petroleum ether as colorless crystals of **9**: mp 148–149°; $[\alpha]^{27}D$ +8° (*c* 1.17, acetone); uv λ^{MeOH} end absorption 208 mμ (ε 17,300); ir λ_{max}^{Nujol} 5.75, 5.82, 6.14, 8.10, 8.58, 9.72, and 10.28 μ.

Anal. Calcd for $C_{20}H_{24}O_8$: C, 61.21; H, 6.17. Found: C, 61.26; H, 6.20.

8-Dehydrovernolepin–Methanol Adduct (10) and 6-Dehydrovernolepin–Methanol Adduct (11).—A solution of vernolepin–methanol adduct (**7**, 305 mg) in acetone (10 ml) was treated with Jones reagent (0.5 ml) at 0°. After 15 min, water (30 ml) was added and the solution was extracted with chloroform (70 ml). The chloroform extract was dried (Na_2SO_4) and evaporated. The residue (315 mg) was chromatographed on silicic acid (20 g), and two discrete fractions were eluted with 0.5% methanol in chloroform. The less polar material was a colorless oil (150 mg), the spectra of which were in accord with the C-8 ketone structure, **10**.

The more polar material was crystallized from acetone–petroleum ether to give colorless plates (26 mg) of **11**: mp 190–193° dec; uv λ^{MeOH} end absorption 211 mμ (ε 11,800); ir λ_{max}^{KBr} 2.84, 3.39, 5.82, 5.89, 6.12, 7.64, 8.45, 9.67, 10.40, and 10.73 μ.

Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.78; H, 5.94.

Lactone Titration of Vernolepin (1).—Vernolepin (26.0 mg) was dissolved in 0.0947 *N* aqueous sodium hydroxide (5 ml), the solution was evaporated to dryness at 40°, and the residue was dissolved in water (1 ml). The solution was heated on a steam bath for 10 min, diluted with water (4 ml), and titrated with 0.121 *N* sulfuric acid using phenolphthalein as indicator; 2.36 ml of acid was required to neutralize the excess of base. On this basis, **1** was found to have equiv wt 138. When the titration was repeated using 29.2 mg of **1** and sodium hydroxide solution (4 ml), the volume of acid required was 1.51 ml, corresponding to equiv wt 149 for **1**.

Vernomenin Acetate (6).—A solution of vernomenin (100 mg) in pyridine (10 ml) and acetic anhydride (5 ml) was left overnight at room temperature, cooled to 0–2°, and diluted with water (50 ml). The mixture was extracted with chloroform and the chloroform extract was washed with diluted hydrochloric acid followed by saturated sodium bicarbonate solution. Evaporation of the dried chloroform extract (Na_2SO_4) gave a crystalline residue (94 mg), which was recrystallized from chloroform–ether to afford colorless plates of **6**: softens at 210–212° but does not melt completely below 300°; $[\alpha]^{26}D$ −135° (*c* 2.00, $CHCl_3$); uv λ^{MeOH} end absorption 210 mμ (ε 17,500); ir $\lambda_{max}^{CHCl_3}$ 3.28, 3.38, 5.63, 5.71, 5.77, 5.96, 6.14, 7.94, 8.06, and 8.58 μ.

Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 63.91; H, 5.59.

Registry No.—**1**, 21887-20-7; **2**, 20107-21-5; **3**, 20107-25-9; **4**, 20107-22-6; **5**, 20107-26-0; **6**, 20071-38-9; **7**, 20107-23-7; **8**, 21887-26-3; **9**, 20107-24-8; **10**, 21887-28-5; **11**, 21887-29-6.

Acknowledgment.—We take pleasure in thanking Dr. Roger M. Smith for stimulating discussions.

Tumor Inhibitors. XLVII.[1a] Vernodalin and Vernomygdin, Two New Cytotoxic Sesquiterpene Lactones from *Vernonia amygdalina* Del.[1b]

S. MORRIS KUPCHAN,[2] RICHARD J. HEMINGWAY, AZIZ KARIM, AND DIETER WERNER

Department of Pharmaceutical Chemistry, University of Wisconsin, Madison, Wisconsin 53706

Received June 30, 1969

A chloroform extract of *Vernonia amygdalina* Del. was found to show significant inhibitory activity *in vitro* against cells derived from human carcinoma of the nasopharynx (KB) carried in tissue culture. The isolation and structural elucidation are reported of vernodalin (**1**) and vernomygdin (**8**), two new cytotoxic sesquiterpene lactones. Mass spectrometry indicated a $C_{19}H_{20}O_7$ molecular formula for vernodalin. Acidic hydrolysis in methanol gave methanol adduct **2**, identical with the methanol adduct of vernolepin. An additional interrelation with vernolepin (**5**) was effected by conversion of vernodalin to hexahydrovernolepin isobutyrate (**4**). Elemental analysis and mass spectrometry indicated a $C_{19}H_{25}O_7$ molecular formula for vernomygdin (**8**). Its structure and relationship to vernolide (**7**) was established by catalytic hydrogenation to tetrahydrovernolide (**9**).

In the course of a continuing search for tumor inhibitors from plant sources, a chloroform extract of *Vernonia amygdalina* Del. (Compositae)[3] was found to show significant inhibitory activity *in vitro* against cells derived from human carcinoma of the nasopharynx (KB) carried in tissue culture.[4] Consequently, a systematic study aimed at isolation of the KB inhibitory principles was undertaken. The dried ground leaves were extracted continuously with chloroform to afford active fraction A (see Chart I and Table I). The marc was extracted continuously with methanol to give an inactive fraction (B), which was not investigated further. Partition of fraction A between 10% aqueous methanol and petroleum ether resulted in concentration of the activity in the aqueous methanol fraction (D). This material was fractionated by silicic acid chromatography to give two main cytotoxic fractions, F and H.

Further chromatography of fraction H yielded vernodalin (**1**) as a colorless oil. The molecular formula $C_{19}H_{20}O_7$ was assigned on the basis of mass spectrometry. The ultraviolet spectrum exhibited a high end absorption and the infrared spectrum showed bands at 5.64 and 6.14 μ, characteristic of an α,β-unsaturated γ-lactone. The nmr spectrum exhibited two doublets (J = 3 Hz) at τ 3.77 and 4.30, indicative of the protons of a methylene exocyclic to a γ-lactone. The infrared spectrum also showed a second carbonyl band at 5.81 μ, and the general features of the spectrum were very similar to those of vernolepin (**5**) and vernomenin, previously isolated from *V. hymenolepis*.[1a] Comparison of the nmr spectra of vernodalin and vernolepin suggested that both compounds had a similar sesquiterpene lactone skeleton and that vernodalin might be an ester of vernolepin or vernomenin. The additional signals exhibited by vernodalin, namely, one-proton broad singlets at τ 3.67 and 4.00, a two-

(1) (a) Part XLVI: S. M. Kupchan, R. J. Hemingway, D. Werner, and A. Karim, *J. Org. Chem.*, **34**, 3903 (1969); (b) This investigation was supported by grants from the National Cancer Institute (CA-04500) and the American Cancer Society (T-275), and a contract with Chemotherapy, National Cancer Institute, National Institutes of Health (PH 43-64-551).

(2) Author to whom inquiries should be directed: Department of Chemistry, University of Virginia, Charlottesville, Va. 22901.

(3) Leaves gathered in Ethiopia in 1965. The authors acknowledge receipt of the dried plant material from Dr. Robert E. Perdue, Jr., U. S. Department of Agriculture (USDA), Beltsville, Md., in accordance with the program developed with the USDA by the Cancer Chemotherapy National Service Center (CCNSC).

(4) Assays were performed under the auspices of the CCNSC. The procedures were those described in *Cancer Chemotherapy Rept.*, **25**, 1 (1962).

CHART I

FRACTIONATION OF CYTOTOXIC EXTRACT FROM *V. amygdalina*

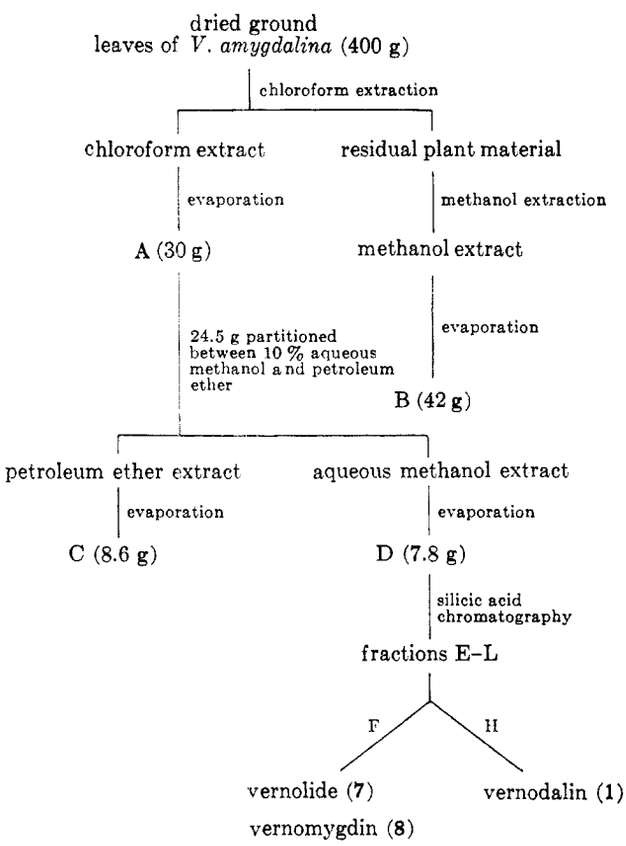


TABLE I

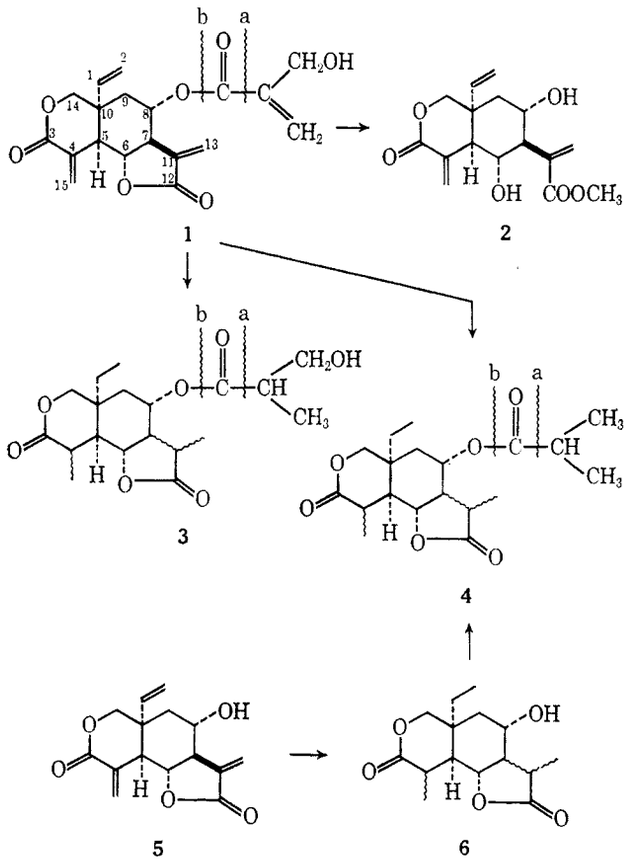
ACTIVITY OF FRACTIONS FROM *V. amygdalina* AGAINST KB CELL CULTURE[a]

Fraction	Activity; ED_{50}, μg/ml
A	6.8
B	>100
C	>100
D	16
E	20
F	1.6
G	12
H	0.62
I	1.6
J	2.4
K	3.2
L	16
1	1.8
7	2.0
8	1.5

[a] Reference 4.

proton broad singlet at τ 5.63, and a signal for one D_2O-exchangeable proton at τ 7.30, corresponded to those expected for a hydroxymethacrylate ester grouping. Support for the presence of this functionality came from the mass spectrum of vernodalin, which showed prominent peaks at *m/e* 57 and 85, attributable to the fragmentations a and b.

Hydrolysis of vernodalin in acidic methanol yielded **2**, identical with the methanol adduct from vernolepin.[1a] The conversion to **2** confirmed the suspected relationship of vernodalin to the elemanolide lactones, but established neither the position of the γ-lactone

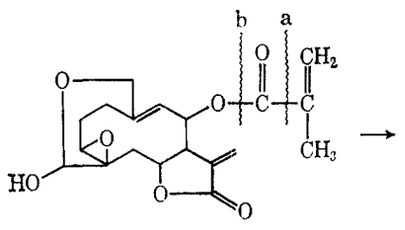


closure (*i.e.*, to C-6 or C-8) nor the nature of the ester function. Hydrogenation of **1** in methanol with 10% palladium-on-charcoal catalyst yielded a mixture of products. The major product, the octahydro derivative **3** ($C_{19}H_{28}O_7$), was isolated by silica gel chromatography. Its nmr spectrum contained no signals due to olefinic protons, but contained a number of new signals at higher field. A three-proton triplet at τ 9.08, similar to that seen in tetrahydrovernolepin,[1a] was indicative of an ethyl group formed by reduction of the double bond at C-1. Three-proton doublets at τ 8.60, 8.72, and 8.82 corresponded to secondary methyl groups formed by reduction of the two double bonds exocyclic to the lactones and that present in the ester. The change from the hydroxy methacrylate side chain in **1** to the hydroxy isobutyrate side chain in octahydrovernodalin (**3**) was also supported by the mass spectrum of **3**, which contained prominent peaks at *m/e* 59 and 87 due to fragmentations a and b. The multiplicity of the signal at τ 5.00 in the nmr spectrum of **3** suggested the lactone closure to C-6. This assignment was based on comparisons with the multiplicity of the corresponding signal in vernolepin acetate (C-6 γ-lactone closure, 1 H, m) and vernomenin acetate (C-8 γ-lactone closure, 1 H, t), which differ only in the nature of the γ-lactone closure.

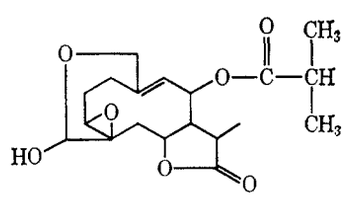
Hydrogenation of **1** in acidic methanol with 10% palladium on charcoal yielded a new product, **4** ($C_{19}H_{28}O_6$), whose mass spectrum contained prominent peaks at *m/e* 43 and 71 attributable to fragmentations a and b. These fragmentations together with the molecular ion peak at *m/e* 352 and the elemental analysis indicated that the hydroxyl group of the side chain had been hydrogenolyzed to yield an isobutyrate ester. Consequently, a sample of vernolepin

(5) was hydrogenated with palladium-on-charcoal catalyst to afford hexahydrovernolepin (6). Acylation of 6 with isobutyric anhydride in pyridine afforded hexahydrovernolepin isobutyrate (4), identical with the product obtained by hydrogenation of 1. This established unequivocally the C-6 closure of the lactone in vernodalin and confirmed the skeleton of the original ester.

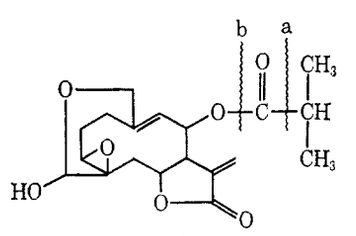
Rechromatography of the cytotoxic fraction F yielded two crystalline compounds with very similar R_f values. The major compound ($C_{19}H_{22}O_7$) was identified as vernolide (7)[5] by direct comparison with an authentic sample. The other, which we designate as vernomydgin (8), was assigned the molecular



7



9



8

formula $C_{19}H_{24}O_7$ on the basis of elemental analysis and mass spectrometry (M^+ *m/e* 364). The high end absorption in its ultraviolet spectrum, the band at 5.65 μ in the infrared spectrum, and nmr signals at τ 3.55 and 3.98 (a pair of doublets of doublets, J = 3.5 and 0.8 Hz) suggested the presence of an α,β-unsaturated γ-lactone. The presence in the infrared absorption spectrum of a peak at 2.92 μ and in the nmr spectrum of one D_2O-exchangeable proton signal at τ 5.00 indicated that vernomygdin contains a single hydroxyl group. A pair of doublets of doublets (2 H) at τ 5.38 and 6.32 (J = 13.5 and 0.5 Hz) suggested the presence of a $-OCH_2CR{=}CH-$ group, as in vernolide. The infrared peak at 5.82 μ was assigned to ester carbonyl. These spectroscopic properties closely resembled those of vernolide. The main difference between the two compounds became apparent from a study of their nmr and mass spectra. The spectrum of vernolide contained two one-proton broad signals at τ 3.86 and 4.48 and a three-proton singlet at τ 8.05, which were assigned to a methacrylate ester side chain.[5] These signals were absent from the spectrum of 8, which contained signals characteristic of an isopropyl group (two 3 H doublets, J = 7 Hz, at τ 8.79 and 8.83) indicative of the presence of an isobutyrate group in the side chain. Vernolide's mass spectrum showed prominent peaks at *m/e* 41 and 69 due to the fragmentations a and b. The corresponding fragmentations in vernomygdin gave peaks at *m/e* 43 and 71. Both vernolide and vernomgydin gave the same fragmentation peaks at *m/e* 276 (M^+ − side chain), 258, 230, and 212. The similarity of the fragmentation patterns in the high-mass region suggested that the difference between the two resided only in the side chain. The structure of vernomygdin was confirmed by catalytic hydrogenation to give the known tetrahydrovernolide (9). The structure of vernomygdin has thus been derived by interrelation with vernolide.

(5) R. Toubiana and A. Gaudemer, *Tetrahedron Lett.*, 1333 (1967). We thank Dr. R. Toubiana cordially for an authentic sample of vernolide.

Experimental Section

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are corrected. Infrared spectra were determined on a Beckman Model IR9 recording spectrophotometer. Ultraviolet absorption spectra were determined on a Beckman Model DK2A recording spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian A-60A spectrometer in deuteriochloroform using tetramethylsilane as internal standard. Specific rotations were determined on a Zeiss–Winkel polarimeter and are approximated to the nearest degree. Petroleum ether refers to the fraction with bp 60–68°. Evaporations were carried out at temperatures less than 40° under reduced pressure. Thin layer chromatography was carried out on silica gel (E. Merck) precoated plates and chromatograms were visualized by spraying with a 3% $Ce(SO_4)_2$–3 N H_2SO_4 solution followed by heating; the developing solvent was 5% MeOH in $CHCl_3$. Microanlyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Preliminary Fractionation of *V. amygdalina* Extract.—The dried ground leaves of *V. amygdalina* (400 g) were extracted continuously for 16 hr with chloroform and the resulting extract was concentrated to afford a thick green oil (A, 30 g). The marc after chloroform extraction was extracted continuously with methanol for 16 hr and the extract was concentrated to yield a thick oil (B, 42 g). A portion of fraction A (24.5 g) was partitioned between petroleum ether (300 ml) and 10% aqueous methanol (300 ml) to yield petroleum ether solubles (C, 8.6 g) and 10% aqueous methanol solubles (D, 7.8 g). A portion of the aqueous methanol solubles (D, 6.6 g) dissolved in chloroform (15 ml) was chromatographed on a column of silicAR CC-7 (Mallinckrodt, 600 g) packed in chloroform. Elution with chloroform and combination of fractions on the basis of the tlc patterns gave, successively, fractions E (86 mg), F (359 mg), G (132 mg), H (866 mg), I (64 mg), J (187 mg), and K (177 mg). The column was finally washed with methanol to yield fraction L (2.30 g).

Isolation of Vernodalin (1).—Fraction H (790 mg) was rechromatographed on a column of silica gel (Merck, 200 g) packed in chloroform. Elution with methanol–acetone–chloroform (1:10:190) yielded the major component, a colorless oil (730 mg), which could not be crystallized. A sample of this oil (100 mg) was chromatographed on neutral alumina (50 g, Woelm activity I) with chloroform to yield a colorless homogeneous oil (85 mg): $[\alpha]^{24}D$ +125° (*c* 1.35, $CHCl_3$); uv λ^{MeOH} end absorption 210 mμ (ϵ 20,000); ir λ_{max}^{KBr} 2.92, 5.64, 5.81, 6.14, 7.93, 8.55, 9.52, 10.20, and 12.20 μ; nmr τ 3.26 (1 H, d, J = 1 Hz, C-15 **H**), 4.00 (2 H, br s, C-15 **H** and =C**H** of hydroxy methacrylate), 3.67 (1 H, br s, =C**H** of hydroxy methacrylate), 3.77 (1 H, d, J = 3 Hz, C-13 **H**), 4.30 (1 H, d, J = 3 Hz, C-13 **H**), 4.58 (3 H, m, C-1 and C-2 **H**), 5.41 (1 H, d, J = 14 Hz, C-14 **H**), 5.88 (1 H, d, J = 14 Hz, C-14 **H**), 5.63 (2 H, s, $-CH_2OH$ of hydroxy methacrylate), and 7.30 (1 H, br s, exchangeable with D_2O, −O**H**); mass spectrum *m/e* 360 (M^+), 276, 258, 246, 228, 85, 57, and 39.

Vernodalin is unstable and after 2 weeks at room temperature forms a white amorphous solid which is insoluble in chloroform.

Vernolepin–Methanol Adduct (2).—A solution of vernodalin (50 mg) in hydrochloric acid (1 ml) and methanol (4 ml) was refluxed for 20 hr. The solution was concentrated to 2 ml, diluted with water (5 ml), and extracted with chloroform (25 ml). The chloroform extract was dried (Na_2SO_4) and evaporated to afford an oil (30 mg) which was chromatographed on silicAR CC-7 (12 g). The major fraction (13 mg), eluted with 10% acetone in chloroform, was crystallized from acetone–hexane to yield **2** in the form of colorless needles (6 mg), mp 169–170°. The product was shown to be identical with authentic vernolepin–methanol adduct by mixture melting point, infrared spectral comparison, and mixture tlc comparisons.

Octahydrovernodalin (3).—A solution of vernodalin (146 mg) in methanol (10 ml) was hydrogenated at room temperature and atmospheric pressure with 10% Pd–C (50 mg) catalyst. After the consumption of 4 mol equiv of hydrogen, when the uptake ceased, the catalyst was removed by filtration and the filtrate was evaporated to afford a colorless oil (140 mg). The oil was dissolved in chloroform and chromatographed on silica gel (15 g) using methanol–acetone–chloroform (1:10:190) as solvent. Fractions were collected and examined by tlc. Crystallization of the major component (63 mg) from chloroform–ether yielded octahydrovernodalin (**3**) as colorless prisms (28 mg): mp 160–162°; $[\alpha]^{27}D$ +90° (*c* 0.51, acetone); ir λ_{max}^{KBr} 2.83, 3.35, 3.40, 3.46, 5.62, 5.78, 6.81, 7.20, 8.40, 8.84, 9.65, and 10.30 μ; nmr τ 5.00 (1 H, m, C-8 **H**), 8.60 (3 H, d, J = 7 Hz), 8.72 (3 H, d, J = 7 Hz), 8.82 (3 H, d, J = 7 Hz), and 9.08 (3 H, t, J = 7 Hz, C-1 CH_3); mass spectrum *m/e* 368 (M^+), 264, 220, 191, 143, 133, 97, 87, and 59.

Anal. Calcd for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66. Found: C, 61.83; H, 7.64.

Hexahydrovernolepin (6).—A solution of vernolepin (**5**, 210 mg) in methanol (12 ml) was hydrogenated at room temperature and atmospheric pressure using 10% Pd–C (200 mg) catalyst. After the consumption of 3 mol equiv of hydrogen, the catalyst was removed by filtration and the filtrate was evaporated to afford a solid residue. The residue was crystallized from acetone–hexane to afford colorless needles (68 mg), mp 162–164°. Recrystallization afforded hexahydrovernolepin (**6**) as colorless needles: mp 170–171°; $[\alpha]^{24}D$ +72° (*c* 3.60, $CHCl_3$); ir $\lambda_{max}^{CHCl_3}$ 2.76, 2.86, 5.62, 5.75, 8.47, 8.93, and 10.15 μ; nmr τ 8.60 (3 H, d, J = 7 Hz), 8.62 (3 H, d, J = 7 Hz), and 9.06 (3 H, t, J = 7 Hz, C-1 CH_3).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.67; H, 7.95.

Hexahydrovernolepin Isobutyrate (4). A. From Hexahydrovernolepin (6).—A solution of **6** (60 mg) in pyridine (1 ml) was treated with isobutyric anhydride (200 mg) at room temperature for 20 hr. The reaction mixture was evaporated to afford a colorless oil, which was crystallized from chloroform–hexane to yield colorless needles (71 mg), mp 168–169°. Recrystallization afforded **4**: mp 174–175°; ir λ_{max}^{KBr} 2.83, 3.35, 3.40, 3.46, 5.62, 5.78, 6.81, 7.20, 8.40, 8.84, 9.65, and 10.30 μ; nmr τ 5.00 (1 H, m, C-8 **H**), 8.58 (3 H, d, J = 7 Hz), 8.68 (3 H, d, J = 7 Hz), 8.62 (6 H, d, J = 7 Hz, isopropyl CH_3), and 9.05 (3 H, t, J = 7 Hz, C-1 CH_3); mass spectrum *m/e* 352 (M^+), 191, 97, 71, and 43.

Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.81; H, 8.11.

B. From Vernodalin (1).—A solution of **1** (170 mg) in methanol (10 ml) and hydrochloric acid (1 ml) was hydrogenated at room temperature and atmospheric pressure using 10% palladium on charcoal (210 mg) as catalyst. After the consumption of 5 mol equiv, the reaction mixture was treated with an excess of sodium bicarbonate and filtered to remove the catalyst and undissolved solid. The filtrate was evaporated and the residue was dissolved in water (5 ml) and extracted with chloroform (20 ml). The chloroform extract was dried (Na_2SO_4) and evaporated to afford a colorless oil (160 mg) which was crystallized from ether to afford **4** as colorless needles (60 mg), mp 174–175°. The melting point of this sample was not depressed on admixture with the sample prepared from hexahydrovernolepin. The two samples showed identical mobility on tlc using methanol–acetone–chloroform (1:15:84) as solvent and superimposable infrared absorption spectra.

Isolation of Vernolide (6) and Vernomygdin (8).—Fraction F (282 mg) was rechromatographed on a column of silica gel (100 g) packed in chloroform. The column was eluted with methanol–acetone–chloroform (1:10:90) to give two homogeneous crystalline fractions. Crystallization of the major fraction (200 mg) from acetone–petroleum ether gave plates, identified as vernolide (**7**) by mixture melting point, tlc, and ir and nmr spectral comparisons with an authentic sample.[5] Crystallization of the minor fraction (30 mg) from acetone–petroleum ether gave plates of vernomygdin (**8**): mp 208–210°; $[\alpha]^{28}D$ +65° (*c* 1.00, acetone); uv λ^{MeOH} end absorption 210 mμ (ϵ 20,000); ir $\lambda_{max}^{CHCl_3}$ 2.92, 5.65, 5.82, 7.93, 8.62, 8.66, 9.48, 9.87, and 10.31 μ; nmr τ 3.55 (1 H, dd, J = 3.5 and 0.8 Hz), 3.98 (1 H, dd, J = 3.5 and 0.8 Hz), 5.00 (1 H, s, D_2O-exchangeable), 5.38 (1 H, dd, J = 13.5 and 0.5 Hz), 6.32 (1 H, dd, J = 13.5 and 0.5 Hz), 8.79 (3 H, d, J = 7 Hz), and 8.83 (3 H, d, J = 7 Hz); mass spectrum *m/e* 364 (M^+), 293, 276, 258, 230, 212, 71, and 43.

Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.62; H, 6.64. Found: C, 62.21; H, 6.46.

Tetrahydrovernolide (9). A. From Vernolide (7).—Vernolide (100 mg) in ethyl acetate (15 ml) was hydrogenated with 10% palladium on charcoal (60 mg) as catalyst. After 15 min, 2 mol equiv of hydrogen had been absorbed. The catalyst was removed by filtration and the solvent was evaporated to give a crystalline residue which was recrystallized from ether to yield plates (**9**, 65 mg): mp 186–188° (lit.[5] mp 185–188°).

B. From Vernomygdin (8).—Upon catalytic hydrogenation of vernomygdin using the same conditions, 1 mol equiv of hydrogen was absorbed in 12 min, to yield a crystalline product, mp 186–188°, identified as tetrahydrovernolide by mixture melting point, tlc, and infrared spectral comparison with the hydrogenation product obtained from vernolide.

Registry No.—**1**, 21871-10-3; **3**, 21871-11-4; **4**, 21871-12-5; **6**, 21871-13-6; **8**, 21871-14-7.