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TWO NOVEL ALKALOIDS FROM *EVODIA RUTAECARPA*

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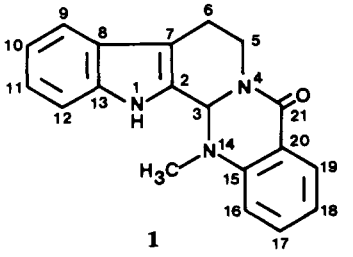
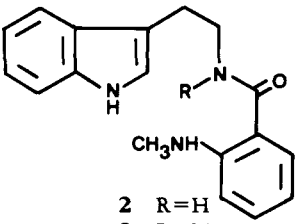
ABSTRACT.—Two novel alkaloids, goshuyuamide-I [**4**] and goshuyuamide-II [**5**] were isolated from the fruits of *Evodia rutaecarpa*, and their structures were determined on the basis of spectral data.

The fruits of *Evodia rutaecarpa* Bentham (Rutaceae) have been used as a Chinese drug (Chinese name "Wu-Chu-Yu," Japanese name "Goshuyu") in the treatment of headache, abdominal pain, dysentery, postpartum hemorrhage, and amenorrhea (1). Phytochemical studies on the drug have shown the presence of numerous constituents including alkaloids such as evodiamine [**1**] (2), which was reported to increase arterial pressure (3). Our recent bioassay-directed research on the same drug led to the characterization of **1** as a powerful cardiotonic principle (4). During the fractionation, we also isolated *N*-(2-methylaminobenzoyl)tryptamine [**2**] and evodiamide [**3**], which are possibly key precursors of rarely occurring indolequinazoline alkaloids (5–10). Furthermore, our continuing in-depth study on the same material resulted in the isolation of two novel alkaloids, goshuyuamide-I [**4**] and goshuyuamide-II [**5**], whose structures are described in the present paper.

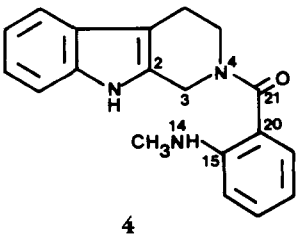
The presence of an amide carbonyl and an indole chromophore in goshuyuamide-I [**4**], as observed in **1**, was demonstrated by the ir and uv spectra (1620 cm^{-1} and 225, 281.5, and 290 nm, respectively) (11). The molecular formula of $C_{19}H_{19}N_3O$



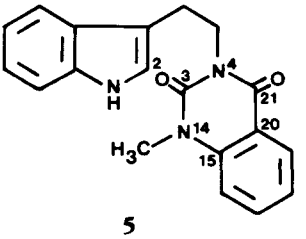
1



2 R=H
3 R=Me



4



5

for **4** was determined by hreims (*m/z* 305.1511 $[M]^+$, Δ −1.7 mmu). The formula is by two hydrogen atoms greater than that of **1**, suggesting that **4** might be a ring-opened structure of **1**. The chemical shifts and multiplicities for **4** corresponded to those for **1** except those assignable to C-3. A doublet at δ 69.9 in **1** was replaced by a triplet at δ 44.8 in **4**. In the ^{1}H-nmr spectrum, an aminomethyl appeared as a doublet (J = 5.1 Hz) at δ 2.69, which was changed to a singlet by adding D_2O. These data could be readily interpreted in the terms of only one possible structure, that is, goshuyuamide-I [**4**] was concluded to be 2-(2-methylaminobenzoyl)-1,2,3,4-tetrahydro-β-carboline.

Goshuyuamide-II [**5**] analyzed for $C_{19}H_{17}N_3O_2$ by hreims (*m/z* 319.1310 $[M]^+$, Δ −0.1 mmu). The functionality of the two oxygen atoms was established to be due to two amide carbonyls, because the ir spectrum showed a band at 1650 cm^{-1} and the ^{13}C-nmr spectrum revealed the absence of any C-O single bonds. In the ^{1}H-nmr spectrum there were three signals in the aliphatic regions. A three-proton singlet at δ 3.49 and two two-proton triplets (J = 8.1 Hz each) at δ 3.46 and 4.65 were assigned to an aminomethyl and an ethylene adjacent to an indole nucleus, respectively. From the above observations **5** was deduced to be 3-[2-(3-indolyl)ethyl]-1-methyl-2,4-quinazolinedione. Compound **5** was previously prepared with **2** and methyl chloroformate by Bergman and Bergman (12). Out synthetic **5** was completely identical with the natural compound. The possibility that **5** was an artifact formed from **1** was ruled out, because no acidic conditions were used in any isolation processes of **5**. As far as we know, **5** was obtained for the first time from natural sources.

Further biogenetic and pharmacologic studies of **4** and **5** are in progress.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—The dried fruits (2.5 kg) of *E. rutaecarpa* were purchased from Nippon Hunmatsu Yakuhin, Osaka, Japan, and a voucher specimen is on deposit in our laboratory. The tlc plates Si gel F_{254} (Merck, art. 5715) were used for tlc. Si gel 60 (Merck, art. 9385) and silanized Si gel 60 (Merck, art. 7719) were used for cc. Sephadex LH-20 (Pharmacia) was employed for gel filtration. Methyl chloroformate was from Aldrich Chemical. The following instruments were used: Yanagimoto micro melting point apparatus (melting points), Hitachi 200-20 spectrophotometer (uv), Shimadzu IR-27 photometer (ir), JEOL JMS-HX-100 mass spectrometer (hreims), JEOL JNM-GX-400 FT NMR spectrometer (^{1}H- and ^{13}C-nmr).

ISOLATION OF GOSHUYUAMIDE-I [**4**] AND GOSHUYUAMIDE-II [**5**].—Part of the isolation procedure was performed as described previously (4). The fruits were defatted with *n*-hexane and extracted with Me_2CO. The Me_2CO extract was chromatographed on a Si gel column with the aid of celite. Elution was carried out with *n*-hexane/Me_2CO mixtures of increasing polarity. Fractions eluted with *n*-hexane–Me_2CO (9:1) were combined and were repeatedly subjected to chromatography on Si gel columns with NH_4OH-saturated C_6H_6-Me_2CO (19:1) and on silanized Si gel columns with MeOH-H_2O (3:2) and to gel filtration with Sephadex LH-20 and MeOH, to yield **4** (190 mg) and **5** (85 mg). The R_f values of Si gel tlc for **4** and **5** were 0.32 and 0.31, respectively, using $CHCl_3$-MeOH (9:1) as a developing solvent.

GOSHUYUAMIDE-I [**4**].—Compound **4**: $C_{19}H_{19}N_3O$, colorless prisms; mp 178–180° (recrystallized from C_6H_6/Me_2CO), uv λ max (EtOH) nm (log ε) 225 (4.65), 253 (4.04), 281.5 (3.90), 290 (3.84), 313 (3.47); ir ν max (KBr) 3400, 3280, 2900, 1620, 1500, 1350, 1300, 1020, 990, 890, 740; hreims *m/z* $[M]^+$ 305.1511 (calcd 305.1528 for $C_{19}H_{19}N_3O$); ^{1}H nmr (pyridine-d_5) δ 2.69 (3H, d, J = 5.1 Hz, NHMe), 2.84 (2H, m, H-6), 3.85 (2H, m, H-5), 4.99–5.08 (2H, m, H-3), 6.08 (1H, q, J = 5.1 Hz, H-14), 6.75 (1H, d, J = 8.1 Hz, H-16), 6.80 (1H, t, J = 7.3 Hz, H-18), 7.25–7.33 (2H, m, H-10 and H-11), 7.36–7.40 (1H, m, H-17), 7.37 (1H, d, J = 7.3 Hz, H-19), 7.57 (1H, d, J = 8.1 Hz, H-12), 7.56 (1H, d, J = 7.3 Hz, H-9); ^{13}C nmr (pyridine-d_5) δ 22.1 (t, C-6), 30.0 (q, NHMe), 42.3 (t, C-5), 44.8 (t, C-3), 108.0 (s, C-7), 111.1 (d, C-16), 111.7 (d, C-12), 115.8 (d, C-18), 118.3 (d, C-9), 119.4 (d, C-10), 120.7 (s, C-20), 121.6 (d, C-11), 127.7 (s, C-8), 128.1 (d, C-19), 131.3 (d, C-17), 131.4 (s, C-2), 137.4 (s, C-13), 148.2 (s, C-15), 171.0 (s, C-21).

GOSHUYUAMIDE-II [**5**].—Compound **5**: $C_{19}H_{17}N_3O_2$, colorless prisms; mp 216–218° (recrystallized from EtOH) [lit. (12) mp 216–

218° (recrystallized from EtOH)], uv λ max (KBr) 3330, 1690, 1650, 1610, 1490, 1430, 1400, 1360, 860, 840 cm^{-1} [lit. (12) 3332, 1696, 1650, 1613, 1488, 1433, 1398, 1355, 858, 847 cm^{-1}]; hreims *m/z* $[M]^+$ 319.1320 (calcd 319.1321 for $C_{19}H_{17}N_3O_2$); ^{1}H-nmr (pyridine-d_5) δ 3.46 (2H, t, J = 8.1 Hz, H-6), 3.49 (3H, s, NMe), 4.65 (2H, t, J = 8.1 Hz, H-5), 7.13 (1H, d, J = 8.8 Hz, H-16), 7.21 (1H, dd, J = 8.1 and 6.3 Hz, H-18), 7.30 (2H, m, H-9 and H-11), 7.38 (1H, d, J = 2.2 Hz, H-2), 7.60 (2H, m, H-12 and H-17), 8.33 (1H, m, H-10), 8.40 (1H, dd, J = 8.1 and 1.5 Hz, H-19), 11.85 (1H, d, J = 2.2 Hz, H-1); ^{13}C-nmr (pyridine-d_5) δ 24.5 (t, C-6), 30.5 (q, NMe), 42.9 (t, C-5), 112.0 (d, C-12), 112.5 (s, C-7), 114.2 (d, C-16), 116.0 (s, C-20), 119.3 (d, C-9), 119.5 (d, C-10), 121.9 (d, C-11), 122.7 (d, C-18), 123.5 (d, C-2), 128.6 (d, C-19), 135.0 (d, C-17), 137.7 (s, C-8), 140.9 (s, C-13), 150.9 (s, C-15), 161.7 (s, C-3), 161.7 (s, C-21). The numbering system tentatively employed for **4** and **5** follows that for **1**.

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