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SYNTHESIS OF SINAPYL ALCOHOL DIISOVALERATE, A NEW PHENYLPROPANOID FROM *ARTEMISIA ASSOANA*

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ABSTRACT.—Sinapyl alcohol diisovalerate (syringenin diisovalerate), a new phenylpropanoid isolated from the roots of *Artemisia assoana*, has been synthesized in four steps from syringaldehyde.

Derivatives of substituted cinnamyl alcohols, especially coniferyl and sinapyl alcohols, have a widespread distribution in the plant kingdom, as they play a crucial role in the biosynthesis of lignin (1). The release of these and similar monomeric phenols by depolymerization of lignin in the course of digestive processes or during smoking has aroused interest recently, mostly because of the possible implications with regard to human health (2).

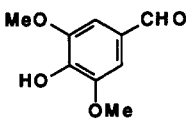
Three years ago, we isolated a new phenylpropanoid from roots of *Artemisia assoana* Willk. (Compositae) (3). On the basis of its spectral properties, deduced mainly from nmr data, we assigned the product the structure of sinapyl alcohol diisovalerate (syringenin diisovalerate) [**1**]. The isolation of cinnamyl alcohol derivatives with isovaleroyl or similar acid residues from diverse plant sources, especially the Compositae, is well precedented (4–8). In order to confirm the proposed structure, we have synthesized compound **1** by acylation of sinapyl alcohol (syringenin) [**6**], which was itself prepared in four steps from syringaldehyde [**2**] as the starting material. A modification of Freudenberg's original procedure (9,10) was performed, leading to improved yields.

Sinapic acid [**3**] was prepared by Knoevenagel condensation of syringaldehyde [**2**] with malonic acid under Pearl and Beyer's conditions (11); it is also commercially available from Aldrich. Reduction of **3** to **6** was effected on the acetylated methyl ester **5** using the $LiAlH_4/AlCl_3$ reagent of Corey *et al.* (12). Finally, acylation of **6** with isovaleroyl chloride gave **1**, identical with the natural product in all its chromatographic and spectral properties.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were measured in a Reichert apparatus and are not corrected. Short cc (13) was performed on Si gel Merck G.

4-HYDROXY-3,5-DIMETHOXYCINNAMIC



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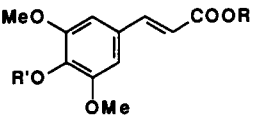
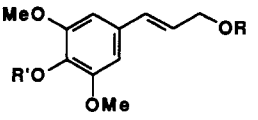


3 R=R′=H
4 R=Me, R′=H
5 R=Me, R′=Ac



1 R=R′=$COCH_2CH(Me)_2$
6 R=R′=H

ACID (SINAPIC ACID) [**3**].—Obtained in 91% yield by Knoevenagel condensation of syringaldehyde and malonic acid (11): colorless needles (95% EtOH), mp 189–191° [lit. (9) mp 192°].

METHYL 4-HYDROXY-3,5-DIMETHOXYCINNAMATE (METHYL SINAPATE) [**4**].—Obtained in 98% yield by Fischer esterification of **3**: colorless needles (95% EtOH), mp 92–93°.

METHYL 4-ACETOXY-3,5-DIMETHOXYCINNAMATE (METHYL ACETYLSINAPATE) [**5**].—Obtained in 83% yield by acetylation of **4**: colorless needles (95% EtOH), mp 151–152°.

4-HYDROXY-3,5-DIMETHOXYCINNAMYL ALCOHOL (SINAPYL ALCOHOL, SYRINGENIN) [**6**].—Obtained in 70–80% yield by reduction of **5** with $LiAlH_4/AlCl_3$ (12), mp 62–66° (pentane/Et_2O) [lit. (9) mp 66–67°].

4-ISOVALEROYLOXY-3,5-DIMETHOXYCINNAMYL ISOVALERATE (SINAPYL ALCOHOL DIISOVALERATE, SYRINGENIN DIISOVALERATE) [**1**].—Sinapyl alcohol (525 mg, 2.5 mM) was dissolved in dry CH_2Cl_2 (10 ml). Dry pyridine (0.8 ml, 10 mM) and 4-dimethylaminopyridine (122 mg, 1 mM) were then added at room temperature under Ar, followed by isovaleroyl chloride (0.73 ml, 6 mM). The mixture was left at 5° for 2 d and worked up in usual form, yielding a dense oil, which was then submitted to short cc on Si gel [length 12 cm, i.d. 3 cm, elution with hexane-Et_2O-CH_2Cl_2 (4:2:1), flow 3 ml/min). Compound **1** was obtained as a colorless oil (710 mg, 75%), ^1H-nmr pure, which was crystallized in poor yields (40%) from hexane: white microcrystalline powder, mp 68–69° [lit. (3) oil]. The spectral (ir, uv, nmr, and ms) and chromatographic properties of the synthetic product are identical with those of the natural compound (3).

Full experimental details of the synthetic procedures, including complete spectral data (ir, ms, nmr) of all compounds, can be obtained from the authors.

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