

SYNTHESIS OF SAFRANAL

By

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## INTRODUCTION

Winterstein and Teleczky<sup>1</sup> first isolated safranal in 1922 from picrocrocin obtained from the plant Safran Aquila. Picrocrocin was purified and hydrolyzed with 1 % sulfuric acid. The hydrolysis products were glucose and safranal in a 1 to 1. ratio.

Many attempts have been made to synthesise safranal, but up to the present time, no satisfactory synthesis has been devised. In the work which has thus far been reported in the literature, either the yields have been too low to be practical, or after isolation of a satisfactory intermediate, the desired final product was not forthcoming.

In 1936 Kulm and Wendt<sup>2</sup> succeeded in converting  $\beta$ -cyclocitral into safranal by treatment with Selenous acid in a dehydrogenation reaction. Unfortunately, the yields in this reaction were found to be from 1 to 3%. If the conditions were so adjusted that all the  $\beta$ -cyclocitral was converted to safranal, the safranal which was formed underwent decomposition.

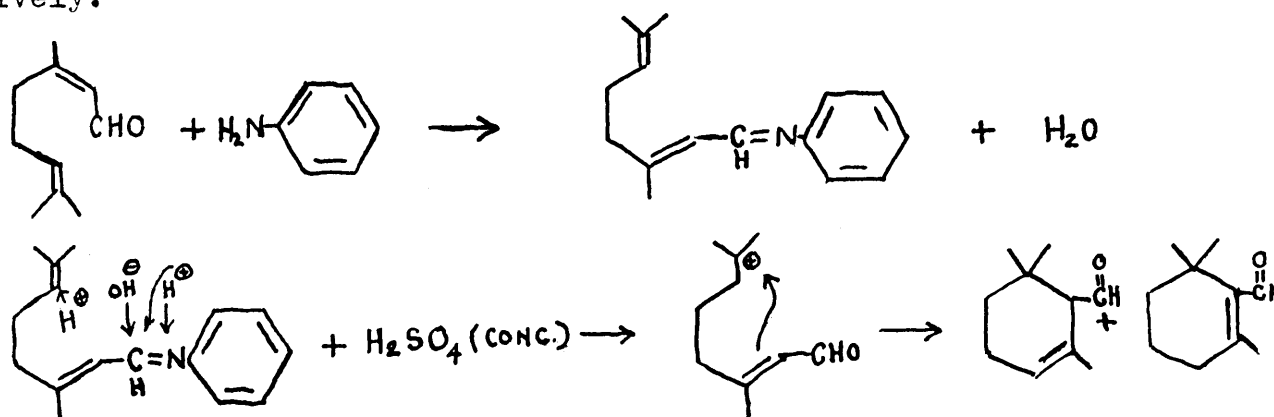
Of the many other attempts which have been made to synthesise safranal, only two will be mentioned. Two atoms of bromine were added to  $\alpha$ -cyclocitral and by double dehydrobromination, safranal was to be formed. The intermediate product was isolated in good yield, but the 2 moles of

hydrogen bromide could not be eliminated to form the final product.<sup>3</sup>

The other noteworthy attempt made by Karrer and Ochsner involved the reaction of  $\beta$ -cyclocitral with N-bromosuccinimide in order to brominate in the allyl position. They then dehydrohalogenated this bromo compound with collidine. The elimination of hydrogen bromide was followed by a rearrangement of the ring double bonds so that safranal was not obtained.<sup>4</sup>

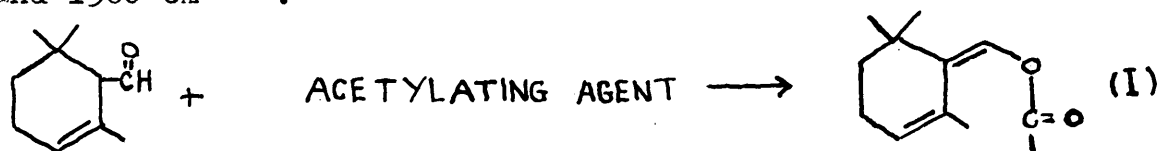
THEORETICAL DISCUSSION

In this thesis, an attempt is made to synthesize safranal by methods which have thus far not been attempted. It was first proposed that with citral as the starting material, a cyclization should be effected. Citral was condensed with aniline and concentrated sulfuric acid was used as the cyclizing agent. These reactions were carried out first with the prescribed amounts of reagents. The yields of  $\alpha$ - and  $\beta$ -cyclocitral were found to be as expected. When double or triple quantities of the reagents were used, the overall yields were little affected by the increase in the quantities of the reactants used; but the ratio of  $\alpha$ - to  $\beta$ -cyclocitral was more nearly 1 to 1 rather than the expected 2/3 to 1/3 ratio of the  $\alpha$ - to  $\beta$ -aldehydes respectively.



The enol acetate of  $\alpha$ -cyclocitral was then made by three different methods. First isopropenyl acetate was used with p-toluene sulfonic acid as a catalyst. Second, sodium acetate and acetic anhydride were used, and last of

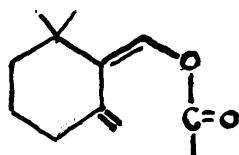
all, acetyl chloride and acetic anhydride were used. It was found that the last method gave the poorest yield and the first method gave the best yield of the acetate. In each case the acetate which was formed gave the same infra red curve having characteristic bands at 829, 913, 1200 and 1360  $\text{cm}^{-1}$ .



The enol acetate of  $\beta$ -cyclocitral was also made by the three methods mentioned above. An acetate was formed which was identical with the acetate formed from  $\alpha$ -cyclocitral.



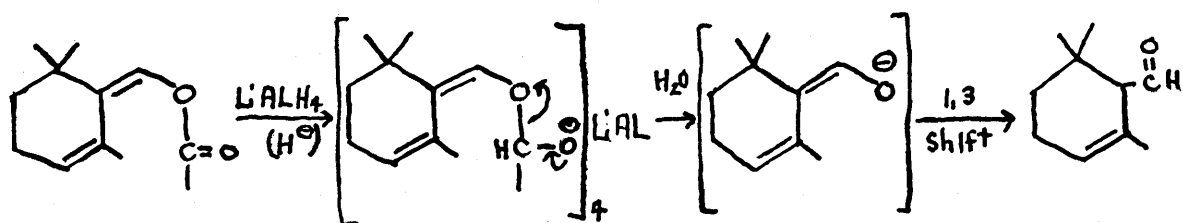
Although (I) is the formula assigned to the enol acetate of  $\alpha$  and  $\beta$ -cyclocitral that was formed, no conclusive proof has been obtained that this is the structure and not



A strong band is present in the infra red spectrum of this ester at 918  $\text{cm}^{-1}$  which could be the slightly displaced band of a semi-cyclic double bond similar to that present in the  $\beta$ -ionone and  $\delta$ -ionone series.

The enol acetate was then subjected to reduction by lithium aluminum hydride in order to determine whether or

not a  $\gamma$ -aldehyde could be isolated in the reduction products. The reduction was carried out three times. In the first attempt a calculated amount of lithium aluminum hydride was used. An unidentified crude product gave a red 2,4-dinitrophenylhydrazone melting at 183.8-184.5°. In the second attempt, again a calculated amount of lithium aluminum hydride was used, but this time a larger quantity of ester was reduced. Two products were isolated from this reaction. These were  $\alpha$ -cyclocitral and a high boiling yellow fluid which is at the present time unidentified. This yellow compound gave a 2,4-dinitrophenylhydrazone which decomposed at 265-266°. At present, indications are that this compound is an aldo-ketone but no definite proof has been obtained at this time. The third time the reduction was made, a large excess of lithium aluminum hydride was used. Again  $\alpha$ -cyclocitral and the high boiling yellow liquid were obtained.

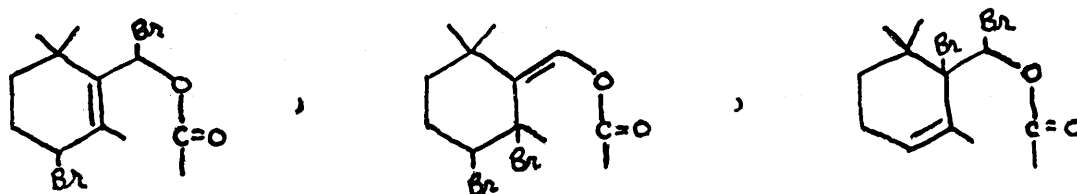


An attempt was then made to hydrolyze the enol-acetate to the corresponding aldehyde, using potassium carbonate in an alcohol-water solution. The 2,4-dinitrophenylhydrazone of the products were made. Two derivatives of two different



compounds were isolated. One was the 2,4-dinitrophenylhydrazone of  $\beta$ -cyclocitral. The other was yellow needles which melted at 185.3-186.8°. The latter compound has not been identified but carbon-hydrogen analysis indicate that it is an isomer of  $\alpha$ - and  $\beta$ -cyclocitral.

The enol acetate was then brominated. Assuming (I) to be the structure of the ester, three different brominated products could be obtained. These are:



The brominated product which was obtained was halved. Half was reacted with sodium acetate and acetic acid, and half was reacted with dimethyl aniline. In the first of these reactions, one 2,4 dinitrophenylhydrazone was formed from the reaction products. In the second reaction, two different 2,4-dinitrophenylhydrazone's were made from the product.

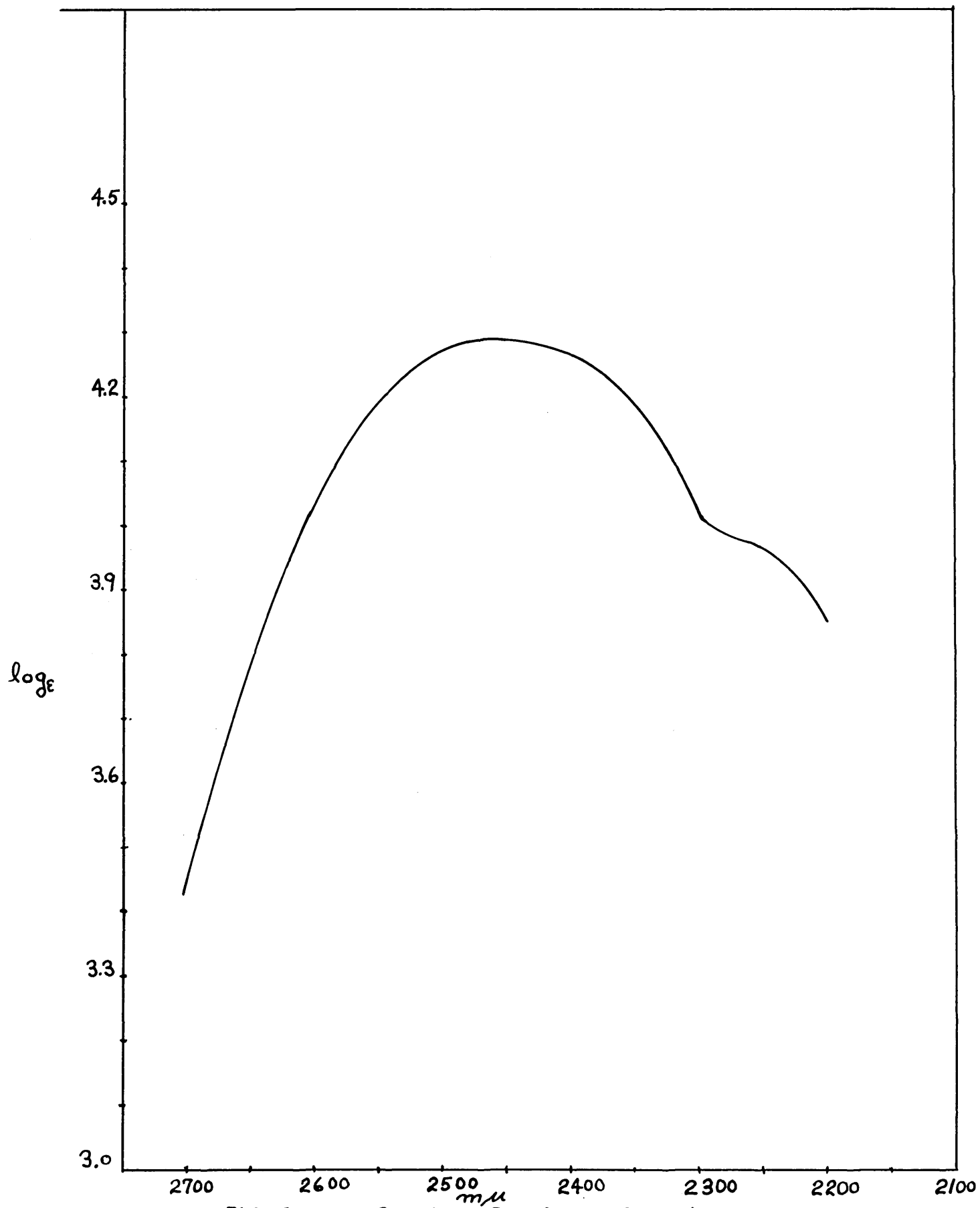


FIG. I - ULTRAVIOLET ABSORPTION SPECTRA:  
ENOL ACETATE OF CYCLOCITRAL

EXPERIMENTAL PARTPreparation of and CyclocitralPreparation of the Schiff-Base:

Fifty grams (0.53 moles) of reagent grade aniline and 50 ml. of reagent ether were placed in a 1000ml. three-neck flask. One neck of the flask was closed with a cork stopper. At the other small neck of the flask was placed a separatory funnel from which 77g. (0.51 moles) of redistilled citral, b.p. 126-127<sup>0</sup> (at 29mm.) were added over a period of one hour. The reaction was stirred vigorously by a stirring motor attached to a stirring shaft which passed through the center neck of the flask. The reaction was carried out at -10 to 12<sup>0</sup>. After the citral addition was complete, the mixture was stirred at this temperature for another hour. At the end of the reaction time, the solution was allowed to come to room temperature. It was then placed in a separatory funnel and the water which was formed in the reaction (about 9 ml.) was then separated. This preparation was used immediately in the following cyclization.

Cyclization of the Base:

The same apparatus was used in this step as was used in the preparation of the base. Five hundred milliliters of concentrated sulfuric acid and 20g. of ice were placed in the 1000ml. reaction flask. The acid was then cooled to -20 to -25<sup>0</sup>, and while the acid was vigorously stirred, the ether solution of the base was added at this temperature over the

period of one hour. Stirring of the solution was continued for another hour at this temperature. A thick, red reaction mixture was formed. This mixture was poured into a two liter long-neck flask containing a quantity of ice. Water was then added to the mixture until the volume was approximately  $1 \frac{3}{4}$  liters, and the mixture was steam distilled. One liter of distillate was collected. The distillate was saturated with sodium chloride and was then extracted with reagent ether. The ether solution was first washed with a solution of sodium carbonate and then with water thoroughly and dried with sodium sulfate. The ether was then distilled off on a steam bath and the yellow residue was distilled in an 8" Vigreux column adapted to vacuum distillation in an attempt to separate the  $\alpha$ - and  $\beta$ -cyclocitral. Yield: 68%.

The  $\alpha$ -cyclocitral was colorless,  $n_D^{25} = 1.4730$ . The  $\beta$ -cyclocitral was slightly yellow,  $n_D^{25} = 1.4880$ .

### Preparation of the Enol Acetate

#### Isopropenyl Acetate Method

A large excess of isopropenyl acetate was added to a quantity of  $\beta$ -cyclocitral and a catalytic amount of p-toluene sulfonic acid was added. The resulting solution was placed in an 8" Vigreux type distillation column and the acetone which was formed in the reaction was distilled off at atmospheric pressure. After the acetone was completely removed, the remaining solution was distilled in an efficient column. A greenish-yellow main fraction was obtained, b.p.

118-120.9° (at 12mm.)

Yield: 84%,  $n_D^{25} = 1.4990$

Anal. Calcd. for  $C_{12}H_{18}O_2$ : C, 74.19; H, 9.34. Found: C, 74.37; H, 9.41.

The preparation was repeated using  $\alpha$ -cyclocitral in place of  $\beta$ -cyclocitral. The same ester was obtained.

Sodium Acetate, Acetic Anhydride Method

Forty grams (0.26 moles) of cyclocitral ( $n_D^{20} = 1.4819$ ) were placed in a 300 ml. side arm flask. One hundred and fifty milliliters of acetic anhydride and 20 g. (0.30 moles) of sodium acetate were added and the mixture was then refluxed for 48 hours under a nitrogen atmosphere. After this time, the mixture was poured into a three neck flask containing water and was stirred for one hour in order to hydrolyze the excess acetic anhydride. The solution was then extracted with ether which was then dried overnight with sodium sulfate. While the ether was being evaporated from the solution, acetic acid separated out. The mixture was then placed in a separatory funnel and the water layer containing the bulk of the acetic acid was separated out. The remaining solution which was a reddish-brown oil was distilled in an efficient fractionating column. The main fraction which was obtained was greenish yellow, b.p. 119.4-120° (12mm).  $n_D^{25} = 1.4990$

Anal. Calcd. for  $C_{12}H_{18}O_2$ : C, 74.19; H, 9.34. Found: C, 74.17; H, 9.44.

Acetic Anhydride-Acetyl Chloride Method

Thirty grams (0.20 moles) of  $\alpha$ -cyclocitral were placed in a 250 ml. side arm flask. One hundred milliliters of acetic anhydride and 20 ml. of acetyl chloride were added and the mixture was refluxed under a nitrogen atmosphere for two days. After this time, the excess acetic anhydride and acetyl chloride were evaporated off under vacuum and the product was distilled in an efficient column. The product was greenish-yellow  $n_D^{25} = 1.4981$ .

Anal. Calcd. for  $C_{12}H_{12}O_2$ : C, 74.19; H, 9.34. Found: C, 74.05; H, 9.39.

Ozonization of the Enol Acetate

One gram of enol acetate was dissolved in ethyl acetate. The solution was cooled to  $-80^{\circ}$  and ozonated in a commercial ozonator for about 30 minutes. After this time, the ozonization was stopped and the water in the water trap was tested for formaldehyde by addition of an alcohol solution of methone. Traces of a white flocculent precipitate were formed, but this was not in sufficient quantity for analysis or melting point determination. The ethyl acetate in the ozonated solution was evaporated off at room temperature under vacuum. The ozonide residue which remained was then destroyed by boiling with water, and this solution was then extracted with ligroin. The ligroin was then tested for formaldehyde with methone. After 24 hours, a slight white precipitate was ob-

tained, but the quantity was not enough for analysis.

### Lithium Aluminum Hydride Reduction (I)

Ten grams, (0.05 moles) of the enol acetate were dissolved in reagent grade ether and the solution was placed in a 500 ml. three neck flask. A stirring motor was attached to a stirring shaft which passed through the center neck of the flask. An efficient condenser was placed through the second neck and a separatory funnel containing an ether slurry of an excess of lithium aluminum hydride (0.05 moles) was placed at the third neck of the flask. The three neck flask was then cooled to  $-12$  to  $-13^{\circ}$  with a methanol-dry ice bath. While the ether-enol acetate solution was under vigorous agitation the lithium aluminum hydride slurry was added over the period of 15 minutes. The solution was then stirred for another 2 hours, and 45 minutes at this temperature. After this time, the mixture was poured into a concentrated solution of ammonium chloride, and extracted with ether. The ether solution was then dried and the ether was distilled off after which the residue was distilled in a Hultsman distillation column.  $\alpha$ -cyclocitral and a high boiling yellow compound b.p.  $115-119^{\circ}$  (10mm) were obtained as products. The 2,4 dinitrophenylhydrazone of the high boiling yellow liquid was a dark red powder when crystallized from methanol-chloroform solution.

This liquid is believed to be an aldo-ketone having the same empirical formula as the enol acetate.

Anal. Calcd. for  $C_{12}H_{18}O_2$ : C, 74.19; H, 9.34. Found: C, 74.21; H, 9.44.

### Lithium Aluminum Hydride Reduction (II)

This reaction was carried out in the same apparatus as was the previous lithium aluminum hydride reduction. This time, 5g. (0.03 moles) of the enol acetate were reacted with a calculated amount of lithium aluminum hydride (0.025 moles). The reduction was carried out at  $-40$  to  $-44^{\circ}$ . The products obtained were the same as those obtained in reduction I.

### Base Hydrolysis of Enol Acetate

Twenty grams (0.10 moles) of enol acetate were placed in a 500 ml. glass stoppered erlenmeyer flask. A concentrated water-methanol solution of potassium carbonate was then added and the mixture was stirred overnight with a magnetic stirrer. After this time, the reaction mixture was diluted with water and extracted with petroleum ether. The ether was dried and distilled off on a steam bath, and the product was distilled in a Hickman distillation flask. 2,4-dinitrophenylhydrazones were made from the products. Two different products were isolated. One was the orange derivative of  $\beta$ -cyclocitral, m.p.  $172.2-172.4^{\circ}$ . The other product was yellow needles from methanol-chloroform, m.p.  $185.8-186.8^{\circ}$ . The analysis for this compound was:

Found: C, 77.83; H, 10.49

### Bromination of the Enol Acetate

A carbon tetrachloride solution of 5g. (0.03 moles) of enol acetate were placed in a 500ml. three-neck flask. A stirring motor and shaft was placed at the center neck of



of the flask. At another neck was placed a drying tube containing anhydrous calcium chloride and at the third neck was placed a separatory funnel containing 4.3g. (0.03 moles) of bromine in carbon tetrachloride solution. The reaction flask was cooled to  $-20^{\circ}$  and the bromine solution was then added over a period of 20 minutes. The reaction mixture was continually stirred throughout the bromination. The stirring was continued for 15 more minutes at this temperature after the bromine had been added. After the reaction was complete, the carbon tetrachloride was evaporated off under vacuum at room temperature. The residue was distilled in a Hickman distillation flask. A reddish product was obtained. This product was separated into two halves. One half was placed in a 50ml. round bottom flask, and an excess of dimethyl aniline was added. The mixture was allowed to sit overnight, <sup>and then was refluxed</sup> under vacuum. This mixture was then poured into a beaker containing cold water and extracted with ether. The ether was washed with cold 3N hydrochloric acid. The ether was then distilled off and a 2,4 dinitrophenylhydrazone of the product was made. One derivative was obtained.

The other half of the brominated product was placed in a 50 ml. round bottom flask. Sodium acetate and acetic acid were added and the mixture was allowed to sit for three days. After this time, it was heated on a steam bath for 2 hours. The mixture was then poured into a beaker containing cold water and extracted with ether. The ether solution was washed with a solution of sodium carbonate and then with water after

which it was steam distilled. Five hundred milliliters of distillate were collected. This was extracted with ether and the ether was dried. The ether was then distilled off and the residue was distilled in a Hickman distilling flask. A yellow product was obtained with a wide boiling range. Two 2,4 dinitrophenylhydrazones were obtained from this compound.

Summary

$\alpha$ - and  $\beta$ -cyclocitral were made by cyclization<sup>of</sup> citral and the enol acetates of these compounds were made using three different methods of acetylation. Both  $\alpha$ - and  $\beta$ -cyclocitrals gave the same enol acetate by all three methods. The enol acetate was brominated and the brominated product was reacted with sodium acetate and acetic acid and also with dimethyl aniline. Two products were isolated from the first of these reactions, and one product was obtained from the other reaction. The 2,4-dinitrophenylhydrazones of these compounds did not melt in the range of the corresponding safranal derivative.

Although safranal has not been obtained by this prescribed synthesis, an intermediate has been obtained which upon bromination and subsequent hydrolysis or dehydrohalogenation may result in the formation of the desired final product. The problem that remains now is to determine the structure of all the unknown compounds formed in this attempted synthesis. Once this has been done, it can be determined whether or not safranal can be synthesized by this method.

FOOTNOTES

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