

THE ROBINSON-MANNICH BASE SYNTHESIS  
APPLIED TO SUBSTITUTED ACETOACETIC ESTERS

by

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Dedicated to my wife, Genie

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INTRODUCTION

The purpose of this investigation was to determine the feasibility of synthesizing certain substituted naphthalenes containing a  $C^{14}$  atom placed in a known position in one of the rings. A contemplated study of the mode of reaction of the Jacobsen rearrangement made it desirable to know whether or not these compounds might be made conveniently, in a high state of purity and in good yield.

One such approach is that given by the series of equations in Figure 1. Steps 1 and 2 had been carried out previously and seemed to present no immediate problems as to their adaptation to a radioactive synthesis. Steps 4, 5 and 6 embodied the use of well known organic reactions from which little trouble was anticipated.

Step 3, on the other hand, was a reaction where it was felt that most of the trouble would be experienced. It represented an application of a known reaction to a new set of starting materials in which the structural changes in the molecules were such as possibly to modify the ultimate product or prevent the reaction from taking place altogether.

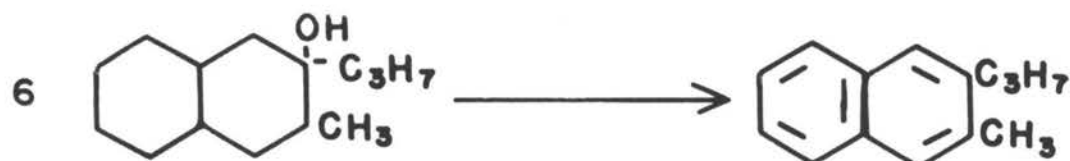
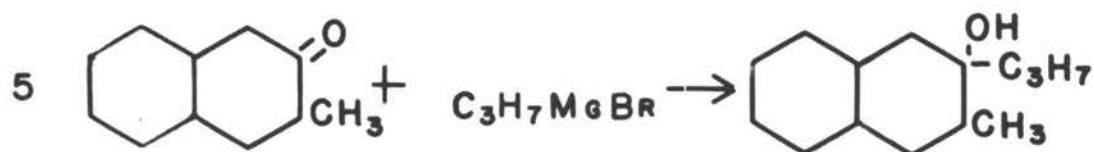
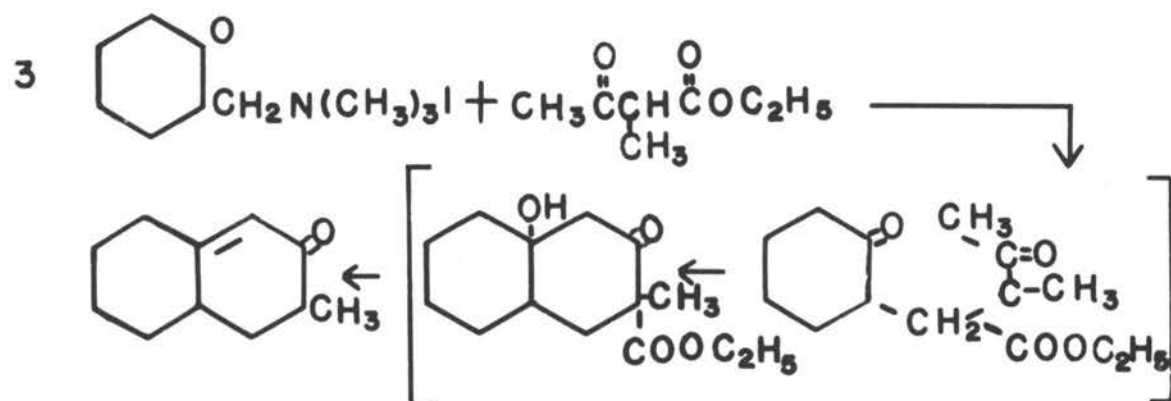
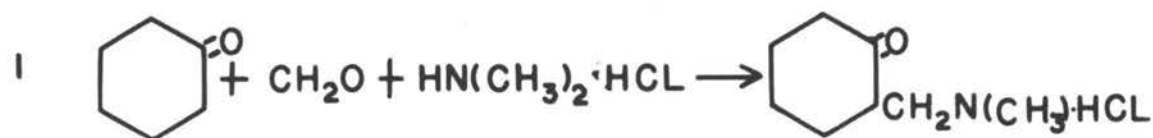
The problem then was to find out whether or not this sequence of reactions would give the end products

needed and in sufficient quantity to make these products useful in the rearrangement studies.



FIGURE 1

3





## HISTORICAL

The reaction between a  $\beta$ -keto ester and a quaternary ammonium salt of a ketonic Mannich base in the presence of equivalent amounts of sodium ethoxide is known as the Robinson-Mannich base synthesis. It has proved useful in preparing many multi-ring compounds which often can be obtained in no other manner.

Essentially, it is the alkylation of an active methylene compound by a Mannich base. In such a reaction the Mannich base acts as a source of an unsaturated ketone which then undergoes a Michael condensation with the active methylene compound.

Mannich (9, pp. 355-359) reported the formation of a  $\beta$ -decalone derivative by the condensation of 2-dimethylaminomethylcyclohexanone with acetoacetic ester in the presence of catalytic amounts of sodium ethoxide. Robinson (2, p. 53) employed a modification of this reaction in his syntheses and studies of substances related to the sterols. The modification consisted in treating the Mannich base with methyl iodide and causing the resulting quaternary ammonium methiodide to react with the active methylene compound in the presence of sodium amide or sodium ethoxide.

The advantage of the methiodide over the Mannich base seems to be in the liberation of the  $\alpha$ - $\beta$  unsaturated

ketone at lower concentrations and greater reactivity, resulting in a reduction of the reaction time from several days to a few hours. Robinson used this modified reaction to synthesize a series of alkyl-substituted ketooctalins (reactions 1 and 2, Figure 2).

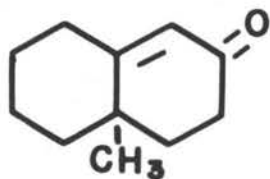
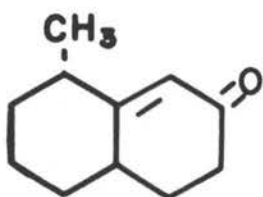
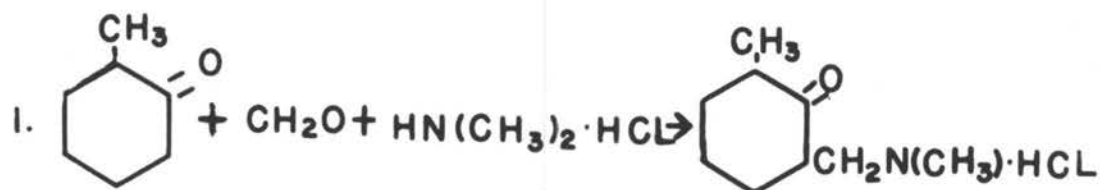
In reaction 1, the initial Mannich reaction takes place on the unsubstituted methylene group adjacent to the carbonyl. This was proved by a series of reactions which gave 2,6-dimethyl phenol as a final product. Condensation of this Mannich base with acetoacetic ester gave 2-keto-8-methyl- $\Delta^{1:9}$ -octalin.

In reaction 2, where the substituted cyclohexanone reacts with 1-dimethylamino-3-butanone (the Mannich base prepared from acetone, formaldehyde and dimethylamine) alkylation takes place at the substituted methylene group to yield 2-keto-10-methyl- $\Delta^{1:9}$ -octalin.

That the two compounds were different was shown by difference in the melting points of the semicarbazones and 2,4-dinitrophenylhydrazones of each. A temperature depression was noted in the melting point of a mixture of the derivatives.

The 2-keto-10-methyl- $\Delta^{1:9}$ -octalin required drastic conditions for dehydrogenation to  $\beta$ -naphthol while the 2-keto-8-methyl- $\Delta^{1:9}$ -octalin was dehydrogenated smoothly to 7-hydroxy-1-methylnaphthalene.

FIGURE 2



Further studies involving this useful reaction were subsequently undertaken, notably by A. L. Wilds and co-workers (14, pp. 469-475; 15, pp. 1149-1153; 16, pp. 1154-1161). They found that careful purification of the Mannich base resulted in higher yields of the alkylation product. They also effectively increased the reactivity of the active methylene group by first formylating the ketone with methyl formate. The resulting  $\alpha$ -hydroxymethyleneketone (considerably more acidic than the parent compound) then could be alkylated in good yield with the methiodide of the Mannich base. The hydroxymethylene group was finally removed by basic cleavage at the same time cyclization was effected.

There is strong evidence in support of the concept that the actual alkylating molecule is not the Mannich base or the methiodide but rather the  $\alpha$ - $\beta$  unsaturated ketone formed by the elimination of either a secondary amine or a tertiary amine from the Mannich base or the methiodide, respectively. Robinson attempted to replace 1-diethylamine-3-butanone with methyl ketone but was unsuccessful due to the polymerization of the unsaturated ketone in the presence of basic catalysts (2, p. 53).

Methyl vinyl ketone later was found to react satisfactorily to give the same results as the corresponding Mannich base, providing only catalytic amounts of the

required basic catalyst were used (15,p.1150).

The Robinson-Mannich base synthesis has been used successfully in forming a new cyclohexanone ring upon many cyclic ketones. The products obtained have had alkyl substituents in many of the ring positions. An examination of all the work previously carried out indicated that this reaction had not been applied to the synthesis of 2-decalone derivatives with alkyl groups substituted in the number three position (i.e., adjacent to the carbonyl group as in either a 2-octalone or a 2-decalone).

Reaction 3 (Figure 1) would be an example of such a reaction. It logically could be considered as an extension of Robinson's original synthesis involving acetoacetic ester (reaction 1, Figure 2) with the only change being the substitution of an  $\alpha$ -alkyl acetoacetic ester for the unsubstituted  $\beta$ -keto ester itself.

## DISCUSSION OF RESULTS

Ethyl  $\alpha$ -methyl acetoacetate, ethyl  $\alpha$ -ethyl acetoacetate and ethyl  $\alpha$ -propyl acetoacetate were prepared according to the procedure given in Organic Syntheses (4, pp.248-250). Little trouble was experienced in the latter two but in the  $\alpha$ -methyl ester it was found necessary to use methyl iodide rather than methyl bromide due to the very low boiling point of the bromide. Because of the appreciable solubility of sodium iodide in alcohol, benzene was used as a solvent in this case so as to avoid complications during distillation caused by the dissolved salt.

2-Dimethylaminomethylcyclohexanone was prepared by the method of Mannich and Braun (8,p.1875). The only modification was to increase the time of heating to 45 minutes and the temperature to 80°. The free base was obtained by making alkaline an aqueous solution of the Mannich base hydrochloride and extracting the free amine with ether. Distillation of the free amine was found to be unnecessary inasmuch as a product of sufficient purity was obtained by the simple extraction procedure.

2-Dimethylaminomethylcyclohexanone methiodide (hereafter referred to as Mannich methiodide) was prepared by the method of Wilds and Werth with no modification (15,p.1151).



2-Keto-3-methyl- $\Delta^{1:9}$ -octalin, 2-keto-3-ethyl- $\Delta^{1:9}$ -octalin and 2-keto-3-propyl- $\Delta^{1:9}$ -octalin were prepared initially by the reaction between the appropriate  $\alpha$  -  $\beta$  substituted acetoacetic ester and the Mannich methiodide catalyzed by sodium ethoxide in anhydrous ethanol. The crude product was obtained by addition of water to the reaction mixture followed by extraction with ether. After drying the ether extracts, initial distillation was carried out under reduced pressure using a short Claisen head.

The following table gives the yields of these reactions based upon the molar amounts of the Mannich methiodide used.

Substituent	Yield*
Methyl	41%
Ethyl	35%
Propyl	32%

\*These percentages were calculated from the products isolated in the initial distillation.

That the second methylene hydrogen in acetoacetic ester is more difficult to remove than the first one is well known. In fact, that is why it is possible to obtain mainly a mono-alkylated product rather than a di-alkylated product in the reaction of acetoacetic ester with the appropriate alkyl halide.



If it is assumed that the reaction takes place in the order given in reaction 3, Figure 1, then it seemed reasonable that an increase in the strength of the basic catalyst might bring about a more effective removal of the second hydrogen as a proton and thus give an increased yield, especially if the amount of product obtained was based upon the initial alkylation.

A series of condensations between ethyl  $\alpha$ -methyl acetoacetate and the Mannich methiodide were run in which only the basic catalyst and the solvent were varied. The results are given in the following table.

Catalyst	Solvent	Yield*
EtONa	EtOH	39-42%
<u>i</u> -PrONa	<u>i</u> -PrOH	41%
<u>t</u> -BuOK	<u>t</u> -BuOH	15% (approximately)
Na	xylene	0

\*Based upon the products isolated in the initial distillation.

These data would tend to indicate that an increase in the strength of the basic catalyst does not bring about an increased yield. Little difference was noted between the results of using either sodium ethoxide or sodium isopropoxide. Both potassium *t*-butoxide or sodium in xylene caused a marked decrease in yield. This perhaps could be attributed to a greater ease of polymerization of

the  $\alpha$ - $\beta$  unsaturated ketone (resulting from elimination of trimethylamine from the Mannich methiodide in the presence of a stronger base). In the case of sodium in xylene the lack of homogeneity in the reaction mixture might also have its effect.

No positive correlation between yield and reaction time could be made. The results of such a series of reactions are given below.

#### Effect of Reaction Time on Yield

Time (hours)	Yield*
4.0	42%
4.5	32%
5.5	38%
5.75	41%
7.50	30%

\*Based upon the products isolated in the initial distillation.

A variation in the molar ratios of the reactants gave some improvement in yield. Initially, all the alkylations had been run with approximately a 0.1 to 0.2 mole excess of the acetoacetic ester and sodium per mole of the Mannich methiodide. A series of reactions were undertaken using ethyl  $\alpha$ -methyl acetoacetate to determine what effect changes in the molar ratios might have upon the yield.

## Effect of Excess Catalyst

Moles Methiodide	Moles Ester	Catalyst	Solvent	Yield
0.11	0.14	0.14	<u>1</u> -PrOH	41%
0.11	0.28	0.28	<u>1</u> -PrOH	59%
0.11	0.42	0.42	<u>1</u> -PrOH	36%
0.30	0.60	0.60	<u>1</u> -PrOH	55%

Such a change indeed affects the yield. It is possible that this increase in yield may be due to the compensation made for the water formed in the reaction by increasing the molar concentration of the sodio-acetoacetic ester. The cyclization of the initial alkylation product takes place by means of an aldol condensation in which water is split out to form the double bond. If this cyclization is rapid as compared to the alkylation there is a good possibility that the water formed may destroy a portion of the sodio-acetoacetic ester before it has a chance to react with the Mannich methiodide. If this is the case, making the molar ratio 2:1 always assures that there is sodio-acetoacetic ester present to react with the Mannich methiodide.

When it had been established that a molar ratio of 2:1 gave the optimum yield, the condensation was carried out on a larger scale using 2 moles of Mannich methiodide, 4 moles of ethyl  $\alpha$ -methyl acetoacetate and 4 moles of sodium. After isolation of the crude reaction mixture by addition of water, ether extraction, and drying, the

low-boiling components were removed by distillation under reduced pressure through a 30 cm silvered vacuum-jacketed Vigreux column. A fraction was removed which boiled at 47-50° at 2.2 to 2.6 mm pressure. This fraction was identified as unreacted ethyl  $\alpha$ -methyl acetoacetate.

The remainder of the crude ketone mixture was distilled twice through a Stedman column 12 inches in length and with a 9.5 mm internal diameter containing Stedman packing number 105. Two distillations through this column resulted in the separation of three main components.

The first fraction was identified as an unsaturated ketone and was collected from 63.5 to 65° at 0.34 mm pressure. The second fraction also was identified as an unsaturated ketone and distilled from 72.5 to 74.5° at 0.3 mm pressure. The third fraction was identified as a keto-ester and distilled from 98 to 102.5° at 0.35 mm pressure. Sixty grams of undistillable tar remained.

2,4-Dinitrophenylhydrazones were prepared for each fraction. Carbon and hydrogen analyses of the two unsaturated ketones and their 2,4-dinitrophenylhydrazones indicated the same empirical formulas even though their physical constants were different. These data are summarized in the following table.



	Ketone 1	Ketone 2
BP	63.5-65° at .34 mm	72.5-74.5° at .3 mm
$n_D^{25}$	1.4983	1.5131
$d_4^{25}$	0.9981	0.9962
% C	80.97	80.28
% H	9.73	9.68

Calcd. for  $C_{11}H_{16}O$ : C, 80.44%; H, 9.85%

2,4-dinitro-  
phenylhydrazone

MP	116-123° 151-156°	162-166° 173-178°
% C	59.21	59.83
% H	5.78	5.87

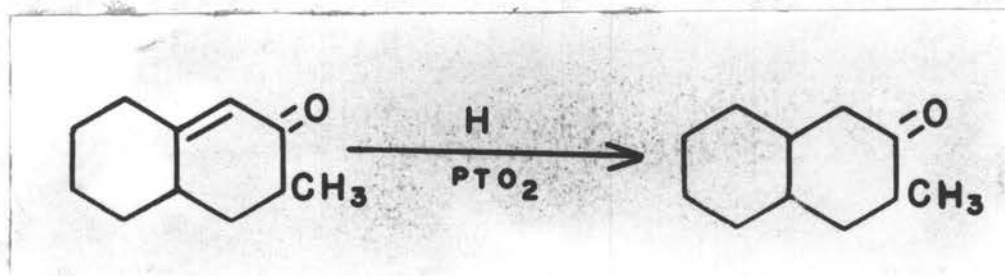
Calcd. for  $C_{17}H_{20}N_4O_4$ : C, 59.29%; H, 5.86%

The physical constants and analytical data led to the conclusion that ketone 1 and ketone 2 were isomeric. A 2-keto-3-methyl- $\Delta$ -octalin possesses two asymmetric carbon atoms which would lead to four possible isomers.

Although the keto-octalins proposed are previously unknown compounds, the 2-keto-3-methyl decalins were prepared and reported by Tsatsas (13, pp. 258-261). He reported the physical constants on both the cis and trans forms.

Such compounds could prove useful in ultimately helping to determine the structure of the two unsaturated ketones if the double bond present could be hydrogenated

and the properties of the resulting decalones compared to those reported. Hydrogenation of the double bond should take place according to the following equation.



In this manner it might be possible to identify our ketoctalins in terms of the known cis and trans decalones.

Each ketone was hydrogenated at room temperature and 2 to 3 atmospheres pressure using platinum oxide as the catalyst. Each was allowed to react until the amount of hydrogen taken up was that necessary to saturate the double bond. In the case of ketone 1, isolation and distillation of the product resulted in a clear slow-running oil possessing a strong terpene-like odor. This oil partially solidified to a wax-like low-melting solid. Its physical constants did not agree with those reported by Tsatsas for the methyl decalones.

The liquid separated from the solid material by filtration showed the presence of a carbonyl group by its

positive reaction with phenylhydrazine reagent. Active unsaturation in the solid was indicated by the rapid decolorization of bromine in carbon tetrachloride. The xanthate test for hydroxyl groups was positive.

This chemical evidence indicated strongly that in the solid material the carbonyl group had been reduced in preference to the normally more hydrogen-susceptible double bond.

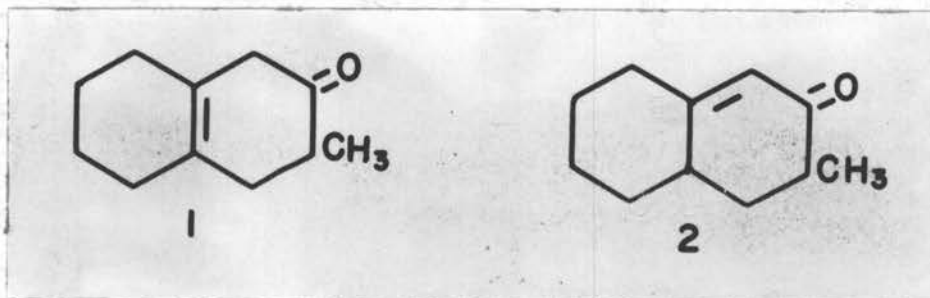
Two derivatives were formed from this hydrogenation product. An  $\alpha$ -naphthyl urethan was made of the solid alcohol while a 2,4-dinitrophenylhydrazone was made of the liquid ketone.

In the case of ketone 2, distillation of the hydrogenation product gave a liquid whose physical constants compared favorably with those reported for the methyl decalones. No positive xanthate test for a hydroxyl group was obtained but a positive test for a carbonyl group was obtained with phenylhydrazine reagent. A very small amount of bromine in carbon tetrachloride was decolorized but not enough to indicate a large amount of unsaturation. A 2,4-dinitrophenylhydrazone was prepared.

The evidence presented so far has shown that two ketones were isolated, each contaminated with a slight amount of the other. These ketones differed in physical constants but possessed the same empirical formulas. Upon

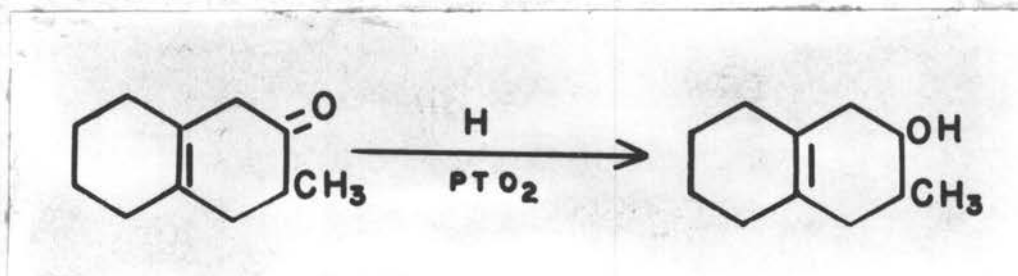


hydrogenation, one ketone gave an unsaturated alcohol while the other gave a saturated ketone. In view of such evidence the following structures were postulated.

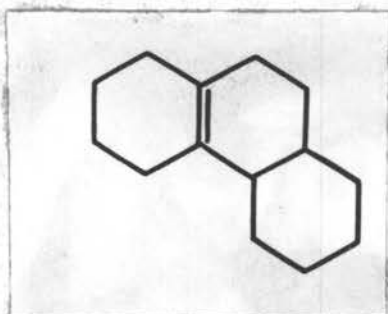


Both of these ketones have the empirical formula  $C_{11}H_{16}O$  but they would possess different physical properties.

Hydrogenation of the double bond produced strong evidence which aided in assigning a specific structure to each compound. In the case of compound 1, the reaction was postulated to go as follows.

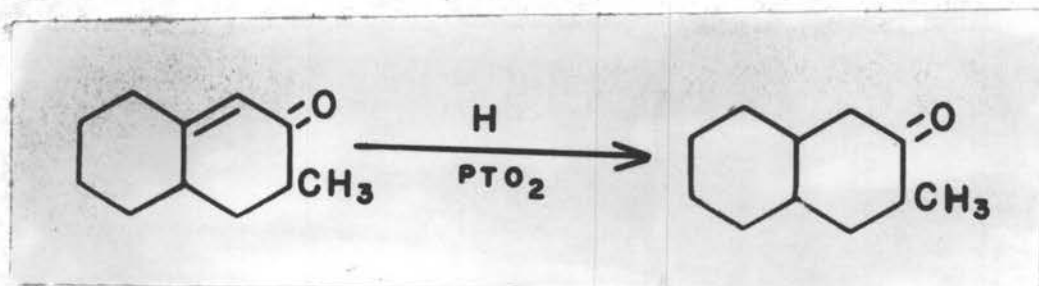


The location of this double bond was based upon the fact that the carbonyl was reduced in preference to the double bond. This could only mean that the ability of the double bond in this compound to take up hydrogen had been curtailed markedly. A double bond between the rings is the logical answer inasmuch as it is well known that a double bond common to two rings may be very resistant to hydrogenation. For example, a temperature of  $250^{\circ}$  was required for the complete hydrogenation of dodecahydrophenanthrene (3,p.1502).



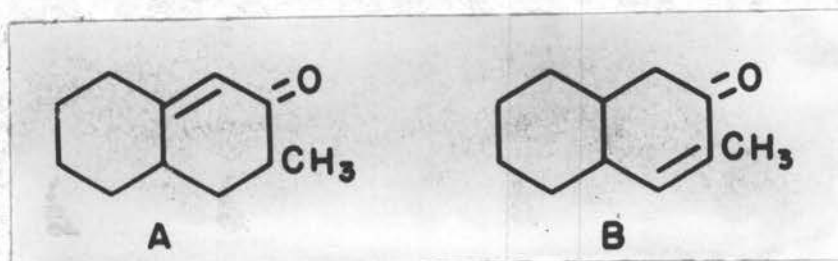
If such is the case, the double bond could not lie in any other position and still exhibit such a resistance to hydrogenation.

In ketone 2, the reaction would be



In such a compound, the double bond would preferentially take up hydrogen before the carbonyl group so that a saturated ketone and not an unsaturated alcohol would be obtained. That the double bond is conjugated is shown in a most striking manner by the location of the carbonyl absorption band in the infrared spectrum of the compound. This will be explained more fully in another section.

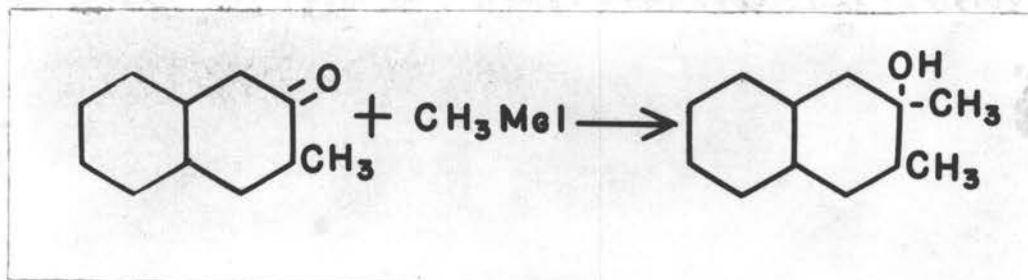
Even with the knowledge that the double bond is conjugated there are still two structural possibilities.



Although the evidence available does not allow one to differentiate between the two it does seem unlikely, in view of the mode of formation of the second ring and the subsequent dehydration, that the double bond initially formed to give compound A would then migrate to form compound B.

Further evidence toward identification of the structure of the 2-hydroxy-3-methyl- $\Delta^{9:10}$ -octalin was obtained by subjecting it to dehydration and dehydrogenation. This was effected by mixing the alcohol with a calculated amount of sulfur and gradually heating to a temperature of 250°. The distillate was identified as 2-methylnaphthalene by the melting point of its picrate. There was a 10° depression of the melting point when this picrate was mixed with pure picric acid.

The 2-keto-3-methyl decalin was reacted with methylmagnesium iodide according to the following equation.





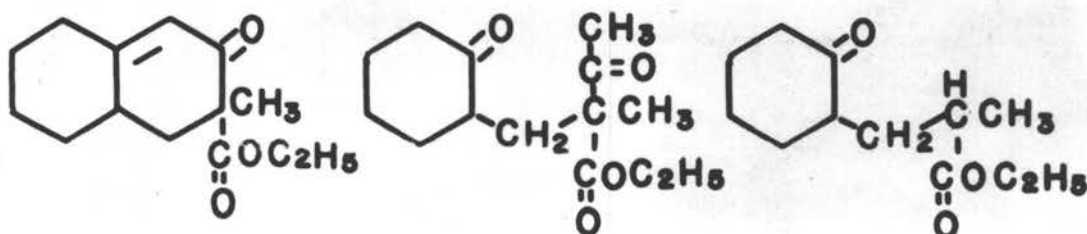
The resulting product was mixed with a calculated amount of sulfur and gradually heated to  $250^{\circ}$ . After two hours crystals of 2,3-dimethylnaphthalene sublimed onto the cold finger used as a condenser. This was identified by means of its melting point and that of its picrate. A melting point of a mixture of the compound and an authentic sample of 2,3-dimethylnaphthalene gave no depression in melting point.

The keto-ester previously designated as the third component could not be identified completely, although some evidence was obtained on which a possible structure could be postulated.

An analysis for carbon and hydrogen gave 71.94% C and 8.81% H.

The 2,4-dinitrophenylhydrazone gave 55.88% C and 5.67% H.

A saponification equivalent of 265 was obtained. Several possible structures might be postulated.



% C	71.2%	66.2%	67.8%
% H	8.5%	8.7%	9.4%
Sap. Eq.	236	254	212

2,4-dinitrophenylhydrazone

% C	57.8%	50.9%	55.2%
% H	5.8%	4.9%	6.2%

An attempt was made to separate the ester from the ketone contaminant by allowing it to stand in 10% alcoholic potassium hydroxide for several hours. The white insoluble salt that settled out was used in an effort to further characterize the compound.

When mixed with 2,4-dinitrophenylhydrazone reagent, a small amount of golden yellow solid was formed which could not be recrystallized. The hot alcoholic solution gradually turned to a lighter yellow color and upon addition of water gave residual amounts of a light yellow solid.

The original ester was also reacted with both aniline and 4-bromoaniline to see if the corresponding anilide would form. Oils were obtained which could not be made to form crystalline derivatives.

No results were obtained in attempts to form the S-benzylthiuronium salt of the potassium salt obtained from the saponification.

Very valuable confirmatory evidence for the structures postulated was obtained from the infrared spectra of

the compounds under investigation. Quantitative studies were not attempted but, rather, efforts were made mainly to locate prominent absorption bands and determine the functional groups characteristic of these bands.

#### Original Ketones

##### 2-keto-3-methyl- $\Delta^9$ -octalin (Figure 3)

Band (cm <sup>-1</sup> )	Strength	Functional Group Assignment
2915	very strong	C-H stretching
1712	very strong	C=O in an unconjugated ketone
1676	slight inflection	C=O in a conjugated ketone
1630	very weak	unconjugated C=C
1447	strong	-CH <sub>2</sub> - deformation

This spectrum was interpreted to mean that the main product was a ketone containing an unconjugated double bond. There was slight contamination by a conjugated ketone. Incomplete separation of the two isomers by the fractional distillation would account for this very nicely.

It might be noted at this time that chemical evidence confirmed the presence of a double bond in this compound and showed that it was quite inert to hydrogenation. The carbonyl absorption band in the infrared spectrum is located exactly where an unconjugated carbonyl should be. This combination of evidence can lead only to the proposed structure where the double bond lies between the rings.



2-keto-3-methyl- $\Delta^{11}$ -octalin (Figure 3)

Band ( $\text{cm}^{-1}$ )	Strength	Functional Group Assignment
2915	very strong	C-H stretching
1668	very strong	C=O in conjugated ketone
1708	slight inflection	C=O in unconjugated ketone
1618	strong	conjugated C=C
1419	strong	-CH <sub>2</sub> - deformation

The main product was a conjugated ketone. The slight inflection indicates a very slight contamination by an unconjugated ketone. This indicates that the distillation did not completely separate the two isomers.

From the relative strength of the absorption bands between the main component and the contaminant it seems reasonable to assume that the main component was obtained in a fairly high state of purity.

The most important thing to note here is to compare the position of this carbonyl band ( $1668 \text{ cm}^{-1}$ ) to that of the other ketone ( $1712 \text{ cm}^{-1}$ ). There is a shift in this band of  $44 \text{ cm}^{-1}$  towards a lower frequency and it lies right in the region where absorption by a conjugated ketone should lie. This clear-cut shift presents very favorable evidence for the two structures postulated for the unsaturated ketones.

## Hydrogenated Compounds

2-hydroxy-3-methyl- $\Delta^9$ -octalin (Figure 4)

Band ( $\text{cm}^{-1}$ )	Strength	Functional Group Assignment
3280	strong	O-H stretching
2880	very strong	C-H stretching
1700	weak	C=O in an unconjugated ketone
1653	weak	unconjugated C=C
1437	strong	-CH <sub>2</sub> - deformation

These spectral data show very well that the carbonyl has been reduced in preference to the double bond. The strongly absorbing carbonyl in the  $\Delta^9$ -ketone has disappeared and a very strong hydroxyl band appears at  $3280 \text{ cm}^{-1}$ . The unconjugated double bond shows up as a weak band in its normal position.

The conjugated ketone present as a contaminant has been hydrogenated to give a saturated ketone. This is shown by the weak band at  $1700 \text{ cm}^{-1}$ . Prior to hydrogenation this carbonyl group absorbed at  $1676 \text{ cm}^{-1}$ . Such a shift clearly shows the course of the hydrogenation.

2-keto-3-methyldecalin (Figure 4)

Band ( $\text{cm}^{-1}$ )	Strength	Functional Group Assignment
3440	very weak	O-H stretching
2880	very strong	C-H stretching
1704	very strong	C=O in unconjugated ketone

Band ( $\text{cm}^{-1}$ )	Strength	Functional Group Assignment
1660	weak	C=O in conjugated ketone
1440	strong	-CH <sub>2</sub> - deformation

This infrared evidence indicated that normal hydrogenation of the conjugated double bond predominated. That the entire amount of  $\Delta^9$ -ketone was not hydrogenated is shown by the weak band at  $1660\text{ cm}^{-1}$  indicating the presence of a small amount of unsaturated conjugated ketone. Some contamination by the unsaturated alcohol is indicated by the weak O-H band at  $3440\text{ cm}^{-1}$ .

High Boiling Fraction from Distillation  
Through Stedman Column (Figure 5)

Band ( $\text{cm}^{-1}$ )	Strength	Functional Group Assignment
2915	very strong	C-H stretching
1736	very strong	C=O in unconjugated ester
1720	very strong	C=O in unconjugated ketone
1672	strong	C=O in conjugated ketone
1608	medium	conjugated C=C

Based on the limited chemical evidence available and the infrared spectrum this compound seems to be a keto-ester contaminated by a conjugated ketone of some sort. It seems unlikely that the impurity is any of the

$\Delta^{119}$ -octalin. The difference in the boiling points of the two is sufficient to permit separation by distillation through the Stedman column. Conceivably it might be a dimer or trimer of the unsaturated ketone formed by elimination of trimethylamine from the Mannich methiodide.

2-Keto-3-ethyl-octalin and 2-keto-3-propyl-octalin (Fig. 5)

Small portions of the original spectra of these compounds are included for comparison to the methyl compound. These curves show the regions of carbonyl absorption. Two broad bands about 30 to 40  $\text{cm}^{-1}$  apart are noted. These compounds were not distilled through the precise fractionation equipment and therefore, if the pattern set by the methyl ketooctalin is followed, mixtures of isomers should be obtained in these two cases. The presence of absorption bands in both the conjugated and unconjugated ketone regions give evidence that such a mixture was obtained.

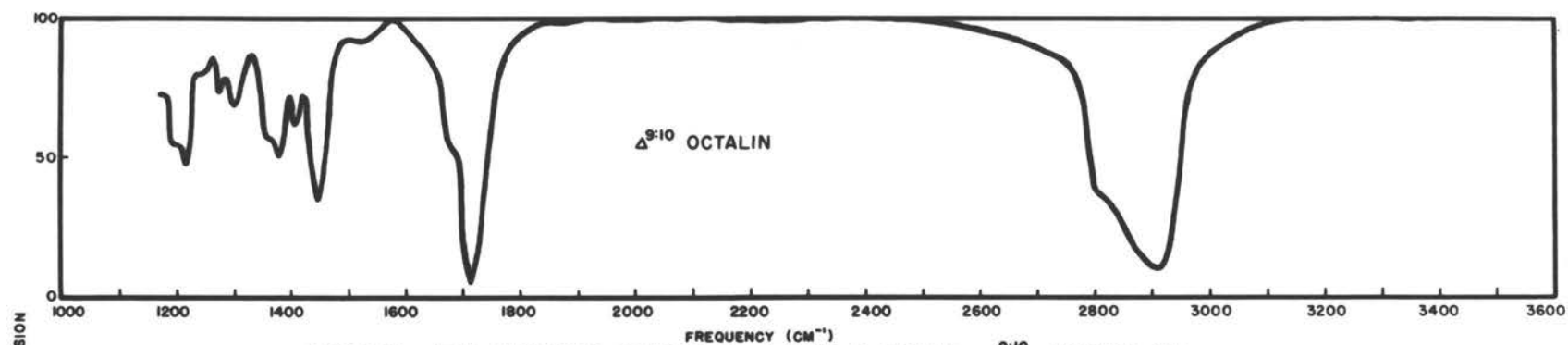
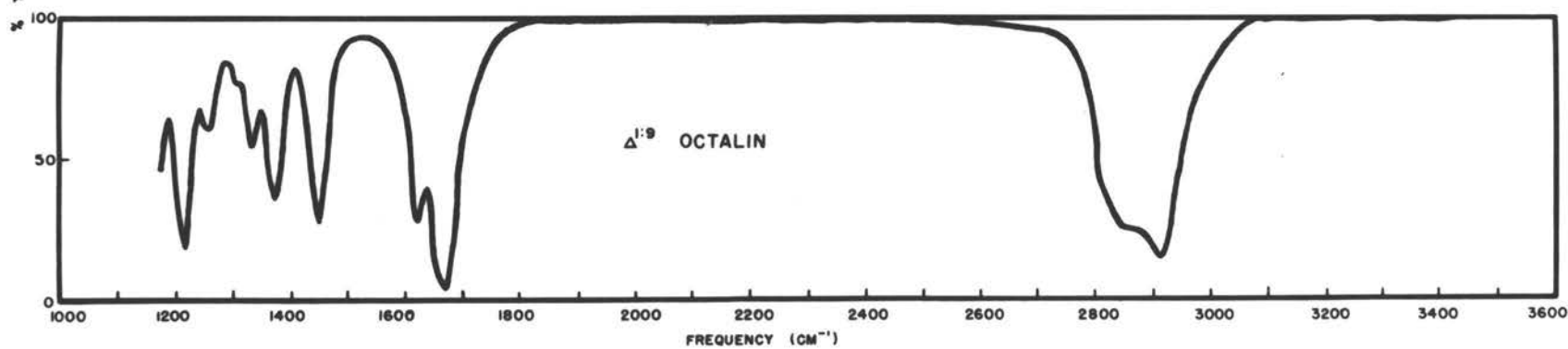


FIGURE 3. THE INFRARED SPECTRA OF 2-KETO-3-METHYL  $\Delta^{9:10}$  OCTALIN AND  
2-KETO-3-METHYL  $\Delta^{1:9}$  OCTALIN



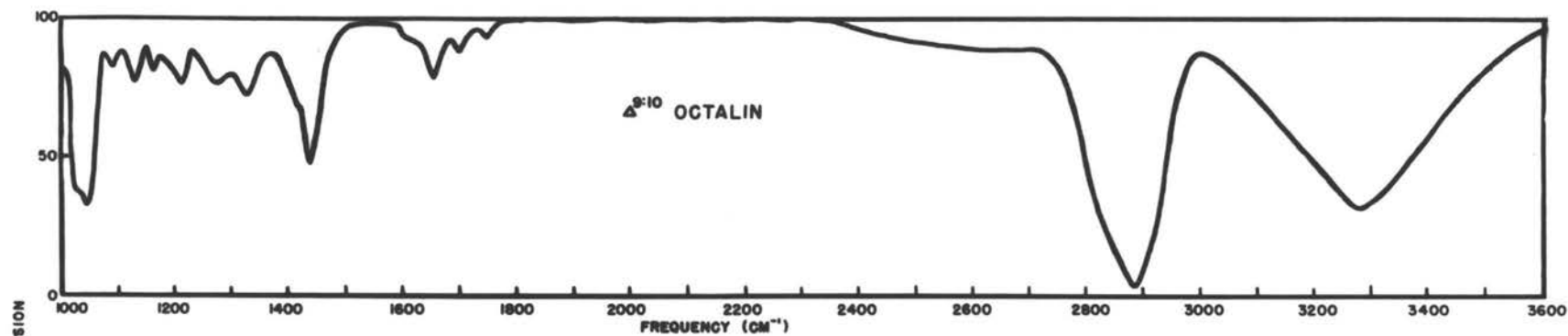
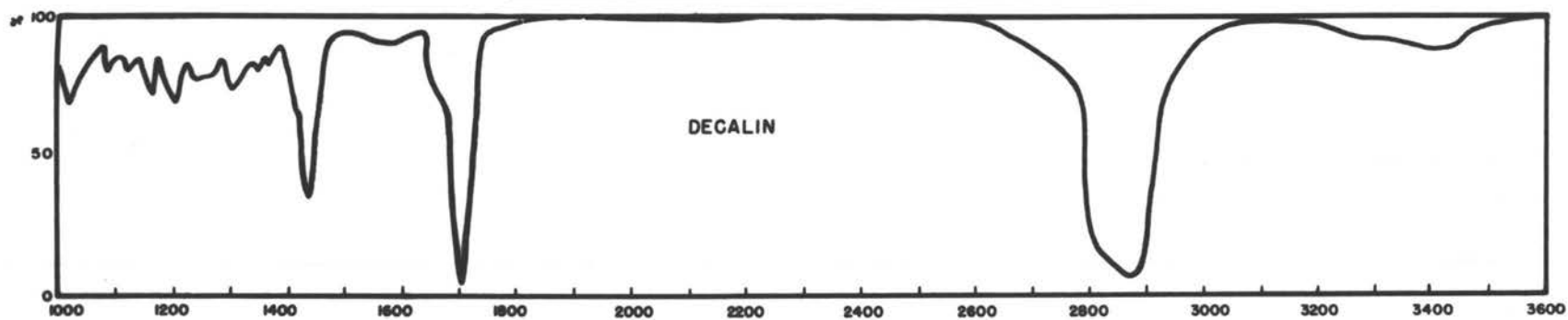


FIGURE 4 . THE INFRARED SPECTRA OF 2-HYDROXY-3-METHYL  $\Delta^{9:10}$  OCTALIN AND  
2-KETO-3-METHYL DECALIN





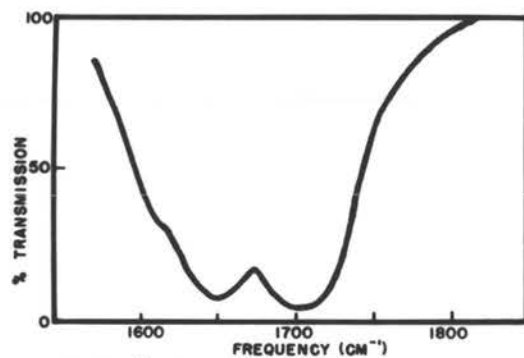


FIGURE 5. THE INFRARED SPECTRUM OF A MIXTURE OF 2-KETO-3-METHYL  $\Delta^{1:9}$  OCTALIN AND 2-KETO-3-ETHYL  $\Delta^{9:10}$  OCTALIN

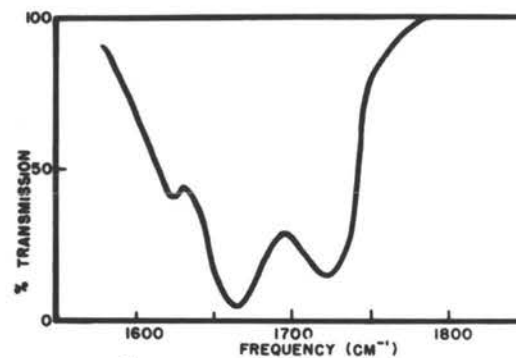


FIGURE 5. THE INFRARED SPECTRUM OF A MIXTURE OF 2-KETO-3-PROPYL  $\Delta^{1:9}$  OCTALIN AND 2-KETO-3-PROPYL  $\Delta^{9:10}$  OCTALIN

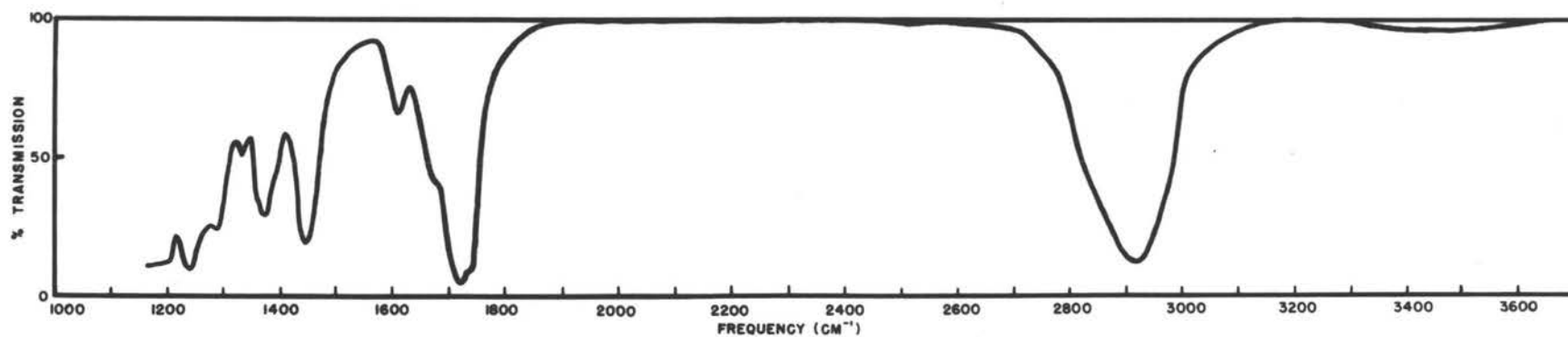


FIGURE 5. THE INFRARED SPECTRUM OF IMPURE KETO ESTER



## EXPERIMENTAL

2-Dimethylaminomethylcyclohexanone hydrochloride

The method used for preparing this compound was based on that described by Mannich and Braun (8,p.1875).

Dimethylamine hydrochloride (242 g., 3 moles) and 37% formalin (244 g., 3 moles) were added to cyclohexanone (1960 g., 20 moles) in a five-liter three-necked flask equipped with a stirring device and a reflux condenser. After heating for 45 to 60 minutes at 90° the solution was allowed to cool. The organic layer was separated and washed once with 200 ml. of water. These washings were combined with the aqueous layer and the entire solution extracted three times with 100 ml. portions of ether in order to remove any excess cyclohexanone. Removal of the water by evaporation under reduced pressure left the crude Mannich base hydrochloride. Yield - 430 g. (75%).

In subsequent preparations of this compound complete isolation was not carried out. After removal of about one-half of the water by evaporation, the concentrated aqueous solution was used as such in preparing the quaternary ammonium salt.

2-Dimethylaminomethylcyclohexanone methiodide (Mannich methiodide)

An aqueous solution of the Mannich base

hydrochloride was made alkaline with 30% NaOH and the free Mannich base extracted with ether. After thorough drying over solid KOH the free base in ether was treated with an equal weight of methyl iodide in dry ether. Care was taken to eliminate moisture by forming the methiodide in a large suction flask. A drying tube was fastened to the side arm while the methyl iodide was added through a moisture-protected dropping funnel. The methyl iodide was added at such a rate that the temperature remained below 30°. Cooling was maintained by immersing the suction flask in an ice bath.

The Mannich methiodide separated as a creamy white solid. The mixture was left in the ice bath for 30 minutes, removed and allowed to stand at room temperature for a few hours. Excess methyl iodide and ether were removed by the placing of the product in a vacuum oven and heating to 30°.

Recrystallization from a mixture of alcohol and ether led to excessive decomposition of the product. Therefore, the methiodide was used in subsequent reactions without recrystallization.

#### Ethyl $\alpha$ -alkyl acetoacetate

The methyl-, ethyl-, and propyl-substituted acetoacetic esters were prepared by the general alkylation reaction which consisted of the condensation of acetoacetic

ester and the appropriate alkyl halide using sodium ethoxide as a catalyst. The general procedure given in Organic Syntheses (4, pp. 248-250) was followed exactly except in the case of the  $\alpha$ -methyl compound in which anhydrous benzene was used as the solvent. The reason for this modification has been explained under "Discussion of Results".

2-Keto-3-methyl- $\Delta^{1:9}$ -octalin

Method A. A twelve-liter three-necked flask equipped with a paddle stirrer and a reflux condenser was charged with five liters of anhydrous ethanol. 92 g. (4 atoms) of metallic sodium was added at a rate which would maintain a constant reflux. After the sodium had reacted completely, 576 g. (4 moles) of ethyl  $\alpha$ -methyl acetoacetate was added dropwise over a period of two hours. At this stage the sodio-acetoacetic ester exceeded its solubility in the solvent and the entire solution became a thick pasty mass. After cooling, a slurry of 591 g. (2 moles) of Mannich methiodide in two liters of anhydrous ethanol was added slowly over a two hour period. Within a few minutes after the slurry was initially introduced the reaction mixture gradually liquified and changed in color to a light tan. The odor of trimethylamine was noticeable at the top of the reflux condenser. Stirring at room temperature was continued for 57.5 hours after the methiodide had been added.

At the end of the reaction time about one-half of the alcohol was removed under reduced pressure and an equal volume of water added to the crude concentrated product. This solution was extracted continuously for 24 hours with ether followed by drying of the extracts over anhydrous sodium sulfate. After removal of the ether by distillation anhydrous potassium carbonate was used for a second drying of the product.

The crude concentrate was stripped of unreacted ethyl  $\alpha$ -methyl acetoacetate by distillation under reduced pressure through a 30 cm silvered vacuum-jacketed Vigreux column. The remaining products were fractionated at a pressure of 0.3 to 0.8 mm using a 12-inch Stedman column with a 9.5 mm internal diameter and containing Stedman packing number 105.

The following main fractions were separated from the mixture: 2-keto-3-methyl- $\Delta^{1'9}$ -octalin, 2-keto-3-methyl- $\Delta^{9'10}$ -octalin, and an unknown ester contaminated with some high boiling carbonyl compound. The physical and analytical data for these compounds have been listed under "Discussion of Results".

Method B, by which the ethyl and propyl keto-octalins were prepared, differed only in the scale of the reaction and the time and temperature of heating. Normally the reaction time ran from three to seven hours and the

temperature maintained was that necessary to cause a mild reflux of the solvent. Several methyl ketooctalin runs were made by this procedure.

2-Hydroxy-3-methyl- $\Delta^{9:10}$ -octalin

11.2 g. (0.69 mole) of 2-keto-3-methyl- -octalin were placed in 75 ml. of absolute alcohol and mixed with 0.25 g. of platinum oxide. This solution was hydrogenated on a Farr low-pressure hydrogenation apparatus at about 2.5 atmospheres. The calculated hydrogen uptake was approximately 5.5 pounds per square inch. The actual hydrogen uptake was 6 pounds per square inch.

The product was isolated by first filtering off the catalyst and evaporating the solvent. The crude product was distilled under reduced pressure through a short Claisen head.

- |   |                           |                     |
|---|---------------------------|---------------------|
| 1 | 88-91.5° at 1.4 to 1.5 mm | $n_D^{27}$ , 1.5025 |
| 2 | 91.5-93° at 1.4 to 1.5 mm | $n_D^{27}$ , 1.5060 |

After standing for several hours the oily distillate of fraction two partially solidified. A solid also separated from fraction one upon cooling in an ice box. These solids were separated by filtration and aspirated for several hours to remove as much of the mother liquor as possible.

This solid alcohol (subsequently identified as 2-hydroxy-3-methyl- $\Delta^{9:10}$ -octalin) rapidly decolorized a



solution of bromine in carbon tetrachloride indicating active unsaturation. A positive xanthate test for a hydroxyl group was obtained.

Melting Point 40-45°

A m-nitrophenylurethan was prepared.

Melting Point 150-154° C, 64.56%; H, 6.92%

Calcd. for  $C_{18}H_{22}N_2O_4$ : C, 65.44%; H, 6.72%

A 2,4-dinitrophenylhydrazone was prepared from the mother liquor.

Softened at 104°, melted at 115-122°

C, 58.35%; H, 6.37%

Calcd. for  $C_{17}H_{22}N_4O_4$ : C, 58.94%; H, 6.43%

#### 2-Keto-3-methyldecalin

8.2 g. (.05 mole) of 2-keto-3-methyl- $\Delta^{11,9}$ -octalin was placed in 50 ml. of absolute alcohol and mixed with 0.25 g. of platinum oxide. This solution was hydrogenated on the Parr apparatus mentioned previously at about 2.5 atmospheres. The calculated hydrogen uptake was approximately 4 pounds per square inch. The actual hydrogen uptake was 4 pounds per square inch.

The product was isolated in the same manner as the 2-hydroxy-3-methyl- $\Delta^{9,10}$ -octalin.

- |   |                         |                     |
|---|-------------------------|---------------------|
| 1 | 81-83° at 1.5 to 1.6 mm | $n_D^{26}$ , -      |
| 2 | 83-85° at 1.5 to 1.6 mm | $n_D^{26}$ , 1.4840 |

3 85-89° at 1.5 to 1.6 mm  $n_D^{26}$ , 1.4858

4 89-94° at 1.5 to 1.6 mm  $n_D^{26}$ , 1.4910

A positive test for a carbonyl group was obtained with phenylhydrazine reagent. The xanthate test for the hydroxyl group was negative. A very small amount of bromine in carbon tetrachloride was decolorized.

Fraction 2 C, 78.97%; H, 10.54%

Calcd. for  $C_{11}H_{18}O$ : C, 79.55%; H, 10.82%

A 2,4-dinitrophenylhydrazone was prepared.

Softened at 104°, melted at 130-140°

C, 58.31%; H, 6.39%

Calcd. for  $C_{17}H_{22}N_4O_4$ : C, 58.94%; H, 6.43%

#### 2-Hydroxy-2,3-dimethyldecalin

In the usual manner a Grignard reagent was prepared from 1.2 g. (.05 mole) of magnesium turnings and 7.8 g. (.05 mole) of methyl iodide in dry ether. After complete reaction of the magnesium, 2 g. (.012 mole) of 2-keto-3-methyldecalin in dry ether was added dropwise to the Grignard reagent. After heating for four hours under mild reflux the intermediate was decomposed by pouring onto an iced solution of 10% ammonium chloride. The organic layer was separated and aqueous layer extracted twice with ether. These extracts were added to the main ether solution and both were shaken with a dilute solution of sodium thiosulfate to remove the small amount of iodine present. The

ether extracts were dried over anhydrous calcium and the crude product obtained by evaporation of the ether.

Dehydrogenation and dehydration of 2-hydroxy-2,3-dimethyl-decalin

Two-tenths of a gram of the crude alcohol was mixed with 0.1 g. of sulfur and this mixture was gradually heated to 250°. After two hours crystals of 2,3-dimethylnaphthalene sublimed on the cold finger used as a condenser. The melting point, after recrystallization from aqueous alcohol, was 101-102°. The melting point given in the literature is 104-104.5°.

No depression in the melting point was noted when the sample was mixed with crystals of authentic 2,3-dimethylnaphthalene.

Dehydrogenation and dehydration of 2-hydroxy-3-methyl-octalin

Two-tenths of a gram of 2-hydroxy-3-methyl-octalin was mixed with 0.1 g. of sulfur and the mixture gradually heated to 250°. After two hours several drops of the distillate were collected and made into the picrate by mixing this distillate with a concentrated alcoholic solution of picric acid. Upon cooling long yellow needles separated. The melting point, after recrystallization from ethanol, was 113-116°. The melting point given in the literature is 116°.

When these long needles were mixed with pure picric acid the melting point depression was  $9.5^{\circ}$ .

Potassium salt of unknown ester

Five-tenths of a gram of the unknown ester was placed in 15 ml. of 10% potassium hydroxide. After standing at room temperature for several hours the white solid which formed was filtered, washed with alcohol and ether and dried.

Attempted formation of 2,4-dinitrophenylhydrazone

The procedure given in Shriner and Fuson (11,p.171) was followed. A golden yellow precipitate was obtained which, when taken up in hot alcohol and diluted with water, could not be recrystallized. Only a small amount of light yellow residual material precipitated.

Attempted formation of the 4-bromoanilide

Five-tenths of a gram of 4-bromoaniline and 0.7 g. of the unknown ester were heated in a sealed tube for six hours at  $150^{\circ}$ . The dark oil was taken up in hot alcohol, decolorized with Norite, and water added to first sign of opalescence. Upon cooling a dark heavy oil settled out.

Benzene and ligroin were used but no positive results were obtained.

The use of aniline in the place of 4-bromoaniline gave a similar dark oil.

Attempted formation of the S-benzylthiuronium salt

An aqueous solution of 0.2 g. of the potassium salt formed by the saponification and 0.2 g. of S-benzylthiuronium chloride were mixed and cooled. Only residual amounts of an amorphous white solid formed.



## SUMMARY

1. The alkylation of substituted acetoacetic esters by the  $\alpha, \beta$ -unsaturated ketone formed from 2-dimethylaminomethylcyclohexanone methiodide was investigated.

2. Investigations and research showed sodium ethoxide or sodium isopropoxide to be the best basic catalyst for the reaction. The length of the time of the reaction did not seem to affect the yield but the molar ratio of the reagents did. It was found that the best results were obtained when two moles each of sodium and the appropriate acetoacetic ester were used per mole of the Mannich methiodide.

3. The cyclized product formed from the initially alkylated substituted ester was found to dehydrate in two directions and to produce isomeric compounds with double bonds in different positions in the ring.

4. A compound previously reported as a new compound turned out to be a mixture of the two isomers, 2-keto-3-methyl- $\Delta^{1:9}$ -octalin and 2-keto-3-methyl- $\Delta^{9:10}$ -octalin (7,p.19).

The isomeric mixture of 2-keto-3-ethyl-octalins and the isomeric mixture of 2-keto-3-propyl-octalins were synthesized. There is no evidence in the literature of the previous existence of these compounds.

2-Hydroxy-3-methyl- $\Delta^{9:10}$ -octalin, produced by hydrogenation of 2-keto-3-methyl- $\Delta^{9:10}$ -octalin was reported for the first time.

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