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ISOLATION OF AN AMIDE, A POSSIBLE KEY PRECURSOR TO EVODIAMINE, FROM *EVODIA RUTAECARPA*

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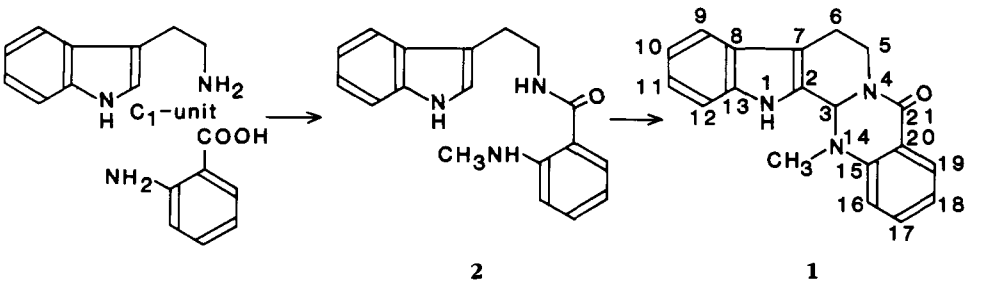
Evodiamine [**1**], one of the main alkaloids of *Evodia rutaecarpa* Benth., belongs to the unique indolequinazoline alkaloids that have been observed so far in rutaceous plants. As to its biosynthesis, Yamazaki *et al.* proposed the tryptophan-anthranilic acid metabolism pathway (1,2). As part of our studies on pharmacologically active constituents in medicinal plants, we previously reported **1** as a powerful cardiotonic principle from the fruits of *E. rutaecarpa* (3). Continued fractionation of the same material led to the first isolation of an amide [**2**], possibly a key precursor in the biosynthesis of **1** (Figure 1), which is described in the present paper.

The $MeCO_2$-soluble portion of the fruits of *E. rutaecarpa* was repeatedly chromatographed in Si gel, Si gel silanized, and Sephadex LH-20 columns to afford **2**. The molecular formula of **2** was determined as $C_{18}H_{19}N_3O$ by hreims (Δ 0.4 mmu). The uv spectrum demonstrated the presence of an indole chromophore (λ max 223, 284, and 292 nm) (4), and the ir spectrum showed a broad band at 1633 cm^{-1}, which could be assigned to an amide carbonyl. The ^{1}H-nmr spectrum revealed an aminomethyl (δ 2.73), two methylenes (δ 3.34 and 4.00), three D_2O-exchangeable protons (δ 8.82, 9.01, 11.75), and nine protons in the aromatic region. One of the methylene signals at δ 4.00 was coupled both to another one at δ 3.34 and to an NH at δ 9.01, thus assigning the unit $-CH_2-CH_2-NH-CO-$. The 1,2-substitution of the aromatic moiety was established from the ^{1}H-nmr coupling pattern. The above spectral data suggest that **2** would be characterized as *N*-(2-methylaminobenzoyl)tryptamine. The deduced structure satisfies the complete ^{1}H- and ^{13}C-nmr assignments which were revealed by the study of the ^{1}H-^{1}H homonuclear and ^{1}H-^{13}C heteronuclear 2D correlation spectra. Further confirmation of the structure was obtained by synthesis. Compound **2** was prepared by the reaction of tryptamine with *N*-methylisatoic anhydride according to Bergman and Bergman (5). The synthetic **2** was completely identical with the



2 **1**

FIGURE 1. Biosynthetic pathway to evodiamine

natural compound. To the best of our knowledge, **2** was obtained for the first time from natural sources.

Compound **2** is of biogenetic significance, because it was previously reported that **2** might be a key intermediate in the biosynthesis of **1** (6). The co-occurrence of **1** and **2** strongly supports the hypothesis, although it still remains to be proven experimentally.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—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 60 F_{254}, Si gel 60, Si gel 60 silanized (Merck), and Sephadex LH-20 (Pharmacia) were used for tlc and cc, respectively. The following instruments were used: Yanagimoto micro melting point apparatus (melting points), Hitachi 200-20 spectrophotometer (uv), Shimadzu IR-27G photometer (ir), JEOL JMS-HX-100 mass spectrometer (hrms), and JEOL JNM-GX-400 FT NMR spectrometer (^{1}H and ^{13}C nmr).

ISOLATION OF COMPOUND **2**.—Part of the isolation procedure was performed as described previously (3). The fractions eluted with *n*-hexane-$MeCO_2$ (9:1) were combined and further subjected to chromatography on Si gel with NH_4OH-saturated C_6H_6-$MeCO_2$ (19:1), on Si gel silanized with 60% MeOH, and on Sephadex LH-20 with MeOH, successively, to yield **2**. Compound **2**, $C_{18}H_{19}N_3O$, colorless needles, mp 114–117° (recrystallized from C_6H_6) [lit. mp 126–127° (recrystalized from toluene) (5)]; uv λ max (EtOH) nm (log ε) 223 (4.40), 259 (3.93), 284 (3.47), 292 (3.45), 346 (3.55); ir ν max (KBr) 3450, 3272, 1633, 1583, 1519, 1280, 1220, 1170, 744, 733 cm^{-1}; hrms *m/z* 293.1532 $[M]^+$ (calcd 293.1528 for $C_{18}H_{19}N_3O$); ^{1}H nmr (pyridine-d_5) δ 2.73 (3H, d, J=4.9 Hz, $NHCH_3$), 3.34 (2H, t, J=7.3 Hz, H-6), 4.00 (2H, q, J=7.3 Hz, H-5), 6.62 (1H, t, J=7.3 Hz, H-18), 6.71 (1H, d, J=8.5 Hz, H-16), 7.23 (1H, t, J=7.3 Hz, H-10), 7.29 (1H, dd, J=8.6 and 7.3 Hz, H-11), 7.34 (1H, s, H-2), 7.36 (1H, dd, J=8.5 and 7.3 Hz, H-17), 7.57 (1H, d, J=8.6 Hz, H-12), 7.90 (1H, d, J=7.3 Hz, H-19), 7.91 (1H, d, J=7.3 Hz, H-9), 8.32 (1H, bq, J=4.9 Hz, H-14), 9.01 (1H, bt, J=7.3 Hz, H-4), 11.75 (1H, s, H-1); ^{13}C nmr (pyridine-d_5) δ 26.4 (t, C-6), 29.6 (q, $NHCH_3$), 41.2 (t, C-5), 111.2 (d, C-12), 111.2 (d, C-16), 113.3 (s, C-7), 114.6 (d, C-18), 116.7 (s, C-20), 119.2 (d, C-10), 119.3 (d, C-9), 121.8 (d, C-11), 123.4 (d, C-2), 128.5 (s, C-8), 128.7 (d, C-19), 132.7 (d, C-17), 137.7 (s, C-13), 151.2 (s, C-15), 170.7 (s, C-21); the numbering system employed tentatively follows that for **1**.

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