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A NEW CLASS OF TWO DIMERIC INDOLE ALKALOIDS, CORYZEYLAMINE AND DEFORMYLCORYZEYLAMINE, FROM THE LEAVES OF *HUNTERIA ZEYLANICA* IN THAILAND

Hiromitsu TAKAYAMA,[a] Sanan SUBHADHIRASAKUL,[b] Junko MIZUKI,[a] Mariko KITAJIMA,[a] Norio AIMI,[a] Dhavadee PONGLUX,[c] and Shin-ichiro SAKAI*,[a]

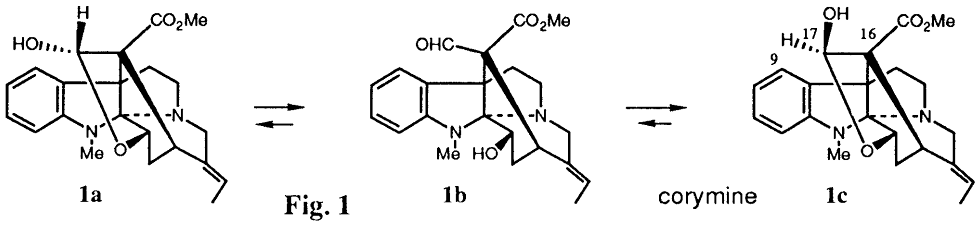
Faculty of Pharmaceutical Sciences, Chiba University,[a] 1-33 Yayoi-cho, Chiba 263, Japan, Faculty of Pharmaceutical Sciences, Prince of Songkla University,[b] Hat-Yai, Songkla, 90112, Thailand, and Faculty of Pharmaceutical Sciences, Chulalongkorn University,[c] Bangkok, 10330, Thailand

Two novel dimeric indole alkaloids, coryzeylamine (**2**) and deformylcoryzeylamine (**3**), which are composed of sarpagine-type and echitamine-type monoterpenoid indole alkaloids, were isolated from the leaves of *Hunteria zeylanica* native to Thailand.

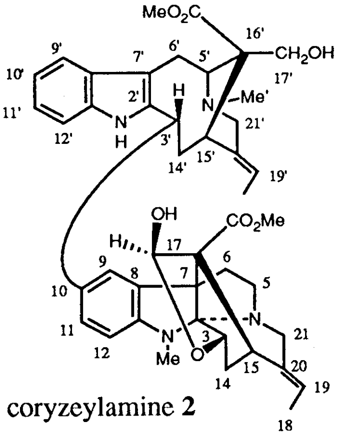
KEYWORDS coryzeylamine; deformylcoryzeylamine; corymine; dimeric indole alkaloid; *Hunteria zeylanica*; Apocynaceae

Hunteria zeylanica (Retz.) Gardn. ex Thw., belonging to the family Apocynaceae, is native to tropical Africa and southeast Asia. The medicinal use of its latex for smearing on the sores of yaws (frambesia) has been recorded in the literature.[1] Previous research by many groups on the chemical components of *Hunteria* has clarified that this genus is a rich source of monoterpenoid indole alkaloids.[2] Because many indole alkaloids are known to play important roles as useful medicines as well as for the lead-compounds to develop new biologically active substances, we have also become interested in the alkaloidal constituents of *Hunteria zeylanica* native to Thailand. From the stem bark of this plant, collected in south Thailand, we have succeeded in the isolation of a biose bounded monoterpenoid indole alkaloid, named hunterioside, together with eight known indole alkaloids.[3] Further investigation of the alkaloidal constituents of the leaves of *Hunteria zeylanica* resulted in the isolation of two novel dimeric indole alkaloids (**2** and **3**). In this communication, studies on the structure of both indole alkaloids are described.

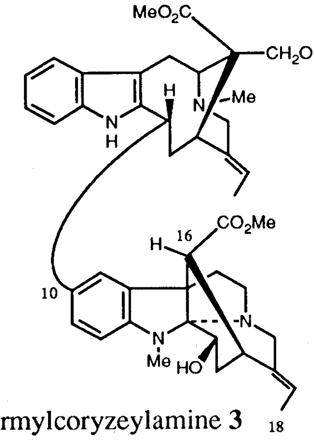
The first new alkaloid (**2**), named coryzeylamine, was obtained as an amorphous powder, $[\alpha]_D^{25}$ -24.0° (*c* 0.25, MeOH). The molecular formula, $C_{44}H_{52}N_4O_7$, obtained by positive high resolution FAB-MS {Calcd. 749.3914, found. 749.3927 $(M+H)^+$}, as well as the UV spectrum [207 (log ε 4.69), 263 (4.27), 287 (4.05), 295 (3.98), and 320 (3.55) nm] indicated that this new compound should be a dimeric molecule composed of two monoterpenoid indole alkaloids having indolic and indoline chromophores. The ^{1}H-NMR spectrum of **2** in $CDCl_3$ gave a complicated chart, but by changing the measurement solvent to DMSO-d_6 or pyridine-d_5[4] it became clear and simple. A similar phenomenon is observed for the NMR spectrum of corymine (**1**),[5] which was simultaneously isolated from the leaves of this plant as a main alkaloidal component. As shown in Figure 1, corymine exists as an equilibrium mixture of two hemiacetal forms (**1a** and **1c**) and an aldehyde form (**1b**) in $CDCl_3$ solution. Their ratio (**1a**:**1c**:**1b**) is approximately 3:1:6. In DMSO-d_6 or pyridine-d_5 corymine takes a hemiacetal form (**1c**), which was confirmed by the observation of NOE between H-9 and H-17. It is quite obvious that corymine (**1**) is one of the components of the dimeric indole alkaloid from the finding that the ^{13}C-NMR spectrum of coryzeylamine (**2**) contains almost superimposable peaks corresponding to those of **1** (see Table I). Based on the molecular formula of **2**, the counterpart of **1**, having an indole nucleus, could be considered to be $C_{22}H_{27}N_2O_3$. The ^{1}H-



1a **Fig. 1** **1b** corymine **1c**



coryzeylamine 2



deformylcoryzeylamine 3

TABLE I. ^{13}C-NMR Data for **1**, **2**, and **3**

Carbon	**1**[a]	**1**[b]	**2**[a]	**2**[b]	**3**[b]
2	96.31	97.31	96.39	97.47	98.63
3	68.52	70.10	68.53	70.12	65.90
5	56.75	57.71	56.69	57.64	55.61
6	39.00	39.88	39.09	39.89	43.85
7	61.87	63.05	61.94	63.15	57.03
8	134.00	135.08	134.29	c	139.34
9	124.01	125.10	123.19	124.74	122.69
10	114.63	115.69	133.34	134.62	135.08
11	127.24	128.07	126.41	127.41	127.00
12	102.85	103.66	102.25	103.23	103.57
13	152.09	153.07	150.49	151.59	150.35
14	29.21	30.41	29.16	30.35	39.81
15	32.75	34.07	33.01	34.22	35.45
16	51.73	52.32	51.04	52.41	49.13
17	94.32	96.02	94.08	95.89	---
18	13.76	14.24	13.71	14.31	13.76
19	120.25	121.15	120.24	121.20	121.93
20	141.18	141.95	141.12	141.80	139.93
21	57.41	58.73	57.40	58.69	58.25
CO	172.63	173.81	172.35	173.34	173.90
OMe	51.73	51.72	51.26	51.46	51.24
NMe	27.10	27.41	27.25	27.61	27.01
2'	---	---	138.76	140.20	140.50
3'	---	---	44.16	45.59	45.76
5'	---	---	60.42	61.47	61.53
6'	---	---	16.67	17.97	17.97
7'	---	---	107.77	109.64	109.52
8'	---	---	129.65	131.09	131.10
9'	---	---	117.15	118.02	118.03
10'	---	---	117.50	118.56	118.43
11'	---	---	120.34	121.33	121.19
12'	---	---	109.78	110.47	110.44
13'	---	---	136.22	137.65	137.67
14'	---	---	c	40.35	40.36
15'	---	---	34.45	35.71	35.74
16'	---	---	52.27	53.70	53.71
17'	---	---	68.53	69.98	70.02
18'	---	---	11.88	12.20	12.12
19'	---	---	118.14	119.05	118.92
20'	---	---	137.68	138.50	138.58
21'	---	---	51.38	52.41	52.37
CO'	---	---	171.76	173.42	173.39
OMe'	---	---	48.81	49.55	49.55
NMe'	---	---	41.99	42.40	42.37

a) In DMSO-d_6. b) In pyridine-d_5. c) The corresponding signals are concealed by the solvent peak.

NMR spectrum of **2** showed that the non-corymine part had an indole ring having no substituents at the C-9', 10', 11', or 12' positions, an *N*-methyl group, a methoxycarbonyl group, and an ethylidene side chain. Furthermore, the presence of two isolated methylene groups (H_2-17' and H_2-21'), and CH-CH2 and CH-CH2-CH functions was demonstrated by the HH-COSY spectrum. In the ^{13}C-NMR spectrum, the existence of one quaternary carbon (C16') three methine carbons (C3', 5', and 15'), four methylene carbons (C6', 14', 17', and 21'), and three methyl carbons (C18', *N*-Me', and OMe') in the aliphatic region and furthermore eleven carbons due to an indole nucleus, an ethylidene, and a carbonyl group in the lower field were observed in regard to the non-corymine unit in **2**. All the above protons were correlated with the corresponding carbons in the phase-sensitive HSQC spectrum. The information from the HMBC spectrum (for example; C2' → H-3', H-6', C5' → *N*-Me', H-15', H-17', H-21', C7' → H-6', C14' → H-15', C15' → H-19', H-21', C16' → H-6', H-17', C17' → H-5', H-15', CO' → H-17') enabled us to construct the molecular structure of the non-corymine part to be a sarpagine skeleton. The stereochemistry of the C16' position was elucidated by an abnormal chemical shift of the methoxy group (δ 2.48), which could be interpreted by the anisotropic effect of the indole ring. Unambiguous assignments of all the protons and carbons in the corymine part in **2** obtained by 2D NMR spectra demonstrated that the corymine unit had a substituent on the benzene ring. In the ^{1}H-NMR spectrum, one singlet and a set of two *ortho*-coupling protons ascribable to the aromatic protons in the corymine unit were observed. In addition, a carbon signal at C10 was shifted to lower field by ca. 20 ppm compared with that of **1**. These facts proved that the corymine part in **2** had a substituent at the C10 position. The connected position between the corymine unit at C10 and the sarpagine unit was determined from the HMBC spectrum, which showed the correlation between C3' and H-9 and -11. This assignment was supported by a phase-sensitive NOESY experiment, which showed the correlation between H-3' and H-11 protons. From the Dreiding model analysis, the orientation of the C3' position could take only the *R* configuration (C3'-βH) in order to avoid serious steric interference between the large corymine nucleus and the methoxycarbonyl function in the sarpagine part, which was supported by the coupling constant of H-3' (broad doublet *J*=11.9 Hz). The stereochemistry at C17 of the hemiacetal position was proved to be *R* by NOE observation between H-9 and H-17, analogous with corymine itself. The ethylidiene's configuration (C19 and C19') was the *E*-form, which was confirmed by NOE experiments. From these data, the structure of coryzeylamine was concluded to be formula **2**.

The second new alkaloid (**3**), an amorphous powder, $[\alpha]_D^{25}$ -90.4° (*c* 0.24, MeOH), exhibited a similar UV spectrum to that of coryzeylamine (**2**), indicating that compound **3** would also be a dimer composed of an indole and an inoline alkaloid. The molecular formula, $C_{43}H_{52}N_4O_6$, obtained from the HR-FABMS spectrum, becomes less than **2** by a CO fragment. The ^{1}H-$^{6)}$ and ^{13}C-NMR spectra of **3**, which were very similar to those of **2**, displayed the existence of sarpagine and corymine units. But the disappearance of both the H-17 (δ 5.87) and the C17 (δ 95.89) signals due to the hemiacetal position from compound **3** was the definite difference in the NMR spectra of **2**. From these data, alkaloid **3** was considered to be a deformyl derivative of coryzeylamine (**2**). According to the procedure for the transformation of corymine to its deformyl derivative,$^{7)}$ **2** was treated with 1% aqueous KOH in dioxane at room temperature to 80°C for 15 min to yield alkaloid **3** in 42% yield, which was identical with the natural product, on the basis of their chromatographic behavior and $[\alpha]_D$, and UV, MS, and ^{1}H-NMR comparisons. The stereochemistry at the C-16 position was determined by the NOE observation between the H-18 and OMe groups. Therefore, the structure of the second new alkaloid was concluded to be deformylcoryzeylamine (**3**).

To the best of our knowledge, these two compounds are the first examples of dimeric indole alkaloids, which are composed of sarpagine-type and echitamine-type monoterpenoid indole alkaloids.

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