A Short, Stereoselective Synthesis of Piperine and Related Pepper-Derived Alkaloids

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Two-step stereoselective syntheses of (*E,E*)-1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]piperidine (piperine; **2**) and the related pepper alkaloids (*E,E*)-1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]pyrollidine (trichostachine; **3**) and (*E,E*)-5-(1,3-benzodioxol-5-yl)-*N*-(2-methylpropyl)-2,4-pentadienamide (piperlonguminine; **4**) are described. The steps consist of first treating piperonal with the ylide derived from (*E*)-4-diethylphosphono-2-butenoate to give methyl (*E,E*)-5-(1,3-benzodioxol-5-yl)-2,4-pentadienoate (methyl piperate; **1b**) followed by methoxide-catalyzed aminolysis of **1b** with piperine, pyrollidine, or (2-methylpropyl)amine. The second step proceeded in 75–86% yield. In contrast to the apparent previously noted limitations to the aminolysis reaction as a useful synthetic tool, the utility of this transformation in producing a variety of pepper-derived alkaloids is discussed.

Piperine ((*E,E*)-1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]piperidine) (**2**) has been shown to be the agent (Grewe et al., 1970) responsible for the biting taste of black pepper, a most important spice. Black pepper extracts have been demonstrated to possess insecticidal properties, although piperine is apparently inactive as a contact toxicant (Su and Horvat, 1981). Pepper extracts containing compounds similar to **2** in structure have exhibited tumor inhibitory activity (Loder et al., 1969), while, on the other hand, a recent report (Concon et al., 1979) points to the possible carcinogenicity of an ethanolic pepper extract which contained piperine among several other constituents. Such interest in **2** dictates that a short, stereoselective synthesis be developed. This idea is reinforced by the fact that, while piperine is easily extracted from the fruit of the pepper plant (*Piper nigrum*), the yield is low (2–4%) and the cost of raw pepper is relativey high.

All previous syntheses of **2**, which began with compounds other than (*E,E*)-5-(1,3-benzodioxol-5-yl)-2,4-pentadienoic acid (piperic acid; **1a**) (tautologically derivable from **2**), have suffered from lack of stereoselectivity (Tsuboi and Takeda, 1979) or low overall yield after several steps (Lurik et al., 1971; Normant and Feugeas, 1964; Dallacker and Schubert, 1975). Herein we report straightforward and stereoselective, two-step syntheses of **2** and the related pepper-derived amides (*E,E*)-1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]pyrrolidine (trichostachine; **3**) and (*E,E*)-5-(1,3-benzodioxol-5-yl)-*N*-(2-methylpropyl)-2,4-pentadienamide (piperlonguminine; **4**).

EXPERIMENTAL SECTION

General. Melting points were deterimined on either a Fisher-Johns or a Melt-Temp hot-stage apparatus and are uncorrected. UV spectra were recorded on a Beckman 24 spectrophotometer, and IR spectra were obtained from a Perkin-Elmer 467 instrument. Either a Perkin-Elmer R24B or Varian EM 360 spectrometer was used to record NMR spectra. 1,2-Dimethoxyethane was refluxed over and distilled from $LiAlH_4$ immediately before use. Methanol was dried by refluxing over magnesium methoxide and then distilling.

Methyl Piperate (1b). A mixture of 16.0 g (0.090 mol) of methyl (*E*)-4-bromo-2-butenoate (Gedye and Nechvatal, 1964) and 15.0 g (0.090 mol) of triethyl phosphite was refluxed for 90 min in a flask fitted with a hot water jacketed condenser. The resulting crude phosphonate and 12.8 g (0.085 mol) of piperonal were dissolved in 100 mL of dry 1,2-dimethoxyethane and cooled to 15 °C under a nitrogen atmosphere. A solution of 4.7 g (0.087 mol) of sodium methoxide, made by addition of 2.0 g of sodium to 25 mL of dry methanol, was added dropwise at such a rate that the temperature of the reaction mixture remained below 20 °C. Then the reaction mixture was stirred for 18 h at room temperature before it was poured into 800 mL of ice-cold water. Stirring for 15 min produced a yellow precipitate which was collected by filtration, dried, and recrystallized from methanol, affording 5.6–6.7 g (28–34%) of **1b** as yellow-gold, glistening plates: mp 144–146 °C [lit. (Posner and Rohde, 1910) mp 146 °C]; UV (methanol) 344 (ϵ 51 300), 308 (ϵ 29 500), and 254 nm (ϵ 16 200); IR ($CHCl_3$) 3020, 2970, 2920, 1708, 1620, 1255, and 1010 cm^{-1}; NMR (acetone-d_6) δ 3.68 (s, 3 H, $-OCH_3$), 5.96 (d, 1 H, J = 15 Hz, *trans*-HC=CH), 6.00 (s, 2 H, methylenedioxy), 6.96 (d, 1 H, J = 15 Hz, *trans*-HC=CH), and 6.75–7.75 (complex, 5 H).

Piperine (2). A mixture of 15.0 mL (12.9 g, 0.177 mol) of freshly distilled piperidine, 3.00 g (0.013 mol) of **1b**, 0.18 g (0.0078 mol) of sodium (first dissolved in dry methanol), and 65 mL of dry methanol was refluxed under nitrogen atmosphere for 40 h. (It is necessary to use freshly distilled amine and freshly dried methanol or an intractable precipitate will form during reflux which must be removed by filtration prior to treatment of the reaction mixture with water.) The resulting red-brown solution was poured into 300 mL of water and stirred for 2 h, and the precipitate which formed was collected by filtration, yielding 3.18 g (86%) of **2** as beige plates: mp 122.5–124 °C. Recrystallization from ethyl acetate–hexane gave fine, yellow-beige needles: mp 128–129 °C [lit. (Rügheimer, 1882) mp 127–128 °C]; UV (methanol) 341 (ϵ 33 000), 309 (ϵ 21 000), and 260 nm (ϵ 10 100); IR (KBr disk) 3010, 2940, 1632, 1440, 1250, 1030, 1015 (*trans*-C=C), and 995 cm^{-1}. The ^1H NMR spectra of piperine and its three other stereoisomers have been previously recorded (DeCleyn and Verzele, 1975), and the spectrum of our compound was fully consistent with that of piperine.

Trichostachine (3). In an exactly analogous manner as above, 3.00 g (0.013 mol) of **1b** was treated with excess freshly distilled pyrollidine in the presence of sodium methoxide–methanol to give 2.81 g (80%) of crude **3**. Recrystallization from ethyl acetate–hexane gave fine, ivory needles: mp 142.5–143.5 °C [lit. (Singh et al., 1969) mp 142–143 °C]; UV (methanol) 342 (ϵ 47 200), 309 (ϵ 29 400), and 260 nm (ϵ 18 800); IR (KBr) 3020, 2970, 2890, 1630, 1610, 1410, 1245, 1072, and 990 cm^{-1}; NMR ($CDCl_3$) δ 1.90

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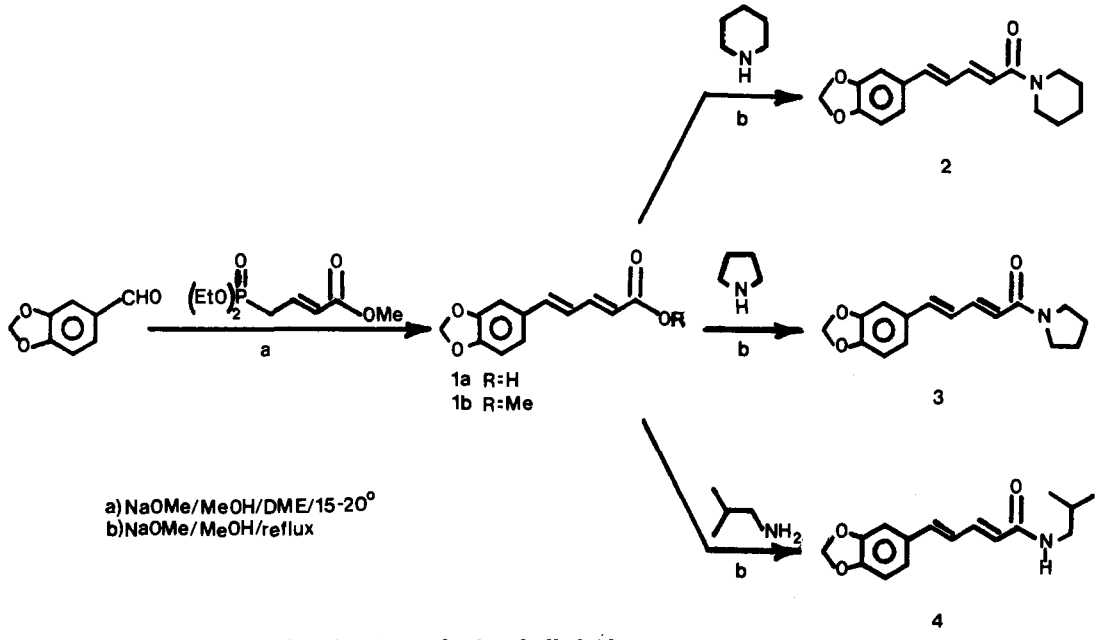

Figure 1. Two-step synthetic scheme for piperine and related alkaloids.

(complex, 4 H), 3.55 (br t, 4 H), 5.98 (s, 2 H, methylenedioxy), 6.30 (d, 1 H, J = 15 Hz, *trans*-HC=CH), and 6.65–7.75 (complex, 6 H).

Piperlonguminine (4). Again methoxide-promoted aminolysis of 3.00 g (0.013 mol) of **1b** gave 2.65 g (75%) of crude **4** as beige, fibrous needles. Recrystallization from ethyl acetate–hexane yielded ivory, fibrous needles: mp 163–164 °C [lit. (Chatterjee and Dutta, 1966, 1967) mp 166–168 °C]; UV (methanol) 342 (ϵ 34 700), 306 (ϵ 21 900), and 260 nm (ϵ 12 300); IR (KBr) 3280 (N–H stretch), 3010, 2950, 1635, 1605, 1495, 1480, 1440, 1248, 1035, and 982 cm^{-1}; NMR ($CDCl_3$–acetone-d_6–Me_2SO-d_6) δ 0.88 (d, 2 H, J = 6 Hz), 1.83 (septet, 1 H, J = 6 H), 3.14 (m, 2 H), 6.03 (s, 2 H, methylenedioxy), 6.22 (d, 1 H, J = 15 Hz, *trans*-HC=CH), and 6.63–7.90 (complex, 6 H).

RESULTS AND DISCUSSION

Our two-step approach (Figure 1) first involved a vinylogous Wadsworth-Horner modified Wittig condensation of readily available and cheap piperonal with the anion derived from methyl (*E*)-4-diethylphosphono-2-butenoate to give methyl piperate (**1b**). The yield of recrystallized **1b** was only 34% based on piperonal, but this is mitigated by consideration of the fact that crude ester could be obtained simply by precipitation from the reaction mixture in 50% yield. Spectral and physical properties of this material were consistent with those expected for stereoisomerically pure **1b**. Moreover, the Arbuzov reaction which yields methyl (*E*)-4-diethylphosphono-2-butenoate from (*E*)-4-bromo-2-butenoate and triethyl phosphite (Burden and Crombie, 1969) proceeded in 70% yield based on the amount of ethyl bromide collected. Therefore, the yield of crude of **1b** based on phosphonate ester was actually ~70%—truly a stereoselective transformation when one considers that two stereoisomers could result. Our synthesis of **1b** is actually one which gives a high yield of the desired product, and in addition, it is an operationally simple one-pot procedure from which the ester may be readily isolated.

Methoxide-catalyzed aminolysis of **1b** with piperidine produced piperine (**2**) in 86% yield based on **1b**. Analogous treatment of **1b** with pyrrolidine and isobutylamine gave the naturally occurring and potentially physiologically active amides trichostachine (**3**) [from *Piper trichostachyon* (Singh et al., 1969)] and piperlonguminine (**4**) [from *Piper longum* (Chatterjee and Dutta, 1966)], respectively, also in good yield. It is instructive to point out that extraction of these two amides from natural sources reportedly (Singh et al., 1969; Chatterjee and Dutta, 1966) affords **3** or **4** in very small amounts (<0.03% yield). Again, the aminolysis procedure is operationally very simple since pure amide precipitates out of the reaction mixture upon treatment with water.

It should be noted that methoxide-catalyzed aminolysis of esters has been known for a number of years (Betts and Hammett, 1937; DeFeoand and Strickler, 1963). However, the successful examples reported to date have employed only ammonia or primary amines. Two examples of reaction of secondary amines with esters to form tertiary amides have involved use of *n*-butyllithium (Yang et al., 1970) or boron tribromide (Yazawa et al., 1974) as the catalyst or coreactant—rather more drastic conditions in contrast to the use of the dilute sodium methoxide solution reported here.

Generally, however, secondary amines are rather unreactive in aminolysis reactions. Perhaps this is due to steric inhibition of formation of the tetrahedral intermediate presumed to be involved in the reaction mechanism (DeFeoand and Strickler, 1963). Piperidine and pyrrolidine are not highly hindered and are used here in large excess. These factors may account for the success in our hands in producing **2** and **3**. Since several piperidyl-, pyrrolidyl-, and other alkylamides have been isolated from pepper species (Shulgin, 1973; Atal et al., 1975), the amidation procedure herein described should represent a generally useful means for synthesis of other pepper-derived amides from corresponding esters.

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Synthesis of New Pyrazines for Flavor Use

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Ten newly synthesized pyrazines, some of which possessed a licorice–woody (isobutylquinoline-like) odor, showed very low odor thresholds (0.2–1.0 ppm in an ethyl alcohol solution). This indicates that these pyrazines have high potential use as flavor ingredients. Eight 5-alkyl-3-methyl-2(1*H*)-pyrazinones were synthesized from 3-methyl-5,6-dihydro-2(1*H*)-pyrazinone, which was prepared from the reaction of methyl pyruvate and ethylenediamine, with aldehydes or ketones. Some pyrazinones synthesized were derived to 2-chloropyrazine derivatives, which were subsequently reacted with sodium alkylate, sodium phenolate, sodium thioalkylate, and sodium thiophenylate to obtain the desired alkoxy-, phenoxy-, (alkylthio)-, and (phenylthio)pyrazines, respectively. The spectral data (IR; NMR; MS) of 8 pyrazinones and 10 new pyrazines are also reported.

Alkoxypyrazines are found in various foods: in coffee beans (Vitzthum et al., 1975), cooked potato (Nursten and Sheen, 1974), green peas (Murray et al., 1976), grape (Bayonove et al., 1975), cooked beets (Parliment et al., 1977), roasted almond (Takei and Yamanishi, 1974), and galbanum oil (Bramwell et al., 1969).

Because of the characteristic flavor and low threshold values (Seifert et al., 1970; Parliment and Epstein, 1973), alkoxy- and (alkylthio)pyrazines have been widely used as flavor ingredients. 2-Methoxy-3-methylpyrazine is used to create a fondant and an ice cream flavor (Firmenich et al., 1967). 2,5-Dimethyl-3-(methylthio)pyrazine is applied to make coffee and sugar syrup flavors (Winter et al., 1972).

Alkoxypyrazines have been synthesized by a condensation reaction of an α-amino amide and an α-dicarbonyl compound via a 2-pyrazinone intermediate (Jones, 1949; Karmas and Spoerri, 1952; Seifert et al., 1972). Because α-amino amides are not readily available, only limited quantities of alkoxypyrazines can be produced by this method.

Masuda et al. (1980) synthesized 5-substituted 3,5-dimethylpyrazines by the reaction of 2,3-dimethyl-5,6-dihydropyrazine, which was obtained from the condensation of diacetyl and ethylenediamine, and aldehydes or ketones using the method reported by Shibamoto et al. (1979).

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This study reports a new method for synthesizing pyrazines including alkoxypyrazines, a phenoxypyrazine, (alkylthio)pyrazines, and a (phenylthio)pyrazine.

EXPERIMENTAL SECTION

Synthesis of 3-Methyl-5,6-dihydro-2(1*H*)-pyrazinone (1). Fifteen grams (0.25 mol) of ethylenediamine was dissolved in 80 mL of methylene chloride in a 200-mL Erlenmeyer flask. To the ice-cooled solution, 20 g (0.20 mol) of methyl pyruvate was slowly added over a 3-h period under constant stirring. The reaction mixture was extracted with 800 mL of methylene chloride. The extract was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residual solid was recrystallized from benzene. Colorless needles (16.5 g) were identified by NMR, IR, and MS as 3-methyl-5,6-dihydro-2(1*H*)-pyrazinone.

Synthesis of 5-Isobutyl-3-methyl-2(1*H*)-pyrazinone (2). An excess amount of isobutyl aldehyde (43.7 g, 0.61 mol) was added to a methanol solution (30 mL) of compound 1 (14.2 g, 0.13 mol). The reaction mixture was cooled in an ice bath and stirred for 30 min. A methanol solution (80 mL) of potassium (18 g, 0.28 mol) was added dropwise to the above cooled reaction mixture over a 30-min period. The reaction mixture was brought to room temperature in ~1 h. The solution was then refluxed for 2 h. After the solvent was evaporated to dryness, 60 mL of water and 30 mL of ethyl acetate were added to the residue. Ammonium chloride (80 g) was added to the above aqueous layer. The solution was then extracted with

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