5 (3.5), 6 (4.2), 9 (-1.5)
CH_3(a)	CH_3(b) (4.1)

NOE Experiments:

Steady State NOE:

236 (C_6D_6): Irradiation (40°) at H3a affects H2a, 5.7%
H5 affects H2a and/or H8a, 1.5%; H7a, 0.7%; CH_3(a), 4.8%; CH_3(b), 2.5%
H7 affects H8, 3.6%
H7a affects H8a, 1.7%; H10, 5.4%
H10 affects H7a, 4.2%; CH_3(b), 1.4%
H12a affects H10a and/or H11a, 2.6%
CH_3(a) and H2a affects H5, 15.1%; H7, 2.7%; H11a, 7.2%; OCH_3, 0.7%; CH_3(b), 6.5%
CH_3(b) affects H5, 6.6%; H7a, 7.4%; H8a, 1.4% H10, 4.8%; CH_3(a), 5.7%

CNOE (1D):

irrad at H5 affects C4 and C6

VNOESY (1.2 s mixing time)

H5 with: CH_3(a) and CH_3(b)
H7a with: CH_3(b)
H8 with: H7, H7a
H8a with: H7, H7a
H12a with: H10a, H11, CH_3(a)
CH_3(a) with: CH_3(b), H10, H10a, H11, H11a

252 (C_6D_6): Steady State NOE:

irrad CH_3 (a,b) affects H2a (13%) ($CDCl_3$; separate experiment)
irrad H2 affects H3 (14%)
irrad H2a affects H3 (15%)
irrad H3 affects H2 (15%), H2a (10%), H5 (6%)
irrad CH_3(a) affects H3 (5%), H5 (15%)
irrad CH_3(b) affects H3 (4%), H5 (15%)

1D Difference NOE:

irrad H3: large NOE with H2a, small with H2, OCH_3, faint with H5.

VNOESY (1.2 s mixing time) (likely interactions are underlined for pairs of overlapping signals):

H2 with H2a
H3 with H2, H2a, CH_3(a)
H5 with $NOCH_3$, CH_3(a) (more intense), CH_3(b) (less intense)
H8,H8a with H7 and H7a
H12a with H11a, H10a/H11, H12/H10, CH_3(a)
CH_3(a) with H10a/H11
CH_3(b) with H7a/H11a, H8/H8a

H-NOESY:

H3 with both H2 and H2a (equal intensity)
H5 with H2, CH_3(a), CH_3(b) (all weak)
H8/H8a with H11 and H12
H11a with H10, H10a
H12a with H10, H10a, H11a

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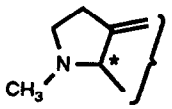

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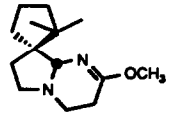

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