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A New Synthesis of Piperine and Isochavicine

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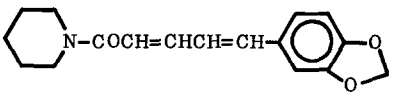
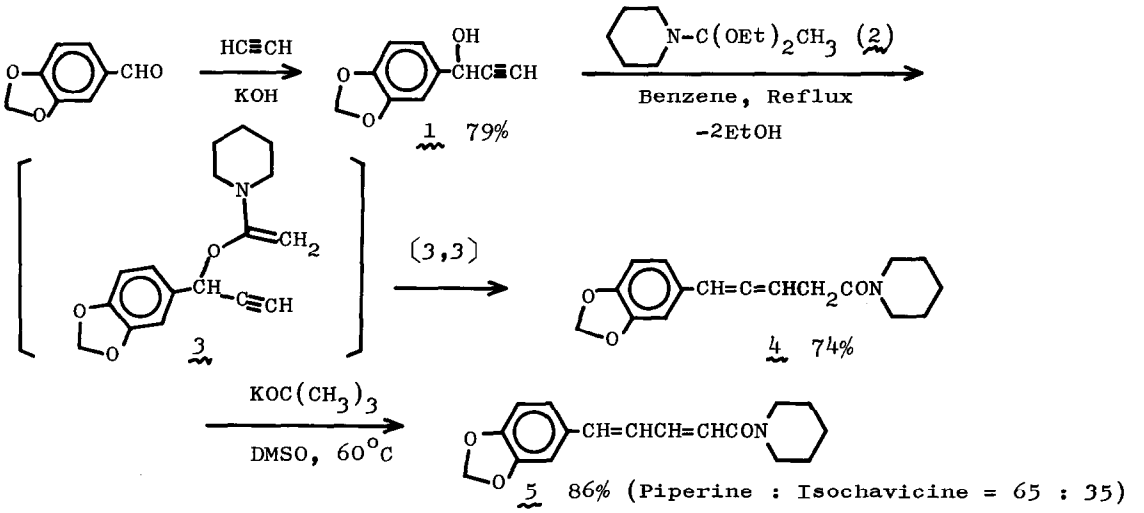
Pepper is by far one of most important spice, and still structures of some of its major components remained ambiguous.[1,2,3] Cleyn and Verzele[3] have recently isolated four diene alkaloids described below, and elucidated the



Piperine (E-E), Isochavicine (E-Z)
Chavicine (Z-Z), Isopiperine (Z-E)

structures by 100 MHz NMR.[3,4] Piperine and its analogs are reported useful as an insecticide synergist as well as a digestive.[2,5] Total syntheses of piperine were established by two groups[1c,6] since the first synthesis by Rügheimer.[7] These synthetic methods depended on the condensation of piperoyl chloride with piperidine.

We present here an efficient synthesis of piperine and isochavicine, in three steps from piperonal. The synthetic route is summarized below. The key



step was a thermal condensation of propargylic alcohol (1) with acetal (2) to give allene amide (4), which was converted with base to a mixture of piperine

and isochavicine (65 : 35). The reaction can be explained by (3,3)-sigmatropic rearrangement through an intermediate 3.[8]

Propargylic alcohol 1 was prepared in the same way as in the preparation of 1-ethynylcycloheptanol.[9] Acetylene was bubbled through a mixture of finely powdered KOH (9 g) in 1,2-dimethoxyethane (12 ml) at -40°C for 20 min. To the stirred suspension was added a solution of piperonal (5 g, 33 mmol) in 1,2-dimethoxyethane (50 ml) during a period of 1.5 h, with bubbling acetylene. After 0.5 h, the mixture was poured onto 50 ml of crushed ice and then worked up as usual to give a clean oil of 1 (4.6 g, 79%): bp 128-130°C (0.6 mm); NMR ($CDCl_3$) δ 2.64 (d, J = 3 Hz, C≡CH), 3.10 (s, OH), 5.36 (s, CHOH), 5.96 (s, $-O-CH_2-O-$), 6.7-7.3 (m, aromatic H). Thermal condensation of 1 (0.26 g, 1.5 mmol) with N-acetylpiperidine diethyl acetal (2)[10] (0.60 g, 3 mmol) was carried out under reflux in benzene (5 ml) for 4 h. Concentration of the mixture in vacuo gave a pale brown oil showing three spots on tlc analysis. Preparative tlc gave a pure allene 4 (0.32 g, 74%): IR (neat) 1950 (C=C=C), 1630 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.60 (s, $NCH_2(CH_2)_3CH_2$), 3.20 (m, CH_2CO), 3.50 (m, CH_2NCH_2), 5.6-6.3 (m, CH=C=CH), 5.92 (s, OCH_2O), 6.78 (m, aromatic H). For isomerization, the solution of 4 (0.15 g, 0.54 mmol) in 6 ml of dry dimethyl sulfoxide (DMSO) was heated at 60°C for 1 day in the presence of potassium tert-butoxide (0.01 g, 0.14 mmol). The mixture was poured into 50 ml of water, extracted with ether, and the evaporation of the solvent gave 0.13 g (86%) of diene amide (5), which was shown by NMR analysis to be a mixture of piperine and isochavicine (65 : 35) Each components were isolated by preparative tlc. NMR spectra of these isomers were identical with those reported in the literature.[4]

References and Notes

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