Alkaloidal Insect Antifeedants from *Virola calophylla* Warb

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Wood extracts of the Peruvian plant *Virola calophylla* Warb. (Myristicaceae) were shown to have antifeedant activity against the cotton boll weevil (*Anthonomus grandis* Boh.). Five compounds with antifeedant activity were isolated. They include 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT), 2-methyl-6-methoxytetrahydro-β-carboline (6-MeO-THC), nicotine, friedelan-3-one, and β-sitosterol.

In a continuing search for natural insect antifeedants, a species of the myristicaceous genus *Virola*, *Virola calophylla* Warb., was shown to possess antifeedant properties (Ly, 1985) against the cotton boll weevil (*Anthonomus grandis* Boheman), one of the most destructive cotton pests in the United States. During the past 25 years, an extensive interest has developed in the myristicaceous genus *Virola* for its wood products, seed pod fatty oils, and for its pharmacological properties as potential new therapeutic agents (Schultes and Hofmann, 1973; Schultes, 1979).

Phytochemical and toxicological interest in *Virola* was first evidenced in 1954 (Schultes and Holmstedt, 1971) with the discovery that several species of plants (*V. calophylla*, *Virola calophylloidea*, *Virola elongata*) of the Amazon basin of Colombia represented the source of yakee-snuff, a potently hallucinogenic narcotic made from the red bark resin. The psychoactivity is apparently due to the presence of various unsubstituted and substituted (5-MeO, 5-OH) tryptamines. Also, some snuffs contain carbolines either in free form or in combination with the simple tryptamines (Holmstedt and Lindgren, 1967). The β-carbolines are monoamine oxidase inhibitors (Agurell et al., 1968) and could potentiate the action of the simple indoles.

The tryptamines *N*,*N*-dimethyltryptamine and 5-methoxydimethyltryptamine have also been identified as the primary hallucinogenic constituents of the *Virola* resins (Holmstedt and Lindgren, 1967). No report was found of nonalkaloidal constituents in *V. calophylla* although sitosterol and stigmasterol were found in several other *Virola spp.* (Filho et al., 1973; Gottlieb et al., 1973), and sitosterol, stilbenes, neolignans, and lignans were found in *V. elongata* (MacRae and Towers, 1985).

MATERIALS AND METHODS

General Experimental Procedures. The infrared spectra were recorded as KBr pellets on a Perkin-Elmer Model 283 B infrared spectrophotometer. Proton nuclear magnetic resonance spectra were recorded on a General Electric Nicolet Model NT-200 high-resolution spectrometer (200 MHz), using $CDCl_3$ as solvent with Me_4Si as the internal standard.

Gas chromatography (GLC) analysis was performed on a Varian Model 3300 gas chromatograph equipped with a DB-5 column. Gas chromatography–mass spectrometry (GLC–EI-MS) was obtained with a DB-1 column (60 m

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× 0.322 mm) interfaced to a Hewlett-Packard 5985-B^R quadrupole mass spectrometer through an open-split interface for acquisition of mass spectra. Alternatively, the column output was directed to an fid detector.

Column chromatography was performed with silica gel (Woelm 63–200 mesh). Thin-layer chromatography (TLC) was carried out on chromatoplates also prepared with 110 C activated silica gel (Woelm, 63–200 mesh), 0.25 mm thick for analytical and 1.0 mm for preparative TLC. Ultraviolet light (254, 366 nm) and exposure to I_2 vapors were used as detecting agents. Alkaloids were located with Dragendorff and Van Urk-Salkowski reagents.

Cotton boll weevils and dehydrated cotton bud powder were supplied by the USDA Boll Weevil Research Laboratory at Mississippi State.

Reference Compounds. 5-Methoxy-*N*-methyltryptamine and 5-methoxy-*N*,*N*-dimethyltryptamine were provided by Dr. H. Weidmann and Dr. H. Friedli, Sandoz A.G., Basel, Switzerland. 2-Methyl-6-methoxytetrahydro-β-carboline was synthesized from 5-methoxy-*N*-methyltryptamine and formaldehyde. All other reference compounds were obtained from Sigma Chemical Co. (St. Louis, MO).

Boll Weevil Antifeedant Bioassay. The agar plug bioassay feeding stimulant procedure developed by Hedin et al. (1966) as modified for antifeedant evaluation by Miles et al. (1985) was used with a few additional modifications. The agar plugs (d = 13 mm, l = 3.6 cm) were formed by boiling 3 g each of agar and freeze-dried cotton bud powder in 100 mL of distilled water and then poured into glass tubes to gel. Upon cooling, the gelled plugs were extruded from the tubes and cut to the aforementioned lengths. Known quantities of the plant samples were applied to 4-cm squares of Whatman 1 chromatography paper. The papers were wrapped around the agar plugs and fastened with staples. Twenty newly emerged boll weevils were place in 14 × 2 cm Petri dishes containing test and control plugs. The bioassay was carried out in the dark at 80 °F for 4 h, after which the papers were removed and the punctures counted.

Antifeedant activity was expressed as a percent T/C value:

$$\% \ T/C = \frac{\text{no. punctures of test paper } (T)}{\text{no. punctures of control paper } (C)} \times 100$$

Extraction of Plant Material. Wood of *V. calophylla* Warb. was collected on March 12, 1980, near the village of Santa Rosa (district of Iquitos) on the Rio Momon, a Peruvian tributary of the Amazon. The plant identification was carried out by Dr. Sidney McDaniel, the Institute for Botanical Exploration, Mississippi State University (IBE Voucher No. 6883).

Sequential Solvent Extract Procedures. Air-dried plant chips were extracted in a Soxhlet apparatus with methylene chloride for 16 h, followed by evaporation of the solvent in vacuo to give 75 g of methylene chloride residue. After hexane was added to the methylene chloride

residue, the mixture was heated at 60 °C for 5 min, and the solvent was removed by decanting. This procedure was repeated until the hot hexane solution was clear. The mixed pale yellow hexane solutions were evaporated in vacuo to yield 12 g of the hexane-soluble residue. The remaining insoluble residue was exhaustively extracted with benzene at room temperature to give, after evaporation of the solvent in vacuo, 14.3 g of a dark brown benzene-insoluble residue.

The marc was Soxhlet-reextracted with ethanol for 16 h. The solvent was evaporated in vacuo to dryness to give 63.6 g of ethanol-dry extract, which was partitioned between chloroform and water (1:1). After separation of the layers, the chloroform phase was evaporated to yield 47.1 g of dry extract. Extraction of the dry extract with hexane yielded 14.0 g of hexane solubles. Subsequent extraction of the dry extract with benzene yielded 10.2 g of benzene solubles. Further extractions of the remaining dry residue with CHCl$_3$ and MeOH yielded 14.3 g of CHCl$_3$ solubles and 4.6 g of MeOH solubles.

The benzene Soxhlet extract (10.2 g) and CHCl$_3$ Soxhlet extract (14.3 g) possessed high antifeedant activity and therefore were mixed together, dissolved in 5% acetic acid, and filtered. The filtrate was made alkaline with 5% ammonium hydroxide and extracted repeatedly with chloroform until the aqueous solution gave negative Dragendorff and Van Urk-Salkowski tests. The combined chloroform extracts were then dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to give 1.2 g of crude alkaloid residue, which gave strong positive tests with Van Urk-Salkowski and Dragendorff reagents.

Preparative TLC. The concentrated extract of crude alkaloids was subjected to preparative TLC using chloroform–methanol–1 N ammonium hydroxide (80:15:1) for development. Five zones or bands were located by UV light and separately eluted with ethanol. Each of the five solutions were tested with Dragendorff and Van Urk-Salkowski reagents. Band 1 (R_f 0.15), band 3 (R_f 0.36), and band 5 (R_f 0.59) gave positive alkaloid tests and were designated 1–3, respectively.

Data for Isolated Compounds. *5-Methoxy-N,N-dimethyltryptamine (5-MeO-DMT)* (*1*). The ethanol extract was evaporated and redissolved in ether–petroleum ether (1:1), from which a colorless solid separated (compound 1): mp 67–68 °C; GLC-MS, *m/e* (rel intens) [M]$^+$ 218 (11), 173 (2), 160 (5), 117 (4), 103 (2), 58 (100); TLC, R_f(I) [propanol–1 N NH$_4$OH (5:1)] 0.13, R_f(II) [methanol–glacial acetic acid–water (75:10:15)] 0.58, R_f(III) [chloroform–methanol–1 N NH$_4$OH (80:15:1)] 0.36.

2-Methyl-6-methoxy-1,2,3,4-tetrahydro-β-carboline (6-MeO-THC) (*2*). The ethanol eluate was concentrated in vacuo to give a yellow residue that was dissolved in methanol and rechromatographed on preparative TLC using methanol–ammonia (50:1). Three bands were located by UV light; however, only band 2 gave a positive reaction with Dragendorff reagent and a negative reaction with Van Urk-Salkowski reagent. The eluate from band 2 was evaporated in vacuo, and the residue was recrystallized from heptane–ethyl acetate (10:1) to give small needles: mp 207–208 °C; GLC-MS, *m/e* (rel intens) [M]$^+$ 216 (13), 173 (100), 158 (37), 130 (10), 115 (7), 103 (1), 77 (5); TLC, R_f(I) 0.36, R_f(II) 0.41, R_f(III) 0.47. No depression was observed in the melting point on admixture with a synthetic sample of 6-MeO-THC.

Nicotine (3). The ethanol solution eluted from this band was concentrated in vacuo to give a yellow oil with a strong pungent odor: GLC-MS, *m/e* (rel intens) [M]$^+$ 162 (17), 133 (32), 119 (11), 105 (6), 92 (9), 84 (100), 57 (8);

TLC, R_f(I) 0.39, R_f(II) 0.44, R_f(III) 0.63. Compound 3 gave a picrate, mp 223–224 °C, undepressed when mixed with nicotine picrate.

Synthesis of 2-Methyl-6-methoxytetrahydro-β-carboline. 5-Methoxy-*N*-methyltryptamine (50 mg) was dissolved in 1 mL of 0.3 N aqueous H$_2$SO$_4$ and 1 mL of 10% formaldehyde. The mixture was heated for 0.5 h at 50 °C, cooled, and mixed with an excess of Na$_2$CO$_3$ to form a solid precipitate. The solid was dissolved in dilute HCl, filtered, made basic with dilute NaOH, and repeatedly extracted with Et$_2$O. Upon evaporation of the Et$_2$O, 2-methyl-6-methoxytetrahydro-β-carboline remained. The product was recrystallized from heptane–ethyl acetate (10:1) to give fine needles, mp 208–209 °C, undepressed when mixed with isolated 6-MeO-THC. The GLC analysis showed the same retention time as isolated 6-MeO-THC of 6.45 min (Akabon and Saito, 1980).

Isolation of the Nonalkaloid Constituents 4 and 5. The residue remaining after extraction of the alkaloids from the benzene and chloroform extracts was dried at room temperature to give a dark brown solid (18.59 g) that was chromatographed on a silica gel column (200 g). The column was prepared with hexane and eluted successively with the following solvent systems (250-mL fractions being collected): A, hexane–toluene (4:1): B, toluene–chloroform (9:1 → 0:10); C, chloroform–ethyl acetate (9:1 → 0:10); D, ethyl acetate-methanol (9:1 → 0:10). The only significant result was obtained from elution with hexane–toluene (fraction A).

Isolation of 4 and 5 from Fraction A. Concentration of fraction A afforded a colorless crystalline solid that gave a green color in the Liebermann–Burchard reaction. Analytical TLC plates developed with toluene–ethyl acetate (1:3) revealed the presence of compounds 4 (R_f 0.52) and 5 (R_f 0.60) upon detection with iodine vapor. Separation of the two compounds was performed by fractional recrystallization. The crystalline solid was dissolved first in hot methanol to give a soluble fraction and an insoluble residue. Removal of methanol in vacuo from the decanted solution followed by recrystallization resulted in the isolation of compound 4. The insoluble residue was recrystallized from toluene–hexane (1:1) to give compound 5.

β-Sitosterol (4) was isolated as colorless flakes: mp 134–135 °C; IR (ν_{max}) 3380, 2900, 1460, 1365, 1050, 795 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.65 (3 H, s), 0.86 (14 H, m), 1.0 (7 H, m), 1.23 (9 H, m), 1.56 (16 H, m), 1.93 (5 H, m), 3.51 (1 H, m), 5.36 (1 H, m); GLC-MS, *m/e* (rel intens) [M]$^+$ 414 (47), 396 (21), 329 (29), 273 (33), 255 (38), 213 (40), 199 (29), 159 (71), 145 (83), 119 (62), 105 (100), 91 (90). Admixture of isolated compound with an authentic sample of β-sitosterol showed no depression in the melting point. *Friedelan-3-one (5)* was isolated as long colorless needles: mp 260–261 °C; IR (ν_{max}, KBr) 2910, 1710, 1450, 1385 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.71 (3 H, s), 0.95 (11 H, m), 1.27 (11 H, m), 1.54 (12 H, m), 1.74 (1 H, s), 1.74 (1 H, s) 217 (1 H, s), 2.39 (1 H, s); GLC-MS, *m/e* (rel intens) [M]$^+$ 426 (52), 411 (14), 341 (10), 302 (31), 273 (59), 246 (43), 205 (50), 179 (38), 163 (45), 137 (38), 123 (76), 109 (83), 95 (100), 69 (83). No depression was observed in the melting point of isolated friedelan-3-one on admixture with the same compound isolated from *Heritiera littoralis*.

RESULTS AND DISCUSSION

V. calophylla wood chips were extracted in a Soxhlet for 16 h with CH$_2$Cl$_2$. The residue from the extract was extracted successively with hexane and benzene. The initial CH$_2$Cl$_2$ extract showed boll weevil antifeedant activity (% T/C = 7.9 at 20 mg), the residue of which when ex-
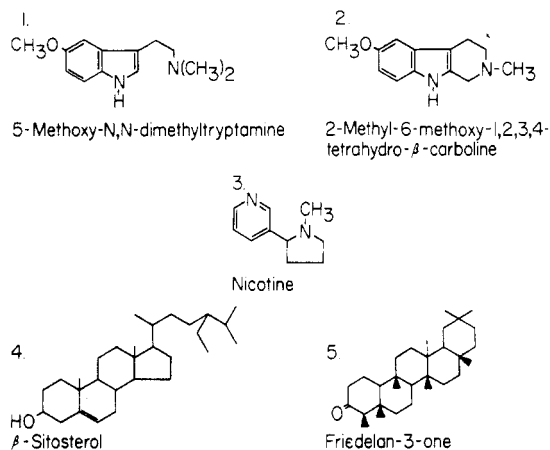
Figure 1. Compounds isolated from *V. calophylla* Warb.

tracted with benzene was active (% T/C = 4.8 at 20 mg). The CH_2Cl_2-extracted pulp when extracted with EtOH was also active (% T/C = 5.4 at 20 mg). Partioning of the ethanol extract between chloroform and water resulted in the concentration of the antifeedant activity in the chloroform phase (% T/C = 2.0 at 20 mg). The water phase was only slightly active (% T/C = 58.0 at 20 mg).

Because of its demonstrated activity, a large quantity of the chloroform phase (47.1 g) was accumulated and extracted successively with hexane, benzene, chloroform, and methanol. While all extracts possessed some activity, the benzene (% T/C = 0.3 at 40 mg) and chloroform (% T/C = 0.7 at 40 mg) fractions were the most potent. The chloroform and benzene fraction gave positive Dragendorff (Zweig and Sherma, 1972) and Van Urk-Salkowski (Ehmann, 1977) tests, thus suggesting they contained indole alkaloids.

Consequently, the chloroform and benzene fractions were combined, and their resultant residue was fractionated according to the general procedures for the isolation of crude alkaloids. Separation of the crude base mixture was effected by preparative TLC using $CHCl_3$-MeOH-1 N NH_4OH (80:15:1) for development. The distinct zones obtained in this fashion were eluted separately with ethyl alcohol. Only the eluates that presented a positive reaction with the Dragendorff and/or Van Urk-Salkowski reagents were considered for further analysis. These eluates were designated compounds 1-3 (Figure 1).

The major alkaloid, compound 1, was identified as 5-methoxy-*N,N*-dimethyltryptamine (5 -MeO-DMT). It was eluted from zone 1 of the TLC plate (R_f 0.15) and isolated as colorless crystals, mp 67-68 °C. The ethyl alcohol eluate gave an orange precipitate with Dragendorff reagent and a blue color [cornflower blue (Horticultural Colour Chart, 1938)] with the Van Urk-Salkowski reagent. Identification of 5-MeO-DMT was based on congruence of the GLC-MS with an authentic sample and by comparison of its spectral features with published data (Holmstedt and Lindgren, 1967; Agurell et al., 1969). In addition, only one spot was obtained when 5-MeO-DMT was chromatographed separately and in admixture with the authentic compound on analytical silica gel TLC with three different solvent systems. The occurrence of 5-MeO-DMT in several other species of the genus *Virola* was previously reported (Holmstedt and Lindgren, 1967).

Compound 2 was isolated as colorless small needle crystals, mp 207-208 °C. This alkaloid gave a red-orange precipitate with Dragendorff reagent but a negative reaction with Van Urk-Salkowski reagent, suggestive of an indole substituted in the 2-position. The mass spectrum of alkaloid 2 gave a M^+ of 216 and two prominent frag-

ments at m/e 173 (base peak) and 158, essentially identical with that previously reported (Agurell et al., 1968, 1969) for 2-methyl-6-methoxy-1,2,3,4-tetrahydro-β-carboline (6-MeO-THC).

Further confirmation of the identity of compound 2 was achieved by the synthesis of 6-MeO-THC from 5-methoxy-*N*-methyltryptamine and formaldehyde to give fine needles, mp 208-209 °C. The TLC, GLC, and mass spectra of the isolated and synthetic compounds were identical.

6-MeO-THC is a minor constituent of *Virola theiodora* and *Virola rufula*, but its occurrence in *V. calophylla* has never been reported. 6-MeO-THC has also been isolated from plants that are not members of the genus *Virola* (Agurell et al., 1969; Frahn and O'Keefe, 1971).

The occurrence of both tryptamines and β-carbolines in the same plant is pharmacologically interesting. The β-carbolines are monoamine oxidase inhibitors (Agurell et al., 1968) and may potentiate the hallucinogenic effects of tryptamines (Holmstedt and Lindgren, 1967). However, the tetrahydro-β-carbolines are less active inhibitors than the corresponding fully aromatic β-carbolines (Undenfriend et al., 1958).

Compound 3 was isolated as a yellow oil with a strong pungent odor. Compound 3 produced a red precipitate with Dragendorff reagent but gave a negative reaction with the Van Urk-Salkowski reagent. The mass spectrum of alkaloid 3 gave M^+ of 162 with prominent fragments at m/e 133 and 84 (base peak). This alkaloid was identified as nicotine by GC-MS, GLC, and TLC by comparison with an authentic sample and with mass spectral data reported in the literature (Dow and Hall, 1978). The base peak of nicotine (m/e 84) is produced by α-cleavage of the α-substituted pyrrolidine with the loss of pyridine (Budzikiewicz et al., 1964).

Nicotine has been isolated from at least 18 species of *Nicotiana*, among which *Nicotiana tobacum* and *Nicotiana rustica* are the most common. However, it is also found in species completely unrelated to *Nicotiana* [*Asclepia syriaca*, *Atropa belladona*, *Equisetum arvense*, *Lycopodium clavatum* (Jacobson and Crosby, 1971)]. Nicotine has also been reported to be present in several *Acacia* species (Fikenscher, 1960).

Two nonalkaloidal compounds were isolated by silica gel column chromatography of the solid residue left after extraction of the crude alkaloids. Elution with a mixture of hexane-toluene (4:1) yielded a crystalline solid, which under examination by TLC revealed two compounds designated herein as 4 and 5 (Figure 1). Separation was performed by fractional recrystallization. Compound 4 was identified as β-sitosterol by GC-MS, IR, and TLC comparison with data from an authentic sample.

Compound 5 was identified as friedelan-3-one (friedelin) by comparison of the spectral data and chemical properties with those of friedelin as published in the literature (Braun, 1954; Stenhagen et al., 1969).

The isolated compounds 5-MeO-DMT, β-sitosterol, and friedlan-3-one were bioassayed at 10 mg, and 6-MeO-THC was bioassayed at 6 mg. An authentic sample of nicotine was bioassayed at 1.5, 3, 6, and 10 mg. Nicotine was found to be lethal to the insects at 10 mg (Table I). At 1.5, 3.0, and 6.0 mg, it was as antifeedant as 5-MeO-DMT (% T/C = 3.5 at 10 mg). Friedlan-3-one, 6-MeO-THC, and β-sitosterol were progressively less antifeedant.

For comparison of relative antifeedant properties, methyl linolenate, which has been shown to be primarily responsible for the feeding deterrency of Rose of Sharon *Hibiscus* (Bird et al., 1987) *Syriacus* L. Calyx tissue to the

Table I. Boll Weevil Antifeedant Activities of Compounds Isolated from *V. calophylla* Warb

compound	concn	av % T/C
5-MeO-DMT	10.0	3.5
6-MeO-THC	6.0	49.0
nicotine	1.5	17.0
	3.0	12.5
	6.0	11.0
	10.0	0.0[a]
friedelan-3-one	10.0	22.4
β-sitosterol	10.0	79.5

[a] 10 mg of nicotine was also lethal to 100% of the insects.

boll weevil, decreased feeding by this insect to 40% of control when applied to a test disc at 0.56 μg/mm². When 5-MeO-DMT was tested at 5.0 μg/mm² with the same insect, feeding was decreased to 3.5% of control. Thus, a 10-fold greater activity was obtained at a 10-fold higher concentration, and therefore the relative activity appears to be approximately the same. For further comparison, the well-known bitter principles in citrus, nomilin, and obacunone gave responses similar to azadirachtin, the bitter principle from the neem tree (PC_{95} = 6 μg/cm² disk) against *Heliothis zea* (Kubo and Klocke, 1982). The potency of these liminoids at PC_{95} = 6 μg/cm² is equivalent to 0.06 μg/mm² at T/C = 5% and approximately 100-fold more potent than 5-MeO-DMT, which showed a T/C value of 3.5% at 5.0 μg/mm².

The antifeedant activity of 5-MeO-DMT might have a relationship to the finding (Graleffi et al., 1983) that 5-MeO-DMT, nicotine, and, to a lesser extent, 6-MeO-THC evidently account in a large measure for the reported pharmacological properties of this plant. The pharmacological properties appear to be generally correlated with the antifeedant properties.

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