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ISOLATION OF A NEW ALKALOID FROM *EVODIA RUTAECARPA*

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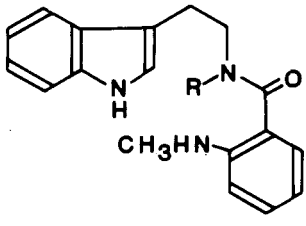
Our recent isolation from *Evodia rutaecarpa* Bentham (Rutaceae) of *N*-(2-methylaminobenzoyl)tryptamine [**1**] (1), which is possibly a key intermediate in the biosynthesis of evodiamine [**2**] (2–4), prompted us to reinvestigate the alkaloidal fraction in more detail. As a result, we wish to report the isolation and structural elucidation of a new alkaloid **3**, named evodiamide, which is also considered to be a precursor of **2**.

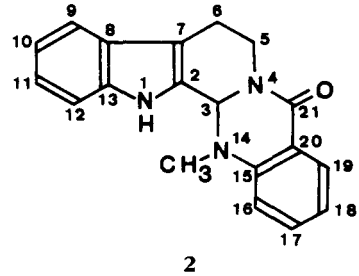
Evodiamide was obtained as colorless prisms. The uv absorptions (221, 284, and 291 nm) demonstrated the presence of an indole nucleus (5). The ir spectrum showed an absorption (1620 cm^{-1}) due to an amide carbonyl. The hrms determined the molecular formula as $C_{19}H_{21}N_3O$ (Δ 0.2 mmu), which differs from **1** by CH_2. The appearance of a new three-proton signal (δ 3.00) in the ^{1}H-nmr spectrum strongly indicated that **3** should be an *N*-methyl derivative of **1**. Unlike **1**, however, **3** showed unusual behaviors in the ^{1}H- and ^{13}C-nmr spectra. Both the methyl and ethylene groups adjacent to the nitrogen of the amide appeared as extremely broadened signals (δ 3.00, 3.21, and 3.86, respectively) in the ^{1}H-nmr spectrum. Furthermore, in the ^{13}C-nmr spectrum, the signals expected for the two carbons next to the nitrogen function could not be found. The interpretation of these observations could be made in the terms of the influence of the amide carbonyl. Compound **3** underwent ready reduction with $LiAlH_4$ to afford an amine **4**, which gave typical ^{1}H- and ^{13}C-nmr spectra as expected. The final structural information of **3** was obtained by synthesis. Evodiamide was prepared with *N*ω-methyltryptamine and *N*-methylisatonic anhydride in the manner similar to that reported for **1** (6). The physicochemical data of the synthetic **3** were identical with those of the natural one. We propose the name evodiamide for **3**, which was assigned the structure *N*-methyl-*N*-(2-methylaminobenzoyl)tryptamine. Compound **3** seems to be a precursor in the biosynthesis of **2**, although it still remains to be proven experimentally.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—



1 R=H
3 R=Me



2

The dried fruits of *E. rutaecarpa* were purchased from Nippon Hunmatsu Yakuhin Ltd., Osaka, Japan, and a voucher specimen is on deposit in our laboratory. The tlc plates, Si gel F_{254}, Si gel 60, Si gel 60 silanized (Merck), and Sephadex LH-20 (Pharmacia) were used for tlc and cc, respectively. *N*ω-methyltryptamine and *N*-methylisatonic anhydride were from Aldrich Chemical Co. The solvent system used for tlc was C_6H_6-Me_2CO (9:1). The following instruments were used: Yanagimoto micro melting point apparatus (melting points), Hitachi 200-20 spectrophotometer (uv), Shimadzu IR-27 photometer (ir), and JEOL-GX-400 FT NMR spectrometer (^1H and ^{13}C nmr).

ISOLATION OF EVODIAMIDE.—Part of the isolation procedure was performed as described previously (1). The fractions eluted with *n*-hexane-Me_2CO (9:1) were combined and were further subjected to chromatography on Si gel with NH_4OH-saturated C_6H_6-Me_2CO (19:1), on Si gel silanized with 60% MeOH, and on Sephadex LH-20 with MeOH, successively, to yield **3**. The R_f value of **3** was 0.33. Compound **3**, $C_{19}H_{21}N_3O$, colorless prisms, mp 208–209° (recrystallized from C_6H_6), uv λ max (EtOH) nm (log ε) 221 (4.65), 250 (4.00), 284 (3.84), 291 (3.82), 311 (3.44); ir λ max (KBr) 3350, 3200, 1620, 1600, 1580, 1518, 1285, 1235, 1120, 750 cm^{-1}; hrms *m/z* $[M]^+$ 307.1683, calcd 307.1685 for $C_{19}H_{21}N_3O$); ^1H nmr (pyridine-d_5) δ 2.66 (3H, d, J = 4.4 Hz, NHMe), 3.00 (3H, bs, NHMe), 3.21 (2H, m, H-6), 3.86 (2H, m, H-5), 5.71 (1H, m, NH-14), 6.71 (1H, d, J = 8.8 Hz, H-9), 6.75 (1H, d, J = 7.3 Hz, H-18), 7.24–7.36 (6H, m, H-2, H-10, H-11, H-12, H-17, H-19), 7.58 (1H, d, J = 7.3 Hz, H-9), 11.86 (1H, s, H-1); ^{13}C nmr (pyridine-d_5) δ 24.1 (t, C-6), 30.0 (q, NHMe), 110.9 (d, C-16), 112.0 (d, C-12), 115.8 (d, C-18), 119.1 (d, C-9), 119.2 (d, C-10), 121.8 (d, C-11), 123.4 (d, C-2), 128.0 (d, C-19), 128.3 (s, C-8), 130.6 (d, C-17), 137.6 (s, C-13), 147.6 (s, C-15), 171.0 (s, C-21); the numbering system employed tentatively follows that for **2**.

REDUCTION OF EVODIAMIDE.—Reduction of **3** (100 mg) with $LiAlH_4$ (30 mg) in THF (10 ml), followed by Si gel cc with NH_4OH-saturated C_6H_6-Me_2CO (19:1), yielded **4** (62 mg). The R_f value of **4** was 0.38. Compound **4**, $C_{19}H_{23}N_3$, colorless oil, uv λ max (EtOH) nm (log ε) 224 (4.55), 284 (3.87), 292 (3.86); ir ν max ($CHCl_3$) 3470, 3000, 1600, 1511, 1462, 1448, 1205, 750, 720, 655 cm^{-1}; ^1H nmr (pyridine-d_5) δ 2.18 (3H, s, NMe), 2.52 (3H, d, J = 3.7 Hz, NHMe), 2.81 (2H, t, J = 7.3 Hz, H-5), 3.07 (2H, t, J = 7.3 Hz, H-6), 3.56 (2H, s, H-21), 6.16 (1H, bs, NH-14), 6.60 (1H, d, J = 8.1 Hz, H-16), 6.75 (1H, t, J = 7.3 Hz, H-18), 7.77 (1H, d, J = 7.3 Hz, H-9), 11.76 (1H, s, NH-1); ^{13}C nmr (pyridine-d_5) δ 23.7 (t, C-6), 29.7 (q, NHMe), 41.3 (q, NH_3), 58.1 (t, C-5), 62.4 (t, C-21), 109.5 (d, C-16), 112.0 (d, C-12), 113.9 (s, C-7), 116.0 (d, C-18), 119.1 (d, C-10), 119.2 (d, C-9), 121.8 (d, C-11), 123.1 (s, C-20), 123.2 (d, C-2), 128.5 (s, C-8), 129.0 (d, C-17), 130.3 (d, C-19), 137.7 (s, C-13), 150.0 (s, C-15); the numbering system employed tentatively follows that for **2**.

SYNTHESIS OF EVODIAMIDE.—A mixture of *N*ω-methyltryptamine (1 g) and *N*-methylisatonic anhydride (1 g) was refluxed in 1 h in diglyme (3.4 ml). The solution was evaporated, and the residue was crystallized from C_6H_6 to yield **3** (360 mg).

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