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SYNTHESES OF *CIS* AND *TRANS* 2-METHOXY-4,5-METHYLENEDIOXYCINNAMOYLPIPERIDIDE AND REVISED STRUCTURE OF A NEW ALKALOID FROM *PIPER PEEPULOIDES*

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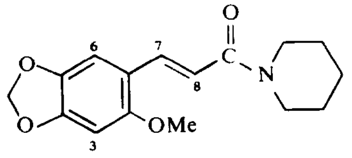
Key Word Index—*Piper peepuloides*; Piperaceae; 2-methoxy-4,5-methylenedioxycinnamoylpiperidide; *cis* and *trans* isomers; syntheses; revised structure.

Abstract—The structure of a new alkaloid isolated from *Piper peepuloides* has been revised as 2-methoxy-4,5-methylenedioxy-*cis*-cinnamoylpiperidide. The revision is based upon spectral evidence and syntheses of both isomers. The synthesis of the *cis* isomer has been accomplished through an intermediate obtained by a novel ring opening of the coumarin 'ayapin' using sodium hydride and methyl iodide in tetrahydrofuran.

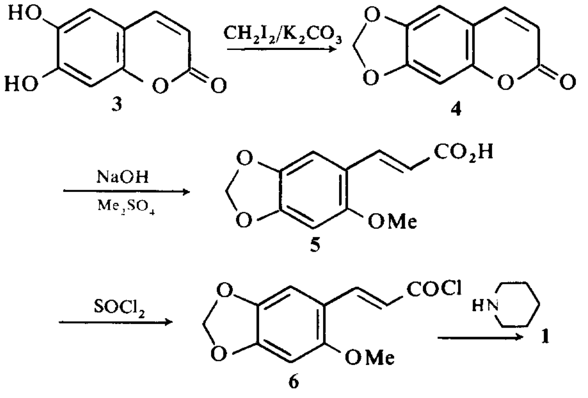
INTRODUCTION

Recently Gupta *et al.* [1] reported the presence of a new piperidine alkaloid which was characterized as 2-methoxy-4,5-methylenedioxy-*trans*-cinnamoylpiperdide (**1**) on the basis of spectral data. However, a careful study of the high resolution ^1H NMR of the above alkaloid raised some doubts regarding the geometry of protons at $\Delta^{7,8}$ in the proposed structure. These protons were located a little upfield from their expected positions. These doubts were further substantiated by the fact that the coupling constant for the $\Delta^{7,8}$ protons was found to be 12.3 Hz and not 14 Hz as reported earlier. Moreover, the presence of two multiplets, instead of a broad singlet for the methylene protons adjacent to nitrogen in the piperidine moiety, also could not be explained on the basis of the proposed structure. These facts led us to the speculation that the structure may have a *cis* configuration at $\Delta^{7,8}$ rather than *trans*. It was, therefore, decided to synthesize both geometrical isomers to confirm the structure.



1 (7, 8) *trans*
2 (7, 8) *cis*

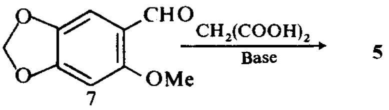
RESULTS AND DISCUSSION



Scheme 1

Two different methods were adopted to synthesize the *trans* isomer. In the first method 6,7-dihydroxycoumarin (esculetin) (**3**) was initially converted into 6,7-methylenedioxycoumarin (**4**) [2] using di-iodomethane in presence of a base. (**4**) was converted to 2-methoxy-4,5-methylenedioxy-*trans*-cinnamic acid (**5**) by the simultaneous ring opening and methylation according to the method of Rao *et al.* [3] using dimethyl sulphate and sodium hydroxide. The *trans* acid chloride **6** obtained from **5** was then subjected to condensation with piperidine to give **1**. The synthesis is outlined in Scheme I.

In the second method for the synthesis of the *trans* isomer, 2-methoxy-4,5-methylenedioxybenzaldehyde (**7**) [4] was used as the starting material. The compound was subjected to Knoevenagel condensation in the presence of malonic acid, pyridine and piperidine. The trans acid **5** was converted to *trans* amide (**1**) in the usual manner (Scheme 2).



Scheme 2

In both cases the resultant product was found to be similar in all respects. However, when the physical constants and spectral data of synthetic and natural alkaloid were compared, there was a marked difference between the two. The synthetic *trans* compound has mp 117°, whereas the natural product has mp 99°. The UV spectra (MeOH) of the reported alkaloid shows absorption bands at 333, 275 and 240 nm, whereas in the synthesized compound these bands are at 360, 290 and 235 nm, respectively. In the ^1H NMR spectra ($CDCl_3$), the $\Delta^{7,8}$ *trans* protons were located at δ 7.85 and 6.70, respectively, as doublets ($\Delta\delta = 1.15$, $J = 15.8$ Hz), whereas in the case of the natural alkaloid these protons were located at δ 6.86 and 5.95, respectively ($\Delta\delta = 0.91$, $J = 12.3$ Hz); the reported values of $\Delta\delta$ for the *cis* and *trans* olefinic protons in cinnamic acids are 0.95 and 1.15 and $J = 12.3$ and 15.8 Hz, respectively [5]. Besides there is a broad signal centred at δ 3.66 attributed to 4 protons ($-N(CH_2)_2$) of the piperidine moiety. In the case of the reported amide there were two clear multiplets at δ 3.30 and 3.55, respectively, for these protons. The UV also indicates, as expected, a red shift in the case of the synthetic *trans* compound. From these observations it is clear that the reported alkaloid has a *cis* rather than *trans* geometry at $\Delta^{7,8}$.

For the final confirmation of the structure, the synthesis of the *cis* isomer was undertaken by a novel method. In this synthesis, the opening of the 6,7-methylenedioxycoumarin (**4**) was achieved by NaH and MeI in THF at room temperature. After the completion of the reaction, a mixture of the *cis*- and *trans*-2-methoxy-4,5-methylenedioxycinnamic acids **5a** and **5b** was obtained in the ratio of 4:1. The mixture was converted to the required amide by usual method (*cis*:*trans*, 3:1). The pure *cis* isomer, mp 99°, was separated by repeated fractional crystallization. The spectral data of the synthesized compound coincided in all respects with the natural amide. Incidentally this appears to be a new approach for the synthesis of *cis*-cinnamic acid derivatives.

Further confirmation of the structure was made when both the isomers were hydrogenated separately in the presence of Pd/C. Both the isomers gave a dihydro derivative, the identity of which was confirmed by superimposable IR and NMR.

This gives us the first confirmed report of any piperamide with a *cis* geometry at a double bond in conjugation with the carbonyl. All previous reports indicate a *trans* geometry of double bonds in the side chain of the amides. The presence of a multiplet instead of a singlet for the two methylene protons adjacent to nitrogen in the *cis* isomer can be attributed to the restriction of the free rotation of the $>N-C=O$ bond, thereby making the two methylenes non-equivalent. This observation was made when Dreiding molecular models were constructed for both *cis* and *trans* isomers.

EXPERIMENTAL

Mps are uncorr. NMR was recorded with TMS as internal standard and chemical shifts are reported in δ (ppm) units.

Synthesis of 4,5-methylenedioxycoumarin (*ayapin*) (**4**). Esculetin (1 g) was dissolved in 90 ml dry Me_2CO and 10 ml *N*,*N*-dimethylformamide. To this soln were added 25 g K_2CO_3 and 10 ml CH_2I_2. The mixture was refluxed on a water bath for 40 hr. The product crystallized from EtOAc–petrol (500 mg), mp 230° (lit. mp 232°) [2]. It analysed for $C_{10}H_6O_4$. ^1H NMR ($CDCl_3$): δ 6.13 (2H, *s*, $C\underline{H}_2O_2$), 6.33 (1H, *d*, $J = 9.5$ Hz, $-CH{=}C\underline{H}-CO-O-$), 7.63 (1H, *d*, $J = 9.5$ Hz, $-C\underline{H}{=}CH-CO-O-$), 6.90 (2H, *s*, $Ar-\underline{H}$).

Synthesis of 2-methoxy-4,5-methylenedioxy-trans-*cinnamic acid* (**5a**). A soln of **4** (300 mg) in aq. NaOH (60%) was warmed on a water bath until the coumarin was completely dissolved. To this was added Me_2SO_4 (3 ml) slowly with continuous stirring. The mixture was warmed at 50° and stirred for 6 hr. The reaction mixture was then cooled to 0° and acidified with dil HCl. The ppt. was collected, dried and crystallization from Me_2CO gave **5a** (200 mg), mp 244°. It analysed for $C_{11}H_{10}O_5$. ^1H NMR (DMSO-d_6): δ 3.92 (3H, *s*, $Ar-OC\underline{H}_3$), 6.08 (2H, *s*, $C\underline{H}_2O_2$), 6.40 (1H, *d*, $J = 15.8$ Hz, $-CH{=}C\underline{H}-CO-O-$), 7.86 (1H, *d*, $J = 15.8$ Hz, $-C\underline{H}{=}CH-CO-O-$), 6.93 (2H, *s*, $Ar-\underline{H}$).

Synthesis of 2-methoxy-4,5-methylenedioxy-trans-*cinnamoylpiperidide* (**1**). 2-Methoxy-4,5-methylenedioxy-*trans*-cinnamic acid (**5a**) (200 mg) was converted into the acid chloride by reacting with $SOCl_2$ in presence of a little Py. The acid chloride in dry C_6H_6 and piperidine (1 ml) was warmed on a water bath for 0.5 hr. The C_6H_6 soln was cooled and washed with dil HCl until free from piperidine, washed several times with H_2O and concd. The amide was crystallized from EtOAc–petrol, mp 117° (100 mg) and analysed for $C_{16}H_{19}O_4N$. UV λ_{max}^{MeOH} nm: 360, 290, 235. IR ν_{max}^{Nujol} cm^{-1}: 1650, 1600, 1270, 1240, 1190, 1020, 970, 915, 840 and 705. ^1H NMR ($CDCl_3$): δ 1.26–1.83 (6H, *bs*, $-N(CH_2C\underline{H}_2)_2C\underline{H}_2$), 3.40–3.80 (4H, *bs*, $-\underline{N}(C\underline{H}_2)_2$), 3.90 (3H, *s*, $Ar-OC\underline{H}_3$), 5.96 (2H, *s*, $-(\underline{CH}_2O_2)$, 6.7 (1H, *d*, $J = 15.8$ Hz, $-CH{=}C\underline{H}-CO-N<$) 7.85 (1H, *d*, $J = 15.8$ Hz, $-C\underline{H}{=}CH-CO-N<$), 6.50 (1H, *s*, $Ar-\underline{H}$, 6.96 (1H, *s*, $Ar-\underline{H}$).

Synthesis of 2-methoxy-4,5-methylenedioxybenzaldehyde (**7**). The compound was synthesized from piperonal by the method of ref. [4].

Synthesis of 2-methoxy-4,5-methylenedioxy-trans-*cinnamic acid* (**5**) *from* **7**. 2-Methoxy-4,5-methylenedioxybenzaldehyde (500 mg), malonic acid (625 mg), piperidine (0.035 mg) and Py were heated at 100° for 3 hr. After cooling, the reaction mixture was poured into 0.2 ml conc HCl and 10 g ice. The product crystallized from Me_2CO, mp 244°.

Synthesis of 2-methoxy-4,5-methylenedioxy-cis-*cinnamic acid* (**5b**). 6,7-Methylenedioxycoumarin (450 mg) was dissolved in 20 ml dry THF. 500 mg of NaH (60%) dispersed in oil were added slowly to the stirred soln, the temp. being maintained at 25°. MeI (3 ml) was then added and stirring continued for a further 4 hr. The mixture was cooled and 40 ml 0.5 N HCl was added. It was then extracted with EtOAc and the organic layer was washed and dried. After removal of the solvent, 300 mg of a mixture of *cis*- and *trans*-(4:1) 2-methoxy-4,5-methylenedioxycinnamic acid was obtained.

Synthesis of 2-methoxy-4,5-methylenedioxy-cis-*cinnamoylpiperidide* (**2**). The amide was synthesized from the mixture of *cis*- and *trans*-4,5-methylenedioxycinnamic acid by the method discussed earlier. The *cis* isomer was separated from the mixture by repeated crystallization from EtOAc–petrol, mp 99°. It analysed for $C_{16}H_{19}O_4N$. λ_{max}^{MeOH} MeOH nm: 333, 275 and 240. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1660, 1550, 1200, 1140, 1040, 1000, 930, 970. ^1H NMR ($CDCl_3$): δ 1.20–1.90 (6H, *bs*, $-N(CH_2C\underline{H}_2)_2C\underline{H}_2$), 3.30 and 3.55 (*m*, 4H, $N(C\underline{H}_2)_2$), 3.90 (3H, *s*, $Ar-O\underline{CH}$), 5.96 (2H, *s*, $C\underline{H}_2O_2$), 5.95 (1H, *d*, $J = 12.3$ Hz, $-CH{=}C\underline{H}-CO-N<$), 6.86 (1H, *d*, $J = 12.3$ Hz, $-C\underline{H}{=}CH-CO-N<$), 6.52 (1H, *s*, $Ar-\underline{H}$), 6.96 (1H, *s*, $Ar-\underline{H}$).

Hydrogenation. The compounds, 125 mg each in MeOH (100 ml), were hydrogenated separately over 10% Pd/C (25 mg) at room temp. After the absorption of H_2 was complete, the catalyst was filtered out and the solvent removed. The residue (25 mg) on purification over neutral alumina afforded a pure colourless waxy compound which analysed for $C_{16}H_{21}NO_4$.

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