EXPERIMENTS TOWARD THE SYNTHESIS OF SOME SUBSTITUTED BICYCLO [4.3.0] NONAN-6-ONES

by 6408

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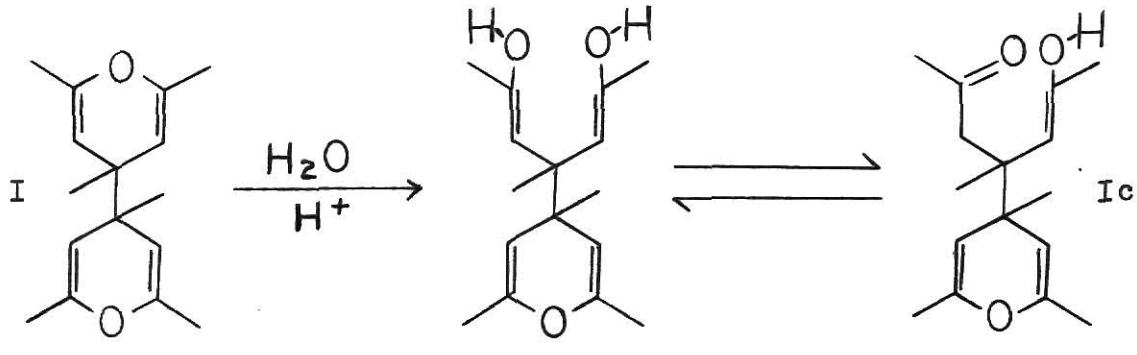
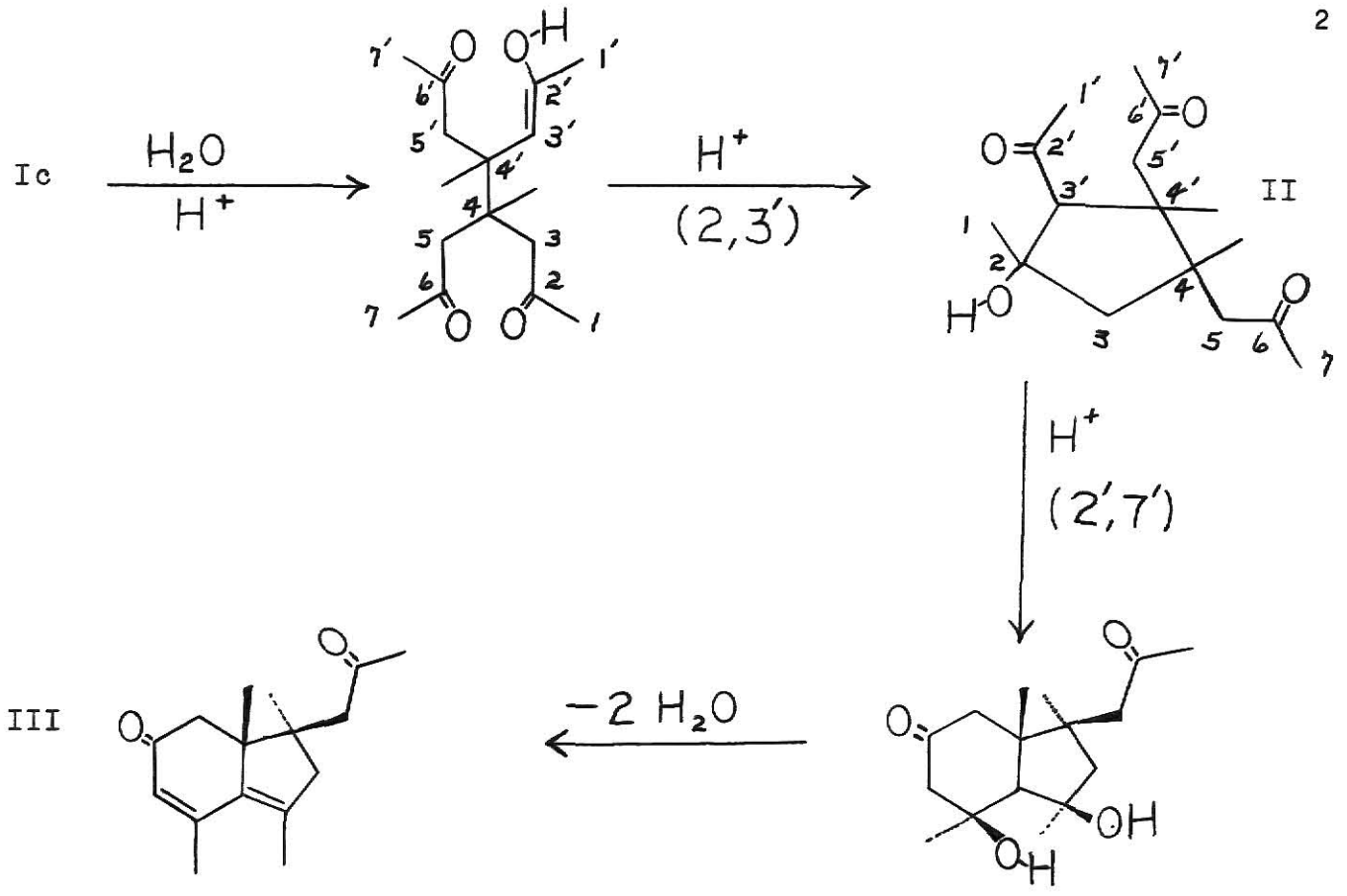
Introduction

The compound 2,2',4,4',6,6'-hexamethyl-4,4'-bi-4H-pyran (I) has been synthesized.[1] Its successive hydrolyses can theoretically give rise to a very large number of compounds. However, only a comparatively few hydrolysis products, some of which have been shown to be precursors of others, have in fact been isolated.[1-2] Considerable difficulty is encountered in deducing the structures of these compounds because of the existence of such a large number of possible reaction pathways. Therefore, it would be highly desirable to synthesize one of the bipyran (I) hydrolysis products by an independent route in order to confirm the product's presumed structure and thus to provide a firmer basis for deducing the structures of other bipyran hydrolysis products which have been related to the synthesized compound by stepwise hydrolyses. It is toward this goal that the work reported in this paper was directed.

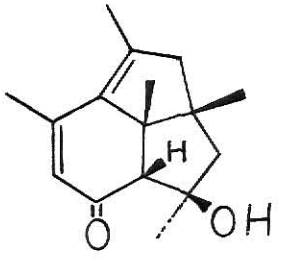
The compound chosen for synthesis was 1β-acetonyl-1α,3,4,7aβ-tetramethyl-2,7-dihydro-6-indanone (III). It presumably arises from the acid hydrolysis of bipyran in the following manner:



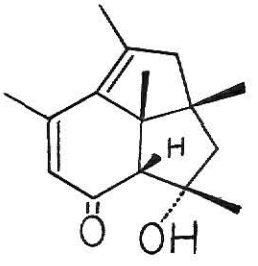


Compound II has been postulated to be an early precursor of III.[2]

If the stereochemistry is appropriate, the final hydrolysis above will be accompanied by ring closure of II to form other products such as IV and V, which have been isolated,[2] and which presumably have the structures shown below:



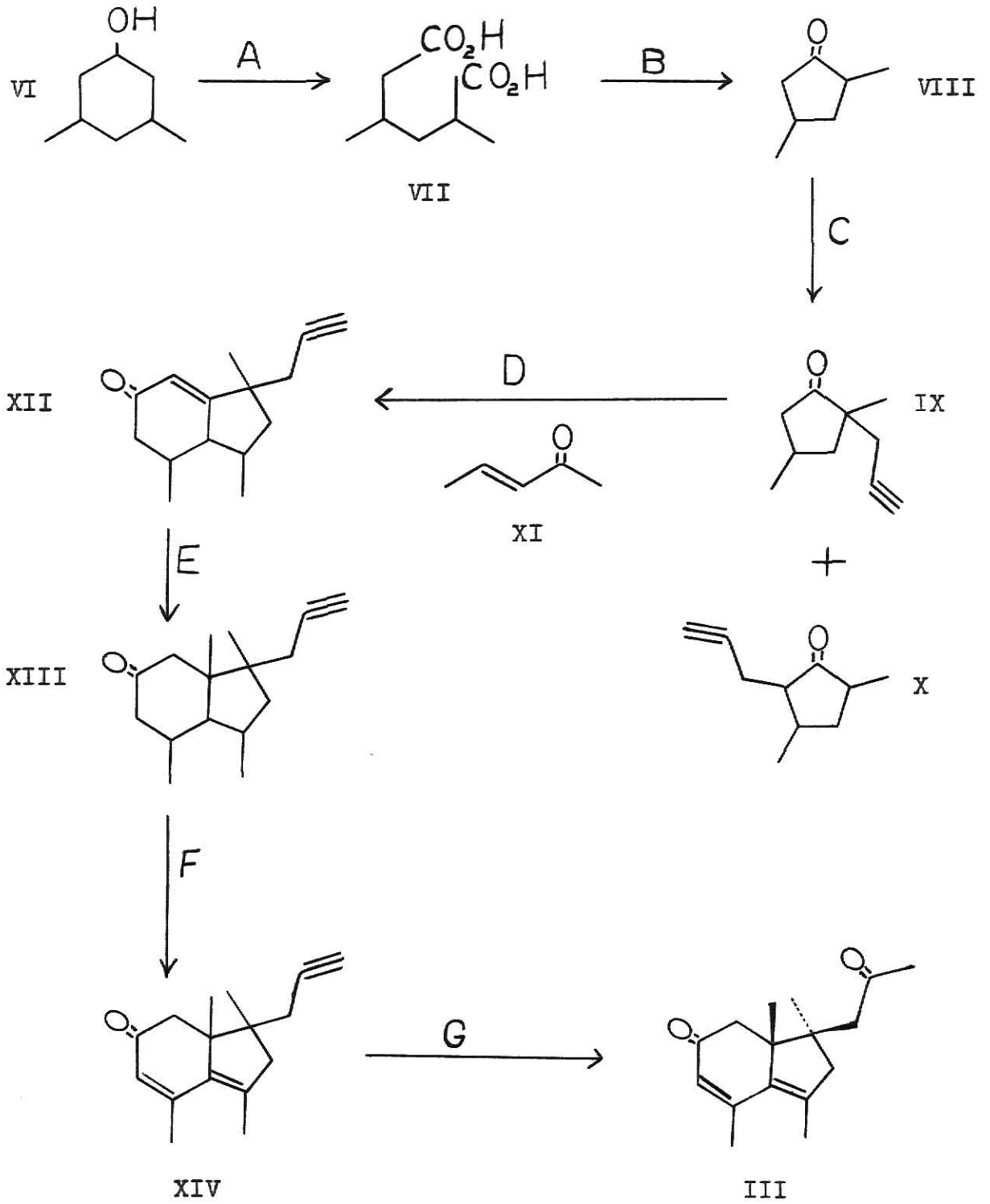
IV



V

Proposed Synthesis

The proposed synthesis of III is as follows:



Stereochemistry

Starting material VI exists as a mixture of three isomers: two meso (cis) forms which can be represented as having axial, axial, axial and equatorial, axial, axial configurations, and a set of d,l enantiomers. Oxidation of either meso form of VI yields a racemic set of erythro enantiomers of VII, and oxidation of the d or l enantiomers of VI yields + or - threo acid VII. Thus VII can exist as two geometrical isomers. (Note that all of the geometrical isomers throughout the proposed synthetic sequence, with the exception of the two meso forms of VI, can exist as racemic mixtures of enantiomers.) The erythro acid VII gives rise to erythro ketone VIII (cis), and the threo acid VII produces threo ketone VIII (trans). Thus, overall, cis (meso) VI gives rise to cis (erythro) VIII, and trans (d,l) VI gives rise to trans (threo) VIII.

Propargylation (Procedure C) of VIII produces both 2,2,4-/ and 2,3,5-trialkyl compounds IX and X, respectively. The desired compound, IX, consists of cis and trans isomers, but X can exist as four geometrical isomers. Cyclized product XII has four geometrical isomers, and the addition of an optically active bridgehead carbon atom in the 7a position of XIII gives rise to a total of eight geometrical isomers. However, dehydrogenation of the rings at the 3,4a and 4,5 positions removes the asymmetry at these two sites, so compound XIV exists as only two geometrical isomers. Likewise, the final product, III, exists as two geometrical isomers.

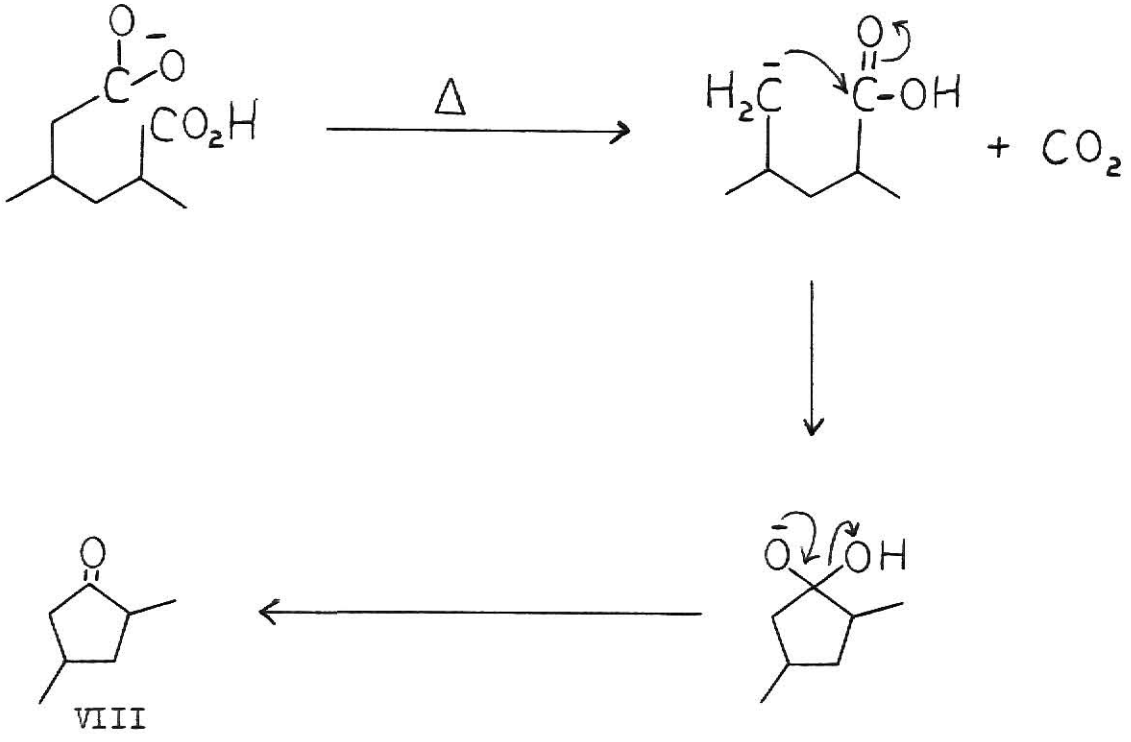
It would be desirable to separate the geometrical isomers of the earliest possible intermediate in the synthesis. This is compound IX, since the extremely basic conditions employed in Procedure C permit stereochemical equilibration of the methyl groups. However, attempts to separate the isomers of

IX by gas-liquid chromatography (GLC) were unsuccessful, and separation was effected only between IX and X. The next most convenient place in the synthetic sequence to attempt a separation of isomers is after Procedure F, when again only two geometrical isomers of the intermediate product (XIV) exist.

Discussion of the Synthetic Sequence

Procedure A is a straightforward oxidation of a cyclic alcohol to a dicarboxylic acid. Nitric acid was used as the oxidizing agent.

Procedure B is a cyclization of the dicarboxylic acid with decarboxylation to form a cyclic ketone. Potassium fluoride was the catalyst employed. The mechanism of this reaction, House [3] suggests, involves the decarboxylation of the salt to form a carbanion which is preferentially cyclized to form the enolate.



VIII

It was observed by House[3] and also by us that the yield of cyclic ketone increases and the amount of polymeric residue correspondingly decreases as the relative amount of KF is decreased. This was attributed to the formation of the dicarboxylate ion, which cannot decarboxylate with cyclization.

Procedure C is the propargylation of the cyclic ketone in the α position. The simplest way to effect this is to form the enolate of ketone VIII by reaction with a strong base, and then to react this with the alkyl halide. However, it is seen that alkylation can occur at either of two positions to the carbonyl group. Early work on the alkylation of VIII[4] using NaH and CH_3I yielded almost exclusively the 1,3,4-trimethyl compound, which is analogous to ketone X, rather than the 1,1,4-trimethyl compound corresponding to the desired ketone IX.

The equilibrium between the two possible enolates of some analogous alkylated cycloalkanones has been studied[5]. It was found that changing the cation of the enolate from lithium to either sodium or potassium favors the formation of the more highly substituted enolate. It was also found that if enolates are generated in the presence of the alkylating agent, 1,3-alkylation is favored greatly over 1,1-alkylation. Our synthesis was designed accordingly[6].

An increase in solvent polarity, in going from 1,2-dimethoxyethane (DME) to dimethyl sulfoxide (DMSO), was found to increase the relative amount of the more highly substituted enolate somewhat[5]. Dimethyl sulfoxide was accordingly tried as a solvent in our synthesis, but was found to be unsatisfactory because of its reaction with the alkylating agent to form the salt XV.

$$\left[C_3 H_3 S (CH_3)_2 \right] Br$$

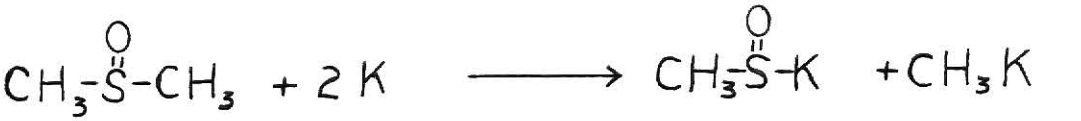
XV

This is analogous to the trimethylsulfonium halides which have been extensively studied[7].

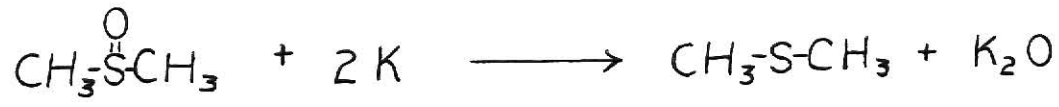
It is known that the triphenylmethyl anion is reasonably stable in DMSO[8], with $\frac{(\phi_3C^-)\ (DMSO)}{(\phi_3CH)\ (DMSO^-)} = 8 \times 10^3$

However, the characteristic deep red color of the triphenylmethyl anion was not observed when DMSO was employed as a solvent. The addition of potassium to redistilled DMSO containing ϕ_3CH or ϕ_3CCl resulted in an immediate, highly exothermic reaction from which a gas was evolved.

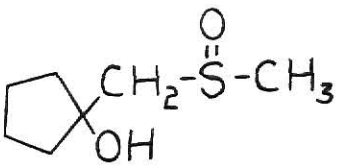
It may be that, although the equilibrium is favorable for the formation of ϕ_3CK in a DMSO solution, the kinetics of the exchange are slow enough to allow side reactions to occur[9]. Other workers[10] have shown that the predominant reactions are:



Also occurring to a lesser extent are:



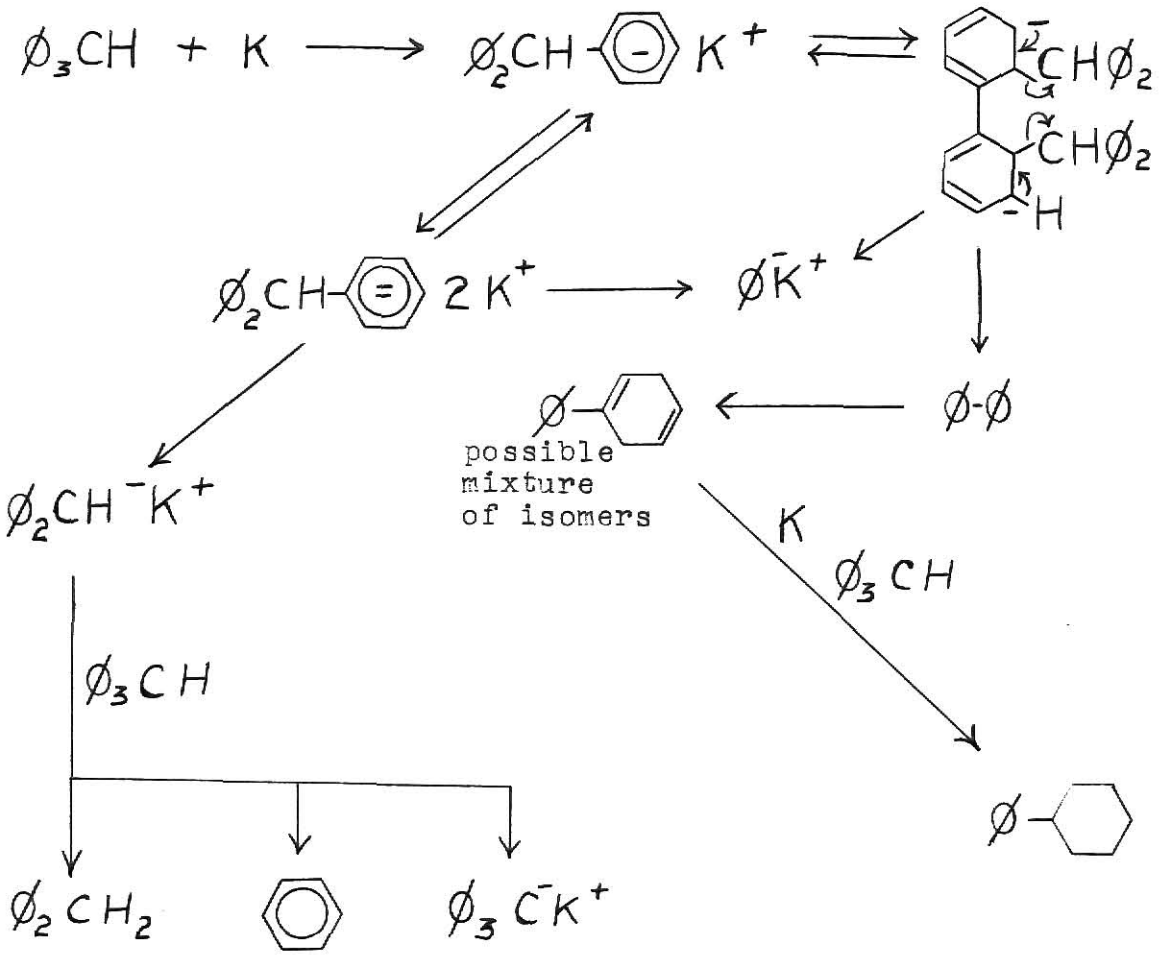
The anion $CH_3\overset{O}{\overset{\|}{S}}CH_2^-$ can also add to the cycloalkanone to form a hydroxysulfoxide. Corey[11] has shown that for unsubstituted cyclopentanone, the addition product



XVI

is formed in 17% yield, with an 80% yield of enolate.

It has been shown[3] that triphenylmethyl anion upon standing in an inert atmosphere at room temperature slowly undergoes fragmentation and rearrangement to yield a number of biphenyl-type hydrocarbons:



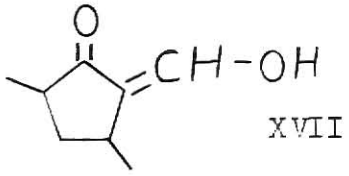
Some of these hydrocarbons produced by fragmentation of the triphenylmethyl anion were not completely separated from ketones IX and X by our spinning band distillation at reduced pressure. Partial resolution of the ketone/hydrocarbon mixture was effected by preparative gas-liquid chromatography (GLC) employing a 6-foot 10% NPGS (neopentyl glycol succinate) column. Considerably better resolution was obtained with a 15-foot 10% FFAP column,

but apparently neither IX nor X were separated into their respective stereoisomers. The hydrocarbons were not further characterized. The nmr spectrum of Component 3 showed a peak at 8.63 τ which was not seen in that of Component 1. Shielding of $-CH_3$ by a geminal propargyl group could cause such a shift from its usual range near 9 τ . Because of the complexity of the nmr spectrum in the 9 τ region, these data were not used for structural assignments.

In future work, it would seem worthwhile to try to separate the hydrocarbons from ketones IX and X either by preparative GLC[13] or by chemical means before attempting Procedure D. Probably IX and X could be complexed in moderate yield with $NaHSO_3$ or a Girard's reagent and the water-soluble complexes separated from the hydrocarbons. Branching near the carbonyl group, however, can be expected to significantly lower the yield of the reaction. It should be possible to form the oxime in good yield; unsubstituted cyclopentanone oxime can be formed in 93% yield[14]. The water-soluble oxime could be easily extracted from the hydrocarbons, and the ketone regenerated by reaction with pyruvic acid.

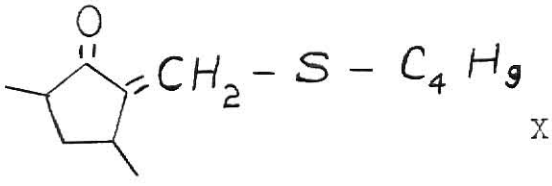
It is seen that the propargylation of VIII (Procedure C) produces both ketones IX and X, with the desired product, IX, being produced in only about 30% relative yield under the reaction conditions described in this paper. Alternate, lengthier procedures could be employed which would yield ketone IX only, probably in yields comparable to those achieved in our synthesis. The most attractive of these procedures uses n-butylthiomethylene as a blocking group. This method has been used to synthesize 2,2-dimethylcyclohexanone from 2-methylcyclohexanone with an overall yield of 77%[15]. The procedure using this method would be as follows: The hydroxymethylene derivative of

VIII could be made by the method of Johnson and Posvic[16] to give XVII.



XVII

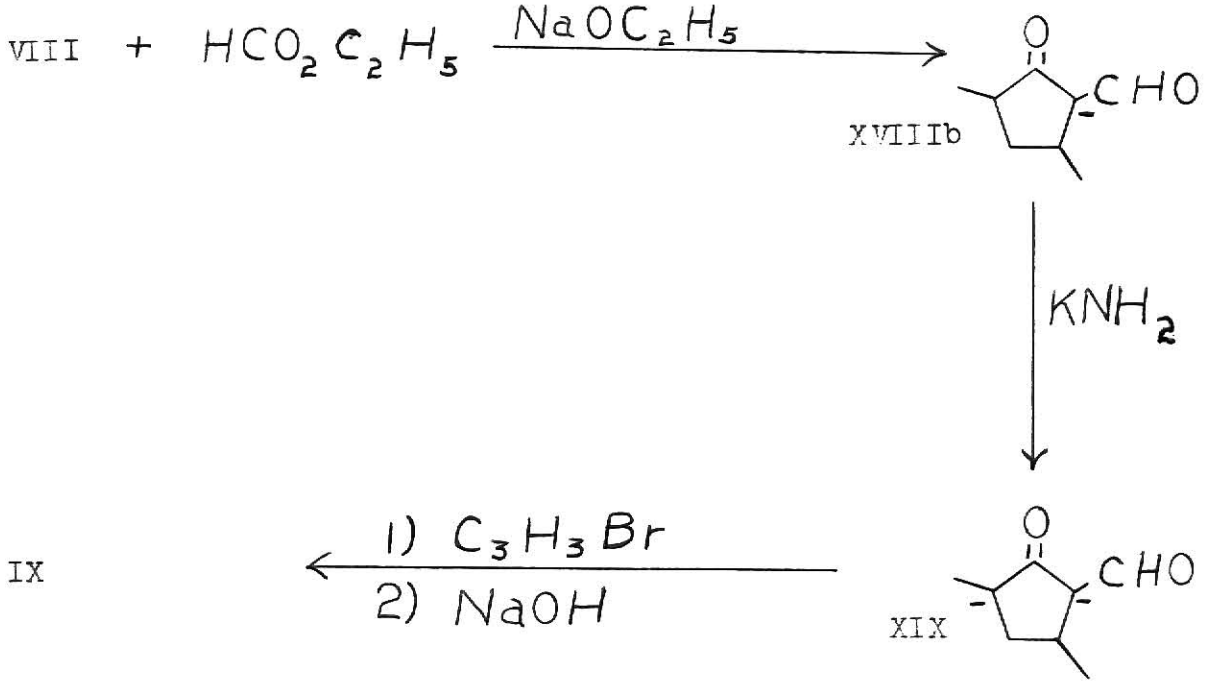
Product XVII could be refluxed with n-butyl mercaptan and a catalytic amount of p-toluenesulfonic acid in benzene under a nitrogen atmosphere to give the thioether XVIII.



XVIII

Propargylation of XVIII could then be carried out in the same manner as that employed for VIII. The n-butylthiomethylene group is stable to the highly basic conditions employed in Procedure C. After propargylation is accomplished, the blocking group could be removed by refluxing with aqueous KOH and diethylene glycol for several hours and then steam distilling.

A similar procedure employing the α-CHO group as a blocking group[17] could be employed. The reaction conditions are more basic and the yields would perhaps be lower than the procedure using the n-butylthiomethylene group, but this procedure appears to be shorter and faster, with the work-up of only one intermediate being necessary, the dicarbonyl compound XVIIIb.

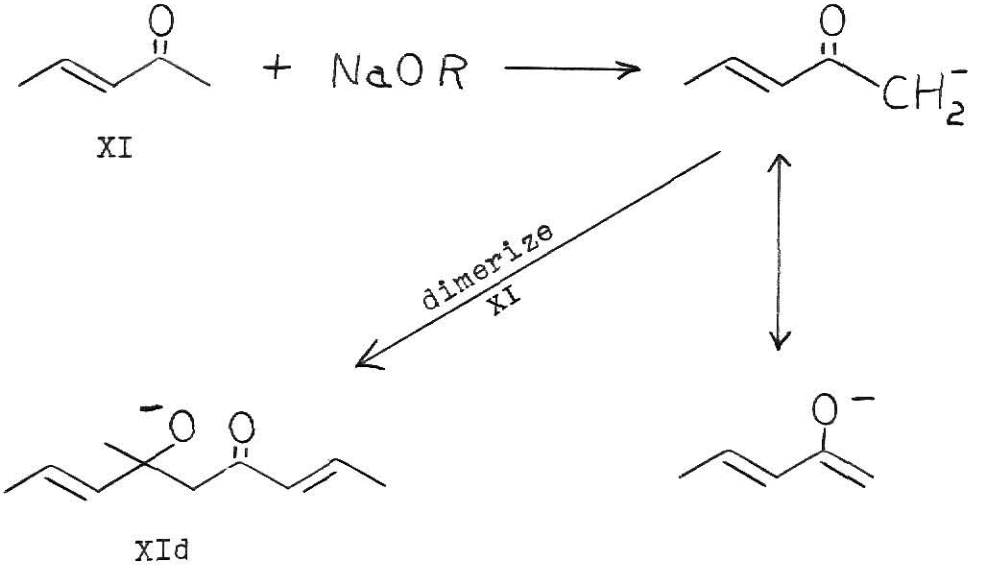


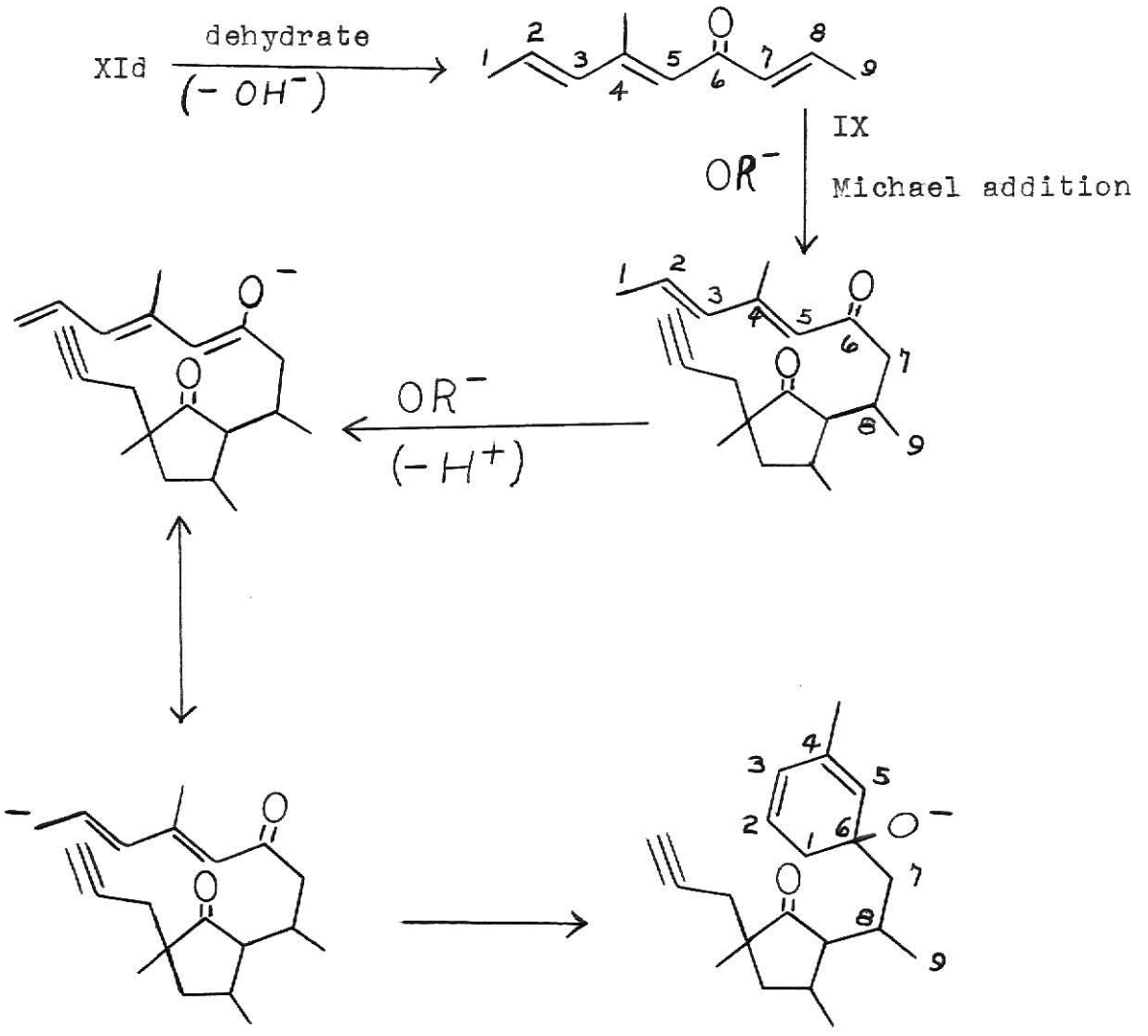
In the dianionic species XIX, one negative site is doubly resonance stabilized by the two carbonyl groups, and alkylation has been reported to occur almost exclusively at the less stable negative site.

Procedure D is a Robinson annelation, which consists of a Michael addition of α,β-unsaturated ketone XI to cyclic ketone IX, followed by intramolecular ketone condensation and dehydration to give cyclized product XII. Descriptions in the literature of the reaction conditions for a Robinson annelation vary widely. Lowenthal[18] has used initial cooling only, no solvent, fast addition of α,β-unsaturated ketone, and a molar excess of sodium methoxide. Others[19], however, have used cooling throughout the reaction, an alcoholic solvent, slow addition of α,β-unsaturated ketone, and only a catalytic amount of base. The reported yields from these two methods were comparable, in the 50-70% range. However, our attempts to apply each of these methods to Procedure D led to virtually zero yields, and our projected synthesis failed at this point. One difference between our procedure and

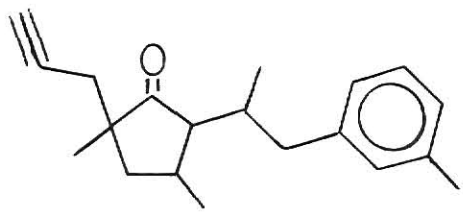
those described in the literature is that we employed an α, β-unsaturated ketone with a β methyl group on the double bond, whereas theirs were unsubstituted in this position. The methyl group could serve to sterically hinder the Michael addition of XI to the enolate of IX to such a point that the condensation of XI becomes the dominant reaction, even with slow addition of XI to the reaction mixture.

The infrared spectra of the resins isolated from the attempted Robinson annelations all indicated the presence of an aromatic system. These resins apparently were not simply contaminated by an aromatic compound, but actually have an aromatic nucleus incorporated into the structure, since all efforts to purify them by complexation with hydrazine, by steam distillation, and vacuum distillation with a spinning band column failed to remove the aromatic component of the resin (or its complex). Since aromaticity was observed in virtually every product, and since the desired Robinson annelation product was never obtained, the following interesting possibility suggests itself as an example of the way in which an aromatic nucleus might arise:



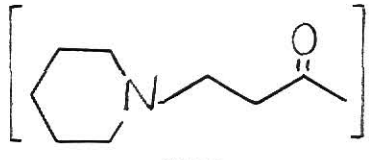


XIi

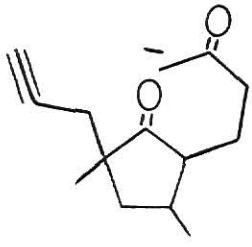
XIi $\xrightarrow{-OH^-}$ 

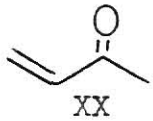
The resins obtained from the first and third attempted Robinson annelations show infrared absorption bands at 1140, 1070, and 1020 cm^{-1}, plus two strong bands at 740 and 700cm^{-1}. Together, these bands suggest 1,3-substitution of an aromatic nucleus[20]. Thus, perhaps the ready polymerization of ketone XI which was observed, followed by a presumed Michael addition of the dimer to ketone IX under the severely basic reaction conditions employed, accounts for our observations.

It should be possible to overcome this difficulty by employing an alternate synthesis, involving either the Robinson-Mannich reaction, or a Robinson annelation with (unsubstituted) methyl vinyl ketone XX and subsequent methylation:

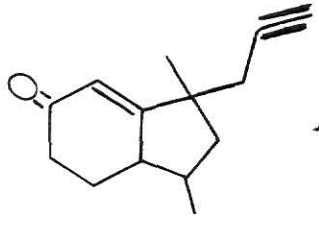
IX +  . CH_3I

XXI

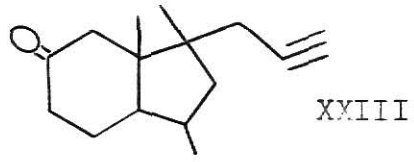
$\xrightarrow{OR^-}$ 

IX + 

XX

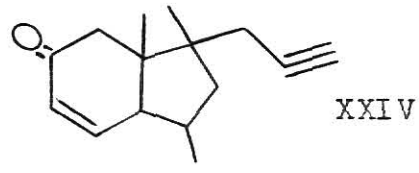
XXII 

The product of these reactions, XXII, differs from ketone XII by the absence of a methyl group in the 4-position. Conjugate addition of CH_3MgI (Procedure E) would give the analog of XIII:



XXIII

Dehydration of XXII by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) should give the α,β-unsaturated ketone XXIV[21]:



XXIV

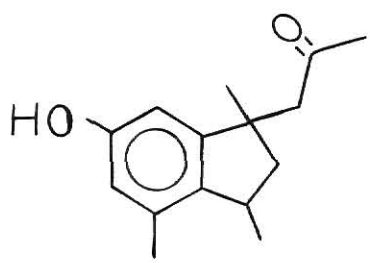
Another conjugate addition of CH_3MgI to XXIV would yield ketone XIII.

Reaction conditions for the Michael addition of substituted ketone XI to IX enolate in the Robinson reaction apparently must be rather severe. No reaction of IX was observed in the second attempt at this reaction, and IX was recovered almost quantitatively from the reaction mixture. Only a catalytic amount of methoxide ion was present, whereas in the other attempts, molar amounts of base were used.

Polymerization tends to occur in the final dehydration step of the Robinson reaction, and the reaction solution darkened in every case. If further attempts are made to utilize the Robinson reaction in this synthetic sequence, it would seem advisable to work up the reaction mixture before dehydration is attempted, determine if the appropriate ketol has in fact been formed, and then seek a milder method for dehydrating the ketol.

An attempted Robinson-Mannich reaction utilizing 4-piperidinobutan-2-one methiodide (XXI) was unsuccessful, probably because of the accidental introduction of atmospheric oxygen into the system. Resin formation from the labile methyl vinyl ketone produced from XX apparently occurred before it could react to any detectable extent with the enolate of IX, and the starting material was recovered almost quantitatively.

Procedure E, the conjugate addition of methyl Grignard reagents to α, β-unsaturated ketones, is known to occur, and Marshall *et al.*[22] have reported the reaction in systems similar to ours. However, the fact that a second quaternary methyl group adjacent to a first is to be introduced may make the reaction more difficult than if the methyl group in the 9-position were not present. Even if the reaction sequence had failed at this step, ketone XII is of interest because its hydrated dehydrogenation product, XXV, should be the same as the dehydrogenation product of III with loss of the quaternary methyl group:



XXV

Procedure F, the dehydrogenation of ketone XIII, could probably be accomplished in a variety of ways. Both DDQ[21] and chloranil have been used to introduce conjugated unsaturation in steroidal systems. However, if these reagents should fail in this case, dehydrogenation based on halogenation and dehydrohalogenation could be used. Product XIII is of intrinsic interest because its hydration product is identical to "tetrahydro-III", which should be available by appropriate reduction of III.

Procedure G, the final step in the proposed synthetic sequence, is

simply the hydration of the propargyl group to form the acetonyl group, and should be easily accomplished by Hg(II) in H_2SO_4 solution.

Although the goal of the total synthesis of III and the investigation of its relationship to the hydrolysis products of bipyran was not achieved, the exploratory experiments reported here do serve to form a basis for future work in this area. Several suggestions for improving the synthetic schemes have been advanced in the course of the preceding discussion, the utility of which, we believe, will be proved in the further development of this problem.

Experimental Procedures

2,4-Dimethyladipic acid (VII). The method of Robertson[23] was used for the oxidation of 3,5-dimethylcyclohexanol. The oxidation of the corresponding ketone by this general method has been reported[24]. Concentrated HNO_3 (600 ml) and H_2O (100 ml) were heated to 80° in a 1-liter flask equipped with a mechanical stirrer and thermometer. Over a period of two hours, 3,5-dimethylcyclohexanol, b.p. 185° (760 mm),(200g) was added to the flask. The reaction vessel was cooled during this time in an ice bath to keep the temperature between 85° and 95°. Large quantities of NO_2 were evolved. The temperature was held at 90° for one hour after the addition was completed, and the HNO_3 solution was evaporated under reduced pressure (approx. 400 mm) until the temperature reached 120°. The remaining viscous yellow liquid was transferred to a 500 ml three-necked flask equipped with a thermometer, a nitrogen source, and a gas outlet. Distillation was continued under a nitrogen atmosphere until the pot temperature reached 200°. Above 140-160°, polymerization occurred, and the light yellow liquid rapidly became darker and more viscous. Therefore, the crude 2,4-dimethyladipic acid, b.p. 206-212° (14 mm), was used without further purification.

2,4-Dimethylcyclopentanone (VIII). The method of Rand et al.[25] was used for the pyrolysis of VII. A nitrogen atmosphere was maintained throughout the pyrolysis. To the crude acid in the apparatus described above, KF (3.0 g) was added, and the temperature gradually increased. A negligible amount of material was recovered between 200° and 260°, and 4 ml of a two-phase system was recovered between 260° and 275°. The main fraction was collected between 275° and 305°. Less than 0.5 ml of distillate was obtained

between 305° and 350°. The residue was an amorphous black solid. The pyrolysis at 275 - 305° was essentially complete within 100 minutes. Yield of impure VIII: 74.5 g.

The distillate was washed with 10% $NaHCO_3$ solution until the evolution of CO_2 ceased. The remaining 2,4-dimethylcyclopentanone, b.p. 152.5° (770 mm), was dried over $MgSO_4$. Yield: 63.5 g. Overall yield for the conversion of VI to VIII: 36.2%.

The dried ketone VIII was redistilled, and the fractions boiling over the range of 155-192° (760 mm), whose infrared spectra were virtually identical, were kept. Yield: 43.7 g. Ketone VIII in the vapor phase exhibited the expected ultra-violet spectrum: λ max = 300 mμ , logϵ = 1.43.

2,4-Dimethyl-2-propynylcyclopentanone (IX). Triphenylmethyl anion was prepared by the method of House and Kramar[5]. Triphenylmethane (130.4 g) was dissolved in 600 ml of 1,2-dimethoxyethane (DME) which had been dried for three hours over sodium, in a 1-liter flask equipped with a constant-pressure addition funnel and a nitrogen source and outlet. The nitrogen was dried over KOH pellets and Drierite. A nitrogen atmosphere and magnetic stirring were maintained throughout the reaction. A total of 17.4 g of metallic potassium was added in small pieces to the DME solution. The intense red color of the triphenylmethyl anion became stable in solution after about 10 minutes. After 19 hours at 25°, most of the potassium had reacted. The remaining potassium (approx. 0.5 g) had formed an aggregate of very small particles. This was removed by pipette.

(In another preparation of triphenylmethyl anion, approx. 2 g of mercury were added to the reaction mixture after six hours. This formed a Hg/K amalgam, which, when vigorously stirred, was dispersed into fine droplets which

presented a much larger surface area for reaction than that of the chunks of potassium alone.)

Ketone VIII (40.2 g) was introduced, which was slightly more than enough to decolorize the solution. After 20 minutes, 77.9 g of propargyl bromide (a 2:1 excess) was added as rapidly as the exothermicity of the reaction permitted (approx. 5 minutes), while the reaction vessel was packed in ice. Because of the very small particle size of the KBr precipitate, the resulting creamy suspension was filtered only with difficulty. The addition of water to the filtrate produced a two-phase system consisting of a yellow aqueous layer and a heavier organic layer containing a large volume of hydrocarbon crystals. The layers were separated and filtered, and the aqueous layer was extracted with diethyl ether which was then added to the organic layer. The crude organic layer was cooled to -12° for 48 hours, and a large quantity of hydrocarbon crystals was recovered. The resulting liquid was distilled at 0.5 mm pressure under a nitrogen atmosphere on a stainless steel spinning band column. Seventeen fractions were collected. Total yield of distillate: 42.1 g. The residue (approx. 40 g) after cooling consisted of large hydrocarbon crystals in a dark resinous matrix.

Gas-liquid chromatography of the distillate using a 6-foot column of 10% neopentyl glycol succinate (NPGS) on 60/80 mesh chromosorb W separated the entire distillate into four components. Infrared spectroscopy showed that the first and third components were ketones, and the second and fourth components were hydrocarbons. (Cf. p. 8 et seq. of this report.) A 15-foot column of 10% FFAP (the half-acid ester of 2-nitroterephthalic acid and polyethylene glycol) on 60/80 mesh Chromosorb W separated the entire distillate into 11 components, but apparently neither ketones IX nor X were separated

into their respective stereoisomers.

In a different preparation of IX, triphenylchloromethane (13.9 g) was added to 50 ml of redistilled DMSO. Magnetic stirring and a nitrogen atmosphere were maintained throughout the reaction. Potassium (1.9 g) was added in small pieces. Reaction was immediate and very exothermic. A turbid brown solution resulted. After 10 minutes, 5.8 g of ketone VIII were added, and after another 20 minutes 23.8 g of propargyl bromide were rapidly introduced. No exothermicity was detected. Stirring was continued for two hours longer. The solution was filtered, and 10 g of a brown solid, m.p. approx. 90°, was recovered. Infrared spectroscopy indicated this to be primarily triphenylmethane and triphenylchloromethane. Distillation of the filtrate at atmospheric pressure yielded the major fraction, a turbid liquid with an acrid odor, at 63°. A white solid began to crystallize out of the distillate after standing approximately an hour, and after two days the distillate became almost completely crystalline. The crystals were insoluble in carbon tetrachloride, acetone, diethyl ether, and petroleum ether, but were soluble in water. At 190-200°, they decomposed with an acrid odor characteristic of the freshly distilled liquid. The product was tentatively identified as compound XV. Ketone VIII was quantitatively recovered from the reaction mixture.

Pentan-2-ol-4-one. This reagent was prepared by the method given in Beilstein[26]. Acetone (105 g), freshly distilled acetaldehyde (40 g), and a solution of 5 g of KCN in 10 ml of H_2O were separately cooled to -12°, mixed, and allowed to stand at -12° for 10 hours. (Note: It is necessary for all the components to be cooled to 0° or below before mixing. Otherwise, the reaction quickly becomes uncontrollably exothermic.) Diethyl ether (150 ml) was added to the resulting brown solution. Approximately 30 ml of a viscous

dark liquid slowly separated out. This was extracted with three 30-ml portions of ether and discarded. The combined extracts were added to the major ethereal solution, which was then dried over $MgSO_4$ and filtered. The ether was evaporated at reduced pressure, and a clear orange liquid with a characteristic spicy odor remained. Yield: 49 g.

Distillation of the crude ketol, even with a nitrogen atmosphere near 50° at reduced pressure, resulted in extensive polymerization. Therefore, in most preparations the product was dehydrated without further purification.

4-Penten-2-one. The ketol was dehydrated by the method of Rapson[27]. A crystal of iodine was added to the crude ketol and the solution held at 155-170° in an oil bath until no more distillate was obtained. Saturation of the distillate with K_2CO_3 produced a two-phase system. The organic layer was dried over K_2CO_3 and then over $MgSO_4$. Yield: 13 g. This dried layer was distilled at atmospheric pressure, and the fraction with b.p. 107-119° was retained. Yield of XI: 3.7 g.

Extensive decomposition occurred in almost every redistillation. Distillation of XI at reduced pressures is not recommended for this reason. Also, particles of $MgSO_4$ appeared to effectively catalyze the decomposition; the extent of decomposition could be appreciably reduced by careful filtration of XI. The best yield from a distillation of the crude product, 42%, was afforded by a trap-to-trap distillation at 20 mm pressure, with the receiver cooled in a 2-propanol/dry ice bath. The major contaminant boiled near 140° at atmospheric pressure, or 40° at 20 mm. At room temperature, 4-penten-2-one polymerizes to a brown liquid in a few weeks, and is best kept at low temperatures.

1,3,4-Trimethyl-1-propynyl-2,3a,5-trihydro-6-indanone (XII). A Robinson annelation employing the Marshall[19] technique was attempted. Magnetic

stirring and a dry nitrogen atmosphere were maintained throughout the reaction. To 40 ml of dry methanol 1.6 g of sodium were added, and the solution was cooled to -4°. After the reaction was complete, 3.36 g of a hydrocarbon solution containing 45% ketone IX and 8% ketone X was added. After 20 minutes, 1.5 g of ketone XI (a 1.5:1 excess) in 10 ml of methanol was introduced over a 20-minute period. The solution was then held near 0° for 6 hours and at 25° for 16 hours. The brown solution was then refluxed at 64° for one hour.

The solvent was evaporated at reduced pressure, 30 ml of water was added, and the solution acidified with glacial acetic acid. The turbid, very dark solution changed to a clear orange color. After extraction with six 25-ml portions of ether the water solution was light yellow and the ethereal solution was orange. After washing the ethereal solution with three 25-ml portions of 5% NaOH solution, the organic layer remained orange, but the aqueous layer was orange and turbid. The ethereal layer was dried over $MgSO_4$ and reduced in volume to 15 ml. Petroleum ether was then added as evaporation continued, such that a constant volume was maintained, in an attempt to induce crystallization of product. The volume of the solution was then increased to 40 ml. A turbid solution containing some precipitate was produced. Cooling at -12° for one hour yielded a clear orange solution and a resinous brown residue. Attempted reprecipitation of the residue yielded only the oily resin again.

The resin was distilled under a nitrogen atmosphere at temperatures up to 170° at 0.3 mm pressure. Some hydrocarbons, b.p. less than 65° (0.3 mm), (1.25 g) were obtained. These were identified by infrared spectroscopy as Components 2 and 4 from the previous propargylation reaction. A red resinous residue remained after distillation.

Column chromatography of the residue using a 1 x 5 inch tapered column of neutral alumina yielded two components. (Solvents used for this and all

column chromatographic separations reported in this paper were carbon tetrachloride, chloroform, and acetone. All columns were of 60/300 mesh neutral alumina.) The infrared spectrum of Fraction 1 obtained on a Perkin-Elmer Model 237 IR Spectrometer showed that it contained a cyclopentanone ring and a double bond. Fraction 2 was an unresolved mixture and was re-chromatographed on a 0.75 x 11 inch column. Separation was still incomplete, but the infrared spectrum showed three salient features: 1) a hydroxyl stretching absorption at 3500 cm^{-1}, 2) cyclopentanone and unstrained ketone absorptions in almost equal intensities near 1700 cm^{-1}, and 3) bands at 1660-1665 cm^{-1} and 1620-1630 cm^{-1} implying the presence of an α, β- unsaturated ketone and a conjugated double bond, respectively.

An aliquot of the residue was dissolved in a fresh 2,4-dinitrophenylhydrazine solution for 16 hours. Light orange crystals, m.p. 119-121.5°, precipitated within 16 hours. These crystals were chromatographed on a 1 x 7 inch column, but no separation of components was effected.

An aliquot (0.1 g) of the resin was dissolved in 0.4 ml of absolute ethanol and raised to reflux temperature. To this was slowly added 0.35 ml of 99% hydrazine hydrate, and the solution was refluxed for 30 minutes. Most of the solvent was later evaporated. When the solution was cooled, a two-phase system consisting of an orange bottom layer and a yellow oily, top layer resulted. The bottom layer was chromatographed on a 1 x 6 inch column, and two bands were completely separated from each other: a wide first band whose components were partially separated, and an apparently homogeneous second band. However, neither these nor the 2,4-dinitrophenylhydrazone produced above possessed the infrared spectra expected for ketone XII derivatives.

In the second attempted Robinson annelation reaction, employing a modified Marshall technique, the general method given above was employed. Magnetic

stirring and a dry nitrogen atmosphere were maintained throughout the reaction. To 100 ml of methanol, 0.69 g of sodium was added, and the methoxide solution was cooled to -4°. Ketone IX (3.95 g), uncontaminated by ketone X, which was dissolved in 7.23 g of hydrocarbon Component 4 from the propargylation reaction, was introduced. After 30 minutes, 2.78 g of XI in 80 ml of methanol was added dropwise over a four hour period. The solution was held near 0° for an additional 10 hours and then near 25° for 10 hours. At this point, the solution was slightly turbid and light yellow, with little darkening of color, as occurred in the previous attempt at Robinson annelation. The solution was refluxed one hour, 9.6 g of KOH was added (making the solution 2 N in base), and refluxing was continued for one hour. Upon standing, a cream colored paste separated out from the clear orange solution. This was removed by filtration.

The volume of the filtrate was reduced to approximately 50 ml by evaporation at reduced pressure. Upon cooling to -12°, a two-phase system appeared. The aqueous layer was extracted with ether, and this was added to the organic layer. The organic layer was acidified with glacial acetic acid, extracted with six 25-ml portions of ether, and washed repeatedly with 10% NaOH solutions until the aqueous extract was almost colorless. The clear orange ethereal layer was dried over $MgSO_4$ and evaporated at reduced pressure to a volume of approximately 10 ml. This was steam distilled, and the distillate extracted with three portions of ether. A very small amount of dark red residue remained after the steam distillation. The ether was evaporated at reduced pressure, yielding 10.73 g of material. Infrared spectroscopy showed it to be the unreacted starting material. (Total weight of ketone X plus hydrocarbon solvent used was 11.18 g.) Infrared spectroscopy did indicate that some propargyl-to-allenic

rearrangement had occurred in ketone X. This is to be expected in the highly basic medium employed. The rearrangement would not interfere with the overall synthesis, since both the propargyl and allenic systems hydrate under the reaction conditions of Procedure G to give the desired ketone.

Samples of both the acidic and basic aqueous solutions from the work-ups of both attempts to effect the Robinson reaction were evaporated to dryness. Their infrared spectra showed no carbonyl absorption in any residue.

In the third attempted Robinson annelation reaction, the Lowenthal[18] technique was employed. Magnetic stirring and a dry nitrogen atmosphere were maintained throughout the reaction. Potassium (5.39 g) was refluxed for 30 minutes with 50 ml of tert-butyl alcohol, and the mixture was then held near 25° for 4.5 hours. The resulting alkoxide formed a white mass of greater volume than the original liquid. The remaining potassium was reacted with 20 ml more of tert-butyl alcohol and the mixture refluxed for an additional 30 minutes. The solution was cooled, and 30 ml of dry tetrahydrofuran (THF) was added in order to lower the solidification temperature of the tert-butyl alcohol, m.p. 25.2°. The alkoxide solution was further cooled in an ice bath to -4°.

(It was found that the sodium tert-butoxide could be formed only with difficulty and in poor yields, since the alkoxide film which forms on the surface of the metal prohibits further reaction.)

A 27% hydrocarbon solution containing 4.00 g of ketone X was added to the potassium alkoxide solution. The solution almost immediately turned reddish-brown. (No color change was observed at this point in the two previous attempts to effect the Robinson annelation.)

After 25 minutes, the introduction of 2.25 g of ketone XI in 35 ml of tert-butyl alcohol was begun. This was added at a constant rate over a period

of five hours, while the reaction flask was held near 0° in an ice bath. Cooling was maintained an additional six hours, and then the solution was held near 25° for ten hours. The solution was dark and almost opaque. The solution was refluxed at 80° for two hours, and the solvent evaporated at reduced pressure. The residue was a black, oily resin.

To the residue was added 50 ml of water, which was then acidified with glacial acetic acid. The solution separated into two phases. The yellow aqueous layer was extracted with three 15-ml portions of ether, and the extracts added to the organic layer. The organic layer was washed repeatedly with 15-ml portions of 5% KOH solution until the colored water-soluble organic material was extracted. The organic layer was dried over $MgSO_4$, filtered, and the solvent was evaporated at reduced pressure. Distillation at 1.5 mm pressure yielded 3.3 g of distillate, b.p. 103-123°. No further distillate was obtained up to 180°.

Infrared spectra of the distillate showed no carbonyl or hydroxyl absorptions, but appeared to be the hydrocarbons previously isolated from the synthesis of ketone IX. The residue from the distillation showed an infrared spectrum not qualitatively different from the residue from the first attempted Robinson reaction.

An attempt was made to hydrolize the polymeric residue by a retrograde aldol reaction. The residue was refluxed with 50 ml of 5% aqueous KOH solution for two hours. A 15-ml aliquot was removed, extracted with ether, and the solvent removed at reduced pressure. The infrared spectrum showed the presence of both cyclopentanone at 1745 cm^{-1} and unstrained ketone at 1715 cm^{-1}. The relative intensity of absorption in the 1580 cm^{-1} region (probably due to alkene stretching) was much less than in the original residue.

Another aliquot taken after refluxing for six hours showed an infrared spectrum identical to that of the two-hour hydrolysis product.

The hydrolysis product was chromatographed on a 1.5 x 8.0 cm column. Three fractions were obtained. No carbonyl absorptions in the infrared were observed in Fraction 1, but Fraction 2 contained an unstrained ketone. Fraction 3 showed absorptions indicating the presence of both unstrained ketone and cyclopentanone. Fraction 3 was chromatographed again on a 2.0 x 28 cm column. A broad, red band moved ahead of the yellow major component, but complete separation was not effected. The infrared spectrum of this minor component showed little or no propynyl or allenic absorptions in the 2100 or 1900 cm^{-1} regions, respectively, where they had been prominent in other spectra.

4-Piperidinobutan-2-one Methiodide. The Mannich base and its methiodide were prepared by the method of Wilds and Werth[28]. Piperidine hydrochloride (3.60 g), paraformaldehyde (1.06 g), acetone (11 ml), and methanol (1.5 ml) were refluxed for six hours and then treated with excess 45% aqueous KOH. The solution was extracted with ether and then dried over $CaCO_3$ and $MgSO_4$. The solvent was removed at 15 mm pressure, and a small amount of distillate, b.p. 70° (15 mm), was obtained. The amine appeared to decompose above approximately 120°, so distillation was discontinued. Infrared spectroscopy showed the amine to be fairly pure 4-piperidinobutan-2-one[29]. Yield: 2.3 g.

The Mannich base above and an equal weight (2.3 g) of methyl iodide were cooled to 0° in an ice bath and then mixed. In a somewhat exothermic reaction, the solid methiodide rapidly formed. This was allowed to stand for 16 hours, washed with three portions of dry ether to remove the excess methyl

iodide, and the resinous, yellow methiodide was immediately reacted in the following procedure. Yield: 4.8 g.

1,3-Dimethyl-1-propynyl-2,3a,4,5-tetrahydro-6-indanone (XXII). Magnetic stirring and a dry nitrogen atmosphere were maintained throughout the Robinson-Mannich reaction. A 25 ml three-necked flask was equipped with a nitrogen inlet, reflux condenser, and thermometer. To 5 ml of dry methanol and 5 ml of thiophene-free benzene, 0.1 g of sodium was added. After the reaction was complete, a 27.5% hydrocarbon solution containing 0.73 g of ketone IX uncontaminated by ketone X was introduced. The solution, which soon became darkened, was refluxed for 15 minutes and then cooled to 3°. Over a period of approximately 20 minutes, 1.5 g of 4-piperidinobutan-2-one methiodide dissolved in 5 ml of dry methanol was added dropwise. Cooling in an ice bath was maintained for one hour, and the solution was kept near 25° for 22 hours. The solution was refluxed at 60° for one hour and then cooled. At this point, the solution was dark brown and clear. The addition of 15 ml of water caused the precipitation of a large volume of yellow amorphous material. The solution was extracted with four portions of benzene, and the benzene solution washed with four portions of dilute aqueous HCl. Evaporation of the benzene at reduced pressure left a brown oil. Gas-liquid chromatography of this oil on a 15-foot column of 10% FFAP on 60/80 mesh firebrick at 180° showed that almost no reaction had occurred; only the starting material could be detected. As expected, no methyl group migration (ketone IX → ketone X) occurred under the reaction conditions.

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EXPERIMENTS TOWARD THE SYNTHESIS OF SOME SUBSTITUTED BICYCLO [4.3.0] NONAN-6-ONES

by

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Abstract

Successive hydrolyses of 2,2',4,4',6,6'-hexamethyl-4,4'-bi-4H-pyran (I) and its hydrolysis products can theoretically give rise to a very large number of compounds. It is difficult to deduce the structures of the comparatively few hydrolysis products which have in fact been isolated because of the existence of a large number of reaction pathways. Therefore, a synthesis by an independent route of one of the hydrolysis products of I was undertaken in order to confirm the product's presumed structure and to provide a firmer basis for deducing the structures of other hydrolysis products of I which have been shown to be related to the synthesized compound by stepwise hydrolysis. The compound chosen for synthesis was 1β-acetonyl-1α,3,4,7aβ-tetramethyl-2,7-dihydro-6-indanone (II).

A 7-step synthetic route to II is proposed: The starting material, 3,5-dimethylcyclohexanol (III) is oxidized to 2,4-dimethyladipic acid (IV), which is cyclized to 2,4-dimethylcyclopentanone (V). Propargylation gives a mixture of 2-propynyl-2,4-dimethylcyclopentanone (VI) and the corresponding 2,4,5-trialkylated product. A Robinson annelation with 4-penten-2-one should produce 1-propynyl-1,3,4-trimethyl-2,3a,5-trihydro-6-indanone (VII). Methylation and double dehydrogenation should produce II.

The stereochemistry of the reaction sequence is discussed. Each compound III→II in the synthetic sequence can have from 2 to 8 geometrical isomers. The considerations which governed the choice of synthetic route and reaction conditions are discussed. Alternate routes are proposed for the reaction sequence V→II. To problems of specificity and yield which were encountered in the synthesis possible solutions are proposed. Anomalous

results are rationalized. Experimental procedures used in the proposed reaction sequence III→VII are reported.