Phytochemistry, 1981, Vol. 20, pp. 345–346. Pergamon Press Ltd. Printed in England. 0031–9422/81/0201–0345 $02.00/0

PIPLARTINE-DIMER A, A NEW ALKALOID FROM *PIPER TUBERCULATUM*

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(*Received* 12 *May* 1980)

Key Word Index—*Piper tuberculatum*; Piperaceae; alkaloids; piplartine-dimer A; piplartine; 3,4,5-trimethoxycinnamic acid.

Abstract—Piplartine-dimer A (**1**), a dimer of the known pyridone alkaloid piplartine, was isolated from root bark of *Piper tuberculatum*. It is accompanied by piplartine (**3**) and 3,4,5-trimethoxycinnamic acid.

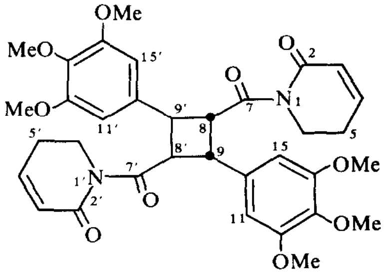
The new compound **1**, isolated from *Piper tuberculatum* Jacq. was recognized as a dimer of piplartine (**3**) [1] by its spectral characteristics. The mass spectrum (see Experimental) is practically superimposable on the spectrum of piplartine (M$^+$ 317, $C_{17}H_{19}O_5N$), except for the M$^+$ at *m/e* 634 ($C_{34}H_{38}O_{10}N_2$). The ^{1}H NMR spectrum, however, is different (see Experimental), the most notable difference being the signals due to the ethylenic *trans*-related hydrogens. Thus, the two doublets (δ 6.69, 7.50, J 15 Hz) that appear in the spectrum of piplartine are replaced by an AA′BB′ system (δ 5.06–4.46) in the spectrum of the dimer (**1**). Consequently, the double bond must have been involved in the formation of the cyclobutyl ring. Additional evidence was obtained on comparison of the proton chemical shifts of the aryl of piplartine (δ 6.86), tetrahydropiplartine (δ 6.48), dimer (δ 6.50) and tetrahydrodimer (δ 6.55). Only the aryl group of piplartine is conjugated with a double bond.

The four cyclobutane protons of dimer **1** are represented in the tetrahydroderivative (M$^+$ 638) by a broad singlet whose chemical shift (δ 4.75) is comparable with that of the analogous signal due to the photodimer of chalcone (δ 4.90) [2]. These data suggest the *trans*, *trans*, *trans* (head-to-tail) structure for the dimer **1** [2, 3]. The alternative structure **2** is incompatible with the lack of the peaks at *m/e* 360 and 274 in the mass spectrum [2, 4]. Indeed, this spectrum shows only fragment **4**, *m/e* 317 (100%) while the base peak of the tetrahydroderivative appears at *m/e* 319.

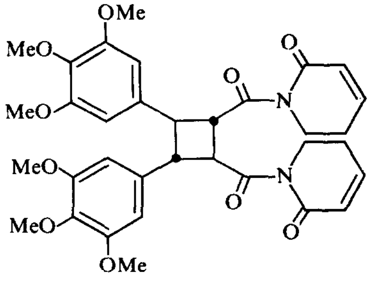
The ^{13}C NMR spectrum is again compatible with structure **1**. The signal assignments (see Experimental) were carried out by means of known chemical shift rules [5], comparative analyses of proton noise decoupled and single-frequency off-resonance decoupled spectra [5] and comparisons with model compounds [6, 7].

Irradiation of a crystalline layer of piplartine **3** with sunlight resulted in two dimers. Structure **1** was attributed to the dimer with the higher mp and, indeed, this photoproduct was proved to be identical by direct comparison (IR and ^{1}H NMR, TLC and mmp) with the natural isolate.

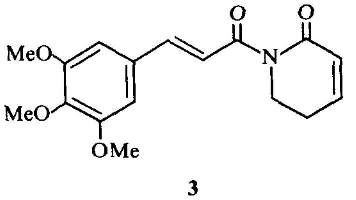
TLC of a fresh extract again revealed the presence of **1**. This result and the difficulty of formation of **1** (**3** must be exposed to sunlight for 10 hr before **1** can be spotted on TLC plate) provides strong evidence for the natural origin of the dimer.



1



2



3

$[4]^{\cdot+}$

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EXPERIMENTAL

Isolation of constituents. The C_6H_6 extract (45 g) of a root bark sample (2.75 kg) was chromatographed on Si gel. Elution with C_6H_6, C_6H_6–Me_2CO and Me_2CO–MeOH gave fractions A, B and C, respectively. A was recrystallized from C_6H_6, yielding white crystals of piplartine (30 g), mp 128–130° (lit. [1] 124°). B was recrystallized from MeOH, yielding piplartine-dimer **1** (0.7 g). C was recrystallized from MeOH, yielding 3,4,5-trimethoxycinnamic acid (20 mg), mp 124–126° (lit. [8] 125–126°).

Piplartine-dimer A. (**1**), white crystals, mp 269–272 (MeOH), $C_{34}H_{38}O_{10}N_2$ by ^{13}C NMR. ^1H NMR counts and MS ν_{max} (KBr, cm^{-1}): 1690, 1670, 1625, 1590, 1510, 1480, 1120, 810. ^1H NMR (100 MHz, $CDCl_3$, δ): 6.75–6.45 (*m*, 2 H-4, 4′), 6.5 (*s*, 4 H-11, 11′, 15, 15′), 5.72 (*dq*, $J = 10$, 1.5 Hz, 2 H-3, 3′), 5.06–4.46 (AA′BB′ system, 4 H-9, 9′, 8, 8′), 4.15–3.66 (*m*, 2 Heq-6, 6′), 3.6–3.04 (*m*, 2 Hax-6, 6′), 3.86 (*s*, 12 H, 4 OMe-12, 12′, 14, 14′), 3.77 (*s*, 6 H, 2 OMe-13, 13′), 2.40–1.44 (*m*, 4 H-5, 5′). ^{13}C NMR (25.2 MHz, $CDCl_3$, δ): 164.3 (*s*, 2 C-2, 2′), 125.3 (*d*, 2 C-3, 3′), 145 (*d*, 2 C-4, 4′), 24.1 (*t*, 2 C-5, 5′), 40.8 (*t*, 2 C-6, 6′), 173.7 (*s*, 2 C-7, 7′), 51.2 (*d*, 2 C-8, 8′), 42.2 (*d*, 2 C-9, 9′), 136, 136.5 (2*s*, 4 C-10, 10′, 13, 13′), 105 (*d*, 4 C-11, 11′, 15, 15′), 152.6 (*s*, 4 C-12, 12′, 14, 14′), 56 (*q*, 4 C, 4 OCH_3-12, 12′, 14, 14′), 60.7 (*q*, 2 C, 2 OCH_3-13, 13′). MS (*m/e*): 634 (8 %) M^+; 537 (3), 440 (4), 412 (3), 317 (100), 221 (23), 193 (2), 191 (2). *Tetrahydropiplartine-dimer A*, white crystals, mp 266–269 (MeOH). ν_{max} (KBr, cm^{-1}): 1687, 1672, 1587, 1507, 1480, 1250, 1130, 1005, 840. ^1H NMR (60 MHz, $CDCl_3$, δ): 6.55 (*s*, 4 H-11, 11′, 15, 15′), 4.75 (*s*, 4 H-8, 8′, 9, 9′), 3.88 (*s*, 12 H, 4 OCH_3-12, 12′, 14, 14′), 3.79 (*s*, 6 H, 2 OCH_3-13, 13′), 3.50–3.20 (*m*, 4 H-6, 6′), 2.5–2 (*m*, 4 H-3, 3′), 1.9–1.2 (*m*, 8 H-4, 4′, 5, 5′). MS (*m/e*): 638 (8 %) M^+; 571 (10), 539 (4), 472 (6), 440 (8), 412 (5), 320 (41), 319 (100), 317 (6), 291 (5), 276 (7), 252 (20), 237 (8), 221 (44).

Synthesis of piplartine-dimer A (**1**). A $CHCl_3$ soln of piplartine (10 g) was placed in a Petri-dish and allowed to evaporate. The crystalline layer was irradiated with sunlight. The mixture obtained after 30 hr was chromatographed on a Si gel column, yielding upon elution with C_6H_6, piplartine (0.8 g) and with C_6H_6–Me_2CO, **1** (80 mg). The identity of this photodimer with the corresponding natural product was established by direct comparison. Another photodimer was isolated in very small amounts (TLC and MS) and probably has the structure **2** [2].

Acknowledgements—This work was supported by fellowships (to R. B. F.) and grants by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Financiadora de Estudos e Projetos S.A. (FINEP). The authors are indebted to Dr. Paul M. Baker, NPPN, Universidade Federal do Rio de Janeiro, for determination of the mass and ^{13}C NMR (25.2 MHz), ^1H NMR (100 MHz) spectra.

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