Caffeic Acid Phenethyl Ester (CAPE): Synthesis and X-Ray Crystallographic Analysis

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The structure of caffeic acid phenethyl ester [2-propenoic acid, 3-(3,4-dihydroxyphenyl)-2-phenethyl ester] (I), C_{13}H_{16}O_{5}/1/2C_{6}H_{5}O, synthesized by base-catalyzed alkylation of caffeic acid salt with β-bromoethylbenzene in HMPA (hexamethylphosphoramide) and recrystallized from benzene, was confirmed by single crystal X-ray diffractometry. The crystals are triclinic, space group P1, Z = 2, unit cell dimensions a = 5.8129 (9) Å, b = 11.022 (2) Å, c = 13.226 (2) Å, α = 97.080 (3)°, β = 101.467 (3)°, γ = 95.405 (3)°, V = 825.4 (2) Å³, Dcalc = 1.301 g/cm³, F(000) = 342. The packing of the molecule is stabilized by intermolecular O₁H⋯O₄ (2.69 Å) and O₁⋯H₂O₂ (2.82 Å) hydrogen bonds.

Key words caffeic acid phenethyl ester; alkylation reaction; X-ray diffraction; hydroxycinnamic acid derivative; phenolic compound

Caffeic acid phenethyl ester (CAPE), a plant-derived phenolic compound and an active component of propolis from honeybee hives, is known to have antiviral, antibacterial, anti-inflammatory, antiatherosclerotic, antioxidative, and immunostimulatory and tumor growth inhibition activities. This compound has also been shown to be a potential inhibitor of some enzymes such as ornithine carboxylase, and human immunodeficiency virus (HIV)-1 integrase.

CAPE has been chemically synthesized from caffeic acid and phenethyl alcohol via acid-catalyzed esterification using p-toluenesulfonic acid as a catalyst. It can also be prepared by base-catalyzed alkylation of caffeic acid with β-bromoethylbenzene in dipolar aprotic solvents such as hexamethylphosphoramide (HMPA). The latter reaction has been reported to give a high yield (ca. 70%) of product compared to the first two reactions which give only 40% yield.

To confirm the structure of CAPE, which we synthesized by alkylation of caffeic acid salt with β-bromoethylbenzene using HMPA as solvent, we subjected the product of the reaction to single crystal X-ray crystallography. The X-ray diffraction data showed that the ester structure (I) is the reaction product and not the ethers (II, III) (Chart 1).

Experimental
Thin-layer chromatography (TLC) was performed on precoated Silica gel F₂₅₄ plates (Merek) and on microscope slides (2.5×7.5 cm) coated with Silica gel G containing fluorescent indicator (Fluorescent Brightener 50). Detection was by iodine vapor and by UV light (UV lamp, model UVG-54). Column chromatography was performed on Silica gel H (32—63 mesh) from Seleco Scientific. MgSO₄ was used as the drying agent for organic extracts. Solvents were evaporated under vacuum. Melting points were determined on a Fisher—Johns melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 683 IR spectrophotometer. Single crystal X-ray analysis was performed using a Bruker SMART with 1K CCD detector. Data were collected using SMART Software. Cell refinement and data reduction were performed using the SAINT program. SHELXS86(22) was used to solve the structure and SHELXL93(23) to refine the structure. SHELXTL was used to display molecular graphics and to prepare publication material.

Materials
Caffeic acid (3,4-dihydroxyceinnamic acid, 98%); β-bromoethylbenzene (phenethylbromide); HMPA (99%); diethyl ether; and ethyl acetate were from Aldrich.

Synthesis
CAPE was synthesized according to Hashimoto et al. To a solution of caffeic acid (1.98 g) in 25 ml of HMPA, 2.28 ml of 25% NaOH was added. After stirring for 1 h, a solution of β-bromoethylbenzene (5.7 ml) in 10 ml HMPA was added dropwise with a separatory funnel and the solution was stirred for 52 h at room temperature. The reaction mixture was poured into ice water (50 ml), and the product was extracted with diethyl ether (2×50 ml). The ether extract was washed successively with 1 N HCl (20 ml) and water (20 ml), dried over MgSO₄ (10—15 g), and evaporated under vacuum. The product dissolved in ether was chromatographed on a silica gel column (150 g), eluted with CHCl₃ and then with increasing proportions of ethyl acetate. The fraction eluted with 30% ethyl acetate contained the desired product. Recrystallization from ether/hexane gave compound (I) (CAPE) as a pale-yellow powder; mp 124.5—126 °C; yield ca. 70%. IR (neat) cm⁻¹: 3490, 3100, 1685, 1640—1610, 1100.

Single-Crystal X-Ray Analysis of CAPE
Single crystals of I suitable for X-ray analysis were obtained by slow evaporation from benzene. Data were collected from a colorless thin plate crystal of dimensions 0.20×0.10×0.02 mm on a Bruker SMART with 1K CCD detector with MoKα radiation (λ = 0.71073 Å; graphite monochromated) employing 0.3°ω scanning technique. The final refinement of the structure was achieved by the full-matrix least-squares method with anisotropic displacement parameters for all non-hydrogen atoms and fixed isotropic displacement parameters for all hydrogen atoms. Crystallographic data are listed in Table 1.

Results and Discussion
The IR spectrum showed a peak for phenolic OH (br, 3490 cm⁻¹), a peak for C—H stretch (m, 3100 cm⁻¹), a peak

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for carbonyl group (s, 1685 cm\(^{-1}\)), peaks for C=\(\text{C}\) stretch (m, 1610—1640 cm\(^{-1}\)) and a peak for C–O stretch (1100 cm\(^{-1}\)) consistent with structure I. However, the one dimensional \(^1\text{H}-\text{NMR}\) spectrum was not of sufficient quality to allow reliable assignment of proton signals to distinguish between structures I, II, and III. X-ray analysis showed that the reaction product had structure I corresponding to CAPE.

A perspective view of compound (I) with atomic numbering is shown in Fig. 1. The X-ray crystallographic data and the selected geometric patterns are shown in Tables 1—4. The structure of compound (I) has two rings, A and B. Both rings are planar within experimental observations. Ring B makes an angle of 42.21 (0.15)° to the linker (C7–C8–C9–C10). The linker makes an angle of 10.75 (0.21)° to ring A. This ring makes an angle of 52.96 (0.13)° with the best plane through B. The bond C7–C8 is a trans-double bond. The molecules are linked in unit cell by two types of intermolecular hydrogen bonds \(\text{O}_2\text{H} \cdots \text{O}_1\) (2.69 Å) and \(\text{O}_3\text{H} \cdots \text{O}_2\) (2.82 Å) (Fig. 2, Table 3). X-ray data has also shown that the crystal of I (recrystallized from benzene) contains one-half molecule of solvent benzene for each molecule of CAPE giving a molecular formula of \(\text{C}_{17}\text{H}_{34}\text{O}_4\).
Thus, we have confirmed by single crystal X-ray diffraction that the major product of the reaction of caffeic acid salt with $\beta$-bromoethylbenzene in HMPA solvent is CAPE and not the two ethers II and III.

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References