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Vinylketenes. Synthesis of (+)-Actinidine‡

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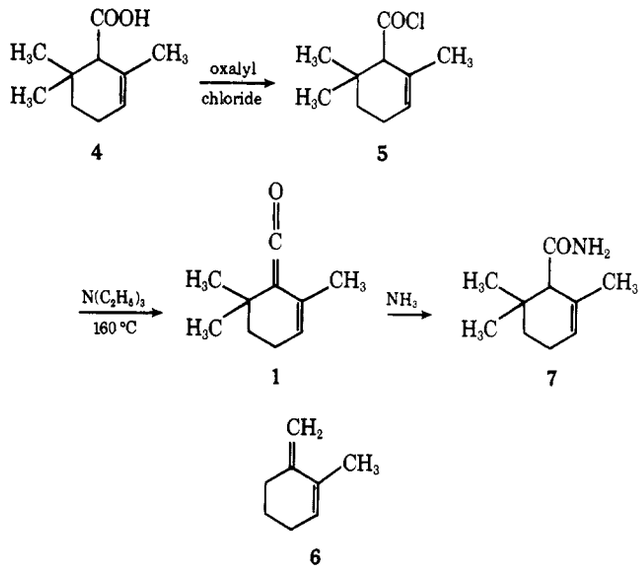
Dehydrochlorination of 2,6,6-trimethylcyclohex-2-ene-1-carbonyl chloride (**5**) yielded 2,6,6-trimethyl-1-carbonylcyclohex-2-ene (**1**), a vinylketene which could be isolated and characterized. Dehydrochlorination of (1*S*,5*R*)-5-methyl-2-(1-methylethylidene)cyclopentane-1-carbonyl chloride (**9**) led presumably to (*R*)-5-methyl-2-(1-methylethylidene)-1-carbonylcyclopentane (**2**), but this vinylketene quickly rearranged by a [1,5] migration of hydrogen into (*R*)-5-methyl-2-(1-methylethenyl)cyclopent-1-ene-1-carboxaldehyde (**10**). Aldehyde **10** could be converted directly into (+)-actinidine (**12**).

Valence isomerizations of cyclobutenones[1a] and cyclohexadienones,[1b] [1,5] sigmatropic migrations of hydrogen in α,β-γ,δ-unsaturated aldehydes,[2] and pyrolyses of β,γ-unsaturated acid chlorides[2] apparently produce vinylketenes. Although these reactive intermediates have been detected spectroscopically and trapped chemically, the isolation and complete characterization of a vinylketene has not yet been reported. We therefore would like to describe the synthesis and physical properties of 2,6,6-trimethyl-1-carbonylcyclohex-2-ene (**1**), the behavior of (*R*)-5-methyl-2-(1-methylethylidene)-1-carbonylcyclopentane (**2**), and an application of our observations in a synthesis of the enantiomer of (−)-actinidine (**3**), a natural product of *Actinidia polygama*[3] and *Valeriana officinalis*.[4] Actinidine, first synthesized by Sakan,[5] has received some special attention since it is one of the rare monoterpenoid alkaloids,[6] since it has been reported to be an attractant of cats,[3] and since it is a close structural relative of the principal alkaloid of the medicinal plant *Valeriana officinalis* L.[7]

Results and Discussion

Vinylketene **1** was synthesized by the sequence of reactions described in Scheme I. 2,6,6-Trimethylcyclohex-2-ene-1-carboxylic acid (**4**) was prepared from geranic acid[8] and converted into 2,6,6-trimethylcyclohex-2-ene-1-carbonyl chloride (**5**). This acid chloride strongly resisted dehydrochlorination but was transformed by the action of triethylamine in benzene at 160 °C into compound **1**, which could be isolated and purified by molecular distillation. The infrared spectrum contained bands at 2115 and 1645 cm^{-1}, and the ultraviolet spectrum, which consisted of absorptions at 234 (ϵ 10 100) and 404 nm (ϵ 33), was simply the sum of the spectra expected for the butadiene **6** (λ_{max} 236 nm)[9] and the ketene portion of a diarylketene (λ_{max} 405 nm).[10] In the ^1H NMR spectrum of compound **1**, a sharp singlet replaced the doublet attributable to the diastereotopic methyl groups at C_6 in compounds **4** and **5**. In addition, treatment with ethereal ammonia converted

Scheme I

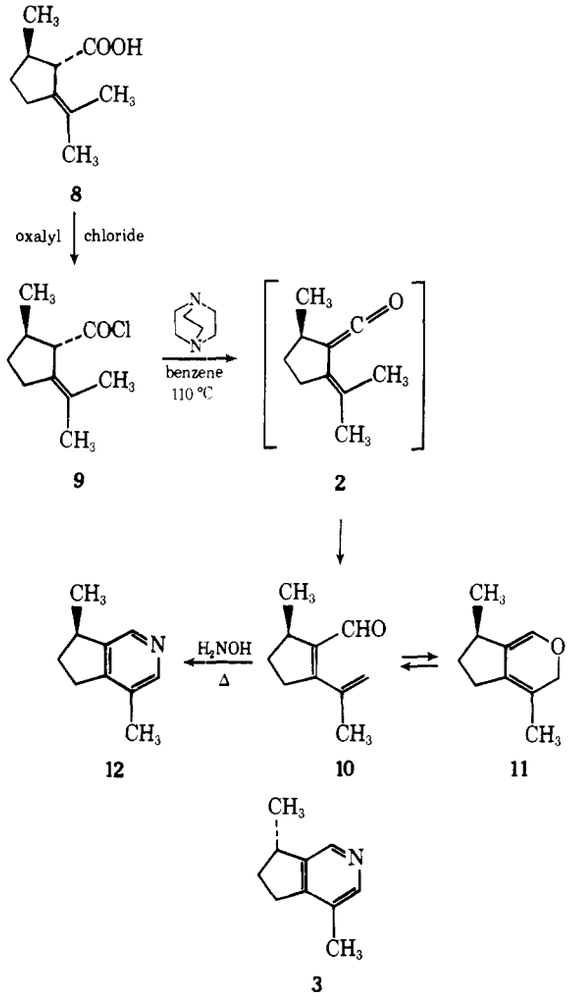


the ketene into 2,6,6-trimethylcyclohex-2-ene-1-carboxamide (**7**), which was identical with a sample of the amide prepared by the method of Bouveault.[11]

Applied to (1*S*,5*R*)-5-methyl-2-(1-methylethylidene)cyclopentane-1-carboxylic acid (**8**), derived from (+)-pulegone by the procedure of Achmad and Cavill,[12] a similar sequence of reactions did not lead to (*R*)-5-methyl-2-(1-methylethylidene)-1-carbonylcyclopentane (**2**). Instead, (*R*)-5-methyl-2-(1-methylethenyl)cyclopent-1-ene-1-carboxaldehyde (**10**) was isolated. A [1,5] sigmatropic migration of hydrogen in ketene **2**, a rearrangement which has been observed recently by others,[1,2] accounts for the formation of aldehyde **10**; and, in fact, when the dehydrochlorination was interrupted, a ketene was detected spectroscopically by an absorption at 2090 cm^{-1} which vanished slowly at 25 °C. However, no bases, including tetramethylethylenediamine, triethylamine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,8-bis(dimethylamino)-naphthalene, pyridine, lithium diisopropylamide, and po-

‡ Dedicated to Professor Robert Burns Woodward on the occasion of his sixtieth birthday.

Scheme II



tassium hydride, converted compound **9** to ketene **2** or aldehyde **10** under milder conditions, and ketene **2** could not be isolated and characterized.

No evidence for the formation of valence isomer **11** appeared in the spectra of aldehyde **10**,[13] but its reaction with hot ethanolic hydroxylamine[14] efficiently yielded (+)-actinidine (**12**). Comparison of the IR, UV, ^{1}H NMR, and mass spectra, the optical rotations, and the melting points of the picrates of compound **12** and natural (−)-actinidine (**3**) showed that the substances were enantiomers.

Experimental Section

All infrared (IR) spectra were recorded on a Perkin-Elmer Model 137 spectrometer. Varian T-60, A-60, HA-100, and XL-100 spectrometers were used to obtain ^{1}H nuclear magnetic resonance (NMR) spectra. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane (δ). Ultraviolet (UV) spectra were recorded on a Cary 14 spectrophotometer. The wavelength (λ) and molar extinction coefficient (ε) of absorption maxima are reported in the form λ (ε). An AEI MS-9 double-focusing spectrometer was used to obtain mass spectra at 70 eV. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points were measured on a Thomas-Hoover capillary apparatus and are uncorrected. Vapor phase chromatographic analyses were performed on columns of SE-30 on Chromosorb W (6 ft × 0.25 in.) and Carbowax 20M on Chromosorb W (6 ft × 0.25 in.) in a Varian Aerograph Model 1420 instrument. Benzene was dried over sodium wire and triethylamine was distilled twice from 1-naphthyl isocyanate and once from lithium aluminum hydride before use.

Preparation of 2,6,6-Trimethylcyclohex-2-ene-1-carbonyl Chloride (5). Under dry N_2 a stirred solution of 2,6,6-trimethylcyclohex-2-ene-1-carboxylic acid[8] (**4**, 6.62 g, 39.4 mmol) in benzene (70 mL) at 5 °C was treated dropwise during 24 min with a solution of oxalyl chloride (6.27 g, 49.4 mmol) in benzene (30 mL). The mixture was stored at 27 °C for 14 h and then solvent and excess oxalyl chloride were removed by evaporation under reduced pressure. Distillation of the residue yielded acid chloride **5** (6.05 g, 32.5 mmol, 82%) as a colorless liquid: bp 44–47 °C at 0.6 Torr (reported[15] bp 103–108 °C at 13 Torr; reported[16] bp 87–88 °C at 12 Torr); IR (liquid film) 1800 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 0.97 (s, 3 H), 1.10 (s, 3 H), 1.1–1.4 (m, 2 H), 1.7–1.9 (m, 3 H), 1.9–2.3 (m, 2 H), 3.06 (broad s, 1 H), 5.5–5.7 (m, 1 H); mass spectrum *m/e* (rel intensity) 186 (1), 150 (49), 135 (72), 123 (100), 122 (43), 107 (97), 91 (89), 81 (76), 79 (68).

Preparation of 2,6,6-Trimethyl-1-carbonylcyclohex-2-ene (1). A solution of acid chloride **5** (2.24 g, 12.0 mmol) and triethylamine (1.45 g, 14.3 mmol) in benzene (9 mL) was heated at 160 °C for 8.3 h under dry N_2 in a sealed Pyrex tube. The mixture was filtered under dry N_2 and the filtrate was concentrated by evaporation under reduced pressure. Molecular distillation of the concentrate (24 °C at 0.01 Torr) yielded ketene **1** (1.12 g, 7.46 mmol, 62.2%) as a yellow-orange liquid: IR (liquid film) 2115, 1645, 1380, 1360 cm^{-1}; UV (hexane) 234 nm (ε 10 100), 404 (33); ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.14 (s, 6 H), 1.42 (t of d, 2 H, J = 6.3, 1.0 Hz), 1.73 (d of t, 3 H, J = 1.3, 1.8 Hz), 1.98–2.22 (m, 2 H), 5.13 (t of q, 1 H, J = 1.3, 3.5 Hz); mass spectrum *m/e* (rel intensity) 150 (62), 135 (95), 107 (100), 79 (68); high-resolution mass spectrum *m/e* 150.1062 (calcd for $C_{10}H_{14}O$, 150.1045).

Preparation of 2,6,6-Trimethylcyclohex-2-ene-1-carboxamide (7). At 0 °C under dry N_2 a stirred solution of ketene **1** (74 mg, 0.49 mmol) in anhydrous ether (1.0 mL) was treated dropwise during 3 min with a saturated ethereal solution of anhydrous ammonia (5 mL). The orange color was not discharged instantaneously, so the mixture was stored at 26 °C for 30 h. Removal of solvent by evaporation left the amide **7** (67 mg, 0.41 mmol, 84%) as a colorless solid: mp 121.0–122.0 °C (reported[11] mp 120–121 °C); IR (KBr) 3450, 3250, 1650 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.97 (s, 3 H), 1.03 (s, 3 H), 1.0–1.4 (m, 2 H), 1.6–1.8 (m, 3 H), 1.9–2.3 (m, 2 H), 2.40 (s, 1 H), 5.69 (broad s, 1 H), 5.8–6.1 and 6.4–6.9 (broad s, 2 H).

Preparation of (1*S*,5*R*)-5-Methyl-2-(1-methylethylidene)-cyclopentane-1-carbonyl Chloride (9). Under dry N_2 a stirred solution of (1*S*,5*R*)-5-methyl-2-(1-methylethylidene)cyclopentane-1-carboxylic acid[12,17] (**8**, 7.3 g, 43 mmol) in benzene (85 mL) at 5 °C was treated dropwise during 30 min with a solution of oxalyl chloride (6.2 g, 49 mmol) in benzene (27 mL). The mixture was stirred at 27 °C for 14 h and then solvent and excess oxalyl chloride were removed by evaporation under reduced pressure. Distillation of the residue yielded acid chloride **9** (6.8 g, 36 mmol, 85%) as a colorless liquid: bp 47–50 °C at 0.55 Torr; IR (liquid film) 1795 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.14 (d, 3 H, J = 7 Hz), 1.2–1.5 (m, 1 H), 1.6–1.7 (m, 6 H), 1.8–2.1 (m, 1 H), 2.2–2.6 (m, 3 H), 3.34 (broad d, 1 H); mass spectrum *m/e* (rel intensity) 186 (2), 123 (100), 107 (20), 81 (75), 79 (21), 69 (20), 67 (22), 55 (20).

Preparation of (*R*)-5-Methyl-2-(1-methylethenyl)cyclopent-1-ene-1-carboxaldehyde (10). A solution of acid chloride **9** (394 mg, 2.11 mmol) and 1,4-diazabicyclo[2.2.2]octane (239 mg, 2.13 mmol) in benzene (3.0 mL) was heated at 110 °C for 8 h under dry N_2 in a sealed Pyrex tube. The mixture was filtered and benzene was removed by evaporation under reduced pressure. Distillation of the residue yielded aldehyde **10** (128 mg, 0.85 mmol, 40.5%), the only volatile component, as a chromatographically pure, yellow liquid: bp 52–57 °C at 1.5 Torr; IR (liquid film) 2730, 1665, 1605 cm^{-1}; UV (95% ethanol) 233 nm (ε 3550); ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.13 (d, 3 H, J = 7.0 Hz), 1.3–1.7 (m, 1 H), 1.9 (m, 3 H), 2.0–2.3 (m, 1 H), 2.6–2.8 (m, 2 H), 3.0–3.3 (m, 1 H), 5.06 (qn, 1 H), 5.21 (qn, 1 H), 9.81 (s, 1 H); mass spectrum *m/e* (rel intensity) 150 (88), 149 (71), 135 (100), 121 (27), 107 (66), 105 (24), 93 (41), 91 (66), 79 (73), 77 (49), 65 (24), 53 (27), 51 (27). Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39; O, 10.65. Found: C, 80.21; H, 9.12; O, 10.67.

Synthesis of (+)-Actinidine (12). A solution of aldehyde **10** (150 mg, 1.00 mmol) and hydroxylamine hydrochloride (145 mg, 2.08 mmol) in a mixture of ethanol (6.0 mL) and water (1.5 mL) was stirred at 0 °C and treated with aqueous NaOH (1.5 mL, 1.7 N). The mixture then was heated at reflux for 25 h, diluted with water, and extracted with dichloromethane. After solvent had been removed by evaporation under reduced pressure, distillation of the residue yielded (+)-actinidine (**12**, 133 mg, 0.90 mmol, 90.5%), the only volatile component, as a chromatographically pure, colorless liquid. The IR, UV, ^{1}H NMR, and mass spectra of this substance were identical with those of natural (−)-actinidine, but the sample proved to be dextrorotatory: $[\alpha]^{20}_D$ +10.8° (*c* 0.360, $CHCl_3$).

The picrate of (+)-actinidine (**12**) was prepared in the usual manner and crystallized from ethanol to constant melting point: mp 146.0–

146.3 °C (reported[5b] mp 146–147 °C); $[\alpha]^{20}_D$ −34.6° (*c* 0.940, $CHCl_3$).

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Registry No.—**1**, 61899-98-7; **4**, 564-24-9; **5**, 61899-99-8; **7**, 61900-00-3; **8**, 7712-68-7; **9**, 61900-01-4; **10**, 61900-02-5; **12**, 15524-81-9; **12** picrate, 61900-03-6; oxalyl chloride, 79-37-8.

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(17) The (+)-pulegone from which acid **8** was derived had $[\alpha]^{20}_D$ +22° (neat).

A Stereocontrolled Synthesis of (±)-Anhydronupharamine. The ^1H and ^{13}C Nuclear Magnetic Resonance of Piperidine Nuphar Alkaloids[1]

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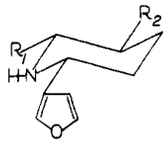
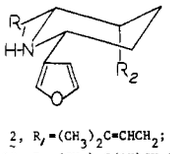
(±)-Anhydronupharamine is prepared in 11 steps starting from 6-methyl-5-hepten-2-one and proceeding through key intermediates *trans*-3-methyl-2-(3-methyl-2-butenyl)cyclopentanone, *trans*-6-(3-methyl-2-butenyl)-5-methyl-2-piperidone, and *trans*-2-(3-methyl-2-butenyl)-3-methyl-6-(3-furyl)-2,3,4,5-tetrahydropyridine. Stereocontrol is based on the greater stability of trans substituents in a 2,3-disubstituted cyclopentanone and the more favorable reduction of a C-2 substituted 2,3,4,5-tetrahydropyridine from the direction opposite the C-2 substituent. The ^1H and ^{13}C NMR characteristics of the various 3-furyl-substituted piperidines obtained in the course of synthesis are given and briefly discussed with regard to conformation.

The structures of (−)-anhydronupharamine (**1**) and (−)-nuphenine (**2**) exemplify the two stereochemical types of Nuphar piperidine alkaloids. The trans disposition of C-2 and C-3 hydrogen atoms in **1** similarly occurs in the Nuphar quinolizidine alkaloids where the carbons of the second ring might be considered constituted by those of the C-2 side chain in **1**. This trans arrangement appeared, until recently, to be the only one in the quinolizidine Nuphar alkaloids. However, the results of new isolation work show that the C-2 and C-3 cis arrangement of hydrogen atoms in **2** also presents itself in the C_{15} quinolizidine 1-*epi*-deoxynupharidine[2] and in some C_{30} thiaspiranes such as 1-*epi*,1′-*epi*-thiobinupharidine.[3] Regardless of the steric disposition of the C-2 and C-3 substituents, the 3-furyl group at C-6 always assumes an equatorial conformation and is cis to the C-2 substituent in the naturally occurring Nuphar piperidines and quinolizidines.



1, $R_1=(CH_3)_2C{=}CHCH_2$; $R_2=CH_3$
20, $R_1=R_2=H$
21, $R_1=CH_3$; $R_2=H$
28, $R_1=(CH_3)_2C(OH)CH_2CH_2$; $R_2=CH_3$



2, $R_1=(CH_3)_2C{=}CHCH_2$; $R_2=CH_3$
29, $R_1=(CH_3)_2C(OH)CH_2CH_2$; $R_2=CH_3$

We sought to prepare the piperidine Nuphar alkaloids by routes which would offer control over the C-2, C-3, and C-6 stereochemistry and which appeared to hold some promise for appropriate elaboration of the C-2 side chain in order that the route could be extended later to the Nuphar quinolizidines. We report here the synthesis[4] of (±)-anhydronupharamine by a route through which the stereocontrol of C-2 and C-3 substituents rests on the far greater stability of trans C-2, C-3 alkyl substituents in a cyclopentanone.[5] As results were to demonstrate, the basis for the C-2, C-6 cis arrangement of substituents is the more favorable reduction of a C-2 substituted 2,3,4,5-tetrahydropyridine from the side opposite the C-2 substituent. In addition we report on the results of the ^1H and ^{13}C NMR investigations of the stereochemistry of the new piperidine compounds which have arisen in the course of the synthesis.

Results and Discussion

Synthesis. The cyclopentenone **6**, substituted by γ,γ-dimethylallyl and methyl groups at C-2 and C-3, was prepared by starting from the 6-methyl-5-hepten-2-one (**3**) and proceeding through **4** and **5** according to an established sequence[6] for preparing 2,3-disubstituted cyclopentenones. Thereafter the key intermediate cyclopentanone **7** possessing C-2 and C-3 trans substituents was prepared through lithium/liquid ammonia reduction of the cyclopentenone. None of the cis isomer