Isolation and Chemical Characterization of a New Constituent of Cape Aloe Having the 1,1-Diphenylethane Skeleton[†]

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The structure of a new constituent of Cape aloe was determined by spectral analysis and confirmed by total synthesis. This 1,1-diphenylethane derivative (6), which occurs in the drug in racemic form, was also obtained by thermal reaction of p-coumaric acid with orsellinic acid (or orcinol). These facts are consistent with a nonenzymatic origin of 6, which can be regarded as the first process product isolated from aloe.

INTRODUCTION

Cape aloe (or aloës) consists of the residue obtained by evaporating the juice of the leaves of various species of *Aloe* (Fam. Liliaceae), mainly *A. ferox* Miller and its hybrids with *A. africana* Miller and *A. spicata* Baker (Tyler et al., 1988). The drug is included in the main national pharmacopoeias as a laxative activating peristalsis (*British Herbal Compendium*, 1992). It is also used as a bittering agent in liqueur formulations in appropriate mixture with other tonic flavors (*Fenaroli's Handbook of Flavor Ingredients*, 1975). In this regard, aloe has the regulatory status of a permitted flavoring both in the United States (*Code of Federal Regulations*, 1991) and in Europe (Council of Europe, 1981). Despite its current use, the chemical composition of Cape aloe is far from being completely known. A number of constituents have so far been isolated and structurally characterized (Figure 1): feroxidin (1a) (Speranza et al., 1991), feroxins A (1b) and B (1c) (Speranza et al., 1992), 7-hydroxy-2,5-dimethylchromone (2) (Speranza et al., 1993a), aloesone (3a) (Holdsworth, 1972), aloesin (formerly aloeresin B, 3b) (Haynes et al., 1970), aloeresin A (3c) (Gramatica et al., 1982), aloeresin C (3d) (Speranza et al., 1985), isoaloeresin A (3e) (Speranza et al., 1988), furoaloesone (3f) (Speranza et al., 1993a), aloins A (4a) and B (4b) (Manitto et al., 1990), 5-hydroxyaloin A (4c), aloinosides A (4d) and B (4e) (Rauwald and Beil, 1993), and feralolide (5) (Speranza et al., 1993b). However, they amount to only 50−60% in weight of the drug, aloeresin A (3c), aloesin (3b), and aloins (4a and 4b) being the most abundant components (ca. 25%, 20%, 5%, and 5%, respectively).

All of the products mentioned above appear to be secondary metabolites formed through the acetate−malonate pathway (O'Hagan, 1991) from hexa- to nonaketide chains (see Figure 1). Two additional peculiarities of these compounds are remarkable: frequent C-glucosylation (of only limited occurrence in plant metabolism) (Franz and Grün, 1983) as well as esterification of the glucosyl residue by p-coumaric acid.

It must be pointed out that, besides natural products, thermal process compounds can be present in Cape aloe.

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In fact, to obtain the commercial drug, the juice draining from the cut leaves of *Aloe* plants is collected over a period of about 6 h and then heated for about 4 h on an open fire. Eventually, the residue is poured while hot into tins, each holding 25 kg, where it solidifies (Trease and Evans, 1983).

We report here the structure elucidation and synthesis of a 1,1-diphenylethane derivative (6) which can be regarded as the first process product isolated from aloe.

EXPERIMENTAL PROCEDURES

Drug Samples. Commercial Cape aloe used in this investigation was purchased from Meihwizen Exporters Pty Ltd. It was produced in the Port Elizabeth region (Cape Town, South Africa).

General Methods. UV spectroscopy was done using a Perkin-Elmer Model 554 spectrophotometer (Perkin-Elmer Co., Norwalk, CT); IR spectroscopy was performed with a Jasco IR 5000 instrument (Japan Spectroscopic Co., Tokyo). Mass spectra were obtained on a VG 7070 EQ mass spectrometer operating at 70 eV (VG Instruments, Manchester, U.K.). ^1H and ^{13}C NMR spectra were acquired at 300.135 and 75.469 MHz, respectively, on a Bruker AC 300 spectrometer (Bruker, Karlsruhe, Germany) equipped with an ASPECT 3000 data system. The ^1H and ^{13}C chemical shifts were referenced to the solvent signal (3.30 and 49.00 ppm, 7.25 and 77.00 ppm for CD_3OD and $CDCl_3$, respectively). Analytical TLC was performed on silica gel 60 F_{254} aluminum sheets (0.2-mm thickness) and preparative TLC on silica gel F_{254} precoated plates (1-mm thickness) (Merck, Darmstadt, Germany). Components were detected by spraying with 0.5% Fast Blue B salt, followed by heating at 140 °C for 5 min. Silica gel (Merck, 40−63 μm) was used for flash chromatography. Droplet counter current chromatography (DCCC) was carried out on a Büchi Model 670 chromatograph equipped with 250 standard glass tubes (40 cm × 2.7 mm i.d.) (Büchi Laboratory, Flawil, Switzerland). Preparative HPLC was performed on a Perkin-Elmer Series 3B liquid chromatograph connected to a variable-wavelength UV detector (Perkin-Elmer LC 85 spectrophotometric detector). Chromatographic conditions were as follows: column, Lichrosorb RP-18 (7 μm, 250 × 25 mm, Merck); flow rate, 10 mL/min; detector, λ 280 nm; mobile phase, CH_3CN-H_2O, gradient elution from 50% to 70% CH_3CN in 15 min and then to 90% CH_3CN for 5 min. A Waters Model 600 E liquid chromatograph with a 745 integrator and a 484 UV−visible variable-wavelength detector (Waters, Milford, MA) were used for analytical HPLC. Analyses were performed using a Lichrospher100 RP-18 column (5 μm, 125 × 4 mm, Merck), a flow rate of 1 mL/min, detection at λ 225 nm, and mobile phase as reported below. Orsellinic acid was obtained

New Constituent of Cape Aloe

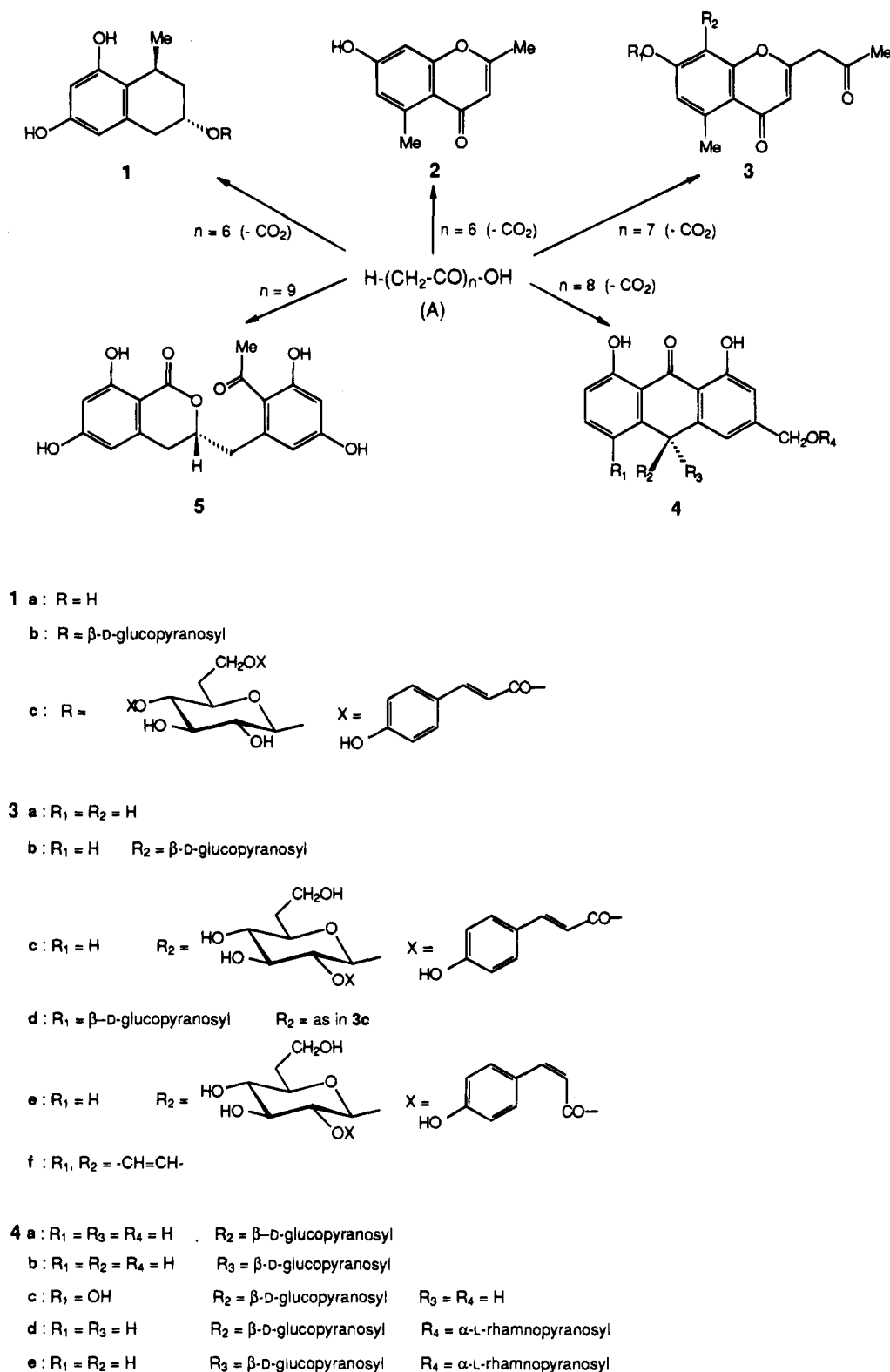*J. Agric. Food Chem.,* Vol. 42, No. 9, 1994 **2003**

Figure 1. Constituents of Cape aloe so far isolated and their apparent origin from a polyketide chain of different length (A).

by alkaline hydrolysis of commercially available ethyl orselli-nate (Sonn, 1928). (R)-$(-)$-2,2,2-Trifluoro-1-(9-anthryl)ethanol was from Fluka (Büchs, Switzerland).

Isolation of Compound CA-12 (6). Powdered Cape aloe (2 kg) was extracted with acetone (2 L) at 40 °C with vigorous mechanical stirring for 3 h. $CHCl_3$ (2 L) was added and the resulting mixture allowed to stand at room temperature overnight. After filtration of the insoluble material, a clear extract was obtained which was concentrated to approximately a half volume under reduced pressure. The residue was then treated with hexane (400 mL), stirred for 3 h, filtered, and

concentrated in vacuo to a brown syrup (21 g). This residue was fractioned by flash chromatography (silica gel, 1.5 kg) eluting with $CHCl_3$ containing increasing amounts of ethyl acetate (20-step gradient from 5% to 100% ethyl acetate, 1.2 L each step). Separation was monitored by TLC (eluent $CHCl_3$—ethyl acetate—acetic acid 10:3:1), and fractions containing compound CA-12 (R_f 0.67) were combined, concentrated (3.5 g) and further purified by flash chromatography (silica gel, 750 g) eluting with a $CHCl_3$—ethyl acetate gradient (from 0% to 100% EtOAc in 20 steps, 600 mL each step). Fractions were combined on the basis of TLC analysis (eluent

Table 1. NMR Data for Compound CA-12 (6) in CD₃OD at 25 °C

carbon	δ ¹H[a]	δ ¹³C[b]
1		157.44
2	6.12 (d, 2.4)	101.76
3		156.52
4	6.06 (d, 2.4)	110.27
5		139.34
6		124.29
7	4.51 (q, 7.3)	35.72
8	1.57 (d, 7.3)	18.53
CH₃Ar	1.98 (s)	21.00
1'		138.59
2',6'	7.02 (d, 8.6)	129.03
3',5'	6.63 (d, 8.6)	115.48
4'		155.62

[a] Splitting patterns and J values (hertz) are given in parentheses. [b] Signal assignments were based on DEPT, HETCOR, and COLOC experiments.

as above) and evaporated to dryness. The residue (1 g) was subjected to DCCC in ascending mode using the lower phase of the solvent system CHCl₃–methanol–H₂O (4:4:3) as stationary phase. The flow rate was 50 mL/h, and 10-mL fractions were collected. Combined fractions 34–58 yielded compound CA-12 (80 mg) in ca. 90% purity. Final purification of compound CA-12 was achieved by preparative HPLC (R_t 11.3 min). Compound CA-12 (55 mg) was obtained as a colorless amorphous powder, pure by TLC (eluent as above) and analytical HPLC (mobile phase, CH₃CN–H₂O, linear gradient from 30% to 60% CH₃CN in 15 min, R_t 7.2 min): mp 108–110 °C (uncorrected); IR (KBr) 3426, 1615, 1514 cm⁻¹; UV (CH₃OH) λ_{max} 250 nm (log ϵ 4.94), 206 nm (4.50); ¹H and ¹³C NMR, see Table 1; EI-MS m/z 244 (M⁺), 229, 136; FAB MS 245 (M + H)⁺; HR EI-MS 244.1109000 (M⁺, calcd for C₁₅H₁₆O₃ 244.1099446).

Conversion of Compound CA-12 (6) into Its Methyl Ether (7). A mixture of compound CA-12 (6) (12 mg), dimethyl sulfate (0.12 mL), and anhydrous K₂CO₃ (400 mg) in dry acetone (2.5 mL) was refluxed with stirring under N₂. After 3 h, the reaction mixture was cooled, diluted with water (5 mL), and extracted with CHCl₃. The CHCl₃ extract was dried over Na₂SO₄ and evaporated to give a residue, which was flash chromatographed using CHCl₃–hexane (1:1) as eluent. Compound 7 (8 mg) was obtained as a colorless oil, pure by TLC (CHCl₃–hexane 1:1, R_f 0.26) and analytical HPLC (mobile phase, CH₃CN–H₂O, linear gradient from 50% to 80% CH₃CN in 15 min; R_t 13.4 min): ¹H NMR (CDCl₃) δ 1.61 (d, J = 7.2 Hz, 3H, CH₃CH), 2.19 (s, 3H, CH₃Ar), 3.62 (s, 3H), 3.76 (s, 3H) and 3.77 (s, 3H) (OCH₃ at 1-, 3-, and 4'-positions), 4.56 (q, J = 7.2 Hz, CH₃CH), 6.30 (d, J = 2.3 Hz, 1H) and 6.32 (d, J = 2.3 Hz, 1H) (H-2 and H-4), 6.77 (d, J = 8.5 Hz, 2H, H-3' and H-5'), 7.11 (d, J = 8.5, 2H, H-2' and H-6'); ¹³C NMR (CDCl₃) δ 17.82 (CH₃CH), 21.08 (CH₃Ar), 34.83 (CH₃CH), 55.17, and 55.54 (3 × OCH₃), 97.25 (C-2), 107.44 (C-4), 113.11 (C-3', C-5'), 126.12 (C-6), 127.88 (C-2', C-6'), 137.99 and 138.25 (C-5 and C-1'), 157.09, 158.35, and 159.02 (C-1, C-3, and C-4'); EI-MS m/z 286 (M⁺), 271.

Synthesis of Compound 7. A stirred solution of orcinol monohydrate (8) (774 mg, 6 mmol) and 4-methoxystyrene (9) (2.4 g, 18 mmol) in dry ethyl ether (3 mL) was cooled to 0 °C and treated with boron trifluoride etherate (0.6 mL) under N₂. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. After this period, the reaction was neutralized with a saturated solution of NaHCO₃ and extracted with CHCl₃ (2 × 5 mL). The combined organic layers were dried over Na₂SO₄, and the solvent was removed under reduced pressure to give a product (3 g) which was submitted to a methylation without further purification.

To an acetone solution (20 mL) of the product previously obtained were added dimethyl sulfate (3.2 mL) and anhydrous K₂CO₃ (5.7 g). The resulting mixture was refluxed with stirring under N₂ for 4 h and then worked up as described above. The crude residue, when analyzed by TLC (eluent CHCl₃–hexane 1:1), consisted of two products which were

separated by flash chromatography (eluent as above). The most polar (R_f 0.26, 35 mg) was identical in all respects with the trimethyl ether of compound 6. The least polar (R_f 0.35, 80 mg) was shown to be pure 10: ¹H NMR (CDCl₃) δ 1.65 (d, J = 7.3 Hz, 3H, CH₃CH), 2.32 (s, 3H, CH₃Ar), 3.71 (s, 6H) and 3.77 (s, 3H) (3 × OCH₃), 4.76 (q, J = 7.3 Hz, 1H, CH₃CH), 6.37 (s, 2H), 6.77 (d, J = 8.6 Hz, 2H) and 7.22 (d, J = 8.6 Hz, 2H) (aromatic protons); ¹³C NMR (CDCl₃) δ 17.97 (CH₃CH), 21.83 (CH₃Ar), 32.43 (CH₃CH), 55.17 and 55.75 (3 × OCH₃), 105.76, 112.93, and 128.19 (aromatic CH), 120.51, 137.08, 138.69, 157.06 and 158.22 (quaternary carbons); EI-MS m/z 286 (M⁺).

Enantiomeric Resolution of Compound 7. Resolution of compound 7 into its enantiomers was achieved by the following methods.

a. HPLC with a Chiral Stationary Phase. The column was a 4.6 × 250 mm β-cyclodextrin (=Daltosil 100, 4 μm) purchased from Serva (Heidelberg, Germany). Separations were obtained isocratically with a flow rate of 1 mL/min using CH₃OH–H₂O (1:1) as eluent. All measurements were carried out at room temperature, and the UV detector was set at 225 nm. Synthetic compound 7 as well as the product obtained by methylation of compound CA-12 exhibited two peaks of equal area having retentions times of 11.20 and 12.35 min, respectively.

b. ¹H NMR Using (R)-(−)-2,2,2-Trifluoro-1-(9-anthryl)-ethanol as Solvating Agent. ¹H NMR spectra were recorded at 300 MHz using CDCl₃ solution ca. 0.05 M in substrate. Addition of 6-fold excess of (R)-(−)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (Pirkle et al., 1977) caused separation of OCH₃ singlet originally at δ 3.76 in two signals at δ 3.762 and 3.767. A similar splitting was observed for the signal at δ 6.77. Enantiomeric composition was found to be 1:1 for both synthetic and extractive trimethyl ethers (7).

Thermal Reaction of p-Coumaric Acid (13) with Orcinol (8) or Orsellinic Acid (11). *a.* A 100-mL two-neck flask equipped with a reflux condenser connected to a CO₂ absorption trap containing 0.1 M Ba(OH)₂ was charged with orcinol monohydrate (8) (850 mg, 6 mmol) and p-coumaric acid (13) (500 mg, 3 mmol). The reaction mixture was heated with stirring in an oil bath maintained at 130 °C for 2 h. After dilution with CHCl₃ (10 mL), the precipitate was filtered off and the organic layer washed with saturated NaHCO₃, dried over Na₂SO₄, and concentrated in vacuo. Purification of the crude residue by preparative TLC (eluent hexane–ethyl acetate 1:1) afforded a compound (20 mg, ca. 3% yield with respect to p-coumaric acid) which was shown to be pure 6 by TLC and analytical HPLC.

b. A mixture of p-coumaric acid (13) (400 mg, 2.4 mmol) and orsellinic acid (11) (400 mg, 2.4 mmol) was heated at 160 °C for 2 h. Workup as described above gave 12 mg of compound 6 (ca. 2% yield).

In two separate experiments (a and b) the crude reaction residue was treated with dimethyl sulfate and anhydrous K₂CO₃ in dry acetone as described for the methylation of compound 6. When the crude reaction product was analyzed by TLC (eluent CHCl₃–hexane 1:1), in neither case was the presence of compound 10 observed.

RESULTS AND DISCUSSION

A minor constituent of Cape aloe, which we call CA-12, was isolated in very low yields (ca. 0.003%) from a commercial sample of the drug through the sequence of separation steps summarized in Figure 2 (see Experimental Procedures).

Its HR EI-MS spectrum showed a parent molecular ion at m/z 244.1109000, consistent with a molecular formula of C₁₅H₁₆O₃. It gave an intensely colored violet spot when TLC plates were sprayed with the diazonium reagent Fast Blue B salt, thus suggesting the presence of phenolic hydroxy groups. Indeed, on treatment with Me₂SO₄, a trimethyl ether (7) was obtained. Inspection of ¹H and ¹³C NMR spectra of compound CA-12 (Table
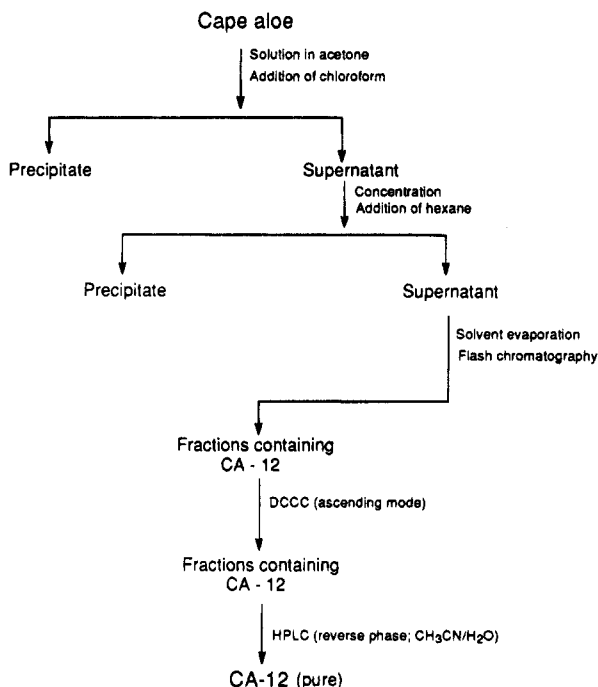
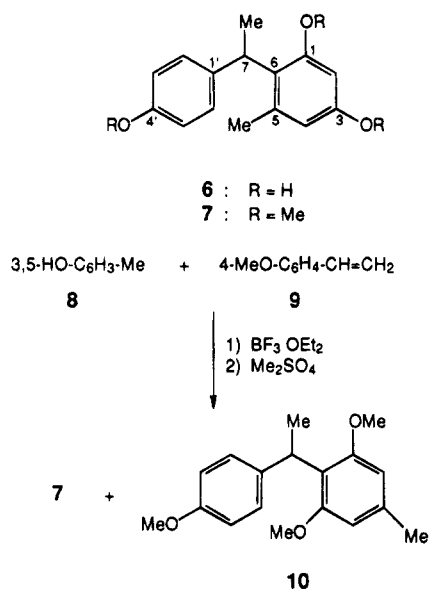**Figure 2.** Schematic diagram for isolating CA-12 (**6**) from Cape aloe.

Figure 3. Chemical structure of CA-12 (**6**) and synthesis of its trimethyl ether (**7**).

Figure 4. Probable reactions involved in the formation of compound **6** during heat treatment of aloe juice.

association between the signal at δ 6.06 and the 5-Me group allowed the former to be assigned to H-4.

Structure **6** for compound CA-12 was also proven through a total synthesis of its trimethyl ether (**7**) (Figure 3). Orcinol (**8**) was arylalkylated with 4-methoxystyrene (**9**) in the presence of $BF_3\cdot OEt_2$ as a catalyst (Zavgorodnii et al., 1960). The crude condensation product was directly subjected to methylation with dimethyl sulfate, giving a 1:2 mixture of products which were separated by flash chromatography. The most polar and least abundant was identical in all respects with the trimethyl ether of compound CA-12 (**7**). The other was found to be the isomeric trimethyl ether (**10**) by NMR spectroscopy.

When compound **6** and its trimethyl ether (**7**) were checked for a possible enantiomeric excess, neither optical activity nor dichroic density was observed.

A comparison of **7**, obtained by methylation of **6**, with a sample prepared by total synthesis was then performed by NMR spectroscopy in the presence of a chiral solvating agent (Pirkle et al., 1977) as well as by chiral HPLC (β-cyclodextrin as stationary phase) (Smolková-Keulemansová, 1982). In the compared experiments the same pairs of peaks in 1:1 ratio, due to the two separated enantiomeric forms, were exhibited both by the synthetic sample and by that arising from the drug, thus proving the latter to be a racemate.

The racemic character strongly suggested a non-enzymatic origin of compound **6**, which could be formed during processing and storage of aloe juice. Four facts appeared to be in favor of this hypothesis: (i) The molecular skeleton of **6** is well explained as resulting from an acid-catalyzed reaction between a meta-dihydroxylated aromatic nucleus (**8** or **11**) and 4-hydroxystyrene (**12**) (cf. Figures 3 and 4). (ii) Orcinol (**8**) or orsellinic acid (**11**) can be regarded as the actual synthetic equivalents of the dihydroxylated aromatic unit, even if neither has been detected in aloe till now. Their occurrence in the drug can be reasonably expected when one considers their polyketide origin, the same that is common to all other secondary metabolites so far isolated (Figure 1). (iii) p-Coumaric acid (**13**) is abundant in aloe, where it is present in esterified form with glucose residues (Figure 1). In addition, thermal decarboxylation of para-hydroxylated cinnamic acids is well documented (Rizzi and Boekley, 1992; Tressl et al.,

1), together with their comparison with those of the trimethyl ether (**7**), indicated the following structural features: (i) a p-hydroxyphenyl residue; (ii) an aromatic ring bearing two meta-coupled protons and a methyl group; (iii) a $CH_3-CH<$ moiety. These data appeared to be consistent with structure **6** for compound CA-12 (Figure 3). It was further supported by homonuclear decoupling experiments, ^1H NOE, DEPT, and one-bond (HETCOR) and long-range heteronuclear (COLOC) correlations which also led to the assignments reported in Table 1. In particular, on irradiation of the quartet at δ 4.51, significant intensity enhancements of the aromatic methyl group at δ 1.98 (2.3%) and H-2' and H-6' (2.4%) were observed. This fact, together with the presence of six different ^{13}C NMR signals for the C-methylated aromatic ring, ruled out the isomeric structure of **6** having the methyl group in para position with respect to the aliphatic chain. In addition, NOE
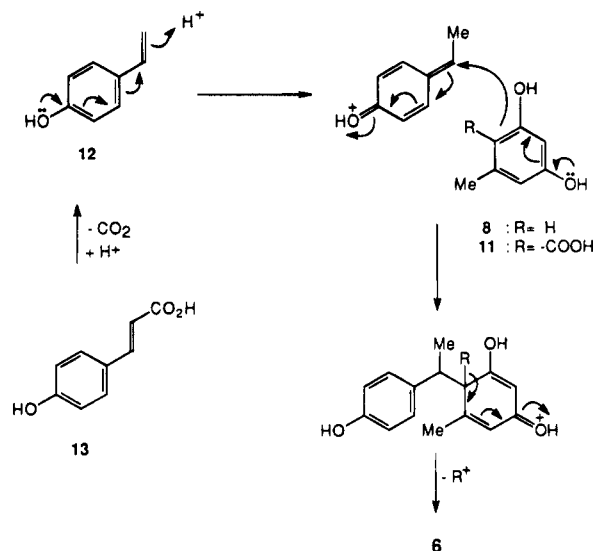
1976; Fiddler et al., 1967), and *p*-hydroxystyrenes (*p*-vinylphenols) have been found in heat-treated food products (Maga, 1978). (iv) Aloe juice does undergo heat treatment during processing as mentioned in the Introduction.

To examine the reliability of the process illustrated in Figure 4, two experiments were carried out by heating mixtures of *p*-coumaric acid (**13**) with orcinol (**8**) or with orsellinic acid (**11**). It was found that compound **6** is formed, though in low yields, in both cases—after 2 h, at 130 °C with orcinol and at 160 °C with orsellinic acid. In neither experiment did the crude reaction residue, when methylated and analyzed by TLC, show the presence of compound **10**, which could be expected from the route to compound **7** described before. The absence of the regioisomer of **6**, among the products formed under the above conditions, can be interpreted in terms of a higher regioselectivity in the electrophilic attack on the meta-dihydroxylated ring by the protonated *p*-hydroxystyrene than in the aromatic alkylation carried out to synthesize compound **7**.

These results, together with the occurrence of compound **6** in racemic form in the drug, strongly support a thermal nonenzymatic origin of that substance. Thus, compound **6** can be considered the first process product found in a commercial sample of Cape aloe.

ACKNOWLEDGMENT

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