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A NEW GARDNERIA ALKALOID, GARDQUINOLONE, HAVING A NOVEL 4-QUINOLONE SKELETON¹

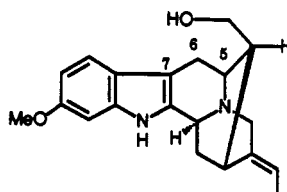
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ABSTRACT.—A new alkaloid, gardquinolone [1], was isolated from the leaves of *Gardneria nutans*. Its unique structure, having a 4-quinolone nucleus corresponding to the monoterpene indole alkaloids, was determined by spectroscopic analysis and chemical transformation from the indole alkaloid, gardnerine [2], which substance is a plausible biogenetic precursor of 1.

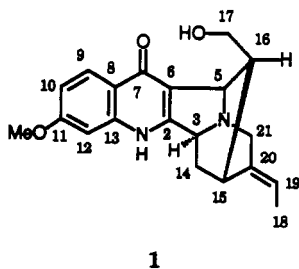
Our comprehensive research on the chemical components of *Gardneria* (Loganiaceae) has clarified that this genus is a rich source of monoterpene indole alkaloids possessing a sarpagine skeleton (2). Starting with the *Gardneria* alkaloids, we have carried out a number of chemical transformations leading to many skeletal types of indole alkaloids (2-4). Reinvestigation of the alkaloidal constituents in the leaves of *Gardneria nutans* Sieb. et Zucc. (5) has resulted in the isolation of a new type of alkaloid, which we wish to report in this paper.

The new alkaloid [1] was obtained from the crude basic fraction of the leaves of *G. nutans*, as a white powder [mp 265–273° (dec), 0.17% yield], together with the known alkaloids, gardnerine [2], gardnutine, gardneramine, 18-hydroxygardnutine, and 18-hydroxygardnerine. Compound 1 could not be detected in the crude basic fraction obtained from the stem and roots of the plant. The high-resolution mass spectrum of 1 is consistent with a molecular formula of



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$C_{20}H_{22}N_2O_3$, and its uv spectrum displayed an unusual pattern of peaks (308, 254, 247, 225 nm), but was similar to that of the 4-quinolones (6, 7). The ¹H-nmr spectrum, which was very similar to that of the main indole alkaloid of this plant, gardnerine [2], revealed the existence of an aromatic methoxy group (δ 3.84), three aromatic protons and an ethylidene side-chain (δ 5.08, 1H, br q, $J=6.6$ Hz, and δ 1.54, 3H, br d, $J=6.6$ Hz). The ¹H-¹H COSY nmr spectrum demonstrated the presence of an isolated AB-type methylene group at δ 3.68 and 3.62 (each 1H, d, $J=17.6$ Hz), which exhibited allylic long-range coupling with the olefinic H-19. These signals could be assigned to H₂-21. The nOe observed between H-19 and H₂-21 suggested an *E*-configuration for the side-chain. All of the remaining eight aliphatic protons showed sequential connectivities in the ¹H-¹H COSY nmr spectrum. Thus, a characteristic signal at δ 3.97 (dd, $J=9.0$ and 2.2 Hz), which corresponded to the H-3 signal of the common indole alkaloids, had a connectivity to the non-equivalent methylene protons at C-14 (δ 1.80 and 1.57). Further, these protons could be successively correlated to H-15



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¹Part 15 in the series "Gardneria Alkaloids."
For Part 14, see Sakai *et al.* (1).

(δ 2.81, br s), H-15 to H-16 (δ 1.90, m), and H-16 to H-17 (δ 3.46, dd, $J=11.3$ and 7.8 Hz, δ 3.12, dd, $J=11.3$ and 7.4 Hz), as in the case of gardnerine [2]. In contrast with 2, the H-5 signal at δ 4.19, showed a connectivity to H-16, appearing as a doublet. By unambiguous assignment of all the carbons in 1 and 2 (5) (Table 1) using the phase-sensitive HSQC (8) and HMBC (9) techniques, it was demonstrated that the signal corresponding to the C-6 methylene group in gardnerine [2] was not present, while a signal due to a carbonyl carbon was observed at δ 172.5 in 1. All the above observations indicated the structure of the new alkaloid to be 1.

With the purpose of confirming the structure, laboratory synthesis was carried out of the new compound 1, starting from gardnerine. Gardnerine [2] was treated with potassium *tert*-butoxide in DMF in an O₂ atmosphere (10) to afford

TABLE 1. ¹³C-Nmr Assignments of 1 and 2.

Carbon	Compound	
	1	2
2	160.97	136.84 ^b
3	58.08	49.21
5	59.34	51.72
6	118.33	22.41
7	172.53	104.58
8	119.69	120.35
9	126.72	117.98
10	113.24	107.78
11	161.40	155.01
12	100.04	94.80
13	141.26	136.78 ^b
14	25.97	26.90
15	29.57	26.07
16	*	42.26
17	60.99	58.99
18	12.36	12.60
19	109.93	111.65
20	142.34	142.06
21	48.83	55.84
OMe	55.42	55.19

*The corresponding signal is concealed by the solvent peak. In pyridine-*d*₅, this signal appears at δ 40.63.

^bThese signals may be interchangeable.

its quinolone analog in 58% yield. The identity of the semi-synthetic compound and the natural product was fully confirmed by comparison of their chromatographic behavior and uv, ¹H- and ¹³C-nmr, and eims spectra. Furthermore, their cd spectra displayed the same Cotton effect curves. Therefore, the structure and absolute configuration of the new alkaloid, named gardquinolone, was determined as represented in formula 1.

The monoterpene indole alkaloid, gardnerine [2], might be a biogenetic precursor of gardquinolone [1], in which the latter compound is generated by oxidative cleavage of the indole α,β -bond and subsequent ring closure to the 4-quinolone nucleus (11,12).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mps (uncorrected) were measured using a micro hot-stage apparatus. Nmr spectra were recorded at 30° using a JEOL JNM-A500 (¹H; 500 MHz, ¹³C; 125 MHz) spectrometer in DMSO-*d*₆. The solvent chemical shifts were used as the internal standards (DMSO-*d*₆: δ_{H} 2.49 ppm, δ_{C} 39.50 ppm). Eims were taken with a JEOL JMS-AM20 spectrometer, and the high-resolution mass spectrum was recorded with a JEOL JMS-HX 110 instrument. Cd spectra were measured with a Jasco J-500 A. Tlc was performed on Merck precoated Si gel 60F-254 plates. Cc utilized Merck Si gel 60 (230–400 mesh) and Merck Al₂O₃ (activity II-III).

PLANT MATERIAL.—The plant material was collected on Mt. Kiyosumi, Chiba Prefecture, Japan, in June 1991. A voucher specimen is deposited in the herbarium department of this faculty.

EXTRACTION AND SEPARATION OF ALKALOIDAL FRACTION.—The dried powdered leaves (1.0 kg) were extracted three times with hot MeOH, and the MeOH solution was evaporated *in vacuo*. The residue was dissolved in 3% HCl solution and filtered. The filtrate was washed with EtOAc. The aqueous layer was basified with NaHCO₃ to pH 10 at 0°, and then extracted with 5% MeOH/CHCl₃. The organic phase was dried over MgSO₄ and evaporated under reduced pressure to give a crude basic fraction (2.71 g).

Isolation of Gardquinolone [1].—The crude bases (2.7 g) were subjected to cc on Al₂O₃ and eluted with a CHCl₃/MeOH gradient. The 10–20% MeOH/CHCl₃ eluate was purified by two successive cc on Si gel by first eluting with 20% MeOH/CHCl₃ and then with a mixture of 10%

MeOH/CHCl₃ containing 1% triethylamine, to give a fraction containing mainly **1**. This substance was further purified by prep. tlc with 10% MeOH/Et₂O to afford 4.5 mg of gardquinolone [**1**] as a white powder from EtOAc; mp 265–273° (dec); uv λ max (MeOH) (log ϵ) 225 (4.55), 247 (4.62), 254 (4.69), 308 (4.16) nm; eims m/z [M]⁺ 338 (100), 321 (32), 307 (31), 293 (49), 227 (34), 214 (45); hrfabms calcd for C₂₀H₂₃N₂O₃ m/z [M+H]⁺ 339.1709, found m/z [M+H]⁺ 339.1708; ¹H nmr δ 8.03 (1H, d, $J=9.0$ Hz, H-9), 6.95 (1H, dd, $J=9.0$ and 2.4 Hz, H-10), 6.91 (1H, d, $J=2.4$ Hz, H-12), 5.08 (1H, br q, $J=6.6$ Hz, H-19), 4.19 (1H, d, $J=8.6$ Hz, H-5), 3.97 (1H, dd, $J=9.0$ and 2.2 Hz, H-3), 3.84 (3H, s, OMe), 3.68 and 3.62 (each 1H, br d, $J=17.6$ Hz, H₂-21), 3.46 (1H, dd, $J=11.3$ and 7.8 Hz, H-17), 3.12 (1H, dd, $J=11.3$ and 7.4 Hz, H-17), 2.81 (1H, br s, H-15), 1.97 (1H, m, H-16), 1.80 (1H, br d, $J=13.1$ Hz, H-14), 1.57 (1H, m, H-14), 1.54 (3H, br d, $J=6.6$ Hz, H₃-18); ¹³C nmr see Table 1; cd (MeOH, $c=0.296 \times 10^{-3}$, 20°) [θ] (nm) 0 (340), -2700 (305), 0 (290), 4060 (275), 2030 (267), 30400 (254), 0 (230), -16900 (219), 0 (200).

PREPARATION OF **1** FROM GARDNERINE [**2**].—

A mixture of gardnerine (**2**; 20 mg, 0.062 mmol) and potassium *tert*-butoxide (11 mg, 0.098 mmol) in dry DMF (0.5 ml) was vigorously stirred in an O₂ atmosphere at room temperature for 1 h. The reaction mixture was poured into chilled H₂O and the whole mixture was extracted with CHCl₃. The organic layer was washed with H₂O, dried over MgSO₄ and evaporated to give a residue, which was purified by cc on Al₂O₃ using 5% MeOH/CHCl₃ to give 12.1 mg (58%) of **1**. The semi-synthetic **1** was identical with the natural sample

upon comparison of their chromatographic behavior and spectral data (eims, uv, ¹H- and ¹³C-nmr, and cd).

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