Potential Hypocholesterolemic Agents: Dicinnamoyl Esters as Analogs of Cynarin

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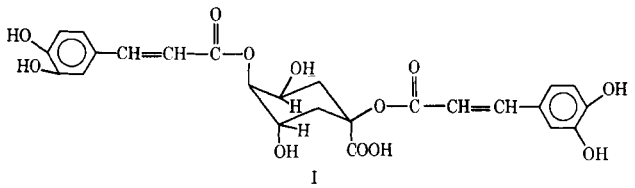
Abstract □ The 1,4-dicaffeyl ester of quinic acid, cynarin, served as a model for the synthesis of potential hypocholesterolemic agents. A scheme to improve upon the cholesterol-lowering activity of cynarin is presented, which involves the synthesis of various diesters of *p*-substituted cinnamic acids. Six alkylene dicinnamates were prepared and tested for their hypocholesterolemic effect. All were inactive due to their insolubility in biological fluids.

Keyphrases □ Dicinnamoyl esters—synthesis, as cynarin analogs, screened as potential hypocholesterolemic agents □ Hypocholesterolemic agents, potential—dicinnamoyl esters □ Cynarin analogs, dicinnamoyl esters—synthesis, screened as potential hypocholesterolemic agents

The 1,4-dicaffeyl ester of quinic acid, cynarin, is a naturally occurring hypocholesterolemic agent (I) (1). Preliminary data suggest that this active constituent of artichoke (*Cynara scolymus*) lowers serum cholesterol by both increasing biliary excretion of the sterol and by choleretic action (2). In light of these important findings, cynarin should represent an important cholesterol-lowering agent. Unfortunately, it must be administered in high doses for long periods of time in the treatment of deranged cholesterol metabolism and atherosclerosis (3).

In preliminary investigations using cynarin as a model for a potent, nontoxic hypocholesterolemic agent, a series of substituted cinnamoyl diesters of a dihydroxy alcohol was synthesized. Structure II is a general representation of cynarin and the proposed analogs. By using the tetramethylene group (R) as equivalent to the quinic acid portion of cynarin and by modifying the substituents (X) on the phenyl ring on the cinnamoyl portion of the molecule, the pharmacological activity might be improved and the compound converted into a useful hypocholesterolemic agent.

The analogs of cynarin were prepared by three methods. Method 1 involved reaction of a carboxylic acid and a dialcohol in the presence of an acid catalyst (4). The water formed in the reaction was removed by azeotropic distillation. 1,4-Butylene cinnamate, 1,4-butylene *p*-methylcinnamate, and 1,4-butylene *p*-methoxycinnamate were prepared by this method. Method 2 involved reaction of alkali metal salts of carboxylic acids with a dihaloalkane in the presence of dimethyl sulfoxide (5). 1,4-Butylene *p*-nitrocinnamate and 1,4-butylene *p*-chlorocinnamate were made by this method. Method 3 involved a transesterification procedure, whereby the tetrahydropyranyl ether of methyl *p*-hydroxycinnamate was reacted with a dialcohol in the presence of dimethyl sulfoxide (6). 1,4-Butylene *p*-hydroxycinnamate was prepared according to this method.



I

Pharmacological screening of the analogs of cynarin by the method of Altman and Honigberg (7) showed no pharmacological activity due to insufficient solubility in biological fluids. This series of compounds was discontinued; a forthcoming paper will report the biological activity of a series of compounds possessing increased solubility. A summary of the pharmacological results is shown in Table I.

EXPERIMENTAL[1]

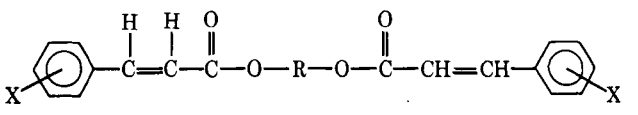
1,4-Butylene Cinnamate (I)—To a solution of 32.5 g. (0.22 mole) of *trans*-cinnamic acid in 200 ml. of benzene were added 9 g. (0.11 mole) of 1,4-butanediol and 1.9 g. (0.01 mole) of *p*-toluenesulfonic acid. The solution was refluxed for 48 hr., during which time the water formed in the reaction was collected in a Dean-Stark trap. The benzene layer was washed well with 5% sodium hydroxide and water. After drying over sodium sulfate, the benzene was removed. The pale-yellow product (26.3 g. or 70.9% yield) gave white needles after one recrystallization from hot ethanol and decolorizing carbon, m.p. 91°. IR (mineral oil): 5.84 (ester), 8.51 (ester), 6.13 (C=C), and 6.35 μ (aromatic). UV (butanol): 278 nm. ($\epsilon = 4.72 \times 10^4$).

Anal.—Calc. for $C_{22}H_{22}O_4$: C, 75.42; H, 6.28. Found: C, 75.72; H, 6.26.

1,4-Butylene *p*-Methoxycinnamate (II)—To 350 ml. of benzene were added 19.6 g. (0.11 mole) of *p*-methoxycinnamic acid, 4.5 g. (0.05 mole) of 1,4-butanediol, and 0.95 g. (0.005 mole) of *p*-toluenesulfonic acid. The water formed in the reaction was collected in a Dean-Stark trap during the 72-hr. reflux. The product, an amorphous white powder, precipitated from the solution on cooling (97.3% yield). Recrystallization from hot chloroform using decolorizing carbon gave a white powder, m.p. 141–142°. IR (mineral oil): 5.88 (ester), 7.84 (ester), 6.10 (C=C), and 6.25 μ (aromatic). UV (butanol): 312 nm. ($\epsilon = 4.83 \times 10^4$).

Anal.—Calc. for $C_{24}H_{26}O_6$: C, 70.24; H, 6.34. Found: C, 69.92; H, 6.09.

1,4-Butylene *p*-Methylcinnamate (III)—To a solution of 17.8 g. (0.11 mole) of *p*-methylcinnamic acid and 4.5 g. (0.05 mole) of 1,4-butanediol in 200 ml. of benzene was added 0.95 g. (0.005 mole) of *p*-toluenesulfonic acid. The water formed in the reaction was collected in a Dean-Stark trap during the 72-hr. reflux. The benzene solution was then washed well with 5% sodium hydroxide and water. Upon removal of the benzene, 14.1 g. (67.8% yield) of crude product was obtained. Recrystallization from hot dioxane–water



II

[1] Melting points were determined on a Thomas-Hoover melting-point apparatus and are uncorrected. IR spectra were determined on the Perkin-Elmer model 237 spectrophotometer. UV spectra were determined on the Perkin-Elmer 202 spectrophotometer. Elemental analyses were conducted by Galbraith Laboratories, Knoxville, Tenn.

Table I—Effect of Alkyl Dicinnamates on Serum Cholesterol

Number	Dose, μmoles/ml.	Number of Animals	Initial Serum Cholesterol
Controls	—[a]	12	101.22 ± 2.60[b]
AY-9944[c]	80	8	47.27 ± 1.91[d]
I	80	12	96.81 ± 2.74
II	80	4	97.70 ± 5.82
III	960	3	115.00 ± 7.64
IV	80	4	101.60 ± 5.42
V	80	4	98.64 ± 2.22

[a] Injected matched volume of solvent only. [b] Standard error. [c] *trans*-1,4-Bis(2-chlorobenzylaminomethyl)cyclohexane dihydrochloride, supplied by Ayerst Laboratories. [d] $p = 0.05$.

and treatment with decolorizing carbon gave a pure white crystalline compound, m.p. 126–127.5°. IR (mineral oil): 5.81 (ester), 7.55 (ester), 6.10 (C=C), and 6.23 μ (aromatic). UV (butanol): 289 nm. ($\epsilon = 4.58 \times 10^4$).

Anal.—Calc. for $C_{24}H_{16}O_4$: C, 76.19; H, 6.87. Found: C, 76.41; H, 6.96.

1,4-Butylene *p*-Chlorocinnamate (IV)—A solution containing 75 ml. of dimethyl sulfoxide, 8.0 g. (0.028 mole) of potassium *p*-chlorocinnamate, and 3 g. (0.014 mole) of 1,4-dibromobutane was stirred vigorously with a mechanical stirrer while heating on a steam bath for 48 hr. As the reaction proceeded, potassium bromide precipitated from the solution. Upon cooling of the dimethyl sulfoxide, the product precipitated. The solid (7.3 g. or 61.9% yield) was washed well with 5% sodium bicarbonate and water. Upon recrystallization from hot dioxane and treatment with decolorizing carbon, the white powdery product melted at 151–153°. IR (mineral oil): 5.88 (ester), 8.51 (ester), 6.11 (C–C), and 6.29 μ (aromatic). UV (butanol): 287 nm. ($\epsilon = 4.16 \times 10^4$).

Anal.—Calc. for $C_{22}H_{20}Cl_2O_4$: C, 63.04; H, 4.78. Found: C, 62.88; H, 4.80.

1,4-Butylene *p*-Nitrocinnamate (V)—Sodium *p*-nitrocinnamate (6.5 g. or 0.03 mole) and 1,4-dibromobutane (3.2 g. or 0.015 mole) were mixed with 75 ml. of dimethyl sulfoxide and stirred with a mechanical stirrer while heating on a water bath for 48 hr. Sodium bromide precipitated during the reaction. When the reaction mixture was cooled, the product precipitated out of the dimethyl sulfoxide. The product was washed well with 5% sodium bicarbonate and water; 7.3 g. (93.2% yield) of crude product was obtained. Upon recrystallization from hot dioxane and treatment with decolorizing carbon, a yellow microcrystalline product was obtained, m.p. 175–177.5°. IR (mineral oil): 5.84 (ester), 8.52 (ester), 6.10 (C=C), 6.28 (aromatic), and 7.41 μ (nitro). UV (dioxane): 306 nm. ($\epsilon = 3.71 \times 10^4$).

Anal.—Calc. for $C_{22}H_{26}N_2O_8$: C, 60.0; H, 4.55. Found: C, 60.17; H, 4.62.

Methyl 4-(2′-Tetrahydropyranyloxy)cinnamate—To 20.0 g. (0.024 mole) of dihydropyran, containing 2 drops of concentrated hydrochloric acid, was added 10.7 g. (0.06 mole) of methyl *p*-hydroxycinnamate. The mixture was warmed to effect solution and allowed to stand for 2 hr. The reaction mixture was diluted with 80 ml. of ether and then washed with 5% NaOH solution and water to remove unreacted phenol. The oil obtained on evaporation of the ether solution crystallized on standing. It was then recrystallized from *n*-hexane to yield 9.4 g. (58.8% yield) of product. IR (mineral oil): 5.83 (ester), 6.1 (C=C), 6.25 (aromatic), 8.2 (ester), and 10.0 μ (ether).

Anal.—Calc. for $C_{15}H_{18}O_4$: C, 68.86; H, 6.92. Found: C, 68.70; H, 6.89.

1,4-Butylene *p*-Hydroxycinnamate (VI)—A mixture of 7.9 g. (0.03 mole) of the tetrahydropyranyl ether of methyl *p*-hydroxycinnamate and 1.35 g. (0.015 mole) of 1,4-butanediol was added to a solution containing 75 ml. of dimethyl sulfoxide, 30 ml. of benzene, and 3.2 ml. of sodium methoxide (1%) in methanol. The solution was heated for 48 hr., and the methanol that formed was removed by azeotropic distillation. The benzene was then removed, and the dimethyl sulfoxide solution was poured into 200 ml. of distilled water. The oil that separated was extracted with diethyl ether and dried over sodium sulfate. The ether was removed, and the oil obtained was crystallized upon scratching (5.2 g. or 54.1% yield). Upon recrystallization from ethanol, a white crystalline product was obtained, m.p. 113–115°.

The protecting group was removed by dissolving the compound in acetone and shaking for 5 min. with 50 ml. of 0.5 *N* hydrochloric acid. The acetone was then diluted with 200 ml. of distilled water. The solid that precipitated from the solution was recrystallized from hot ethyl acetate–benzene. A near quantitative yield of white crystalline product was obtained, m.p. 183–185°. IR (mineral oil): 2.94 (OH), 6.12 (C=C), 6.25 (aromatic), and 8.47 μ (ester). UV (butanol): 319 nm. ($\epsilon = 5.41 \times 10^4$).

Anal.—Calc. for $C_{22}H_{22}O_6$: C, 69.12; H, 5.76. Found: C, 69.19; H, 5.80.

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