The Synthesis of Safranal

by

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Submitted in Partial Fulfillment of the
Requirements for the Degree of
Bachelor of Science

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May 25, 1953

Signature of Author ______________________________

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Acknowledgement

The author wishes to thank Dr. George H. Büchi for his assistance, suggestions, and encouragement with the problem.

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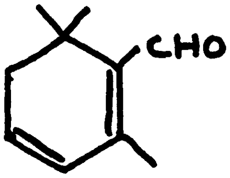
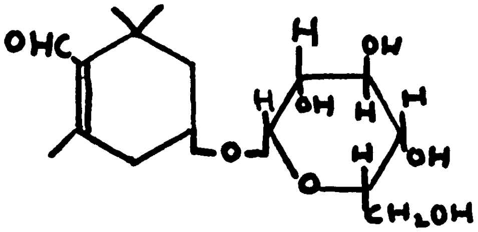
Introduction

Safranal is a cyclic monoterpene which occurs naturally in the saffron plant as a glucoside, picrocrocin. In 1922 Winterstein and Teleczky[1] obtained safranal by hydrolysis of picrocrocin, but its structure was not determined. Kuhn and Winterstein[2] hydrolyzed picrocrocin in 1933 and obtained safranal and glucose in a one to one ratio. The structures for safranal and picrocrocin were determined.



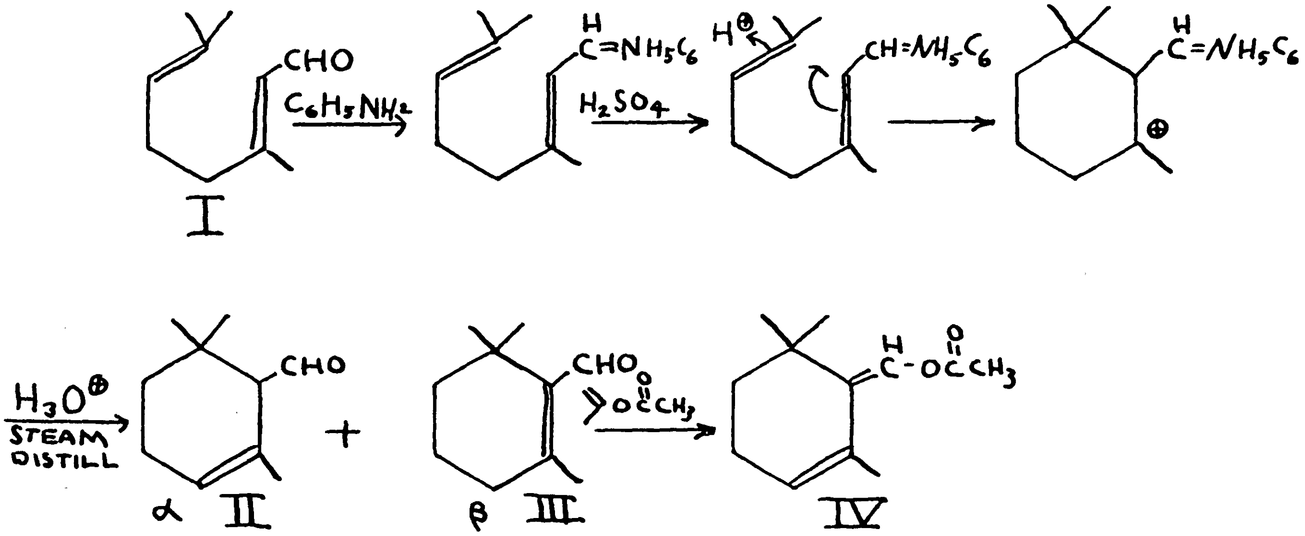
Safranal



Picrocrocin

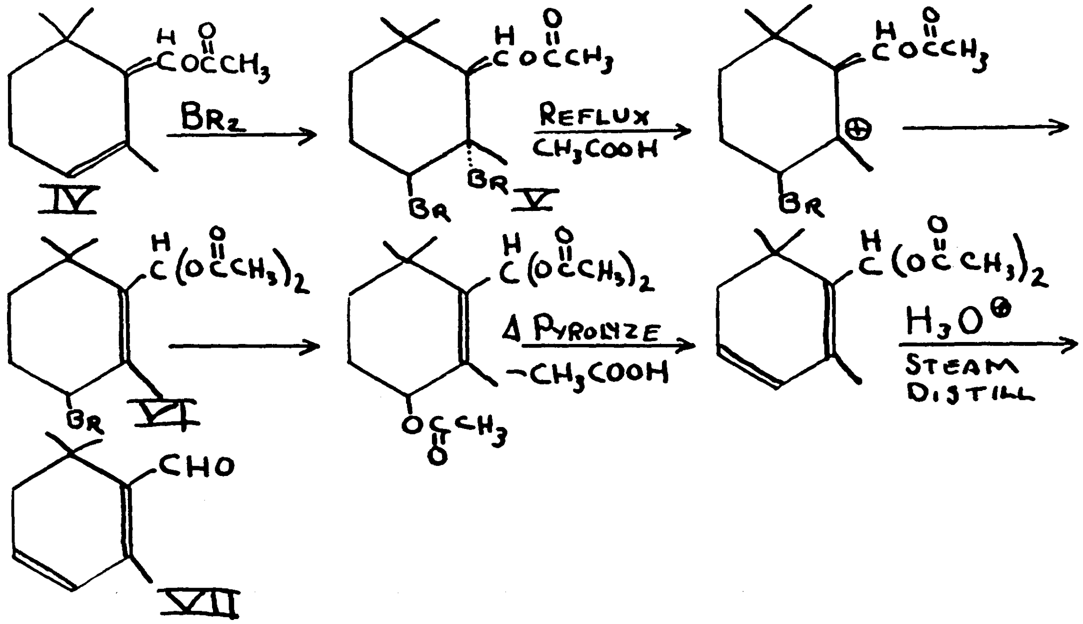
Since this time there have been many attempts to devise a practical synthesis of safranal. Among these has been the work of Kuhn and Wendt,[3] who obtained safranal in 1-3% yield by dehydrogenation of β-cyclocitral. Karrer and Ochsner[4] attempted its synthesis by bromination of α-cyclocitral with N-bromosuccinimide followed by dehydrobromination, but a rearrangement took place. Lunt and Sondheimer[5] obtained a homolog of safranal, 4-methyl safranal, by a Diels-Alder type condensation. Other attempted syntheses have proven unsuccessful.[3,6]

This paper presents the results of attempts to synthesize safranal from the enol acetate of cyclocitral. It is a continuation of the work begun by Vittimberga[7] in 1951. He succeeded in obtaining the enol acetate of cyclocitral in good yield and determined its structure. Cyclocitral was prepared by first forming a Schiff base from citral (I) and aniline. This was cyclized with concentrated sulfuric acid and steam-distilled to give a mixture of α- and β-cyclocitral (II and III) in a ratio of 2/3 to 1/3. This mixture was treated with a large excess of isopropenyl acetate to form the enol acetate of cyclocitral. Both α- and β-cyclocitral give the same enol acetate (IV).

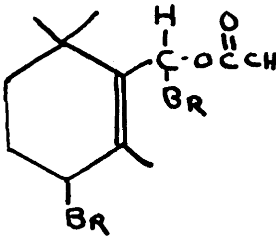


Discussion

In the present work a synthesis was attempted which began with a bromination of the enol acetate (IV). This was prepared by the method of Vittimberga.[7] The brominated product was refluxed in glacial acetic acid, distilled, and pyrolyzed in a Claisen flask. The pyrolyzed product was steam-distilled in the presence of 10% sulfuric acid and the distillate was extracted.



The bromination was carried out in glacial acetic acid, and it was assumed at that time to proceed in the manner indicated by V, although there are two other possible ways in which IV may brominate.



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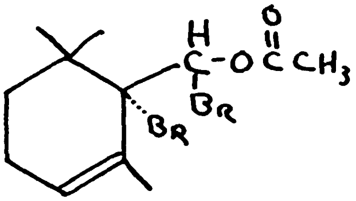


Since the tertiary bromine of V is allylic, it should solvolyze easily, resulting in structure VI. This bromine is now also allylic, and should also be easily removed. Pyrolysis followed by steam-distillation should give safranal (VII).

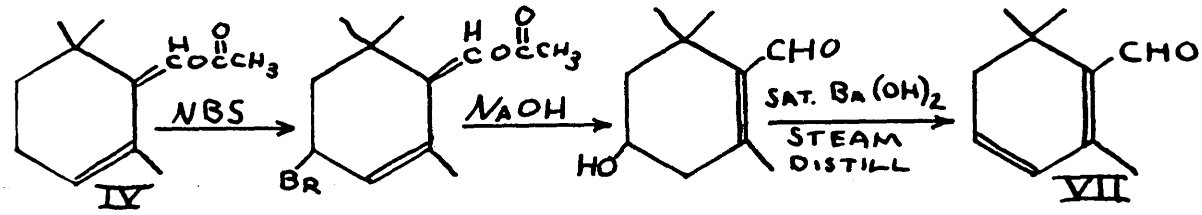
Hydrogen bromide which was formed during the reaction of the dibromoenol acetate with acetic acid caused some decomposition of the product, and more decomposition resulted in the pyrolysis. Only a small yield of a product was formed, which was characterized by a red 2,4-dinitrophenylhydrazone

(2,4-DNP), m.p. 189-195°. A thiosemicarbazone was formed, m.p. 207-208°. The crystalline form of these derivatives corresponded to those reported for safranal. The melting points given in the literature[3] were 186° for the 2,4-DNP and 199-200° for the thiosemicarbazone. These may not have been corrected, and it appears that our product is safranal, but the yield again was very poor.

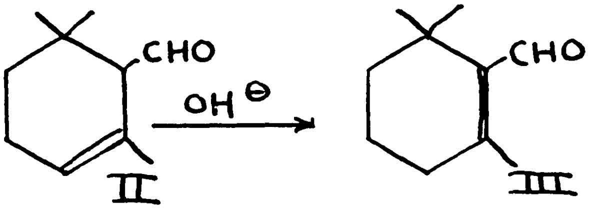
The bromination and solvolysis were repeated. This time the product was not pyrolyzed but was poured into a quantity of ice water and extracted. The product was distilled and passed through an alumina column in an attempt to remove traces of hydrogen bromide. A 2,4-DNP was prepared which was red, m.p. 188-189.5°. A carbon-hydrogen analysis of the liquid, however, did not give the values for safranal, and an infrared spectrum showed only a very weak carbonyl band.

In a third experiment the solvolysis was carried out with an excess of silver acetate to remove the hydrogen bromide as it was formed. In this way it was hoped to prevent decomposition of the product. This time no darkening of the product was observed. A 2,4-DNP of the product was formed. Small dark red crystals formed, m.p. 275°. A Beilstein test indicated the presence of bromine in the liquid and it was thought at this time that the derivative was a bromo-compound.

It was decided at this time to try another synthesis involving a bromination of IV with N-bromosuccinimide. The bromide thus formed was solvolyzed with three equivalents of sodium hydroxide in a 5% solution in order to obtain 4-hydroxy-β-cyclocitral. Kuhn and Löw^8 reported that this product, when steam-distilled in the presence of saturated barium hydroxide, yielded VII.

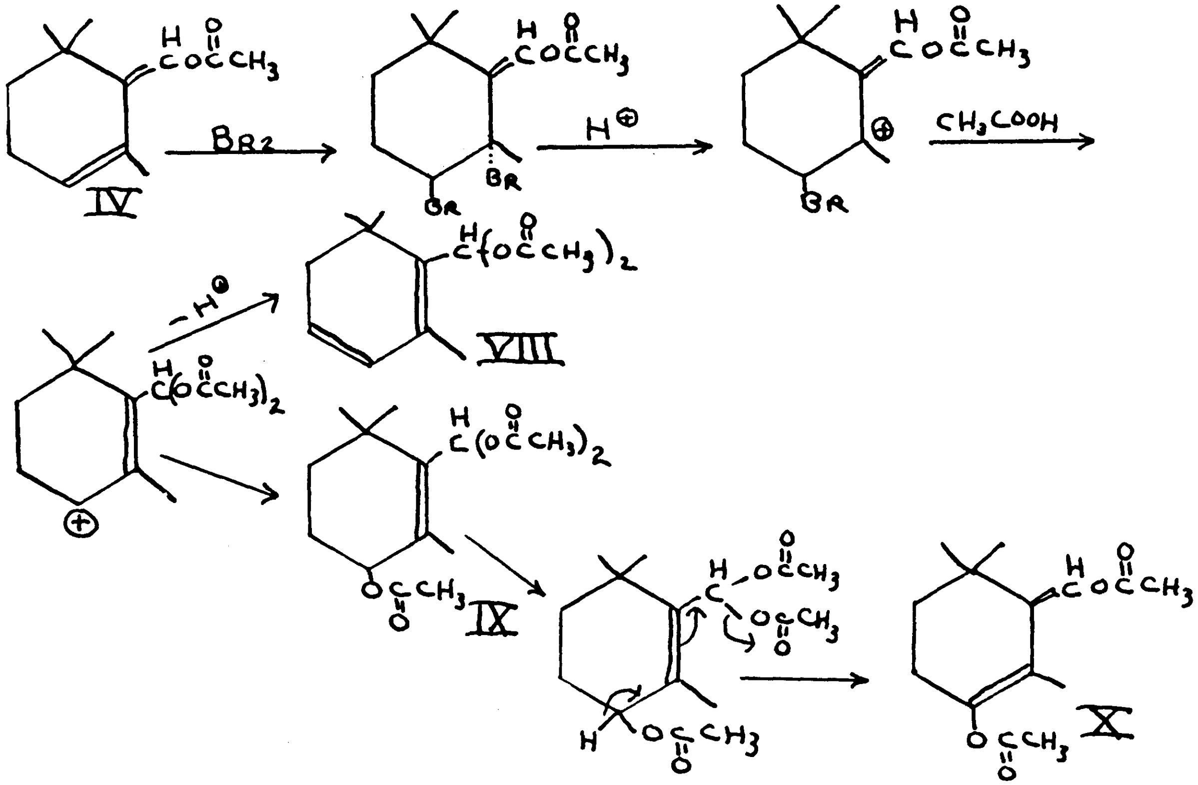


The β-isomer is formed with sodium hydroxide, since it has been shown by Köster^9 that II is converted to III by base.

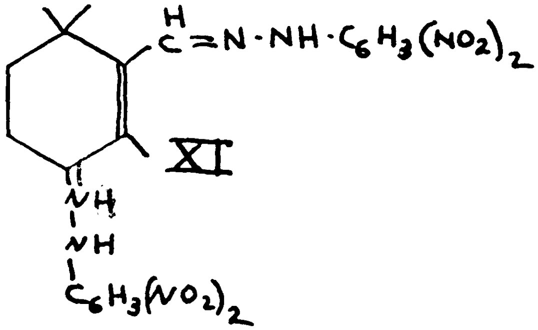


The product obtained, however, gave a mixture of 2,4-DNP's which did not melt in the range of the safranal derivative.

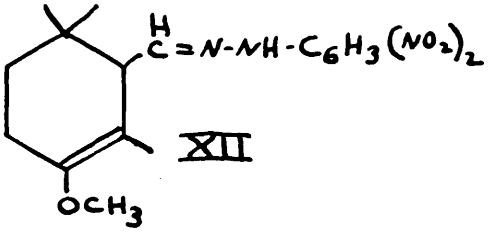
It was decided next to further investigate the product of the silver acetate solvolysis. IV was brominated and solvolyzed with silver acetate as before. A 2,4-DNP was made, and again a high melting, dark red derivative was formed, m.p. 270°. On further standing, an orange derivative formed. A Beilstein test on the product was still positive, but a sodium fusion indicated no bromine, so the test must have been due to traces of hydrogen bromide. Since the compound contains no bromine, there are three possibilities for its structure.



The three possible structures are VIII, IX, and X. A carbon-hydrogen analysis checked for compounds VIII or X, which would have the same analysis. The ultraviolet absorption spectrum indicated two conjugated double bonds, and showed an absorption maximum at 242 mμ (log ϵ 4.03). Compound IX is therefore eliminated by this fact, as well as by the analysis. Compound VIII should give the safranal 2,4-DNP, however, but it does not. Structure X, a dienol diacetate, is therefore indicated as the correct compound. Further evidence for X is the high melting 2,4-DNP formed with excess reagent. This proved to be a bis-derivative. The carbon-hydrogen analysis checked for compound XI.


XI

If a limited amount of 2,4-DNP reagent is used, a mono-derivative forms, orange crystals, m.p. 102-105°. This analyzed for compound XII.

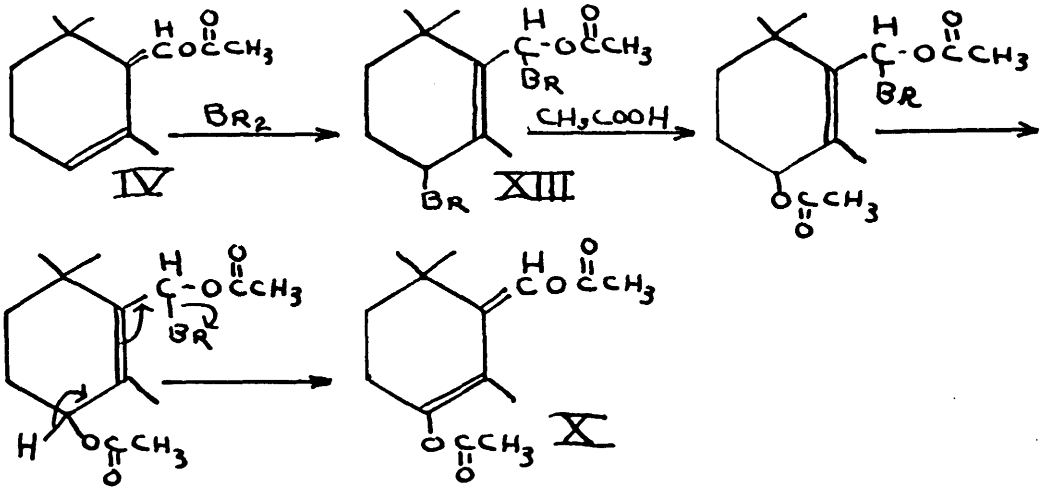


XII

This enol ether results since the 2,4-DNP reagent is made with methanol. The formation of the bis-derivative may go through this stage.

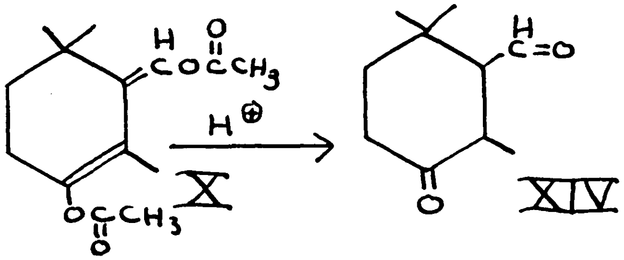
An infrared spectrum indicates an enol acetate system is still present, which confirms the structure of compound X. (See appendix, Curve B).

The formation of X can be explained much more easily, however, if the bromine adds 1,4 to the conjugated system.



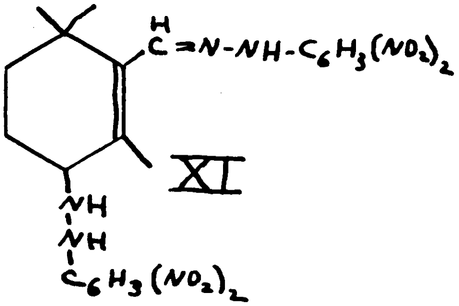
In order to determine how the bromination takes place, a small amount of enol acetate was brominated in carbon tetrachloride with an excess of bromine. An infrared analysis was run on the product. (See appendix, Curve C). The enol acetate bands at 1749 cm.-1 and 1219 cm.-1 were missing or very weak. This indicates that 1,4 addition (XIII) has taken place, since 1,2 addition would preserve the enol acetate system. (See structure V). A 2,4-DNP was formed of the brominated product, and it was identical with the bis-derivative (XI) from X, since a mixed melting point with XI showed no depression.

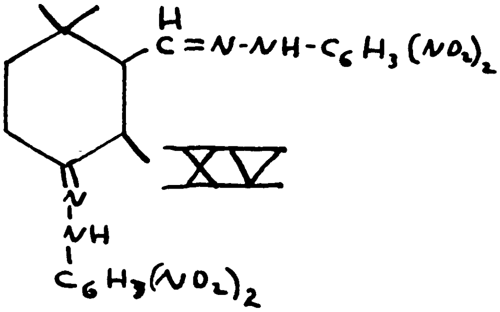
The next step was to hydrolize X to the corresponding aldo-ketone (XIV) by acid hydrolysis.



This hydrolysis was carried out in a dioxane-water mixture. A first attempt with 5% acid gave incomplete hydrolysis, but a second reaction with 20% acid over a longer period of time gave almost complete hydrolysis. This product gave a yellow bis-2,4-DNP, m.p. 242-242.5°, and an orange mono-derivative, m.p. 173-176°.

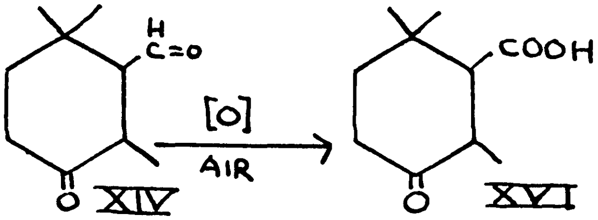
XIV should give the same bis-2,4-DNP derivative as X. Since the analyses of both bis-derivatives are the same, it appears that they are isomers. Two possibilities for the structure are XI and XV.


XI


XV

XI has already been indicated as the correct structure for the derivative of X, since it has more conjugation and should be red. The less conjugated XV would explain the yellow bis-derivative. XV is the normal product expected from XIV. A different manner of attack by the 2,4-DNP reagent on X could give XI.

XIV readily oxidizes in air to form the corresponding keto-acid(XVI), m.p. 173-174°.



This oxidation takes place so rapidly that an analysis could not be run on XIV. Therefore XIV was allowed to oxidize to XVI and an analysis was run on XVI.

Experimental

All melting points were taken in a Hershberg melting point apparatus and were not corrected. Mixed melting points were taken on an electrically heated melting point block. The infrared spectra were done on a Baird Associates' recording infrared spectrophotometer. Spectra and analyses were done in the M. I. T. Microchemical Laboratory, in charge of S. M. Nagy.

All 2,4-dinitrophenylhydrazones (2,4-DNP), were made with a reagent composed of 2.5 g. 2,4-dinitrophenylhydrazine, 100 ml. methanol, 4 ml. concentrated hydrochloric acid.

First Bromination of the Enol Acetate.- Cyclocitral and the enol acetate of cyclocitral (enol acetate) were prepared by the method of Vittimberga[7]. Enol acetate (10.6 g., 0.055 mole) was dissolved in 200 ml. of glacial acetic acid. Bromine (8.7 g., 0.055 mole) dissolved in 100 ml. glacial acetic acid was added slowly to the enol acetate with stirring at room temperature. The bromination proceeded rapidly. The mixture was refluxed for three hours and then the solvent was taken off under vacuum in a nitrogen atmosphere. Considerable decomposition took place during the solvolysis. The bromination product was distilled in a Hickmann flask, b.p. 70-80° (0.1 mm.). Since some splattering occurred in the first distillation, the product was distilled again and yielded 4.87 g., b.p. 60-65° (0.05 mm.).

This product was pyrolized in a Claisen flask and steam-distilled from a 10% solution of sulfuric acid. More decomposition took place on pyrolysis. The distillate was extracted with ether, washed with sodium carbonate solution and water, and dried over anhydrous sodium sulfate. A 2,4-DNP was formed and recrystallized from a mixture of ethyl acetate and methanol; small red rods, m.p. 189-195°. A thiosemicarbazone was formed and recrystallized from methanol; white plates, m.p. 207-208°.

Second Bromination without Pyrolysis.- Enol acetate (21.7 g., 0.11 mole) was brominated with a solution of 17.8 g. of bromine (0.11 mole) in 150 ml. glacial acetic acid. The mixture was refluxed for three hours. Considerable decomposition took place. After refluxing, the reaction mixture was poured into a separatory funnel containing a quantity of cracked ice and was diluted with water. The product was extracted with pentane, dried over anhydrous sodium sulfate, and after removal of the solvent was distilled in a Hickmann flask, b.p. 80-84° (0.05 mm.). A Beilstein test indicated the presence of bromine and a portion of the product was passed through a short column packed with neutral alumina, using pentane as a solvent, to remove traces of hydrogen bromide. After this procedure there was still a trace of hydrogen bromide present. A dark red 2,4-DNP formed which did not contain bromine and was recrystallized from an ethyl acetate-methanol mixture; m.p. 188-189.5°.

N-bromosuccinimide Bromination of the Enol Acetate.- Enol acetate (8.5 g., 0.052 mole) was dissolved in 100 ml. of dry carbon tetrachloride and placed in a three-necked flask fitted with a condenser and stirring motor. N-bromosuccinimide (10.0 g., 0.057 mole) was added in portions. When all the N-bromosuccinimide was added the mixture was refluxed with constant stirring until the reaction was complete(about two hours). After the succinimide was filtered off the solvent was removed under a vacuum.

The bromination product was solvolyzed in 100 ml. of a 75% dioxane-25% water solution containing 4.2 g. (0.15 mole) sodium hydroxide. The mixture was heated to 40° and stirred for one hour under nitrogen. This solution was extracted with six portions of ether, dried, and the solvent removed. The resulting product was steam-distilled in the presence of saturated barium hydroxide. Much polymerization took place. When a 2,4-DNP was formed of the product a mixture of two derivatives formed, one red and one yellow.

Preparation of the Dienol Diacetate (X).- Enol acetate (20.0 g., 0.103 mole) was dissolved in 300 ml. of glacial acetic acid and brominated with a solution of 16.5 g. (0.103 mole) of reagent grade bromine in 50 ml. glacial acetic acid. The bromine solution was added with stirring to the enol acetate solution at room temperature. After the addition of bromine was completed, 42 g. silver acetate (2.4 mole per mole of bromine) was added. The mixture was heated to 40° and stirred for eight hours. At this time the solution gave no precipitate of silver bromide with alcoholic silver nitrate. The silver bromide formed was filtered off and the solution was poured into 300 ml. of water. This mixture was saturated with ammonium sulfate, extracted with six portions of pentane, and dried over anhydrous sodium sulfate. When the solution was dry the solvent was removed and the product was distilled, b.p. 84-85°, (0.2 mm.), $n^{25}D$ 1.4908. Ultraviolet absorption spectra showed $\lambda_{max}^{cyclohexane}$ 242 mμ (log ε 4.03); λ_{max}^{ether} 240 mμ (log ε 3.99).

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.92; H, 8.36.

Preparation of the Bis-2,4-DNP Derivative (XI).- Diacetate (X) (0.2 g.) was added to 40 ml. of 2,4-DNP reagent and refluxed for one hour on a steam bath. The product was recrystallized from ethyl acetate; small, dark red needles m.p. 270°.

Anal. Calcd. for $C_{22}H_{24}O_8N_8$; C, 50.00; H, 4.58. Found: C, 50.11; H, 4.54.

Preparation of the Mono-2,4-DNP Derivative (XII).- A limited amount of the 2,4-DNP reagent was added to a small amount of the diacetate. An orange product formed, m.p. 102-105° after five recrystallizations from methanol.

Anal. Calcd. for $C_{17}H_{22}O_5N_4$; C, 56.34; H, 6.12. Found: C, 56.34; H, 6.21.

Bromination of the Enol Acetate.- Enol acetate (1.5 g.) was dissolved in 50 ml. carbon tetrachloride.

Bromine in carbon tetrachloride solution was added with stirring at 0°, until no more was taken up, as indicated by a bromine coloration in the solution. More than one mole was taken up. One portion was taken up as fast as it could be added, and another portion was taken up less rapidly. Some hydrogen bromide was formed. The carbon tetrachloride was taken off under vacuum and two infrared spectra were run on the product at once. One was run in the pure liquid, and one was in 10% carbon tetrachloride solution. The enol acetate bands at 1219 cm.-1 and 1749 cm.-1 were missing or very weak in both cases, indicating that the enol acetate system had been destroyed. A 2,4-DNP was formed of the bromide and recrystallized from ethyl acetate, small red crystals, m.p. 265°. This derivative was found to be identical with the bis-derivative obtained from the dienol diacetate by mixed melting point.

<u>Preparation of the Aldo-Ketone (XIV)</u>.- Diacetate (2.5 g.) was added to a mixture of 75 ml. pure dioxane, 11 ml. of concentrated sulfuric acid, and 14 ml. distilled water (20% acid solution by weight). The mixture was stirred at room temperature for 24 hours. When the reaction began there were two layers, but the mixture became homogeneous by the end of the hydrolysis. The mixture was neutralized with sodium bicarbonate, saturated with ammonium sulfate, extracted with pentane and dried with anhydrous sodium sulfate. The product was distilled in a Holtzmann column and yielded 2.4 g., b.p. 50° (0.05 mm.), n^{25}_D 1.4793. An

analysis was unsatisfactory because of rapid oxidation to the acid.

Preparation of the Bis-derivative (XV).- The aldo-ketone (0.1 g.) was added to an excess of 2,4-DNP reagent and refluxed for eight hours in order to form a bis-derivative. A yellow product was obtained which when recrystallized from chloroform formed small, dull orange needles, m.p. 242-242.5°.

Anal. Calcd. for $C_{22}H_{24}O_8N_8$: C, 50.00; H, 4.58. Found: C, 49.60; H, 4.66.

Preparation of the Mono-derivative.- In an attempt to make the mono-2,4-DNP of the aldo-ketone, three drops were dissolved in 2 ml. of methanol and 10 drops of the 2,4-DNP reagent were added. On standing, bright orange needles were formed, m.p. 173-176°. Insufficient product was obtained for analysis and the experiment could not be duplicated.

Oxidation to the Keto-Acid (XVI).- A small amount of the aldo-ketone was placed on a watch glass and exposed to the air. The product oxidized almost completely to the keto-acid in a few hours. This acid was recrystallized twice from a water-acetone mixture, m.p. 173-174°.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.28; H, 8.82.

Appendix

Infrared Absorption Curves.

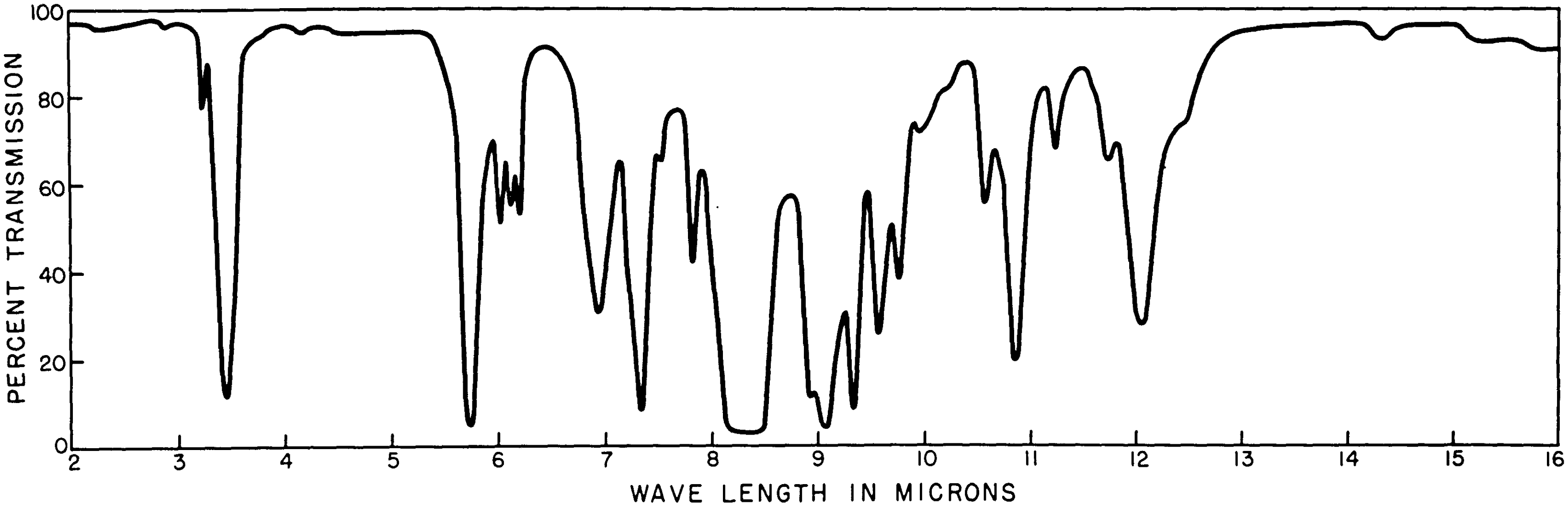
A. Enol Acetate of Cyclocitral (IV).

B. Dienol Diacetate (X).

C. 1,4-Dibromoenol Acetate (XIII).

D. Aldo-Ketone (XIV).

All compounds were run in the pure liquid state.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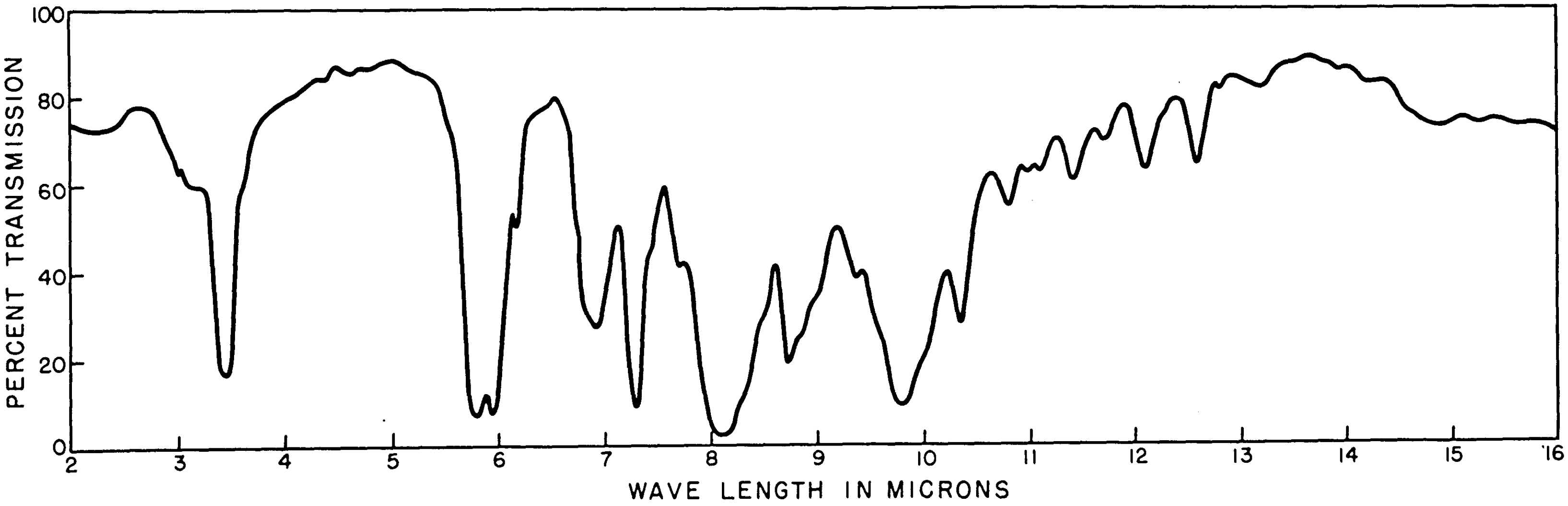
WAVE LENGTH IN MICRONS

A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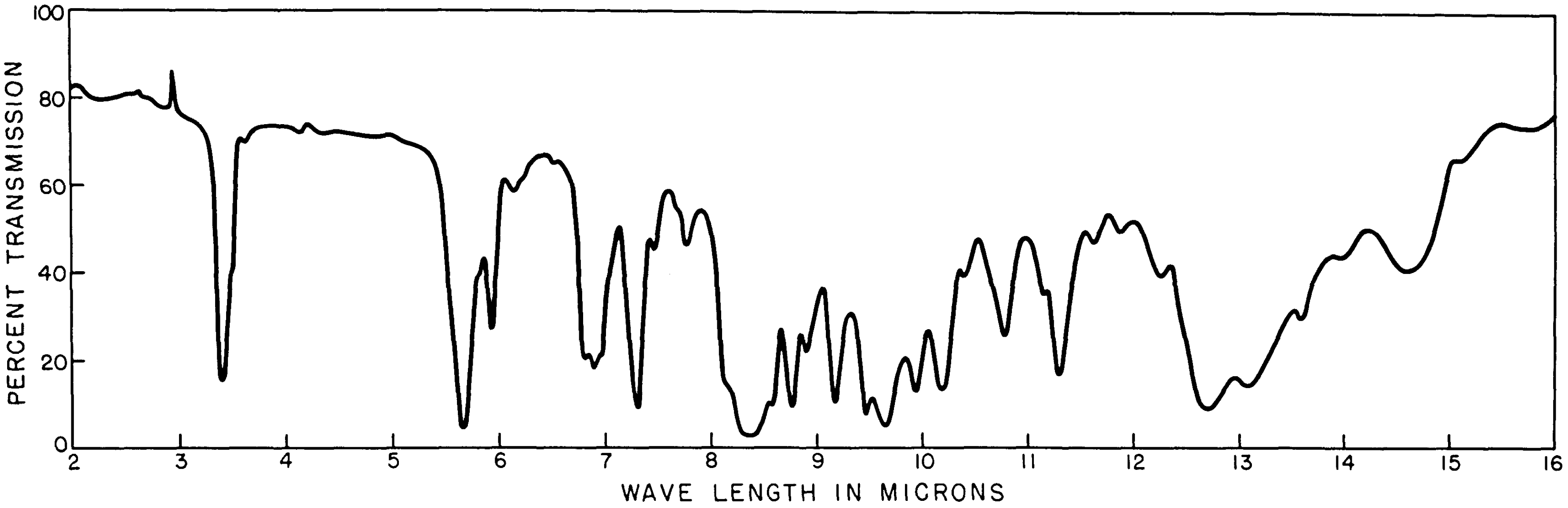
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WAVE LENGTH IN MICRONS

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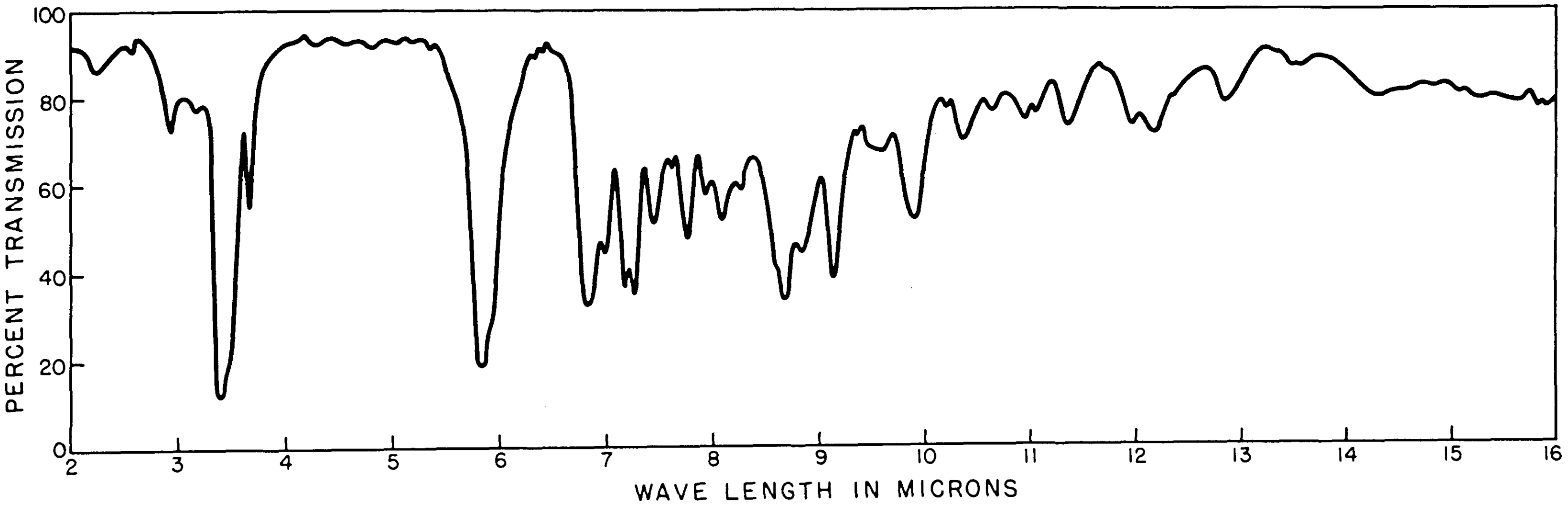
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WAVE LENGTH IN MICRONS

D

Summary

The enol acetate of cyclocitral (IV) $\underline{C(CH_3)_2C(:CHOCOCH_3)\text{-}C(CH_3):CHCH_2CH_2}$ was brominated and solvolyzed with acetic acid. Pyrolysis followed by steam-distillation yielded safranal $\underline{C(CH_3)_2C(CHO):C(CH_3)CH:CHCH_2}$ in poor yield. IV brominated in acetic acid solution and solvolyzed with excess silver acetate in acetic acid yielded a dienol diacetate (X) $\underline{C(CH_3)_2C(:CHOCOCH_3)C(CH_3):C(OCOCH_3)CH_2CH_2}$, b.p. 84-85° (0.2mm.) $n^{25}D$ 1.4908. X formed an orange mono-2,4-DNP, m.p. 102-105°, and a red bis-2,4-DNP, m.p. 270°. X was hydrolyzed in 20% acid solution to form an aldo-ketone $\underline{C(CH_3)_2CH(CHO)CH(CH_3)CO\text{-}CH_2CH_2}$ (XIV), b.p. 50° (0.05 mm.), $n^{25}D$ 1.4793. XIV was oxidized to the corresponding keto-acid by air oxidation, m.p. 173-174°.

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