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New Type of Trimeric and Pentameric Indole Alkaloids from *Psychotria rostrata*

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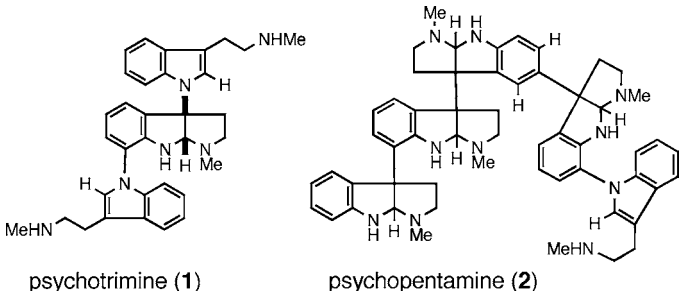
ABSTRACT



psychotrimine (**1**) psychopentamine (**2**)

Two new tryptamine-related alkaloids, psychotrimine and psychopentamine, were isolated from the leaves of *Psychotria rostrata*, and their novel structures were elucidated on the basis of spectroscopic analyses.

The potent antinociceptive activities of polymeric pyrrolidinoindoline alkaloids that interact with opioid or NMDA receptors have been reported.[1] In our continuing chemical and pharmacological studies on indole alkaloids possessing analgesic activity,[2] we have been interested in compounds of this type, which have been isolated from plants belonging to genera *Psychotria*, *Calycodendron*, and *Idiospermum*.[3] We started with the investigation of the alkaloidal constituents of *Psychotria rostrata* Bl., the leaves of which were used as folk medicine for the treatment of constipation in Malaysia. (−)-Calycanthine, (+)-chimonanthine, hodgkinsine, calycosidine, and quadrigemine B were isolated from the bark and twigs of this plant.[4] In the present study, we isolated two new alkaloids, psychotrimine (**1**) and psychopentamine (**2**), from the MeOH extract of *P. rostrata* leaves. We report herein the structure elucidation of the new alkaloids by means of spectroscopic analyses.

New compound **1**, obtained as an amorphous powder (1.30% yield based on the crude base fraction), exhibited $[\alpha]^{18}_{D}$ +179 (*c* 0.2, $CHCl_3$). The molecular formula ($C_{33}H_{38}N_6$) obtained by high-resolution FABMS analysis [*m*/*z* 519.3206 $(M + H)^+$ (Δ −3 mmu)] was identical with those of known trimeric alkaloids hodgkinsine,[5] idiospermuline,[6] and calycosidine.[7] The UV absorption bands [296 (log ϵ 3.99), 222.5

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Table 1. ^{1}H and ^{13}C NMR Data for Psychotrimine (**1**) and Psychopentamine (**2**) (in $CDCl_3$)[a]

psychotrimine (**1**)				psychopentamine (**2**)							
units	position	δ_H	δ_C	units	position	δ_H	δ_C	units	position	δ_H	δ_C
A	2	7.20 (s)	126.0	A	2	2.42 (m)	52.7**	D	2‴	2.34 (m)	52.5**
	3		114.9			2.86 (m)				2.42 (m)	
	3a		128.5		3	1.82 (dd, 12.1, 5.5)	37.8		3‴	1.69 (m)	39.2
	4	7.72 (dd, 8.0, 1.1)	119.4*			3.05 (m)				1.79 (m)	
	5	7.21 (dd, 8.0, 7.4)	119.9		3a		61.1		3a‴		62.3
	6	7.27 (m)	122.4		3b		132.9*		3b‴		138.6
	7	7.27 (m)	111.2		4	7.25 (d, 7.4)	126.9		4‴	6.59 (dd, 7.4, 1.4)	123.3
	7a		136.1		5	6.82 (dd, 7.4, 7.4)	118.8		5‴	6.61 (dd, 7.4, 7.4)	118.8
	8	3.07 (2H, m)	25.6***		6	7.03 (dd, 7.7, 7.7)	128.0		6‴	6.94 (dd, 7.4, 1.4)	125.1
	9	3.00 (2H, m)	52.0		7	6.38 (d, 7.7)	110.5		7‴		120.4
	$N_{10}CH_3$	2.44 (3H, s)	36.4**		7a		152.8		7a‴		144.7
B	2′	3.09 (m)	51.7		8a	4.14 (s)	87.3		8a‴	4.61 (s)	88.4
		2.81 (ddd, 9.6, 9.6, 5.3)			N_1-CH_3	2.11 (3H, s)	34.8		$N_{1‴}$-CH_3	2.27 (3H, s)	35.7
	3′	3.28 (ddd, 11.5, 9.6, 6.8)	39.1	B	2′	2.47 (m)	52.7**	E	2⁗	7.15 (s)	126.1
		2.54 (ddd, 11.5, 5.3, 2.1)				2.90 (m)			3⁗		114.5
	3a′		76.7		3′	2.16 (m)	35.8		3a⁗		128.3
	3b′		132.0			2.42 (m)			4⁗	7.72 (d, 7.1)	119.3
	4′	7.09 (d, 7.6)	123.7		3a′		63.1		5⁗	7.17 (dd, 7.1, 8.0)	111.2
	5′	6.80 (dd, 7.6, 7.6)	119.3*		3b′		132.8*		6⁗	7.22 (dd, 7.6, 8.0)	122.3
	6′	7.18 (d, 7.6)	127.3		4′	7.26 (d, 7.6)	122.1		7⁗	7.20 (d, 7.6)	119.7
	7′		121.5		5′	6.66 (dd, 7.6, 7.6)	116.2		7a⁗		136.0
	7a′		145.9		6′	7.00 (d, 7.6)	126.5		8⁗	2.98 (m)	25.7
	8a′	5.24 (s)	86.1		7′		123.8			3.05 (m)	
	$N_{8'}H$	4.39 (brs)			7a′		151.0		9⁗	2.98 (m)	52.1
	$N_{1'}$-CH_3	2.42 (s)	36.4**		8a′	4.46 (s)	82.4			3.05 (m)	
C	2″	7.27 (s)	124.3		$N_{1'}$-CH_3	2.36 (3H, s)	35.3		$N_{10⁗}$-CH_3	2.48 (3H, s)	36.5
	3″		112.5	C	2″	2.47 (m)	52.6**				
	3a″		129.8			2.86 (m)					
	4″	7.61 (dd, 7.7, 2.2)	119.3*		3″	2.13 (dd, 11.4, 5.1)	37.2				
	5″	7.09 (m)	119.3*			2.63 (m)					
	6″	7.09 (m)	121.7		3a″		64.2				
	7″	7.37 (dd, 7.4, 2.0)	112.2		3b″		132.6				
	7a″		136.1		4″	5.85 (d, 1.6)	121.4				
	8″	2.98 (2H, m)	25.7***		5″		136.2				
	9″	2.91 (2H, m)	52.0		6″	6.67 (dd, 7.7, 1.6)	126.1				
	$N_{10''}$-CH_3	2.49 (3H, s)	36.3**		7″	6.39 (d, 7.7)	108.5				
					7a″		149.8				
					8a″	5.00 (s)	83.4				
					$N_{1''}$-CH_3	2.46 (3H, s)	35.8				

[a] *, **, *** interchengeable.

(4.57), and 206.5 (4.55) nm] and the ^{13}C NMR spectrum (Table 1) that disclosed 22 aromatic carbons and 11 sp^3 carbons including one characteristic aminoacetal carbon (δ 86.1) indicated that **1** was composed of three tryptamine-related moieties containing one indoline and two indolic chromophores. The structures of the three individual parts

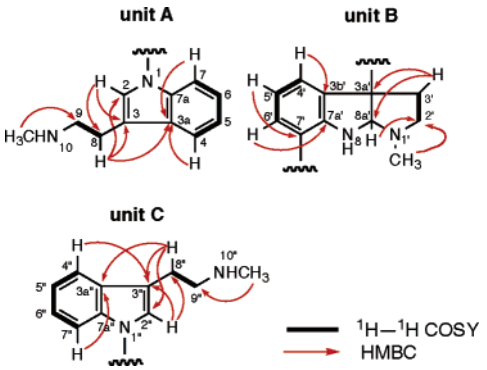

Figure 1. Selected 2D NMR correlations for units A−C in psychotrimine (**1**).

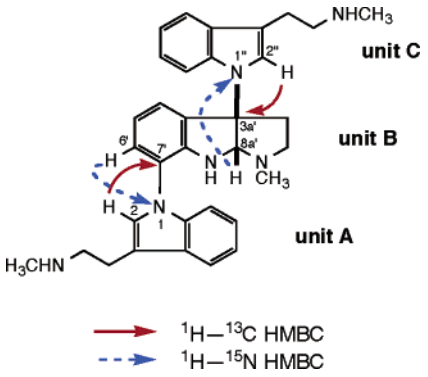

Figure 2. Selected HMBC correlations for psychotrimine (**1**).

in **1** were revealed by detailed analysis of one- and two-dimensional NMR spectra, as follows.

The ^{1}H and ^{13}C NMR, and ^{1}H−^{1}H COSY spectra (Figure 1) suggested that units A and C had one indole nucleus, respectively, and no substituents at C-4, -5, -6, and -7 of the indole nucleus. Further, characteristic proton signals at C-2 and C-2″ in units A and C (δ 7.20, 1H, s, for unit A and δ 7.27, 1H, s, for unit C) were observed. In addition, the HMBC connectivities shown in Figure 1 suggested that each unit possessed a fragment, MeN-CH_2CH_2-, which was connected to C-3 of each indole nucleus. Taken together, new compound **1** had two N_{10}-methyltryptamine units, A and C, which were connected to another unit, respectively, at N_1 and/or N_{10}. The ^{13}C NMR spectrum revealed that unit B had six aromatic carbons and five sp^3 carbons. The characteristic NMR signals ascribable to C-8a′ (δ_H 5.24, 1H, s, and δ_C 86.1) implied that unit B possessed a pyrrolidinoindoline skeleton. The ^{1}H NMR spectrum indicated the presence of one methyl group that was attached to the nitrogen atom in unit B. The chemical shift, i.e., δ 2.42, and the HMBC cross-peak between this proton and C-2′ suggested that the methyl group existed on the N-1′ function. The splitting mode of the protons in the aromatic region (δ 7.09, d J = 7.6 Hz, δ 6.80, dd J = 7.6 and 7.6 Hz, and δ 7.18, d J = 7.6 Hz) in unit B and the HMBC cross-peaks between the aromatic proton at δ 7.18 (H-6′) and C-7a′ (δ 145.9), the proton at δ 6.80 (H-5′) and C-7′ (δ 121.5), and the proton at δ 7.09 (H-4′) and C-3b′ (δ 132.0) indicated the presence of a substituent at C-7′ in unit B. Finally, the connected positions of units A to C were determined by analyzing ^{1}H−^{13}C and ^{1}H−^{15}N HMBC connectivities (Figure 2). The HMBC cross-peaks between H-2″ (δ 7.27) and C-3a′ (δ 76.7), and H-8a′ (δ 5.24) and N-1″ (δ −235) indicated that N-1″ was attached to C-3a′. In addition, the HMBC cross-peaks between H-2 (δ 7.20) and C-7′ (δ 121.5), and H-6′ (δ 7.18) and N-1 (δ −242) implied that N-1 was attached to C-7′. Therefore, the structure of the new alkaloid, named psychotrimine, was deduced to be that shown as formula **1**. All the hitherto known tryptamine-related polymeric alkaloids are composed of pyrrolidinoindoline units (see Figure 5) and rarely additional tetrahydroquinoline units. Psychotrimine is the first example of this class of alkaloid that contains the tryptamine unit in the molecule.

New compound **2**, obtained as an amorphous powder (0.34% yield based on the crude base fraction), exhibited $[\alpha]^{18}_D$ +42 (*c* 0.2, $CHCl_3$). The molecular formula ($C_{55}H_{62}N_{10}$) obtained by high-resolution FABMS analysis [*m*/*z* 863.5244 $(M + H)^+$ (Δ +0.7 mmu)] was identical with those of known pentameric alkaloids psychotridine,[8] psychotridine C,[9] and isopsychotridines A, B, C, and E.[7a,10] All of these known compounds are composed of five pyrrolidinoindoline units that are connected to each other through a linkage between C-3a/C-3a′ and/or C-3a/C-7′. The UV spectrum of **2** [304 (log ϵ 4.10), 250.5 (4.37), and 210 (4.81) nm] showed absorption bands similar to those of simple pyrrolidinoindoline alkaloids.[11] However, the ^{13}C NMR spectrum (Table 1) that revealed 32 aromatic carbons and 23 sp^3 carbons including four aminoacetal carbons (δ 82.4, 83.4, 87.3, and 88.4), and the ^{1}H NMR spectrum that showed a characteristic proton signal at δ 7.15 (1H, s) indicated that **2** was composed of five tryptamine-related moieties containing one indolic and four indoline chromophores. The structures of the five individual parts in **2** were confirmed by detailed analysis of one- and two-dimensional NMR spectra, as follows.

^{1}H−^{1}H COSY, HMQC, and HMBC spectral data (Figure 3) suggested that unit A, which consisted of a pyrrolidinoin-

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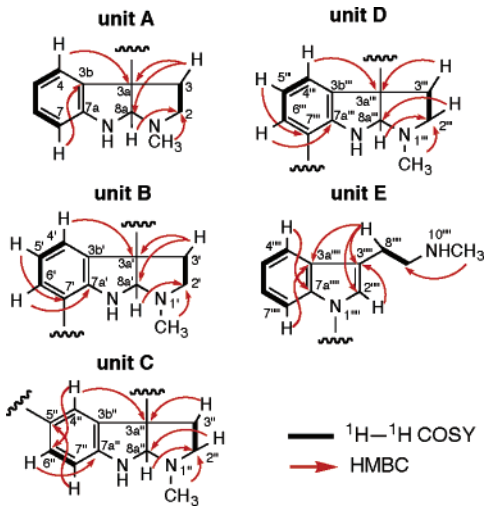

Figure 3. Selected 2D NMR correlations for units A–E in psychopentamine (**2**).

doline framework, had no substituents at C-4, -5, -6, and -7 but had a methyl group at N-1. Both units B and D, which also had the pyrrolidinoindoline structure bearing N-1′ and N-1‴ methyl groups, possessed a substituent at C-7′ and C-7‴, respectively. These findings were supported by the splitting mode of the protons in the aromatic region [δ 7.26, d J = 7.6 Hz (H-4′), δ 6.66, dd J = 7.6 and 7.6 Hz (H-5′), and δ 7.00, d J = 7.6 Hz (H-6′) for unit B and δ 6.59, dd J = 7.4 and 1.4 Hz (H-4‴), δ 6.61, dd J = 7.4 and 7.4 Hz (H-5‴), and δ 6.94, dd J = 7.4 and 1.4 Hz (H-6‴) for unit D] and the HMBC cross-peaks shown in Figure 3. It was deduced next that unit C, which had the pyrrolidinoindoline structure bearing the N-1″ methyl group, possessed a substituent at C-5 on the basis of the splitting mode of the protons in the aromatic region (δ 5.85, d J = 1.6 Hz, δ 6.67, dd J = 7.7 and 1.6 Hz, and δ 6.39, d J = 7.7 Hz) and the HMBC cross-peaks between H-4″ (δ 5.85) and C-3a″ (δ 64.2), H-6″ (δ 6.67) and C-7a″ (δ 149.8), and H-7″ (δ 6.39) and C-5″ (δ 136.2), as shown in Figure 3. The ^{1}H and ^{13}C NMR and ^{1}H–^{1}H COSY spectra (Figure 3) suggested that unit E had an indole nucleus, the C-4⁗, -5⁗, -6⁗, and -7⁗ of which had no substituents. Further, a characteristic proton signal assigned to C-2⁗ in unit E (δ 7.15, 1H, s) was observed. It was suggested that this unit possessed a fragment, MeN-CH_2CH_2-, that was connected to C-3⁗ on the indole nucleus on the basis of information from the HMBC connectivities, as shown in Figure 3. Therefore, new compound **2** was revealed to have an N_{10}-methyltryptamine unit that was connected to another unit at N_1 or N_{10}. Finally, the connected positions of units A to E were determined by analyzing HMBC connectivities (Figure 4).

The HMBC cross-peak between H-8a (δ 4.14) in unit A and C-7′ (δ 123.8) indicated that C-3a is attached to C-7′ in unit B. The HMBC cross-peaks between H-8a′ (δ 4.46) and C-3a″ (δ 64.2), and between H-3″ (δ 2.63) and H-8a″ (δ 5.00) and C-3a′ (δ 63.1) suggested the presence of a bridge between C-3a′ (unit B) and C-3a″ (unit C). Further, the

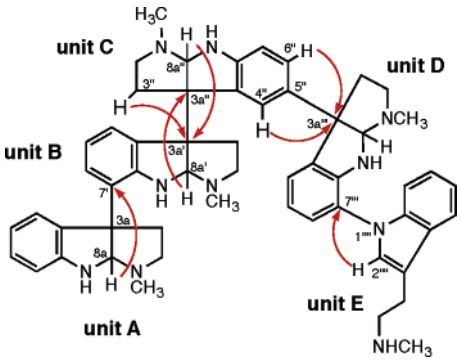

Figure 4. Selected HMBC correlations for psychopentamine (**2**).

HMBC cross-peaks between H-4″ (δ 5.85) and H-6″ (δ 6.67) and C-3a‴ (δ 62.3) indicated that C-3a‴ (unit D) was attached to C-5″ on the benzene ring of unit C, which featured the structure of this alkaloid. In addition, the HMBC cross-peak between H-2⁗ (δ 7.15) and C-7‴ (δ 120.4) indicated the presence of a linkage between C-7‴ (unit D) and N-1⁗ (unit E). Therefore, the structure of the new alkaloid, named psychopentamine, was deduced to be that shown as formula **2**. To date, approximately 20 polymeric (trimeric to octameric) pyrrolidinoindoline alkaloids have been found. All of the compounds have two types of common linkages, i.e., the C-3a/C-3a′ bond (β–β' type of linkage) and the C-3a/C-7′ bond between respective N_1-methylpyrrolidinoindoline units, resulting in the formation of the linear type of sequence structure (Figure 5). Psychopentamine (**2**)

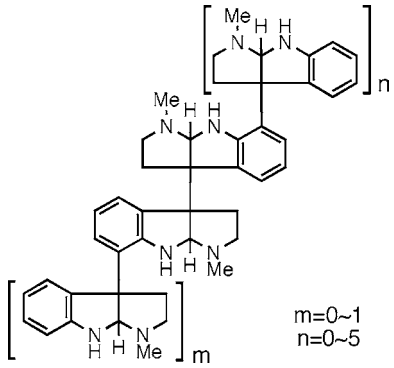

Figure 5. General structure of known polymeric pyrrolidinoindoline alkaloids.

is the first example of a tryptamine-related polymeric-pyrrolidinoindoline alkaloid that contains the C-3a/C-5′ bond, that is responsible to the novel bent-type structure. Studies on the stereochemistry of these new alkaloids are under way.

Supporting Information Available: Experimental procedures and one- and two-dimensional NMR spectral data for **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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