

AN INVESTIGATION OF THE SYNTHESIS OF

$\Delta^{9,10}$ OCTAL-1-ONE

A THESIS

presented to the Department of Chemistry of
Washington and Lee University in partial fulfillment
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BY

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Vita

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Introduction

$\Delta^{9,10}$ Octal-1-one is a proposed intermediate in the synthesis of propellane. Work on the synthesis of propellane was begun in 1964 by Jere D. Cravens¹ on a suggestion from O. B. Ramsey of Northwestern University. Cravens, then an undergraduate of Washington and Lee University, undertook an intensive investigation of the literature to determine the best possible way to synthesize propellane.

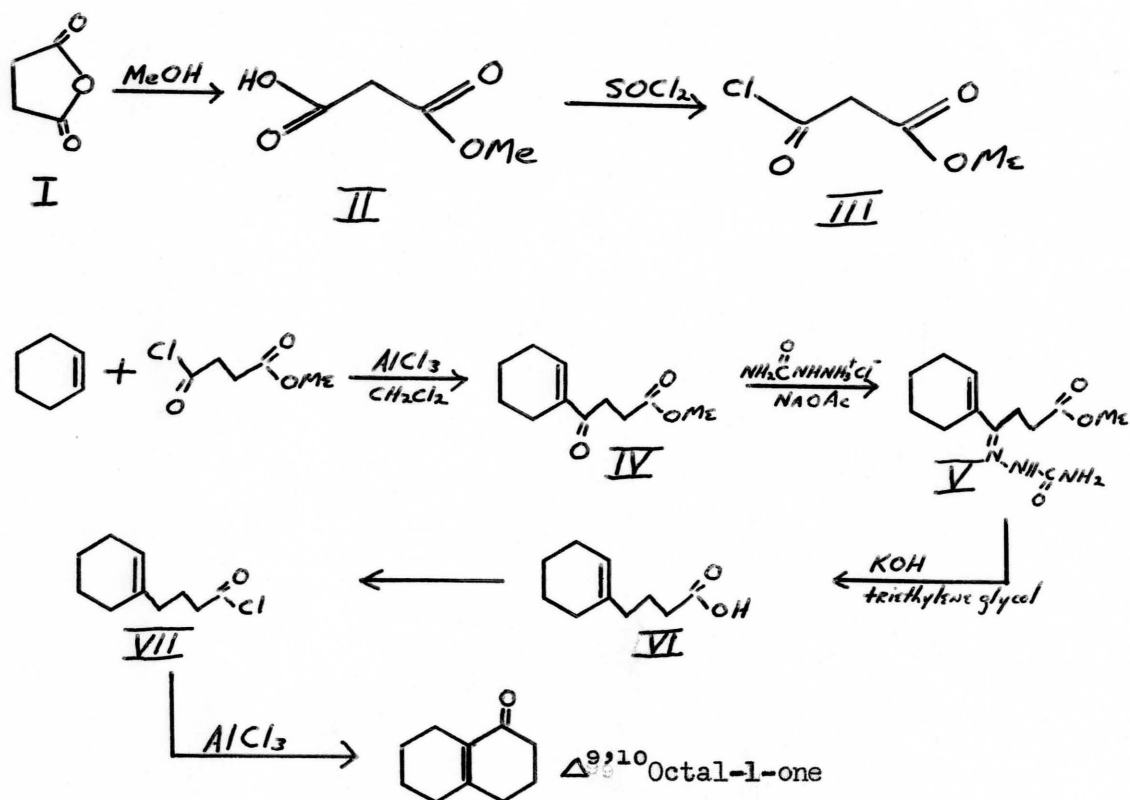
Propellane, Tricyclo [4.4.4.0] tetradecane, consists of three cyclohexane rings, all of which have two carbon atoms and one bond in common. Two possible routes to propellane appeared immediately to Cravens: a ring closure from a 9,10-substituted decalin, and a Diels-Alder reaction with an octalin derivative and a butadiene derivative.

Models seem to suggest that there would be extreme steric problems involved with the ring closure from a 9,10-substituted decalin, so Cravens undertook to make a substituted decalin, and a substituted butadiene. The proposed butadiene was 1-acetoxybutadiene. This would be made by the condensation of ketene and crotonaldehyde:

The 1-acetoxybutadiene has several advantages over butadiene for our purposes: it, too, will undergo a Diels-Alder reaction; it is a liquid at room temperature and easy to handle; and the acetoxy group can be easily hydrolysed from our product. The proposed octalin derivative was $\Delta^{9,10}$ -octalindione-1,5. The synthesis of $\Delta^{9,10}$ -octalindione-1,5 was discontinued in 1965 by F. Scott Kennedy, due to problems in working with the reagents and reactions. Kennedy decided to work on the preparation of $\Delta^{9,10}$ Octal-1-one. This work was carried on by William P. Ridley.² Ridley did a further search of the literature, and discovered a way of preparing methyl- γ -(cyclohexenyl)- γ -oxobutrate, an intermediate in the preparation of $\Delta^{9,10}$ Octal-1-one, which involves using methylene chloride as the solvent and a short reaction time. Kennedy's method involved distillation of the keto ester through a heated column. The methylene chloride method of preparation yielded higher percentages of the keto ester and a one step, relatively simple procedure.

Discussion

The main object of this work was to carry on the work of William P. Ridley from the summer of 1968. Ridley was working on the synthesis of $\Delta^{9,10}$ Octal-1-one by the following method:

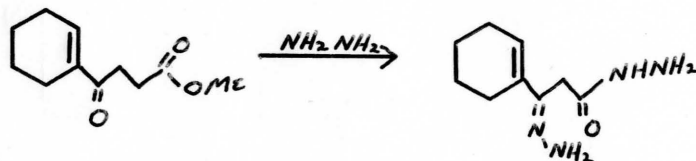


Ridley had prepared compounds II, III, IV, and V in small quantities. It was necessary to repeat his work in larger quantities to get IV in workable amounts, so that the work could continue to VIII.

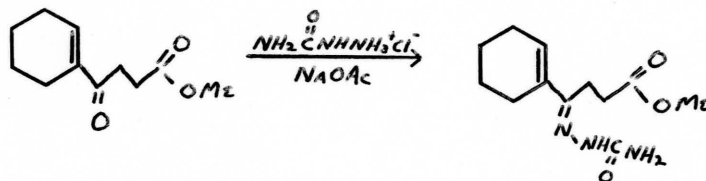
The preparation of II and III proceeded smoothly in accordance with the literature.³ The yields were high, and the compounds easily purified.

It was found in the preparation of IV, that the Friedel-Crafts reaction could only be run in small quantities, which could be later combined for distillation. Combining many runs of the Friedel-Crafts cut down on loss of product due to working with small quantities, and avoided the expense and bother of bringing in dry ice more than once. The small quantities were necessary to insure proper mixing of the reactants and cut down on the side products, which are characteristic of the Friedel-Crafts reaction.

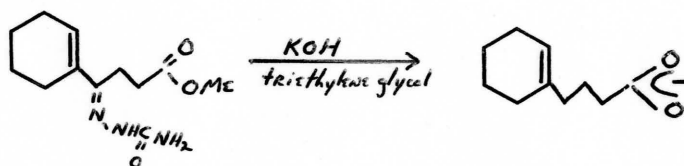
For the reduction of the keto ester IV to the acid IV, there were several possibilities. Ridley and Kennedy had ruled out the traditional Wolff-Kishner reduction, even with the modifications of Huang-Minlon and Cram. The use of hydrazine in the presence of an ester will convert the ester to the hydrazide along with the ketone:



The hydrolysis of this group in the presence of the unsaturation in the cyclohexene ring would prove too difficult. The use of the semicarbazones and the sulfonylhydrazones in a Huang-Minlon modification was considered to be an excellent possibility for the reduction. Semicarbazones and sulfonylhydrazones will make only the derivative of the ketone and leave the ester untouched:



Use of a modified Huang-Minlon reduction also has an advantage in that it hydrolyses the ester as it hydrolyses the semicarbazone or sulfonylhydrazone derivative:



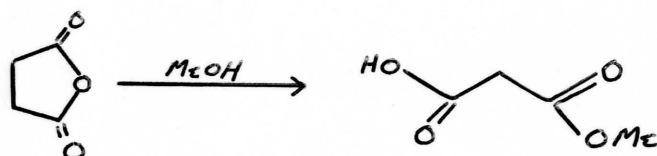
A study of the use of the semicarbazone derivative on aldehydes and ketones, many with unsaturation, was undertaken. Then a study of the use of the thiosemicarbazone was done on three of the same compounds that were used in the semicarbazone study and the results were compared. Two steps were involved in this study. The two steps were:

1. Preparation of the derivatives.
2. The base catalyzed replacement of the derivative group by two hydrogens.

The preparation of the semicarbazone derivatives were simpler, purer, and in higher yields than the thiosemicarbazones. The yields for the semicarbazones ranged from 60-90%, while the yields for the thiosemicarbazones ranged from 55-65%. A minor complication

in obtaining melting points arose with the semicarbazones and thiosemicarbazones in that they have syn and anti isomers. It was found that the syn form in all cases made up the greater portion. Both forms were used since the derivative was only an intermediate.

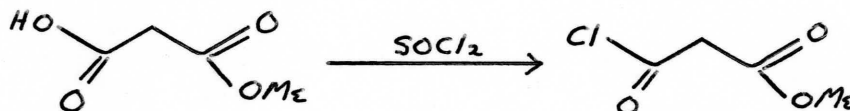
The replacement of the derivative by two hydrogens was brought about by placing the compound in a strong solution of potassium hydroxide in triethylene glycol and refluxing. In his work, Ridley found the best results were obtained by refluxing between 20 and 24 hours. Less than 20 hours of refluxing cut down his yields; more than 24 hours of refluxing had no effect. The reduction of the semicarbazones proved to be better than the reduction of the thiosemicarbazones. The yield from the semicarbazones ranged from 39-59%. The yield from the thiosemicarbazones ranged from 6.8-28%. Purification of the hydrocarbons prepared by way of the thiosemicarbazone was complicated by the presence of byproducts containing sulfur, which were difficult to work with and difficult to isolate from the products. The overall yields from the ketone or aldehydes to the corresponding hydrocarbons were 26-48% for the semicarbazone and 5-18% for the thiosemicarbazone. The better overall yields and the simpler purification indicate that the semicarbazone method should be used for the reduction of methyl-(δ -cyclohexenyl)- γ -oxobutyrate.

ExperimentalMethyl Hydrogen Succinate⁴

A mixture of 400 g. (4 moles) of succinic anhydride and 194 ml (4.8 moles) of methyl alcohol is placed in a one liter flask and set to reflux on a steam bath. The mixture is heated with constant swirling until a homogeneous, clear, colorless liquid is obtained, after about 35 minutes. Once the homogeneous mixture is obtained, the flask is half immersed in the steam bath for 25-30 minutes. It is important to not heat longer, as this leads to side products. The excess methanol is removed by a reduced pressure distillation over steam. Sufficiently low pressure is obtained from a water pump. The distillation should be continued until all methanol is stripped off. The pot contents are then poured into an 18-25 cm evaporating dish which is cooled by placing in an ice/salt bath. As the half ester crystallizes, it is necessary to continuously stir and scrape the sides and bottom of the dish in order to prevent the product from forming a solid cake. The product is ground up with a mortar and pestle and dried in a vacuum dessicator to a constant weight (requiring at least a 24 hour drying period). The product is a white,

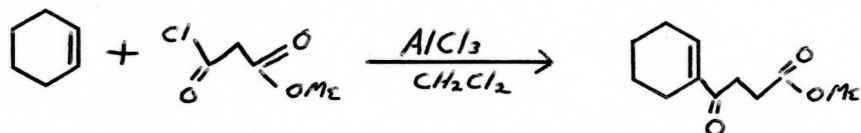
powdery solid. Yield 509 g, 96.5%, M.P. 55-57° (lit. 57-58°), N.E. 115 (lit. 132).

β -Carbomethoxy Propionyl Chloride⁵



A two liter flask is fitted with a Claissen-head with a reflux condenser placed in the side branch and a thermometer, which has been fitted in a bored cork, placed in the center piece and extending down into the pot. The flask is filled with 509 g (3.86 moles) of methyl hydrogen succinate and 334 ml (4.63 moles) of thionyl chloride and the solution is warmed for 3 hours at 40° in the hood. Hydrogen chloride gas is given off as the mixture becomes a homogeneous liquid. The reflux condenser is removed from the Claissen-head and a vacuum distillation is set up. The excess thionyl chloride is removed (violent bumping) on a steam bath at approximately 45-50°/40 mm, using a water pump for the reduced pressure. The excess thionyl chloride is discarded and the final product is distilled over at 93-94°/20 mm or 96°/25 mm. The literature boiling point is 92-93°/18 mm and Ridley⁶ reports 95-98°/40 mm. The product is a clear, colorless solution. Yield 544 g, 94%.

Methyl δ -(1-Cyclohexenyl)- δ -oxobutyrate⁷



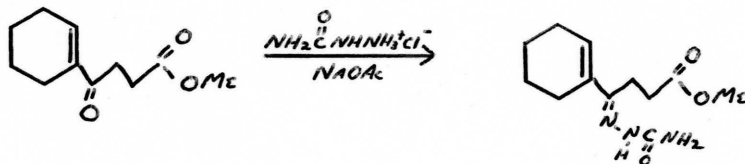
A 500 ml 3-neck round-bottom flask is fitted with a ground-glass mechanical stirrer, thermometer, and a 500 ml ground-glass separatory funnel. After the set up is prepared, the 500 ml flask is cooled using an ice/salt bath. Ridley reports better cooling using the large aluminum pan, wrapped with towels, but it was decided not to use this method since adequate temperatures can be obtained with the enamel pans and the salt is harmful to the aluminum pan. 30.1 g (.20 moles) of the half acid chloride is weighed in a small beaker and taken into the hydrogenation room. There, 40.0 g (.30 moles) of finely powdered aluminum chloride is weighed out and quickly added to 160 ml of previously dried (over calcium chloride) methylene chloride. The half acid chloride is added as quickly as possible to the methylene chloride/aluminum chloride suspension with constant stirring. As the half acid chloride is added, there is a violent reaction; the solution releases gas and heat is given off. The solution is filtered through glass wool into the 500 ml, cooled, round-bottom flask. The stirrer is then started in order to cool the solution to -5°C . 16.4 g (.20 moles, 22.6 ml) of dry (over calcium chloride) cyclohexene is dissolved in methylene chloride and placed in the 500 ml ground-glass separatory funnel. When the temperature of the solution in the 500 ml

round-bottom flask has reached -5°C , the addition of the cyclohexene/methylene chloride is begun and continued at such a rate as to keep the temperature at between -5°C and -4°C . The total addition takes between 1 and $1\frac{1}{2}$ hours. Then the solution is stirred for 15 minutes and poured into a beaker containing 300 g of ice and 150 ml of 5% HCl. The organic layer is separated, washed twice with 100 ml of water and 4 times with 50 ml of 10% sodium carbonate and set to dry over sodium sulfate in the refrigerator. A total of six runs and two of $1\frac{1}{2}$ -times the above run were combined. The set-ups and amounts below are listed for the combined runs.

The combined products are placed in a large round-bottom flask and the methylene chloride is stripped off under reduced pressure (from a water pump) over a steam bath. Approximately 250 ml of solution remained in the pot. A reduced pressure set-up is used with the product being placed in a (24/40) 500 ml round-bottom flask. The receiving unit in this distillation was a (24/40) cow, which had four small flasks attached. 254 g of anhydrous sodium carbonate was placed in the 500 ml flask with the crude product and distilled under a vacuum. After a small forerun, the product is distilled at $75-134^{\circ}\text{C}/3.5$ mm, 170 g. The product was redistilled from 50.4 g of sodium carbonate in a (24/40) 250 ml flask. Yield 139.4 g, 39.3%, B.P. $124-134^{\circ}\text{C}/2.1$ mm, $n_D = 1.481$.

By running the clean-up with more crude product, the yield was increased from 25.2% by Ridley, to 39.3%.

Methyl δ -(1-Cyclohexenyl)- γ -oxobutyrate Semicarbazone



A mixture of 16.6 g of semicarbazone and 24.2 g of sodium acetate, dissolved in 51.0 ml of water, is placed in a 500 ml Erlenmeyer and placed over a magnetic stir plate. Over a period of one hour, while the water solution is vigorously stirred, a solution of 10.0 g (.0507 moles) of the methyl ester, dissolved in 115 ml of methyl alcohol, is slowly added. The solution is refluxed for 1 3/4 hours, corked, and left in the refrigerator overnight. Yield 5.7 g, 44%, M.P. 120-132°C. Ridley got 56.5% yield, M.P. 138-140°C.

Preparation of Semicarbazones

All of the semicarbazones were prepared in the following manner. (The amounts of starting material were changed by adjusting the reactants in molar proportions.)

.083 moles of the aldehyde or ketone was dissolved in 50-60 ml of ethyl alcohol. Water is added until the solution becomes faintly turbid, and then the turbidity is removed with a minimum amount of ethyl alcohol. .089 moles of semicarbazone hydrochloride and .117 moles of sodium acetate are added, the solution is shaken vigorously, and heated on a steam bath. The solution is set to

Semicarbazones

Compound	grams of compound	grams of $\text{NH}_2\text{CONHNH}_2\text{Cl}$	grams of NaOAc	grams of product	% Yield	# of times recrystallized	M. P.	literature M.P.
Cinnamaldehyde	11.1 g	9.93 g	15.9 g	9.8 g	60%	1	211-212°C	215°C
Crotonaldehyde	10.0 g	16.5 g	26.8 g	10.0 g	55%	1	196-197°C	119°C
Benzal Acetone	10.0 g	8.2 g	13.1 g	10.5 g	64%	1	185-186°C	187°C
	10.0 g	16.6 g	24.2 g	5.7 g	44%	0	120-132°C	138-140°C
Benzaldehyde	15.0 g	16.8 g	27.2 g	21.4 g	92%	0	220-221°C	222°C
Acetophenone	15.0 g	20.5 g	32.5 g	19.7 g	55%	1	198-199°C	198°C

cool overnight. The crystals are filtered off, dried, and recrystallized from ethanol and water if necessary.

The following is a table of semicarbazones prepared with physical constants and yields.

Preparation of Thiosemicarbazones

All of the thiosemicarbazones were prepared in the following manner. (The amounts of starting material were changed by adjusting the reactants in molar proportions.)

.010 moles of the aldehyde or ketone is dissolved in 25 ml of ethyl alcohol. .010 moles of thiosemicarbazide dissolved in 75 ml of water is added to the solution and .5 ml of glacial acetic acid is added. The entire mixture is placed on a steam bath and refluxed for one hour. The solution is set to cool overnight. The crystals are filtered off, dried, and recrystallized from ethanol and water if necessary.

The following is a table of thiosemicarbazones prepared, with physical constants and yields.

Thiosemicarbazones

Compound	grams of Compound	grams of $\text{NH}_2\text{CSNHNH}_2\text{Cl}$	grams of product	% Yield	# of times recrystallized	M. P.	literature M. P.
Acetophensone	15.0 g	11.4 g	19.7 g	55%	1	116-118°C	anti 118-119°C syn 90.5
Benzaldehyde	15.0 g	13.6 g	14.2 g	53%	1	155-157°C	159-160°C
Cinnamaldehyde	10.0 g	6.8 g	10.2 g	65%	1	133-135°C	135-136°C

Preparation of Hydrocarbons from their Corresponding Semicarbazones
(or Thiosemicarbazones) by a Modified Huang-Minlon Reduction

All of the following semicarbazones and thiosemicarbazones were reduced to their corresponding hydrocarbons in the following manner. (The amounts of starting materials were changed by adjusting the reactants in molar proportions.)

.035 moles of KOH is dissolved in .10 moles of triethylene glycol by heating and stirring in a 250 ml Erlenmeyer flask. .010 moles of the aldehyde or ketone is added to the KOH/triethylene glycol mixture. The Erlenmeyer flask is then set on a hot plate and fitted with a cork into which a female ground-glass joint has been inserted. A reflux condenser is assembled with the fumes from the reaction being trapped in a beaker of 3 M sulfuric acid. The solution is refluxed for 20-24 hours, and then allowed to cool. 100 ml of water is added, and then the resulting water solution is extracted 4 times with 25 ml of ether. The ether extract is set to dry over sodium sulfate overnight. The ether is stripped off and the crude product is distilled. The following is

The following is a table of the modified Huang-Minlon Reductions run on semicarbazones, with physical constants and yields. Following that is a table of the modified Huang-Minlon Reductions run on thiosemicarbazones with physical constants and yields.

Huang-Minlon Reductions Run on Semicarbazones

Semicarbazone of	grams of compound	ml triethylene glycol	g KOH	grams product	% Yield	B. P.	Lit. B.P.	n_D	Lit. n_D	Dense	Lit. dense
Acetophenone	11.5 g	88.1 ml	12.4 g	4.1 g	59%	134-137°C	136°C	1.494	1.496	.86 g/ml	.88 g/ml
Cinnamaldehyde	8.1 g	57 ml	8.2 g	2.2 g	44%	172-176°C	175°C	1.540	1.549	.90 g/ml	.91 g/ml
Benzaldehyde	14.0 g	116 ml	16.4 g	3.1 g	39%	106-110°C	110°C	1.491	1.496	.85 g/ml	.86 g/ml
Isophorone	12.7 g	112 ml	12.3 g	.5 g	6.2%	134-136°C	138-142°C	1.467	1.445	—	—
α - Ionone	6.1 g	33.1 ml	4.7 g	.7 g	16%	120-121°C/ _{37m}	220-221°C	1.480	1.478	.88 g/ml	.85 g/ml

Huang-Minlon Reductions Run on Thiosemicarbazones

Thiosemicarbazone of	grams of compound	ml triethylene glycol	g KOH	grams product	% Yield	B. P.	Lit. B.P.	n_D	Lit. n_D	Dense	Lit. Dense
Acetophenone	12.0 g	81 ml	11.7 g	1.8 g	28%	133-136°C	136°C	1.492	1.496	.87 g/ml	.88 g/ml
Cinnamaldehyde	10.2 g	72 ml	10.2 g	.4 g	6.8%	168-178°C	175°C	1.510	1.549	.91 g/ml	.89 g/ml
Benzaldehyde	7.7 g	57 ml	8.2 g	.4 g	10%	103-110°C	110°C	1.485	1.496	.85 g/ml	.85 g/ml

Summary

The synthesis of $\Delta^9,10$ Octal-1-one has been begun in large quantities. The intermediate, methyl- γ -(1-cyclohexenyl)- γ -oxobutyrate has been obtained in workable amounts. A study of the use of semicarbazones and thiosemicarbazones in a modified Huang-Minlon reduction has been completed with the following results: the semicarbazones give the higher yields, the purer products, which are easier to clean up. It is suggested that the Huang-Minlon Reduction be continued on the methyl ester semicarbazone, and that it be refluxed with the KOH for the full 24 hours.

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