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A Three-Step Synthesis of Cadin-1(10)-en-11-ol

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Cadin-1(10)-en-11-ol has been synthesized in three steps from the readily available terpene alcohol *l*-isopulegol. Using tosyl chloride in pyridine, *l*-isopulegol was dehydrated to mentha-3,8-diene (4-methyl-1-isopropenylcyclohex-1-ene) in 21% yield. This terpene was then condensed with methyl acrylate (Diels-Alder condensation) to give 4,7-dimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carboxylic acid methyl ester in 75% yield. After treatment with sodium methoxide, the methyl ester was reacted with methylmagnesium iodide to give cadin-1(10)-en-11-ol in 47% yield. The structure was confirmed by ¹H NMR, mass, and IR spectra and by conversion to the known cadinane.

The most commonly found, naturally occurring, cadinene and cadinol sesquiterpenes have the double bonds or hydroxyl group either in the decalin ring or in the methyl side chains leaving the isopropyl group completely saturated with no functional groups. Exceptions are veticadinol (cadin-10(15)-en-11-ol) and khusol (cadin-10(15),5-dien-12-ol) and some related hydrocarbons. In a study involving the volatile products of *Streptomyces* the authors isolated an unusual sesquiterpene alcohol different from those previously reported in *Streptomyces* (Gerber, 1971, 1972). One of the possible structures deduced from the spectral data was cadin-1(10)-en-11-ol. The synthesis of this compound was carried out to test this possibility. Although the synthetic cadin-1(10)-en-11-ol proved to be different from the *Streptomyces* sesquiterpene alcohol it was felt that the synthesis and spectral data of the synthetic compound were of interest because of its close structural relationship to veticadinol and the possibility that it may also occur naturally.

EXPERIMENTAL SECTION

The synthesis is outlined in Figure 1.

Synthesis of Mentha-3,8-diene (II). *l*-Isopulegol (I, Aldrich, 77 g) was dissolved in pyridine (200 ml) and *p*-toluenesulfonyl chloride (tosyl chloride, 96 g) was added gradually at room temperature over 1 h with vigorous stirring (cf. Wintersteiner and Moore, 1943). The mixture was allowed to stand overnight at room temperature. It was then gently refluxed for 3 h. Pyridine was distilled off under vacuum (20 mm). The residue was then extracted with pentane (400 ml) under reflux for 0.5 h. The pentane extract was then washed with water (100 ml) and

dried over anhydrous sodium sulfate. The residue was then further extracted with benzene (200 ml) by refluxing for 0.5 h and the benzene extract poured onto a column (200 × 34 mm) of activated alumina (Woelm No. 1). This was eluted with pentane (400 ml) and combined with the pentane extract from above. Removal of the solvent gave 54 g of crude terpene hydrocarbons which was found by gas-liquid chromatographic (GLC) analysis to contain 26% (21% yield) of mentha-3,8-diene (II).

Diels-Alder Condensation. A distilled fraction (bp 71–74 °C (15 mm)) of the above terpene hydrocarbons (17.9 g, 38% II) was mixed with methyl acrylate (4.75 g) and the mixture heated under nitrogen at 85 °C for 16 h. Distillation of the product under vacuum gave 9.7 g (75% yield) of 4,7-dimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carboxylic acid methyl ester (III) (bp 100–105 °C (0.3 mm)). This material was treated with sodium methoxide (from 1 g of sodium) in methanol (50 ml) solution at room temperature for 24 h. The mixture was then poured into a saturated solution of sodium bicarbonate in water (200 ml) and extracted with pentane. After drying with sodium sulfate the pentane was removed on the steam bath to give III with the ester group in the more stable configuration.

Cadin-1(10)-en-11-ol (IV). III (7.4 g) in ether (20 ml) was added dropwise over 0.5 h to methylmagnesium iodide (prepared from 2.4 g of Mg, 14.2 g of MeI, and 100 ml of ether). The mixture was refluxed for 1 h and then water (50 ml) was added dropwise. The ether layer was then decanted and dried over sodium sulfate. Removal of the ether gave crude IV (6.9 g). Purification of the crude product by packed column GLC separated pure IV as a major peak forming 50% of the total. The overall yield of pure IV was thus 47%.

Dehydration and Hydrogenation to Cadinane. IV (10 mg) was mixed with 200 mg of activated alumina

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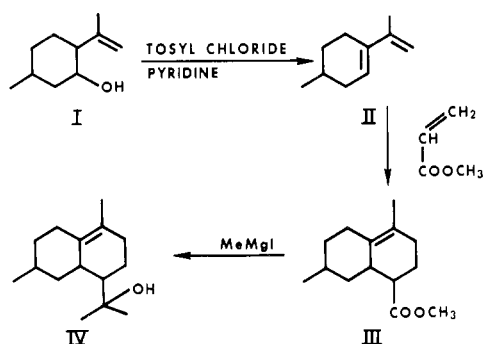


Figure 1. Outline of the synthesis.

(Woelm No. 1) containing 1% pyridine and heated at 200 °C for 1 h under vacuum. The sesquiterpene hydrocarbons formed were eluted with pentane (25 ml) and hydrogenated at 10 psi H₂ with a palladium on charcoal catalyst for 15 h. Removal of the solvent and GLC purification of the product gave the cadinane.

Infrared Absorption (IR) Spectra. These were run on the pure compounds as a film between two salt plates using a Perkin-Elmer 237 instrument.

Mass Spectra. Batch introduction was used with a modified Consolidated 21-620 cycloidal type mass spectrometer. Ionization voltage was 70 V.

Proton Magnetic Resonance (¹H NMR) Spectra. A Varian HA-100 instrument was used with CDCl₃ solutions.

Gas-Liquid Chromatography. The packed column used for separation and collection of samples was 1.7 m long × 0.635 cm o.d. stainless steel packed with 80–100 mesh Chromosorb G-DMCS coated with 10% Carbowax 20M. The column temperature was programmed from 100 to 200 °C. The capillary column was a 150 m long × 0.75 mm i.d. stainless steel capillary coated with Tween-20 containing 5% Igepal CO-880. Its temperature was programmed from 100 to 165 °C and held at the upper limit.

RESULTS AND DISCUSSION

Because isopulegol (I) is readily available and inexpensive, the dehydration of isopulegol seemed to be the most convenient way of obtaining mentha-3,8-diene (II). Several of the usual dehydrating reagents were tried, including phosphoric acid, phosphorus oxychloride in pyridine, and heated activated alumina. Dehydration using tosyl chloride in pyridine (cf. Wintersteiner and Moore, 1943) gave the best yields of II. The products of the dehydration were analyzed and separated by GLC. IR spectra were used to verify the identity of II and other products. The spectra were consistent with those published by Mitzner et al. (1965). The ¹H NMR spectra of II [(100 MHz, CDCl₃) δ 0.97 (d, *J* = 6 Hz, 3, CH₃CH), 1.2–2.4 (complex, ring CH₂), 1.90 (s, 3, CH₃C=C), 4.80 (s, 1, HCH=CC=C), 4.95 (s, 1, HCH=CC=C), 5.83 (s, 1, C=CH)] also confirmed its structure. Dehydration using tosyl chloride gave only two other terpene hydrocarbons besides II, the major one being mentha-2,4(8)-diene. Although II formed only 38% of the distilled terpenes it was possible to use the mixture for the Diels-Alder condensation because the other terpenes in the mixture did not react with methyl acrylate to any significant extent, whereas II reacted completely. This could be followed very conveniently by sampling the reaction mixture at various times for GLC analysis. The unreacted terpene hydrocarbons were readily removed from the condensation product by distillation under vacuum. Treatment with sodium methoxide (which makes the proton α to the carboxy group labile) was used to convert III into its more

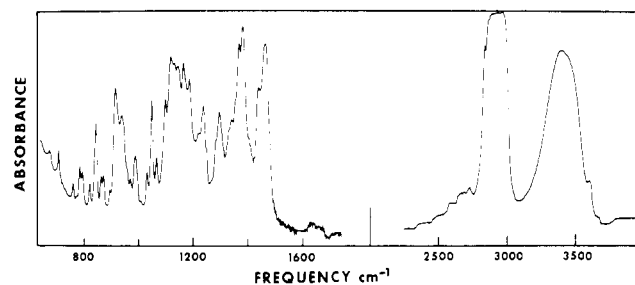


Figure 2. Infrared absorption spectrum of a thin film of pure cadin-1(10)-en-11-ol.

stable configuration (cf. Vig et al., 1969). The identity of III was confirmed by its mass spectrum which showed a molecular ion at *m/e* 222, IR spectra with carbonyl absorption at 5.76 μm, and other general features consistent with III: ¹H NMR spectra (100 MHz, CDCl₃) δ 1.06 (d, *J* = 7 Hz, 3, CH₃CH), 1.62 (s, 3, CH₃C=C), 1.5–2.8 (m complex, ring CH₂), 3.68 (s, 3, OCH₃). Elemental Anal. Calcd for C₁₄H₂₂O₂: C, 75.7; H, 9.9. Found: C, 75.2; H, 9.86.

In the Diels-Alder condensation there are, of course, two possible ways in which II and methyl acrylate could condense. One of these would lead to our desired product III. The other would give the carboxyl group in the β-octahydronaphthalene position. By far the major product, however, seems to be the desired one (III) as shown by the eventual conversion of IV to the known cadinane. It has also been reported (Martin and Hill, 1961; Vig et al., 1969) that similar condensations occur predominantly in this direction.

The conversion of III to IV using methylmagnesium iodide was quite straightforward. The product was purified by GLC separation which showed a major component (IV) comprising 50% of the product, along with three other minor components which are apparently isomers of IV (very similar mass spectra). This major component could not be resolved further using a high-resolution capillary column. It showed the following mass spectrum (two major ions every 14 mass units above *m/e* 34, intensities in parentheses, molecular ion in boldface type): 41 (36), 43 (41); 55 (19), 59 (100); 67 (11), 69 (10); 79 (20), 81 (19); 91 (17), 93 (27); 105 (30), 107 (33); 121 (25), 122 (7); 135 (13), 136 (16); 147 (4), 149 (35); 161 (35), 164 (27); 171 (1); 189 (8); 204 (4), 207 (1); 222 (2). Its IR spectrum is shown in Figure 2. ¹H NMR spectral data are (100 MHz, CDCl₃): δ 1.09 (d, *J* = 6 Hz, 3, CH₃CH), 1.25 (s, 6, (CH₃)₂COH), 1.60 (s, ca. 3, CH₃C=C), 1.4–2.6 (m complex, ring CH₂). Elemental Anal. Calcd for C₁₅H₂₆O: C, 81.08, H, 11.7. Found: C, 80.8; H, 11.7.

The GLC purified IV was readily dehydrated by heating with activated alumina containing 1% pyridine (cf. von Rudloff, 1961). The products from this were hydrogenated with palladium on charcoal. The hydrogenated sample showed only one peak on packed column GLC which was collected and its IR spectrum was measured. This spectrum was consistent with the published spectrum of cadinane (Pliva et al., 1960; Kartha et al., 1963) with the following absorption maxima (between 6 and 14 μm): medium, 6.80, 6.87, 6.92, 7.22, 7.3 μm; weak, 7.75, 7.93, 8.26, 8.47, 8.73, 8.90, 9.01, 9.17, 9.30, 9.52, 9.76, 10.1, 10.3, 10.5, 10.9, 11.0, 11.5, 12.1 μm.

Stereochemistry. As the authors were primarily interested in the mass spectrum of IV, and taking into account that mass spectra are usually extremely similar for these types of isomers, little attention has been paid to the stereochemistry in this synthesis. As mentioned

above, IV (major peak from packed column GLC) gave only a single peak using a high-resolution capillary GLC column (ca. 50 000 plates) and is therefore very likely a single diastereoisomer. Factors involved in determining the stereochemistry include (1) the use of optically active *l*-isopulegol which would probably fix the stereochemistry of the 4-position methyl group (cadinane numbering), (2) the direction of approach of the methyl acrylate in the Diels-Alder condensation, and (3) the use of NaOCH₃ to produce the more stable configuration of III.

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Effects of Dietary Feeding of Organocadmium to Cattle and Sheep

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Adult cattle and sheep were fed a cadmium fungicide, Cadminate, in the diet at levels of 50, 100, 200, 300, and 500 ppm of cadmium. The cattle study continued for 49 weeks and the sheep study for 41 weeks. The toxic effects included abortions, dead or short-lived calves and lambs, and birth defects. The animals fed cadmium at levels greater than 200 ppm in feed developed anemia as detected by decreased RBC counts, decreased PCV, and lowered Hb levels. Greatest residues of cadmium were in the kidney and liver of both cattle and sheep. In sheep, there was a significant difference in feed conversion efficiency due to the level of cadmium in feed. Cadmium, fed as Cadminate in feed, is detrimental to both cattle and sheep.

Many researchers have studied the effects of cadmium on different species of animals but only a few will be mentioned here.

Wilson et al. (1941) observed anemia in rats after they were fed a diet containing 31 ppm of cadmium for 2 months. Friberg (1950) also observed anemia in rabbits exposed to cadmium oxide dust and in rabbits injected with cadmium sulfate (0.65 mg of cadmium/kg for 6 days a week) for 2 months. Decker et al. (1958) observed that hemoglobin (Hb) levels were reduced in rats given 50 ppm of cadmium in drinking water for 2 weeks, but reduced Hb levels were not observed in rats given 10 ppm of cadmium in drinking water for 1 year.

Friberg et al. (1971) noted abortions, damage to reproductive organs, anemia, and neonatal deaths in laboratory animals exposed to cadmium-containing compounds.

Residues of cadmium accumulate most rapidly in the kidney and liver of animals exposed to cadmium-containing compounds. This was observed by Cousins et al. (1973) in swine, by Nordberg (1972) in rats, and by Powell et al. (1964) in calves.

Since very little information could be found on the effect of cadmium-containing fungicides on cattle and sheep, the following experimentation was undertaken.

The plant fungicide, Cadminate, is marketed as a 60% wettable powder. Metallic cadmium accounts for 29% of

the total formulation. This fungicide is used to treat turf grasses for copper spot, dollar spot, and red thread. Before 1973, the grazing of treated areas by livestock was not restricted. In 1973, additional restrictions were placed on the product: namely, do not graze treated areas and do not feed clippings to livestock.

However, even though these restrictions are on the label of the product, accidental exposures can occur. Therefore, we exposed adult cattle and sheep to cadmium as Cadminate in feed for the following objectives: (1) to determine the clinical signs of toxicity in cattle and sheep given cadmium at different levels in their feed; (2) to determine the effect on hemopoietic systems; (3) to determine the amount of cadmium present in blood, urine, and hair at various times during the study; and (4) to determine the accumulation of residues of cadmium in various tissues of cattle and sheep after long-term exposures.

The levels of the fungicide fed in feed to cattle and sheep were based on the cadmium content of the formulation.

MATERIALS AND METHODS

Reagents. Cadminate, 60% active ingredient of cadmium succinate (29% cadmium equivalent), was obtained from Mallinckrodt Chemical Works, St. Louis, Mo. Dipotassium ethylenediaminetetraacetate (K₂EDTA) was obtained from Eastman Kodak Co., Rochester, N.Y. Isoton and Zap-Isoton were obtained from Coulter Diagnostics, Inc., Hialeah, Fla. Cyanmethemoglobin was obtained from Hycel, Inc., Houston, Tex. The reagents for the Echols-ultra-micro method were obtained from Echols Professional Products Co., Houston, Tex.

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