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# PARTIAL SYNTHESIS OF 3-*O*-VANILLOYLVERACEVINE, AN INSECTICIDAL ALKALOID FROM *SCHOENOCAULON OFFICINALE*

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**Key Word Index**—*Schoenocaulon officinale*; Liliaceae; sabadilla; natural insecticide; *Veratrum* alkaloids; 3-*O*-vanilloylveracevine.

**Abstract**—3-*O*-Vanilloylveracevine has been synthesized for the first time in 70% overall yield by conversion of veracevine into its 3-*O*-(4-benzyloxy-3-methoxybenzoate) followed by catalytic hydrogenation. The insecticidal activity of the semisynthetic substance against three pest species is inferior to that of cevadine and veratridine, the major components of the insecticidal sabadilla alkaloid mixture. Copyright © 1997 Elsevier Science Ltd

## INTRODUCTION

The alkaloid mixture, veratrine, obtained from seeds of *Schoenocaulon officinale* A. Gray is a potent natural insecticide [1] and also has antihypertensive properties [2, 3]. The bioactive principles belong to a group of *Veratrum* alkaloids and are esters of veracevine (**1**) [3, 4]. Besides the two major steroidal alkaloids, cevadine (**2**) and veratridine (**3**), a minor component of the seed extract was also isolated and characterized as 3-*O*-vanilloylveracevine (**4**) [3, 4].

Due to their low toxicity to beneficial insects [5] there is a renewed interest in sabadilla preparations. Of the alkaloid components of the plant extract, the insecticidal activity of **4** is unknown, so we sought a sample to determine its contribution to the overall potency of sabadilla powder and to define further the structure–insecticidal activity relationships for natural and semisynthetic *Veratrum* alkaloids [6]. Although partial syntheses starting with **1** of cevadine (**2**) [7] and veratridine (**3**) [8] have been previously described, synthesis of 3-*O*-vanilloylveracevine (**4**) has not been recorded. Thus, a simple synthesis of **4** was developed.

## RESULTS AND DISCUSSION

Monoacylation of the polyol alkamine **1** with an excess of 4-benzyloxy-3-methoxybenzoic acid [9] in the presence of dicyclohexylcarbodiimide under the conditions described earlier [6] afforded the 3-*O* ester **5** in 77% yield. The regioselectivity of the acylation was confirmed by $^1$H NMR, which indicated exclusive formation of the 3-*O* ester leaving the less reactive 16-OH moiety intact.

Characteristically, the protons at C-3 and C-16 appear as a doublet ($J = 4.2$ Hz) at $\delta$ 5.13 (shifted downfield from $\delta$3.74 in **1**) and a triplet ($J = 3$ Hz) at $\delta$4.15 (unchanged with regard to **1**), respectively. Removal of the benzyl protecting group by hydrogenation in the presence of Pd catalyst gave **4** with the structure established unequivocally by IR, $^1$H and $^{13}$C NMR, and high-resolution mass spectrometry.

The insecticidal activity of the synthetic **4** was determined and compared with those of **2** and **3**, the major components of the insecticidal sabadilla alkaloid mixture (Table 1). While compound **4** is about 25-fold less toxic to the housefly (*Musca domestica* L.) than is veratridine (**3**) and is also less toxic to larvae of the mustard beetle (*Phaedon cochleariae* Fab.) than either of the other two natural products, its insecticidal activity to nymphs of the American cockroach (*Periplaneta americana* L.) is comparable with that of **2** and **3**.

## EXPERIMENTAL

*General.* Mps: uncorr. Assignment of C atoms in $^{13}$C NMR spectra was based on previous studies with sabadilla alkaloids [6, 10] and the APT technique [11]. Analytical and prep. TLC was carried out on 0.25 and

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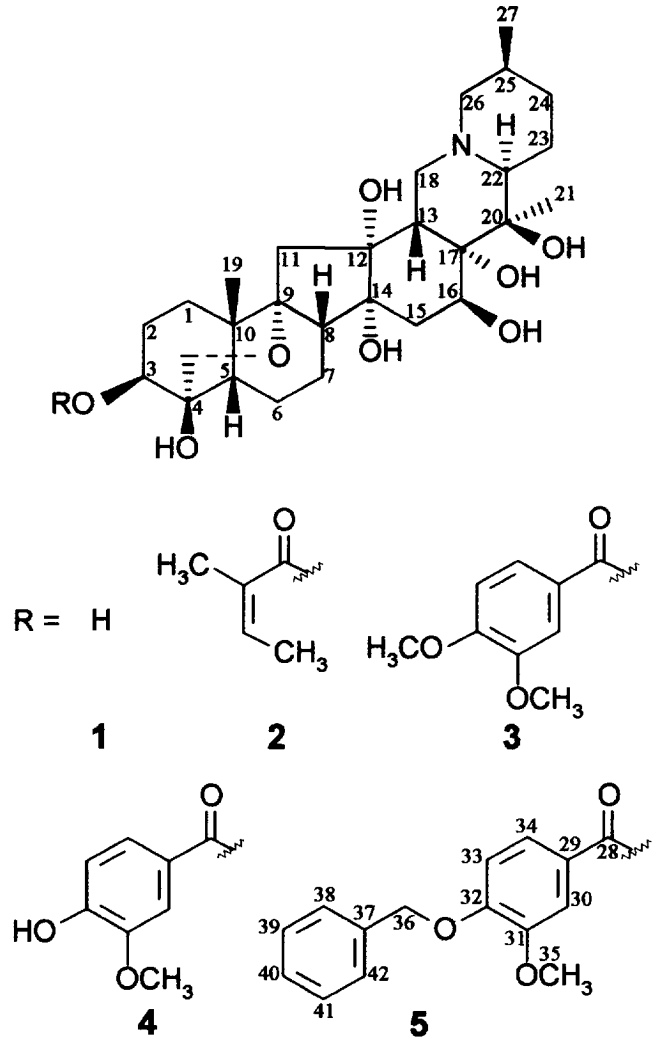


Table 1. Insecticidal activity of sabadilla alkaloids

| Compound | $LD_{50}$ ($\mu g\ g^{-1}$) | | |
|---|---|---|---|
| | Housefly (*Musca domestica*) | Mustard beetle (*Phaedon cochleariae*) | American cockroach (*Periplaneta americana*) |
| Cevadine (**2**) | >50* | 910 | 67 |
| Veratridine (**3**) | 18* | 4800† | 52† |
| Vanilloylveracevine (**4**) | 470‡ | >9000§ | 89 |

* Data from ref. [6].
† Data from ref. [15].
‡ $LD_{50}$ after 48 hr.
§ No mortality at 9000 $\mu g\ g^{-1}$.

2 mm silica gel plates, respectively, using cyclohexane–EtOAc–$Et_2NH$ (7:2:1) (system A) or cyclohexane–EtOAc–$Et_2NH$–MeOH (6:2:1:1) (system B) for development. Visualization was done in UV light (254 nm), $I_2$ vapour or by dipping the plate into an EtOH soln of 3% vanillin containing 1% $H_2SO_4$ and then heating briefly at 110°. Compounds from prep. TLC were recovered by scraping the appropriate band and

elution with $CHCl_3$–MeOH (4:1). Veracevine (**1**) was obtained from veratrine mixt. (Sigma) by mild alkaline hydrolysis at 4° [6]. 4-Benzyloxy-3-methoxybenzoic acid [9] was obtained from the corresponding aldehyde by $KMnO_4$ oxidation [12].

3-*O*-(4-*Benzyloxy*-3-*methoxybenzoyl*)*veracevine* (**5**). To an ice-cooled soln of veracevine (**1**) (100 mg, 196 μmol) and 4-dimethylaminopyridine (10 mg, 81 μmol) in pyridine (0.6 ml) and $CH_2Cl_2$ (2 ml) was added 4-benzyloxy-3-methoxybenzoic acid (100 mg, 387 μmol) followed by dicyclohexylcarbodiimide (80 mg, 387 μmol). After stirring for 4 hr at room temp., TLC analysis indicated the presence of some unreacted **1** ($R_f$ 0.09 in system A). At this point, additional portions of the above acid (20 mg) and dicyclohexylcarbodiimide (10 mg) were added and stirring continued at room temp. overnight. The reaction mixt. was diluted with $CH_2Cl_2$ (4 ml), quenched with a few drops of $H_2O$ and filtered through a short pad of Celite and $Na_2SO_4$ mixt. The solvent was removed and the residue purified by prep. TLC (system A) followed by recrystallization from EtOH–$Et_2O$ to afford ester **5** (114 mg, 77%), mp 142–145°. $R_f$ 0.49 (system A). $^1$H NMR (300 MHz, $CDCl_3$) (only diagnostic peaks listed): δ 7.58 (1H, *dd*, *J* = 1.8, 8 Hz, H-34), 7.54 (1H, *d*, *J* = 1.8 Hz, H-30), 7.4 (5H, *m*, H-38 to H-42), 6.88 (1H, *d*, *J* = 8 Hz, H-33), 5.23 (2H, *s*, H-36), 5.13 (1H, *d*, *J* = 4.2 Hz, H-3), 4.74 (*br s*, OHs, disappear on addition of $D_2O$), 4.15 (1H, *t*, *J* = 3 Hz, H-16), 3.93 (3H, *s*, H-35), 1.15 (3H, *s*, H-21), 1.09 (3H, *d*, *J* = 7.0 Hz, H-27), 1.02 (3H, *s*, H-19). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 166.9 (C-28), 152.4 (C-31), 149.2 (C-32), 136.2 (C-37), 128.6, 128.0 and 127.1 (C-38, C-39, C-40, C-41, C-42), 123.5 (C-34), 122.5 (C-29), 112.8 and 112.4 (C-30 and C-33), 105.0 (C-4), 94.4 (C-9), 81.7 (C-12), 80.3 (C-14), 75.7 (C-20), 75.6 (C-3), 72.0 (C-17), 70.9 (C-16), 70.8 (C-36), 63.5 (C-22), 61.2 (C-26), 56.1 (C-35), 51.3 (C-18), 46.1 (C-5), 45.4 (C-10), 44.7 (C-8), 42.1 (C-11), 36.9 (C-13), 32.6 (C-1), 31.1 (C-15), 29.0 (C-23), 27.4 (C-25), 26.7 (C-6), 19.0 (C-19), 18.9 (C-24), 18.3 (C-2), 17.1 (C-27), 16.9 (C-7), 15.4 (C-21).

*Removal of benzyl protecting group of ester* **5**. A suspension of ester **5** (50 mg, 66 μmol), 10% Pd-C (5 mg), EtOAc (4 ml) and EtOH (2 ml) was stirred under $H_2$ at room temp. overnight. Then, the reaction mixt. was filtered through a short column of Celite. Removal of solvent and subsequent purifications by prep. TLC (system B) and recrystallization form EtOH–$Et_2O$ gave the vanilloyl derivative **4** as fine needles (39 mg, 90%), mp 268–270° (decomp.) (lit. [13] mp 257.5–258.5°; lit. [14] mp 266–270.5°). $R_f$ (system A) 0.06; $R_f$ (system B) 0.24. IR ($CHCl_3$) $\nu_{max}$ cm$^{-1}$ 3690, 3510, 3410, 2960, 2940, 2855, 2790, 1695, 1600, 1515, 1465, 1430, 1330, 1280, 1195, 1115, 1090, 1040, 950, 905, 660. $^1$H NMR (300 MHz, $CDCl_3$) (diagnostic peaks only): δ 7.56 (1H, *dd*, *J* = 1.8, 8.3 Hz, H-34), 7.47 (1H, *d*, *J* = 1.8 Hz, H-30), 6.67 (1H, *d*, *J* = 8.3 Hz, H-33), 5.10 (1H, *d*, *J* = 4.3 Hz, H-3), 4.71 (*br s*, OHs, disappear on addition of $D_2O$), 4.16 (1H, *t*, *J* = 3 Hz, H-16), 3.87 (3H, *s*, H-35), 1.15 (3H, *s*, H-21), 1.09 (3H, *d*, *J* = 7.0 Hz, H-27), 1.00 (3H, *s*, H-19). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 167.4 (C-28), 154.7 (C-31), 147.9 (C-32), 124.7 (C-34), 118.7 (C-29), 115.3 and 112.2 (C-30 and C-33), 105.1 (C-4), 94.2 (C-9), 81.7 (C-12), 80.2 (C-14), 75.7 (C-20), 75.3 (C-3), 72.0 (C-17), 70.9 (C-16), 63.5 (C-22), 61.2 (C-26), 55.7 (C-35), 51.3 (C-18), 46.1 (C-5), 45.4 (C-10), 44.7 (C-8), 42.1 (C-11), 36.9 (C-13), 32.6 (C-1), 31.1 (C-15), 29.0 (C-23), 27.4 (C-25), 26.8 (C-6), 19.0 (C-19, C-24), 18.3 (C-2), 17.1 (C-27), 16.9 (C-7), 15.5 (C-21); HR-MS *m/z*: 660.3378 ($C_{35}H_{49}NO_{11}H^+$ requires 660.3384).

*Biological activity*. Insecticidal activity was determined by topical application of an $Me_2CO$ soln of the test compound to adult houseflies [6], third instar larvae of mustard beetles [15] and last instar nymphs of American cockroaches [15]. $LD_{50}$ values were estimated by probit analysis from mortalities 24 hr after treatment, except for that of **4** for housefly when mortalities were assessed after 48 hr.

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