This is to certify that the

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1. Synthetic Uses of High Surface Sodium and Potassium in Alkylation and Reduction of Ketones and Nitriles
2. Synthesis and Photochemistry of substituted 2-cyclooctenones
3. Synthesis and Photochemistry of 1,5-Dimethy-4-methylene-bicyclo(3.3.0)octa-dienes

presented by

Bing-Lin Chen

has been accepted towards fulfillment
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Harold Hart

Major professor

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PART I

SYNTHETIC USES OF HIGH SURFACE SODIUM AND POTASSIUM IN ALKYLATION AND REDUCTION OF KETONES AND NITRILES

PART II

SYNTHESIS AND PHOTOCHEMISTRY OF SUBSTITUTED 2-CYCLOOCTENONES

PART III

SYNTHESIS AND PHOTOCHEMISTRY OF 1,5-DIMETHYL-4-METHYLENEBICYCLO[3.3.0]OCTADIENES

By

Bing-Lin Chen

A DISSERTATION

submitted to
Michigan State University
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ABSTRACT

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In part I of this thesis, synthetic uses of high surface sodium (HSS) and potassium (HSP), particularly for the alkylation and reduction of cyclic ketones and nitriles, have been explored. Alkylations using HSS (or HSP) have been performed with 2-methylcyclohexanone, cyclohexanone, 4-t-butylcyclohexanone, cycloheptanone and cyclooctanone. The results show that monoalkylation usually predominates; where regioselectivity is involved, the more highly substituted products are obtained. The main competing reactions to alkylation are reduction to alcohols and to pinacols. For example, 2-methylcyclohexanone was alkylated with HSS

and allyl bromide in hexane to give a 68% yield of 2-allyl-2-methyl-cyclohexanone along with some starting ketone and reduction product.

HSS alkylation was also carried out on α,β-unsaturated ketones. An interesting result was obtained for the methylation of isophorone with 20% HSS-C and methyl iodide in hexane. In this case reduction competes very well with alkylation, and a substantial amount of 1,6-diketone (i.e. 1,1',3,3,3',3'-hexamethylbicyclohexyl-5,5'-dione, 38% yield) resulting from the reductive coupling at β-position of isophorone was obtained. The only alkylated product was 2-methylisophorone (32% yield).

The methylation of phenylacetonitrile with HSS and methyl iodide gave a 74% yield of 2-methylphenylacetonitrile with no reduction product. High surface sodium has aslo been used to study the reduction of cyclohexanone and 2-methylcyclohexanone. The reduction of 2-methylcyclohexanone with 2 molar equivalents of high surface sodium on graphite in THF afforded a very good yield of 2-methylcyclohexanol (83%). The more stable alcohol (trans/cis = 85/15) predominated.

A mechanism involving enolate anions is proposed to account for the formation of alkylation products in HSS alkylation of cyclic ketones. The intermediate leading to reduction products is probably a radical anion.

The synthesis and photochemistry of 2-methyl-2-cyclooctenone I, 3-methyl-2-cyclooctenone II, and 2,3-dimethyl-2-cyclooctenone III is

described in part II of this thesis. A method was found to prepare 2-methylcyclooctanone in quantitative yield, involving the methylation of cyclooctanone via its dimethylhydrazone. Bromination-dehydrobromination of 2-methylcyclooctanone gave 2-methyl-2-cyclooctenone in good yield. 3-Methyl-2-cyclooctenone and 2,3-dimethyl-2-cyclooctenones were prepared by oxidizing the tertiary allylic alcohols generated by the 1,2-addition of methyllithium to 2-cyclooctenone and 2-methyl-2-cyclooctenone respectively.

Irradiation of 2-methyl-2-cyclooctenone and 3-methyl-2-cyclooctenone in methanol resulted in the formation of adducts cis-2-methyl-3-methoxycyclooctanone IV and 3-methyl-3-methoxycyclooctanone V respectively, whereas methanol did not add photochemically to 2,3-dimethyl-2-cyclooctenone. The base-catalyzed Michael addition of methanol to I gave an equilibrium mixture of I, trans-2-methyl-3-methoxycyclooctanone VI, and IV in 45 : 35 : 20 ratio. Moreover, the base-catalyzed exchange reaction of IV led to the same product mixture. These results are rationalized by a photoisomerization of I (or II) to its trans isomer which then thermally adds methanol in a regio- and stereospecific syn manner. The reason that no methanol adduct was found in the photolysis of III is probably because other energy dissipation processes compete efficiently with the double bond isomerization.

The synthesis and attempted photochemistry of 1,5-dimethyl-4-methylenebicyclo[3.3.0]octa-2,6-diene, 1,5-dimethyl-4-methylenebicyclo-

[3.3.0]octa-2,7-diene, and 1,5-dimethyl-3,7-diphenyl-4-methylenebicyclo-[3.3.0]octa-2,6-diene is described in part III of this thesis. However, these compounds on irradiation did not give detectable amounts of di-π-methane rearrangement products or the products corresponding to intramolecular cycloaddition of the two endocyclic double bonds.

To my parents and my wife, Yu-I (Yolande)

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PART I

SYNTHETIC USES OF HIGH SURFACE SODIUM AND POTASSIUM IN ALKYLATION AND REDUCTION OF KETONES AND NITRILES

High Surface Sodium and Potassium

Sodium metal and its derivatives have been widely used as reagents in organic synthesis.[10,11a] The rate at which sodium reacts depends on its chemical activity and surface area available for reaction. With bulk sodium, insoluble reaction products may coat the surface and effectively remove the underlying sodium from the reaction zone. This often gives undesirable results. High Surface Sodium (HSS) offers a means of overcoming some of the problems associated with the use of bulk sodium, The term high surface sodium[1] is applied to films of sodium on inert solids of high surface area.

The ease and simplicity of generating HSS make it desirable to prepare sodium in this form at the point of use. Although it seems likely that conditions could be developed for storing HSS without appreciable loss of acitvity, this has not yet been done. The preparation of HSS is accomplished simply by mixing molten sodium with suitable inert solid materials having very large surface areas. Usually, sodium spontaneously spreads over the surface of hot dry solids at temperatures between 100°C and 200°C. Among the substances which may be used as sodium carriers are salt, sodium carbonate, charcoal, metal powders, aluminum oxide, etc. Potassium can also be coated on inert solids to give High Surface Potassium (HSP) which is expected to be more reactive than HSS (see experimental section).

In HSS, the sodium films produced approach atomic dimensions in thickness, the particle size being even smaller than in sodium dispersions. Thus the surface area available for reaction or for catalytic effects is increased tremendously. Table 4[1] shows the calculated sodium film thickness versus the percent of sodium adsorbed on both activated alumina and activated carbon.

Table 4 Average film thickness vs. percent sodium on alumina and carbon

% Sodium	Alumina (1) (160 sq.m/g)	Carbon (2) (750 sq.m/g)
5%	1 atomic layer	1 atomic layer
10%	1.5 atoms thick	1 atomic layer
15%	2.5 atoms thick	1 atomic layer
20%	3.5 atoms thick	1 atomic layer
25%	5 atoms thick	about 1 atom thick

* Sodium atom diameter = 4.2Å

(1) Grade F-20, Aluminum Co. of America.

(2) Columbia LW, Carbide & Carbon Co.

The effective surface area of the solid carrier determines the amount of sodium which can be absorbed. Salt may carry 2 to 10% sodium; soda ash, 10% sodium; alumina, 20% to 25% sodium; and activated or colloidal carbons, over 30% sodium (Table 2)[1]. Within these concentrations a free flowing solid is obtained, while above these concentrations the mixture becomes a pasty mass. This free flowing characteristic can be

maintained at temperatures up to the boiling point of sodium (883°C) depending, of course, on the temperature stability of the carrier.

Table 2 High surface sodium systems

Solid Carrier	Temp** °C	Sodium %	Appearance
Activated Alumina (1)	140-160	20-25	Black or mottled white granules
Activated Carbon Coconut (2)	120	35+	Silver to black pyrophoric powder
Colloidal Carbon (3)	170	30	Black pyrophoric powder
Sodium Chloride 40-80 mesh	150	2-10	Gray to black colored salt

** Optimum dispersing temperature for the system.

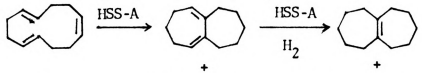
(1) Alcoa F-1 Aluminum Co. of America.

(2) Columbia L-W. Carbide & Carbon Co.

(3) Monarch 71, Godfrey L. Cabot, Inc.

It has been shown that high surface sodium is advantageous for the preparation of finely divided metals, for the purification of hydrocarbons and ethers, and for the preparation of inorganic and organosodium derivatives.[1] There are only a few isolated references in the literature concerning the use of high surface sodium and potassium. Most of the original literature is in patents. For instance, HSS has been used to isomerize and hydrogenate cyclododeca-1,5,9-triene 1

(Eq. 1).[3] The potential of HSS and HSP as reagents to effect the alkylation and reduction of ketones will be discussed in this thesis.



1 + other isomers + other isomers (Eq. 1)

Alkali Metal-graphite Intercalation Compounds

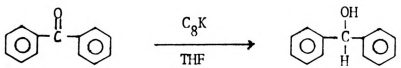
Potassium and the higher alkali metals readily form lamellar compounds[4] with graphite, whereas sodium (or lithium) has a lesser tendency to intercalate in graphite. The best known intercalation compound is C_8K in which all carbon-layers are separated by a layer of potassium of atomic size. With such an arrangement, there is a partial transfer of the 4s electron of potassium to the π-electronic system of graphite. This transfer can markedly influence the reactivity of the 4s potassium electron.

Potassium-graphite (C_8K), though easily prepared,[5] has until now found only a few applications in the synthesis of organic compounds. It has been used as a catalyst in polymerization reactions,[4] in the nuclear and side-chain alkylation of aromatic compounds with ethylene,[6] and in certain base-catalyzed reactions.[4] For example, the Claisen condensation of ethyl acetate to ethyl acetoacetate is catalyzed by

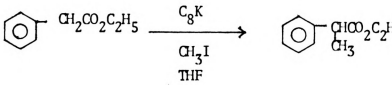
C_8K. C_8K acts essentially as a base (Eq. 2).[7]

$$CH_3CH_2-O-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow{C_8K} CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-O-CH_2CH_3 \qquad \text{(Eq. 2)}$$

Pertinent to this part of the thesis is the reaction of C_8K with ketones, where it functions primarily as a reducing agent by an electron transfer process. For instance, benzophenone was reduced to benzhydrol in 98% yield (Eq. 3).[5] Recently, however, C_8K has been shown to have Lewis base properties toward weak acids,[8] and it also has been used as base to generate anions from nitriles and activated esters.[9] Thus ethyl phenylacetate was metallated with C_8K and subsequently methylated to give ethyl 2-methylphenylacetate (Eq. 4).



(Eq. 3)



(Eq. 4)

Due to reports that the sodium-graphite intercalation compound is unstable, essentially no studies concerning its structure and chemical properties have been made.[4] Sodium-graphite was prepared in very much the same way as HSS, although no attempt was made to determine if it is an intercalation compound. Some of its chemical properties will be discussed in this thesis.

Alkylation of Ketones and Nitriles

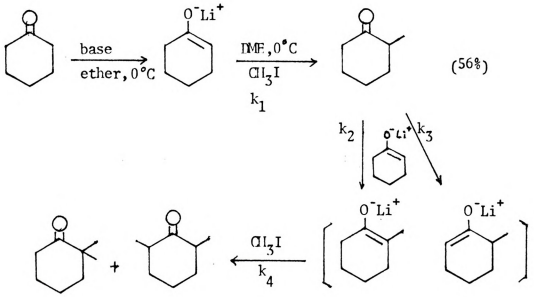
Alkylation reactions of ketone enolate anions[11a] constitutes a very important, well-established and synthetically useful method of elaborating complex molecules. Due to the weak acidity of ketones and nitriles ($pK_a \geq 19$), it is apparent that a stronger base than sodium ethoxide and a solvent less acidic than ethanol must be used in order to obtain an appreciable concentration of their anions. Ketone enolate anions have been generated quantitatively by the action of strong bases or in equilibrium amounts by using weaker bases. A comprehensive list of commonly used strong bases is available.[11a]

Normal monoalkylation of ketones has always been plagued by undesirable side reactions such as di-, and polyalkylation, aldol condensation and, to a much lesser extent, O-alkylation and reduction of the carbonyl group. The importance of these side reactions is largely dependent on the nature of the ketone and the reaction conditions employed. When bases like sodium hydride or sodium amide (or sodium alkoxides) are used, the enolate is formed relatively slowly in solution, and aldol condensation may occur due to the presence of appreciable concentrations of both the free ketone and its enolate anion. Aldol condensation can easily be avoided by slow addition of the ketone to a solution of a strong base in a suitable aprotic solvent. In this way, no excess ketone is present to react with the enolate.

Among the strong bases, the lithium dialkylamides (e.g. lithium diisopropylamide) are particularly convenient to prepare and use. These

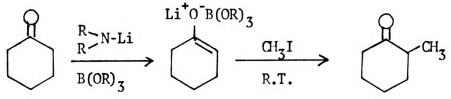
amides possess bulky alkyl groups, and therefore preferentially abstract an alpha proton from a ketone rather than attack the carbonyl group. However, these amides slowly attack ethereal solvents such as THF and 1,2-dimethoxyethane at elevated temperatures. Consequently the ethereal solutions of lithium dialkylamides must be prepared at 25°C or less and used promptly.

When an equivalent amount of a strong base is used in the monoalkylation of ketones, the amount of di- and polyalkylation can be reduced but not eliminated. Polyalkylation is due to a proton exchange between the alkylated product and the starting enolate (reaction k_2 and k_3) as illustrated in the following reaction with cyclohexanone.[12] If reaction k_2, k_3 and k_4 compete with the initial alkylation k_1, complex product mixtures will be formed.



(Eq. 5)

In order to minimize the side reactions encountered in the alkylation of ketone enolates a variety of cations and complexing agents have been used. For example, the problem of dialkylation can be considerably reduced by the use of triethanolamine borate (TEAB) or triethylborane as complexing agents.[13]



Often in the course of a synthesis the need arises to introduce an alkyl group selectively at one of the two alpha positions of an unsymmetrical ketone. Selectivity in the alkylation of unsymmetrical ketones may be achieved by using activating or blocking groups,[11a] or by taking advantage of the fact that kinetic control generally favors creation of the less substituted enolate anion, whereas under equilibrating conditions the more substituted anion usually predominates. Other means of generating a specific enolate ion, such as reduction of α,β-unsaturated ketones,[14] or reaction of enol ethers and esters with organometallic reagents,[12a] have also been used to accomplish specific alkylations.

The alkylation of nitriles usually presents no problem other than the separation of the monoalkylated product from starting material or dialkylated product. Thus the alkylation of nitriles and subsequent

hydrolysis often provides a good synthetic route to α-substituted acetic acids in spite of the rather vigorous conditions required for the hydrolysis (Eq. 6).[11a]

$$n\text{-}C_4H_9\text{-}CH_2\text{-}CN \xrightarrow[n\text{-}C_4H_9Br,\ \phi CH_3,\ \text{reflux}]{NaNH_2} (n\text{-}C_4H_9)_3C\text{-}CN \xrightarrow[H_2O,\ \text{reflux}]{H_2SO_4\ (80\%)}$$

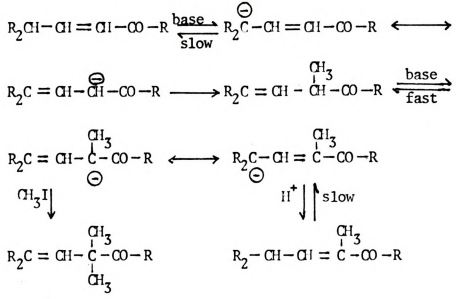
81%

$$(n\text{-}C_4H_9)_3C\text{-}CONH_2 \xrightarrow[HCl,\ HOAc]{n\text{-}C_4H_9\text{-}ONO} (n\text{-}C_4H_9)_3C\text{-}CO_2H \qquad \text{(Eq. 6)}$$

90% 79%

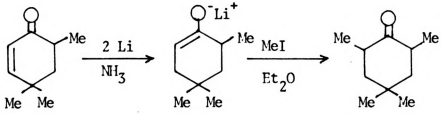
Alkylation of α,β-Unsaturated Ketones

Alkylations of α,β-unsaturated ketones[11a] having enolizable gamma hydrogens proceed almost exclusively at the alpha position to form the α-alkyl-β,γ-unsaturated ketone.[23] This initial product may isomerize to an α-alkyl-α,β-unsaturated ketone or may undergo further alkylation. Dialkylation has often been the major reaction in such cases because a proton is abstracted more readily from the intermediate β,γ-unsaturated ketone than from the starting material or the alkylated α,β-unsaturated ketone. Dialkylation, however, may be diminished either by the slow addition of the alkylating agent or by the use of a less reactive alkylating agent.



(Eq. 7)

When lithium-ammonia[14] was used as the base for the alkylation of α,β-unsaturated ketones, the only monoalkylation product obtained was derived from alkylation of the specific lithium enolate produced in the reduction step (see Eq. 8). This reduction -alkylation procedure provides an excellent method for directing alkylation to the relatively inaccessible α-position of an unsymmetrical ketone. The success of this method depends upon the now well established fact that alkylation

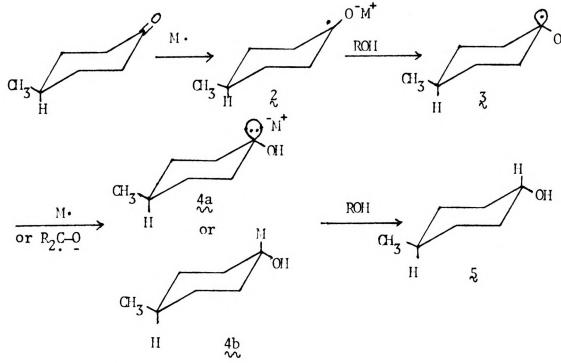


(Eq. 8)

of specific lithium enolates of unsymmetrical ketones with relatively reactive alkylating agents occurs faster in a variety of solvents than does equilibration among the structurally isomeric enolates via proton transfer reactions.

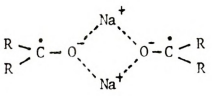
Reduction of Ketones

Ketones can be reduced to alcohols by a wide variety of reducing agents such as lithium aluminum hydride, diborane, hydrogen over a platinum catalyst and dissolving metals.[11b] Pertinent to this thesis are the dissolving metal reductions. These reductions of aliphatic ketones to alcohols are believed to follow the reaction path indicated below.

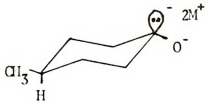


An electron is transferred from the metal to the ketone to form a radical anion 2 which is then protonated to give a free radical intermediate such as 3 with the hydroxyl group in an equatorial position. In a medium containing excess reducing species, rapid reduction of the neutral radical 3 to form an anion 4 or an organometallic intermediate is to be expected. This species would also be expected to adopt the indicated more stable geometry 4. The final protonation of the anionic intermediate with retention of configuration at carbon leads to the observed more stable product.

Radical anion 2 may also exist as a dimeric ion pair 6, especially in relatively nonpolar media when the cation is a relatively small alkali metal cation such as lithium or sodium. Pinacol products may be formed under these conditions. The formation of dianionic intermediates such as 7 from aliphatic ketones, or even from α,β-unsaturated ketones, seems unlikely, since the reduction potential for forming such species is too great, and the commonly used reducing systems[2] just do not have sufficient reduction potential for the second reduction unless the negative charge is first neutralized.



6



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We have seen that ketone alkylations, when carried out in solution using conventional strong bases, often suffer from low to modest yields, lack of regiospecificity, considerable dialkylation and other problems which clearly limit synthetic utility. High surface sodium and potassium are easily prepared, constitute a highly reactive form of alkali metals, and high surface area of solid support. Therefore, it was thought worthwhile to examine and explore the synthetic applicability of high surface sodium and potassium, particularly in the alkylations and reductions of ketones. It was the hope that in these alkylations, the enolate ions generated by HSS would be adsorbed specifically on the surface. In this way, monoalkylated product might be formed regioselectively as compared to the conventional alkylations in solution. The high surface

sodium reduction of ketones might also occur stereoselectively. Results of these studies are presented in this part of my thesis.

RESULTS AND DISCUSSION

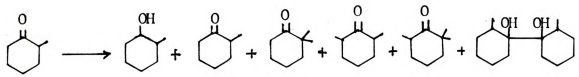
High surface sodium on charcoal (HSS-C), high surface sodium on graphite (HSS-G), high surface potassium on charcoal (HSP-C) and high surface sodium on alumina (HSS-A) were prepared for this study. Procedures for these preparations are given in the experimental section.

1. The Alkylation of Cyclic Ketones

A. Alkylation of 2-Methylcyclohexanone

It was originally thought that an ideal substrate for this study would be a simple, unsymmetrical ketone which could give us information as to whether alkylation using HSS is regioselective. Thus 2-methylcyclohexanone was chosen. Hexane was chosen as the solvent simply because it is inert to alkali metals and relatively easy to dry. Methylation of 2-methylcyclohexanone was carried out with high surface sodium and potassium under various conditions. Results of these methylations are presented in Table 3. The products were isolated by VPC and identified by comparison of their IR,NMR and mass spectra with those of the literature. The product mixture contained 2-methylcyclohexanol 8, 2-methylcyclohexanone 9, 2,2-dimethylcyclohexanone 10, 2,6-dimethylcyclohexanone 11, and 2,2,6-trimethylcyclohexanone 12. In one reaction, 2,2'-dimethylbicyclohexyl-1,1'-diol 13 was isolated in trace amounts.

Table 3 Methylation of 2-Methylcyclohexanone with High Surface Alkali Metals and Methyl Iodide in Hexane.[a,b]



9 8 9 10 11 12 13

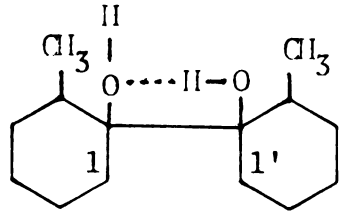
Reaction time	metal(%)	8(%)	9(%)	10(%)	11(%)	12(%)	13(%)
1 hr	HSS-C(10)	15	22.5	28.1	3.0	1.3	-
1 hr	HSS-C(15)	18.5	10.1	38.3	4.2	4.0	-
2 hr	HSS-C(20)	11.8	19.7	45	5	5.7	-
1 hr	HSS-C(25)	20.4	14.2	43	4.6	2.8	-
1 hr	HSS-C(30)	20.1	16.9	42	4.5	2.7	-
2 hr	HSS-G(20)	8.9	2.3	57.6	6.4	14.5	0.5[c]
1 hr	HSP-C(10)	6.7	36.5	18.0	1.8	2.3	-
overnight	HSS-A(15)	10.2	19.8	45	4.4	7.2	-

(a) Equimolar amounts of ketone, metal, and methyl iodide were used.

(b) Yields are calculated by VPC analysis using tridecane as an internal standard.

(c) Isolated yield.

The presence of 2,6-dimethylcyclohexanone 11 was confirmed by comparing its VPC retention time (using a capillary column to effect separation) and its NMR spectrum with those of an authentic sample. The NMR spectrum of the alcohol 8 showed that it consisted of about 85% of trans form and 15% of cis form. The IR spectrum of compound 13 in CCl_4 solution shows absorptions at 3620 and 3550 cm^{-1} ($\Delta\nu$ = 70 cm^{-1}) indicating strong intramolecular hydrogen bonding[15] between the 1- and 1'-hydroxyl groups.



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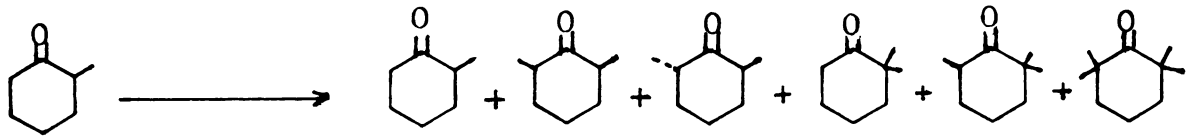
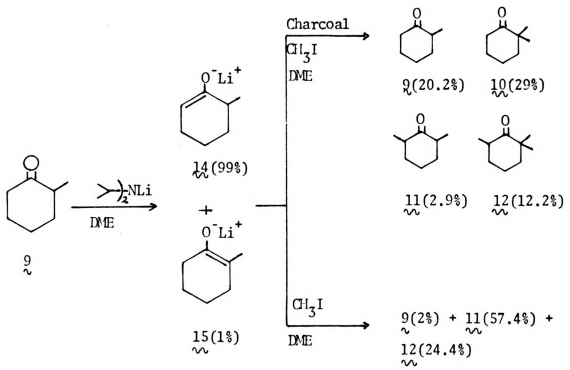
It is apparent from the data in Table 3 that the alkylation of 2-methylcyclohexanone using high surface alkali metals does work, and that monoalkylation predominates, usually to a greater extent than for comparable reactions in solution (for example see Eq. 9). The monoalkylaton product in all cases studied is mainly (≈ 90%) 2,2-dimethylcyclohexanone indicating that the surface may provide some selectivity with regard to different ketone enolates. In solution, the predominance of 2,2-dimethylcyclohexanone over 2,6-dimethylcyclohexanone is usually not so large (see Eq. 9).[11a,12b] The main competing reaction to alkylation is reduction to the corresponding alcohol, and in one case to a pinacol. Methylation with high surface sodium on graphite (in place of charcoal) seems to give more dialkylation product, probably because HSS-G is more reactive than HSS-C. In general, 20% HSS seems to give the best yield of monoalkylation product.



A: ϕ_3CK CH_3I,DME (% yield)	22	9	-	41	21	6
B: NaH,CH_3I DME (% yield)	48	13	13	18	8	-

(Eq. 9)

To see if the solid support would exercise a selectivity between different enolate ions, a mixture of lithium enolate 14 (99%) and 15 (1%) was generated by the reaction of 2-methylcyclohexanone with lithium diisopropylamide under conditions of kinetic control, according to House's procedure.[12a] Charcoal was then added and the resulting enolate solution was alkylated with methyl iodide. Surprisingly, the monoalkylation product found was mainly 2,2-dimethylcyclohexanone, which is the alkylation product of enolate ion 15 (Eq. 10). On the contrary, the same enolate ion mixture 14 and 15, when reacted with methyl iodide directly, gave 2,6-dimethylcyclohexanone as the major monoalkylated product. Apparently charcoal (and other solid supports) shift the enolate composition from predominantly the less substituted enolate ion 14 to predominantly the more substituted enolate ion 15, leading to the geminally substituted ketone.



(Eq. 10)

A plausible explanation for this result can be envisioned as follows. In nonpolar solvents, metal ions are mostly on the surface and most of the enolate ions are adsorbed on the surface. Models of enolate 15 show that the methyl group is in the double bond plane, and can be adsorbed parallel to the surface, whereas in enolate 14 the C-2 methyl group is either in a quasi-equatorial or quasi-axial position which would hinder adsorption on the surface to some extent. Charcoal may contain some proton donor (HR, such as trace of water in this case, and starting ketone in the case of HSS-alkylation) which would catalyze the equilibration between enolate 14 and 15 (Fig. 1) with the result that the thermodynamically more stable enolate 15 predominates and the geminally substituted alkylation product is obtained.

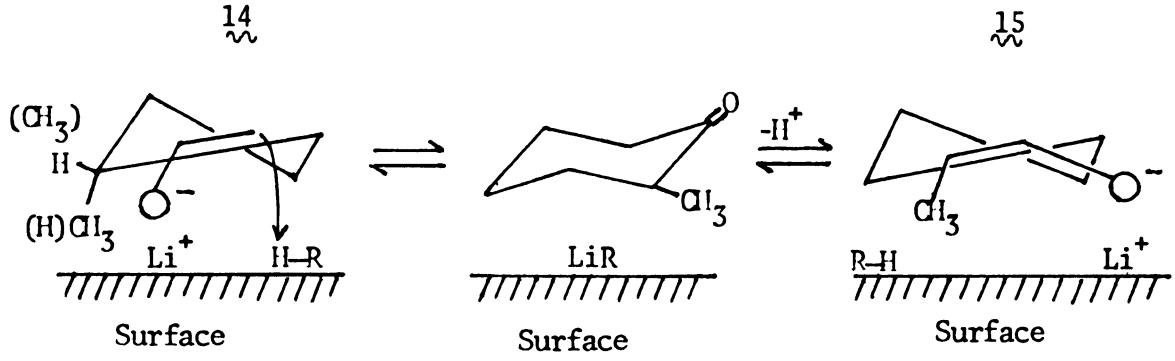
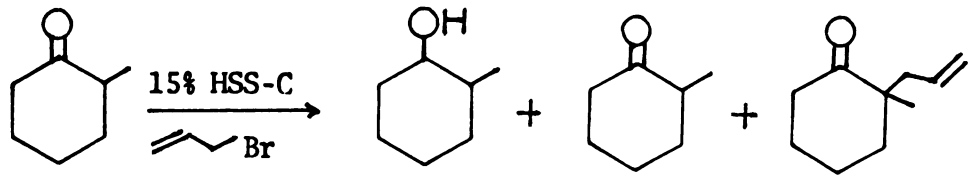


Figure 1. Equilibration of Enolate Ions 14 and 15 on Charcoal

The adsorption of enolates on the surface can also account for the predominance of monoalkylation product over dialkylation product. Since the monoalkylated product has to diffuse to another place on the surface to form enolate again for dialkylation, this process is relatively slow and noncompetitive with monoalkylation. Therefore only a small amount of the dialkylation product would be expected. In contrast to the conventional methods for the alkylation of ketones, side products like aldol condensation and O-alkylation products are not observed in HSS alkylation of 2-methylcyclohexanone.

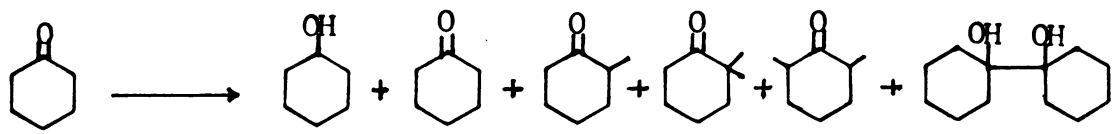
The reactivity of the alkylating agent is also important in the α-alkylation of ketones. When the alkylating agent is more reactive, as with allyl bromide, competing dialkylation and reduction are decreased. Thus, 2-methylcyclohexanone was alkylated with 15% HSS-C and allyl bromide to give a 68% yield of monoalkylated product 16 along with some starting ketone and reduction product.



9 8(11.5%) 9(11%) 16(68%)

B. Methylation of Cyclohexanone

High surface alkali metals were also used to study the methylation of cyclohexanone. The results are summarized in Table 4. Alkylation still predominates over the reduction. In this case dialkylation constitutes a serious side reaction, particularly when THF was used as solvent. One possible explanation is that the enolate ion remains adsorbed on the surface in hexane but is somewhat soluble in THF. Thus in THF equilibration of the initially formed enolate anion with the monoalkylated product will compete with monoalkylation and result in dialkylated product as shown in equation 5. Dialkylation was more serious when HSS-G was used in place of HSS-C.



17 18 17 9 10 11 19

Table 4 Methylation of Cyclohexanone with High Surface Alkali Metals and Methyl Iodide.[a,b]

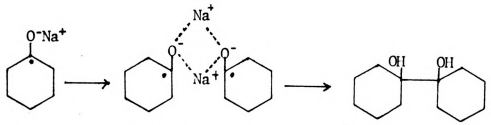
Reaction time	Solvent	Alkali	18(%)	17(%)	9(%)	10(%)	11(%)	19(%)
2 hr	hexane	HSS-G(20)	10.5	7.5	49	15.0	1.7	10.5
2 hr	hexane	HSS-G(20)	3.3	5.0	38	23	2.4	18.5
2 hr	THF	HSS-G(20)	26.8	1.3	22.7	26	2.9	5.0
1 hr	hexane	HSP-G(10)	8.5	18.9	33.3	3.6	0.4	-

(a) Equimolar amounts of ketone, metal, and methyl iodide were used.

(b) Yields are calculated by VPC analysis using p-diisopropylbenzene as an standard.

(c) Isolated yield.

Pinacol is formed in a greater amount than alcohol when hexane is used as the solvent, whereas in THF more alcohol is formed than pinacol. It has been suggested that pinacols normally arise from the dimerization of the ion pair dimer 46 formed form radical anion 45.[11b,19] Radical anion 45 is probably not soluble in a nonpolar solvent like hexane and remains adsorbed on the surface as an ion pair dimer which would favor the formation of pinacol. Radical anion is somewhat soluble in THF: it can either diffuse back to the metal surface for further reduction or abstract a proton from the starting ketone in solution, and subsequent hydrolysis would yield an alcohol (see page 27 for mechanism).



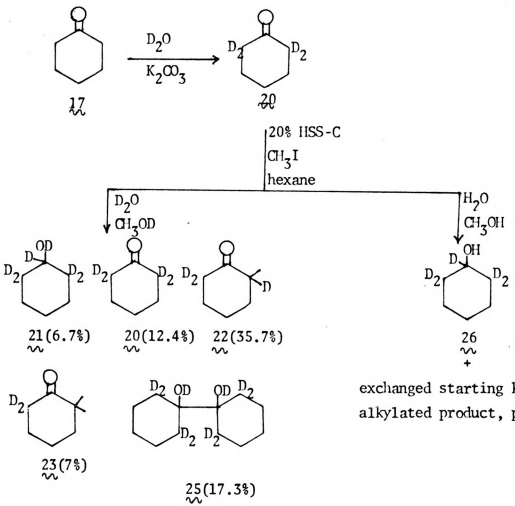
45 46 19

In order to gain some understanding about the mechanism, particularly the source of hydrogen for the unimolecular reduction, a labeling experiment was performed. Treatment of cyclohexanone with D_2O and potassium carbonate gave 2,2,6,6-tetradeuterocyclohexanone 20 (≈ 92% d_4)[20] which has only a singlet at δ 1.80 in its NMR spectrum. Compound 20 was then methylated with 20% HSS-C and methyl iodide in hexane for 2 hr. When the reaction mixture was quenched with D_2O and CH_3OD, there was obtained a mixture of deuterated compounds which was analyzed by VPC (using tridecane as an internal standard) to give the product composition indicated in Eq. 11.

Among the products, 1,2,2,6,6-pentadeuterocyclohexanol-O-d 21 is worth noting. Compound 21 was clearly deuterated at the C-1 position because in its NMR spectrum the area of the peak corresponding to the C-1 methine proton was reduced by 90%; also, the mass spectrum showed a parent peak at m/e 106. When the reaction mixture was quenched with H_2O and ethanol, the alcohol obtained was 1,2,2,6,6-pentadeuterocyclohexanol 26 which also had deuterium at the C-1 position according to its NMR spectrum and to the parent peak at m/e 105 in its mass spectrum. However, the recovered starting ketone in this case had most of its α-deuteriums exchanged with hydrogen (69% d_0, 25% d_1, 6% d_2) and the monomethylated ketone also

had some of its α-deuterium exchanged with hydrogen (19% d_0, 38% d_1, 11% d_2, 12% d_3).

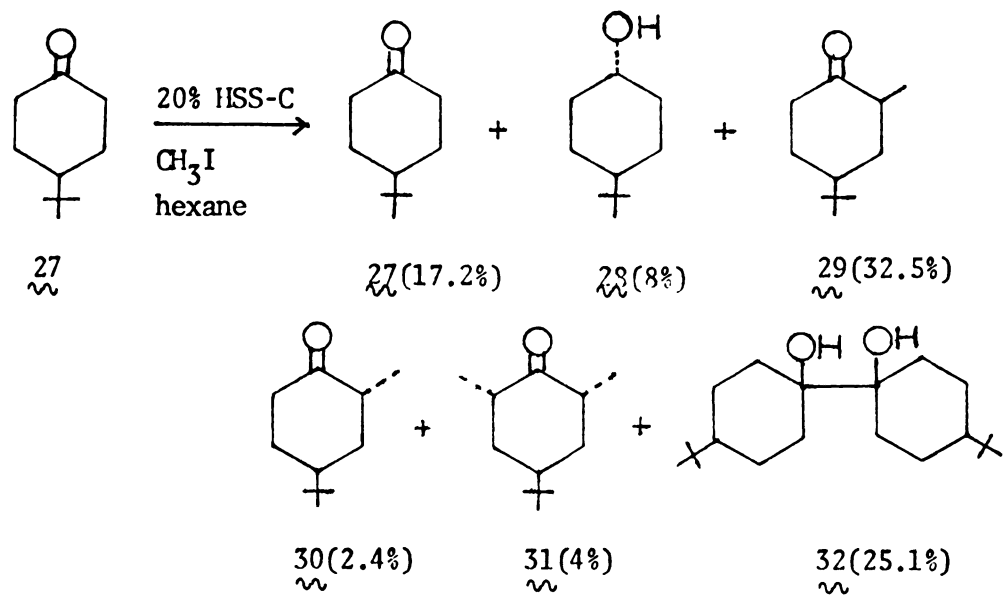
To be sure that the deuterated compound 23 was the 2,2-dimethylated product instead of 2,6-dimethylated product, it was treated with K_2CO_3 and water, to give after workup the non-deuterated 2,2-dimethylcyclohexanone (≈ 90%, ≈ 10% of it is 2,6-isomer).



(Eq. 11)

C. Methylation of 4-t-Butylcyclohexanone

In the case of 4-t-butylcyclohexanone, high surface sodium methylation gave the product composition shown in Eq. 12. The monoalkylated product cis and trans-2-methyl-4-t-butylcyclohexanone were obtained in 93 : 7 relative ratio which is the equilibrium rather than the kinetic ratio.[21] The predominant formation of cis-2-methyl-4-t-butylcyclohexanone may be because in order to have better adsorption on the surface, enolate 33 has to adopt a conformation (possibly half chair, Fig. 2) with its 4-t-butyl group pointing away from the surface: as a result, methyl iodide would have to approach the enolate anion from the side where t-butyl group is sticking up, to give the cis product 29. The reduction products found were trans-4-t-butylcyclohexanol 28 which is the more stable alcohol, and pinacol 32.



27

27(17.2%) 28(8%) 29(32.5%)

30(2.4%) 31(4%) 32(25.1%)

(Eq. 12)

33

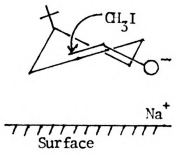


Figure 2. Adsorption of Enolate Ion 33 on Charcoal

D. Methylation of Cycloheptanone and Cyclooctanone

In order to see if ring size would have any effect on the high surface sodium methylation, cycloheptanone and cyclooctanone were studied. The results are summarized in Table 5. They show that monoalkylation still predominates over dialkylation, and that the dialkylated products are 2,2-isomers instead of 2,6-isomers. Reduction to alcohol is less important for cycloheptanone than for cyclohexanone, and even less so for cyclooctanone. The reason for this is not clear.

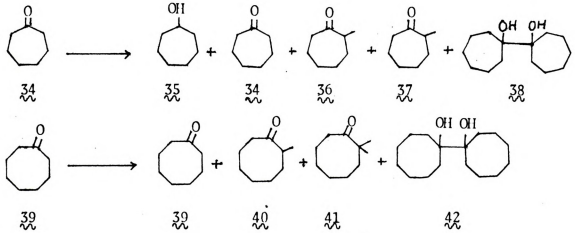


Table 5 Methylations of Cycloheptanone 34 and Cyclooctanone 39

Ketone	Reaction time	Alcohol (%)	Starting ketone(%)	Monoalkylated ketone(%)	Dialkylated ketone(%)	Pinacols (%)
34	overnight	35(6.5%)	34(21.8%)	36(45.8%)	37(7.8%)	38(12%)
39	1.5 hr	-	39(36.2%)	40(41%)	41(14%)	42(5%)

(a) Methylations were done with 20% HSS-C and methyl iodide in hexane.

(b) Product composition calculated by VPC employing triangular method.

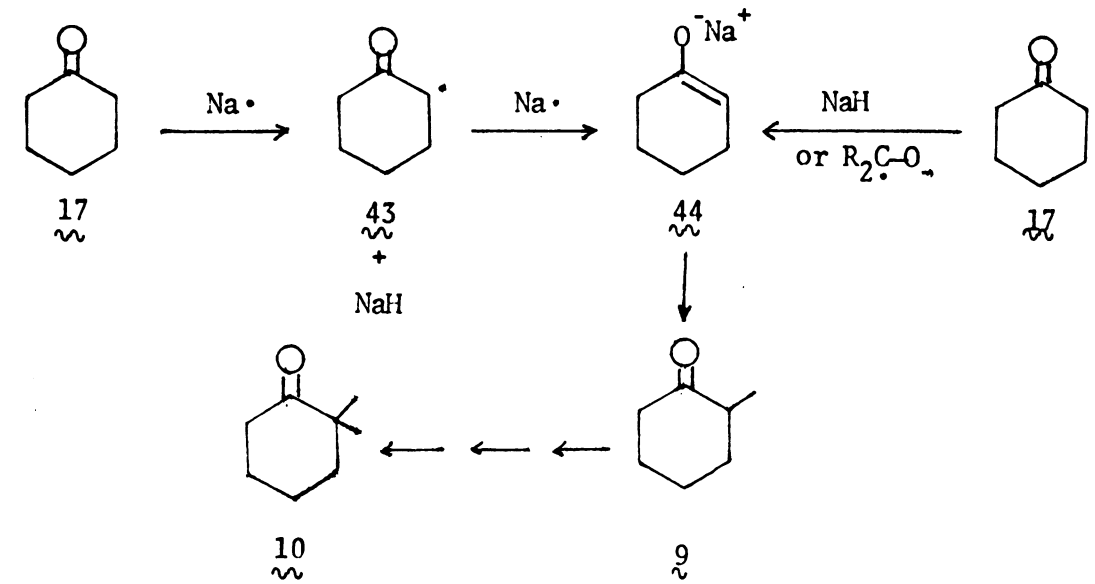
(c) Dialkylated products are predominantly 2,2-isomer in each case.

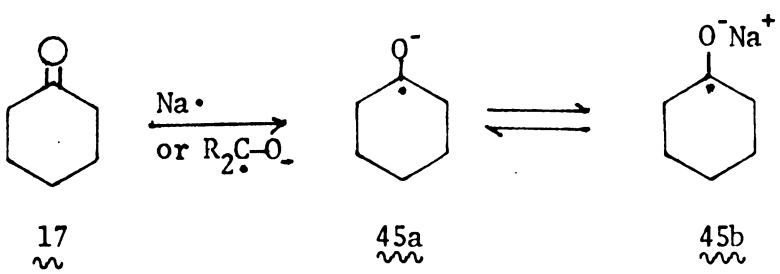
E. Mechanism

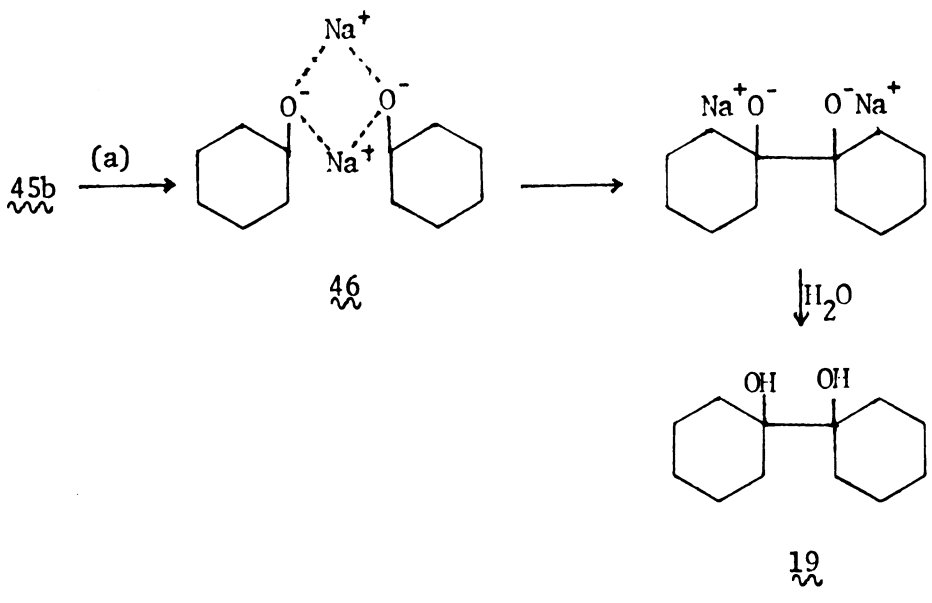
The fact that alkylated products and reduction products are both formed in the alkylation of saturated cyclic ketones with high surface alkali metals indicates that the formation of both the intermediates (enolate ions) leading to the alkylated products and intermediates (radical anion)[16,17] leading to the reduced product are occurring simultaneously. A possible general mechanism to account for the results of the HSS alkylation of cyclic ketones is shown in Scheme 1 (cyclohexanone is taken as an example).

High surface sodium (or potassium), due probably to its atomic dimension, may abstract an alpha hydrogen from ketone 17 to form radical

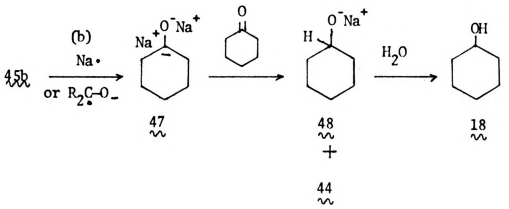
Scheme 1

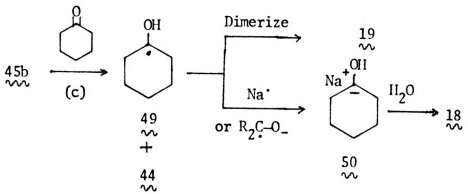

Na•
Na•
NaH
or R2C–O-
17
43
+
NaH
44
17
10
9

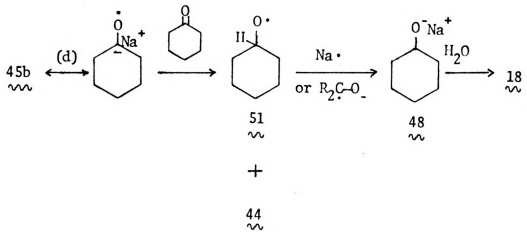

Na•
or R2C–O-
17
45a
45b


45b
(a)
46
H2O
19

Scheme 1 (continued)







43 and sodium hydride. Radical 43 thus formed may further be reduced to the enolate ion 44 which then reacts with methyl iodide to give the monoalkylation product 9. Subsequent enolization and alkylation of 9 should give rise to the dialkylation product 10. Enolate ion 44 may also be produced by the abstraction of an alpha proton from ketone 17 with sodium hydride or radical anion in situ. The reason for the predominant formation of the more substituted enolate ions from the unsymmetrical ketone with HSS is presented on page 19.

Since dissolving metals and alkali atoms have about the same reduction potentials,[2] the mechanism to account for the formation of reduction products of cyclic ketones by high surface alkali metals may be similarily envisioned as those for the reduction of ketones by dissolved metals.[11b] Transfer of an electron from the high surface sodium to the antibonding π^*-orbital of the carbonyl group can give rise to a radical anion 45a (or ketyl)[16] having the greater unpaired electon density on carbon. This radical anion has several competitive reaction pathways open to it.

When proton donors are absent, formation of the tight ion pair 45b and the ion pair dimer 46 derived from it would be expected. The ion pair dimer 46 in a nonpolar solvent can couple to form pinacol 19. However, in the case of 2-methylcyclohexanone, steric hindrance due to the C-2 methyl retards pinacol formation to the extent that only trace of it was observed, thus pathway a would seem to be noncompetitive.

Although it is unlikely that the reduction potential of atomic sodium

is sufficiently negative to form free dianions from aliphatic ketones, tight ion pair 45b might be capable of adding a second electron to form dianion 47, for the negative charge in 45b is already partially neutralized by association with metal ions. The dianion 47, in the absence of added proton donor, can abstract a proton from the weakly acidic starting ketone to form alkoxide ion 48 and enolate 44. Alkoxide ion 48 upon hydrolysis should give alcohol 18.

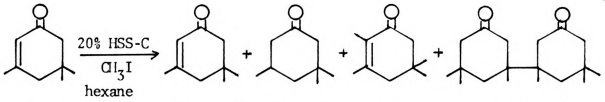
Radical anion 45b, in a less likely reaction, might also abstract a proton from starting ketone to give rise to an hydroxy radical 49 which could then be further reduced to hydroxy anion 50 in the presence of excess reducing species. The hydroxy radical 49 may also couple to yield pinacol 19. Protonation of radical anion 45b can also occur at the carbonyl carbon as suggested by House[19] and Murphy[18] to give alkoxy radical 51 which could be further reduced to an alkoxide ion 48, and finally hydrolyzed to alcohol 18.

It is difficult to tell which pathways would be favored for 45b in the reduction part of the mechanism. However, on the basis of our results some suggestions can be made. Pathway b may not be competitive because no excess reducing agent was used in almost all cases studied. Pathway c may be ruled out based on a labeling experiment which showed that the C-1 methine proton of the reduced product (alcohol) came from the starting ketone (see page 23). Therefore, pathway d seems most likely to be operative. In general, the results showed that the alkylation products were formed in greater amounts than the reduction products in the HSS alkylation of saturated cyclic ketones. Hence, the rate of formation

of enolate ions would be faster than that of the radical anions.

2. Methylation of Isophorone

A high surface sodium alkylation was also done on an α,β-unsaturated ketone. Interesting results were obtained for the methylation of isophorone with 20% HSS-C (10% excess of Na) as indicated in Eq. 13. It is apparent that in this particular case reduction competes very well with alkylation. A substantial amount of 1,6-diketone resulting from the reductive coupling at the β-position of isophorone was obtained.



52 52 (12.6%) 53 (10%) 54 (32.1%) 55 (38.3%)

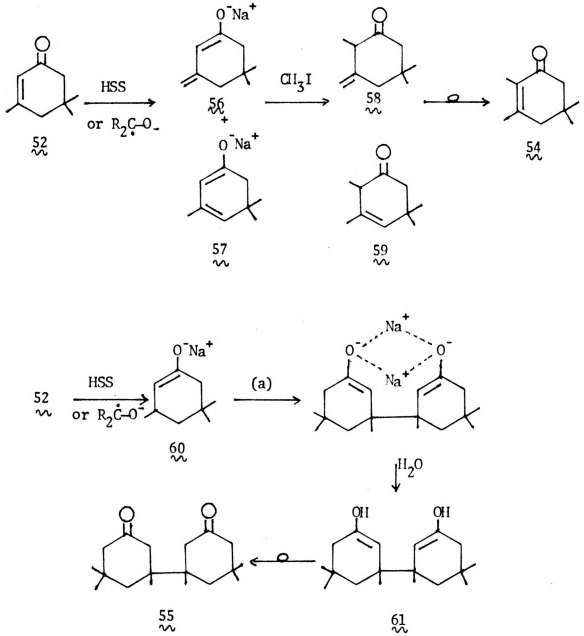
(Eq. 13)

In contrast to the metal-ammonia reduction of isophorone, no corresponding unsaturated pinacol was found.[37] And unlike the reductive alkylation of α,β-unsaturated ketones with lithium-ammonia, no saturated alpha alkylated product was observed in this reaction.[14] The only alkylated product was 2-methylisophorone 54 which presumably arises from alpha alkylation of the dienolate anion formed by abstraction of a γ-proton or γ'-proton from isophorone, and subsequent isomerization.

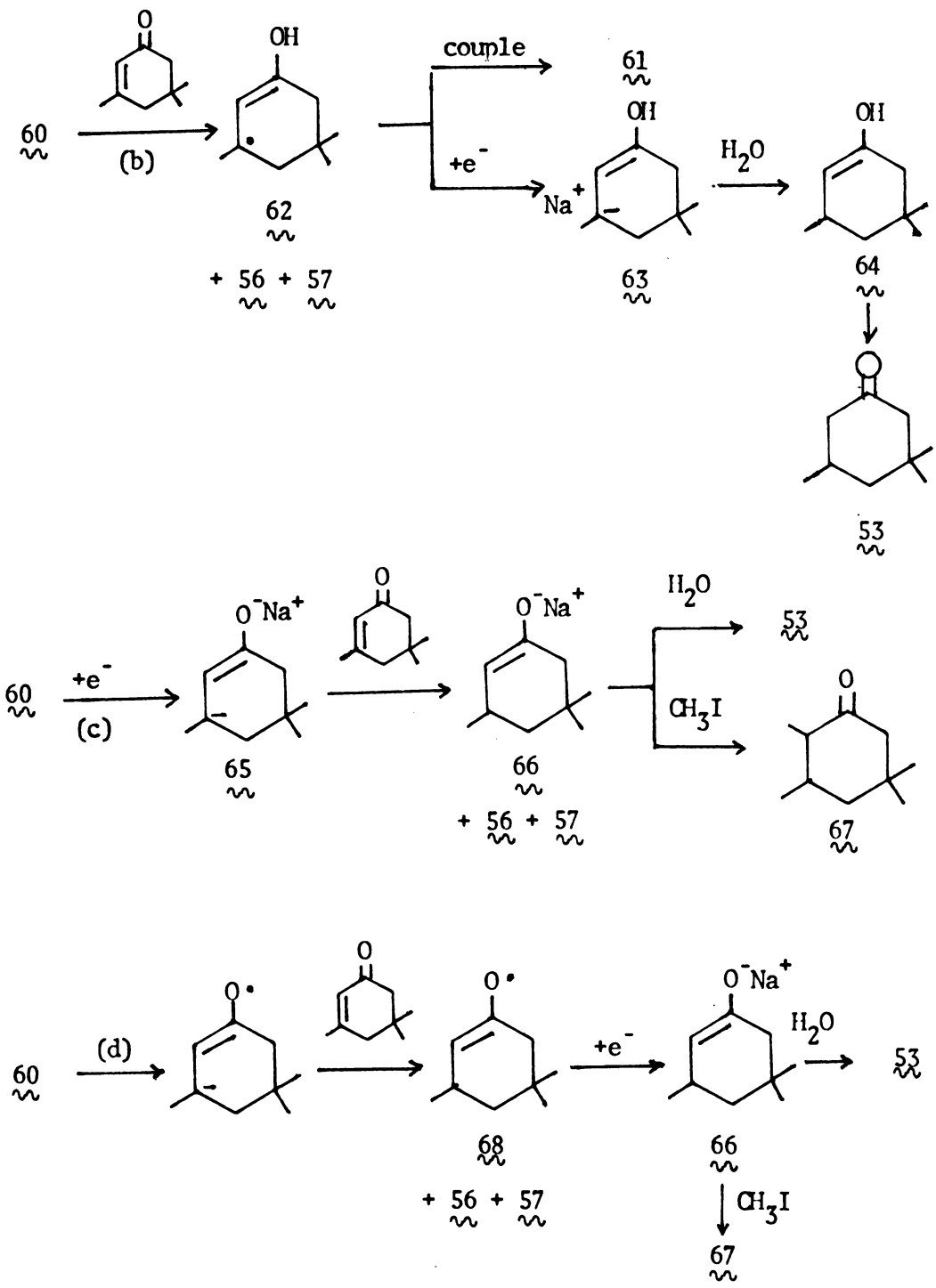
There have been many intensive studies concerning the reactions of α,β-unsaturated ketones, particularly reductions and alkylations with

metal-ammonia.[17] Several possible mechanisms involving a radical anion as a key intermediate have been proposed for these reactions. Similar mechanisms for the high surface sodium alkylation can also be envisioned as shown in Scheme 2.

Scheme 2



Scheme 2 (continued)



Formation of dienolate anions 56 and 57 from starting isophorone may be effected by either high surface sodium (in the same way as with saturated cyclic ketones) or by radical anion. Alkylation of the dienolate anions at the alpha positions would form the β,γ-unsaturated ketones 58 and 59. Isomerization of these initial products then gives the observed product 54. This result suggests that the dienolate anion formed by abstraction of a γ proton (or γ' proton) from an α,β-unsaturated ketone is more stable than its cross conjugated isomer generated by abstraction of a α'-proton.

The initial step in the reduction part of the mechanism is the transfer of an electron from high surface sodium to an antibonding π^*-orbital of the conjugated system, to produce radical anion 60. This radical anion may have four possible pathways for further reaction. In a nonpolar solvent, it may exist as an ion pair dimer which then dimerize to give, after hydrolysis, the intermediate dienol 61 and tautomerization of 61 eventually affords 1,6-diketone 55. In pathway b, in the absence of added proton donor, radical anion 60 can abstract an acidic proton (γ or γ') from isophorone to produce the hydroxyallyl radical 62 and dienolate anion 56 or 57. The hydroxyallyl radical 62 thus generated may be further reduced either by HSS or another radical anion to give a hydroxyallyl anion 63 which would undergo protonation to afford enol 64, and subsequent tautomerization should give a saturated ketone 53. Radical 62 can also couple to give 61. Dienolate anions 56 or 57 would be alkylated to yield the α-alkylated product 54.

Pathway c involves the formation of dianionic intermediate 65 by

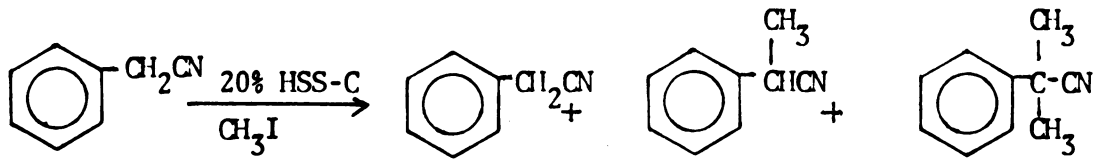
adding a second electron to the radical anion 60. Dianionic species have been suggested as intermediates in the reduction of enones with metals in liquid ammonia.[17] Protonation at the β-position of the dianionic intermediate 65 then gives the enolate anion 66. The hydrogen introduced at the β-position is derived from a proton donor and, in the absence of added proton donor, starting enone can serve as the proton donor. Enolate anion 66 can be alkylated at the α-position to yield the alkylated product 67 or hydrolyzed to give the reduced product 53.

Pathway d, which seems least likely, involves protonation of the radical anion 60 at the β-position[17] to produce the enolate radical 68 which adds an electron to give the enolate 66. Alkylation or hydrolysis of enolate 66 would yield 67 or 53. Since no ketone 67 was found in the HSS methylation of isophorone, pathways c and d may be ruled out. The result that 1,6-diketone 55 was formed in greater amount than the monomeric reduction product is indicative of pathway a being faster than pathway b as far as the radical anion 60 is concerned.

3. Methylation of Phenylacetonitrile

Recently, phenylacetonitrile has been alkylated using potassium-graphite (C_8K) as base by a group of Italian chemists.[9] They employed a molar ratio of nitrile : C_8K : alkyl halide of 1 : 2 : 2, and the yield of monoalkylation products obtained were about 60%. High surface sodium has proved to be useful in the alkylation of nitriles and the yield is better than that reported for C_8K. Thus the methylation of phenylacetonitrile with high surface sodium gave good yield of monoalkylation product as

indicated in Eq. 14; only small amount of the dialkylated product was isolated. The molar ratio of nitrile : HSS : methyl iodide employed was 1 : 1 : 1. The products were isolated by VPC and identified by comparing their spectroscopic and mass spectral data with those of authentic samples. Since no reduction product was found, the α-carbanion is likely to be the only intermediate leading to the formation of alkylated products.



69 69(7.6%) 70(74%) 71(4.4%)

(Eq. 14)

4. Reduction of Ketones

Since the high surface sodium methylations of cyclic ketones are always accompanied by a certain amount of reduction, it was interesting to see to what extent ketones would be reduced in the absence of an alkylating agent. Thus cyclohexanone and 2-methylcyclohexanone were reduced with HSS-C and HSS-G under various conditions, and the results are given in Tables 6 and 7. No proton donor was added in all cases studied.

Table 6 Reduction of Cyclohexanone with High Surface Sodium in the absence of an added Proton Donor.[a]

Metal(%)	Solvent	Reaction time	18(%)[d] Alcohol	17(%)[d] S.M.	19(%)[c] Pinacol
HSS-C(20)	hexane	2 hr	16.8	66.5	6.3
HSS-G(20)	hexane	2 hr	9.4	63.2	20.6
HSS-G(20)	THF	4 hr	52.4	33.3	5.3
HSS-C(20)	THF	4 hr	55.5	31.5	3.6
HSS-G(30)[b]	THF	2 hr	67.6	20.5	3.0

(a) No proton source was used except at workup. Ketone : metal = 1 : 1.
(b) Ketone : metal = 1 : 2 molar ratio. (c) Isolated yield.
(d) Yields determined by VPC analysis using p-diisopropylbenzene as internal standard.

Table 7 Reduction of 2-Methylcyclohexanone with High Surface Sodium in the absence of an added Proton Donor.[a]

Metal(%)	Solvent	Ratio (9:metal)	8(%)[d] Alcohol	9(%) S.M.	13(%)[c] Pinacol
HSS-C(20)	hexane	1 : 1	25.8	62.6	2.0
HSS-C(20)	THF	1 : 1	33.1	54.4	4.0
HSS-G(20)	hexane	1 : 2	30	66	3
HSS-G(20)	THF	1 : 2	83.4	8	3.5

(a) No proton source was added except at workup.
(b) All reactions were stirred at 60°C for 6 hr.
(c) The yields indicated refer to isolated yields.
(d) Yields determined by VPC analysis using p-diisopropylbenzene internal standard, and trans / cis ≃ 85 / 15.

It is clear from the results of both Tables 6 and 7 that the reduction of ketones with high surface sodium in the absence of an added proton donor would not go to completion even after prolonged reaction time. Apparently, the starting ketone has served as a proton donor, becoming converted to an enolate anion which, after workup, gave back the starting ketone. Reductions carried out in THF seem to yield more alcohol and less pinacol. This is probably because the radical anion intermediates formed during reduction are somewhat soluble in THF and subsequent diffusion back to the metal surface or an encounter with another radical anion (or ketone) occurs more readily. The reduction of 2-methylcyclohexanone with 2 molar equivalents of high surface sodium on graphite afforded a very good yield of alcohol, the most successful of the reductions studied. Thus, it seems necessary to use the molar ratio of ketone : metal of 1 : 2 for the reduction of ketones to alcohols without an added proton donor.

The mechanism of the reduction of ketones with high surface sodium should be considered the same as the reduction part of the mechanism for the alkylation of cyclic ketones with HSS (see Scheme 1). When ketone : metal = 1 : 1 molar ratio is employed, pathways b and d are probably competitive processes. In the case of ketone : metal = 1 : 2 molar ratio, dianionic intermediate might be produced predominantly and subsequent hydrolysis would yield an alcohol.

Although reduction of ketones to alcohols can be achieved with high surface sodium in good yield, very little is known about its detailed mechanism, and more research remains to be done in this field.

5. Summary

In this part of the thesis, evidence of the metallating and reducing properties of high surface sodium have been provided. In the alkylations of ketones or nitriles with HSS monoalkylation usually predominates; where regioselectivity is involved, the more highly substituted product is obtained. As to the HSS reduction, alcohol can be obtained in high yields with HSS (2 molar) in THF. The simplicity of workup, good yield of the desired product and the inexpensiveness of the reagent may make high surface sodium a synthetic useful reagent. For instance, HSS has been used to effect the monoalkylation of 1-tetralone and 2-tetralone in excellent yield.[24]

EXPERIMENTAL

1. General Procedures

The general procedures described here apply to all parts of the thesis. Analytical gas chromatography (VPC) was carried out on a Varian Aerograph Model 1400 (flame ionization detector), and preparative VPC was performed with a Varian Aerograph Model 90 P instrument (thermal conductivity detector). Except where otherwise noted, all NMR spectra were measured in $CDCl_3$ or CCl_4 solutions using TMS as an internal standard on a Varian T-60 spectrometer. The 180 MHz spectra were recorded on a Bruker spectrometer. The small number placed next to protons in the structures in the discussion sections are the NMR chemical shifts of those protons relative to tetramethylsilane. The numbers in parentheses beside the chemical shifts are the normalized europium shift numbers. These were obtained by adding small increments of tris- (1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione) Eu (III) to a CCl_4 or $CDCl_3$ solution of the compound being investigated.

Infrared spectra were recorded on a Unicam SP-200 or a Perkin Elmer 167 grating spectrophotometer and were calibrated against a polystyrene film. Ultraviolet spectra were obtained with a Unicam SP-800, using 95% ethanol as the solvent unless otherwise noted. Mass spectra at 70 eV were obtained from a Hitachi-Perkin Elmer RMU-6 operated by Mrs. Ralph Guile. High resolution mass spectra were done in Biochemistry Department, MSU. Melting points were determined with a Thomas-Hoover Melting Point

Apparatus and are uncorrected. Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Michigan, or Clark Microanalytical Laboratories, Urbana, Illinois.

2. Preparation of High Surface Sodium (HSS)

High surface sodium (HSS) and high surface potassium (HSP) of various percentages on different solid supports were prepared according to the following procedure (20% HSS on charcoal is taken as an example): 4.6 g of activated charcoal (predried under vacuum at 200°C for 15-30 min) was placed in a 250-ml 3-necked round-bottomed flask (equipped with mechanical stainless steel stirrer, thermometer, nitrogen inlet and oulet, and sodium dropping port) and heated to 120°C with stirring under nitrogen. Sodium (1.15 g, 0.05 mol) in small pieces was added through the port over a period of 15 min. As soon as the sodium melted, the mixture was stirred more rapidly for about 15 min. Upon cooling to room temperature, the HSS is then ready for use. The abbreviations used are as follow: HSS-C, HSS-G, and HSS-A for high surface sodium on charcoal, graphite or alumina respectively, HSP-C for high surface potassium on charcoal. HSS-C, HSS-G, and HSP-C are highly reactive, pyrophoric powders, black to dark purple depending on the percentage of the metal used. A small sample of each, when exposed to air, becomes red hot (sometimes even catches fire, HSP-C in particular).

2A. Chromatographic Columns

VPC columns that were used for analysis or preparative work in this section are designated as follows:

A. 10' x 0.125 in column, 15% D.C. silicone oil 710 on firebrick.

B. 10' x 0.25 in column, 20% D.C. silicone oil 710 on firebrick.

C. 8' x 0.25 in column, 15% Ucon on firebrick.

D. 5' x 0.25 in column, 5% FFAP on chromosorb G.

E. 150 ft D.C. silicone oil 550 capillary column.

3. Methylation of Cyclohexanone with HSS-C and Methyl Iodide

The methylation of cyclohexanone can be considered as typical for the procedure used with most ketones. Except where otherwise noted, all reactions were carried out under nitrogen or argon. A condenser and dropping funnel were connected to the flask which was used to prepare the 20% HSS-C (0.05 mol). Hexane (50 ml) was added to the cooled HSS-C to make a slurry. A solution of 4.9 g (0.05 mol) of cyclohexanone in 30 ml of hexane was added slowly with constant stirring at room temperature, and the mixture was stirred for about 30 min (the reaction is exothermic; if bubbling became too vigorous or the reaction mixture became too hot the flask was cooled briefly in an ice bath). A solution of 7.1 g (0.05 mol) of methyl iodide in 30 ml of hexane was introduced, and the reaction mixture was first stirred at room temperature for 30 min then refluxed for 2 hr. After the reaction mixture was cooled to room temperature, the unreacted sodium was carefully destroyed first with 10 ml of the methanol, then with 10 ml of water (it is essential to make sure that the unreacted sodium is completely destroyed, or it might catch fire during diltration). A mixture of solvents (ether : methylene chloride : methanol = 1 : 1 : 1; total of 100 ml) was added to the flask. After further stirring for 15 min, the reaction mixture was filtered, and the charcoal was washed with 30 ml of the above solvent mixture. The

combined filtrates were washed with saturated sodium chloride solution, and the organic layer was separated and dried (Na_2SO_4). Removal of solvent gave 5.0 g of the product mixture which was analyzed by VPC (column A, 140°, p-diisopropylbenzene was used as an internal standard) to give the following product composition: cyclohexanol (10.5%), cyclohexanone (7.5%), 2-methylcyclohexanone (49%), 2,2-dimethylcyclohexanone (15%), and 2,6-dimethylcyclohexanone (1.7%). Each of these compounds was collected by preparative VPC (column B, 155°C) and gave satisfactory data (IR, NMR, and mass spectra) as compared to those in the literature. A sample of 2,2-dimethylcyclohexanone 10 collected on the preparative column was found to contain about 10% of 2,6-dimethylcyclohexanone 11 by both analytical VPC (column E at 65°C, retention time 13 min for 10, 14.6 min for 11) and by NMR (for 10 singlet at δ 1.08, for 11 doublet at 0.96). After distilling the product mixture at reduced pressure (45~55°/5 mm Hg), there was left in the flask 0.5 g of solid which was recrystalized from petroleum ether and identified as bicyclohexyl-1,1'-diol (10.5%): MP 126°C; IR (CCl_4) 3620 (m), 3570 (m), 2950 (s), 1450 (s), 965 (s), 910 (m) cm^{-1}; NMR (CCl_4) δ 1.0 1.8 (broad); mass spectrum, m/e (rel. intensity) 198 (0.3), 180 (2), 162 (3), 137 (3.7), 99 (100), 81 (47). The results of methylations of cyclohexanone using 10% HSP-C, 20% HSS-G in hexane, and 20% HSS-G in THF are given in Table 4.

4. Methylation of 2-Methylcyclohexanone 9

The procedure and workup were as described for cyclohexanone. The results are summarized in Table 3. Yields were obtained by VPC analysis (column A, 145°C) using tridecane as an internal standard. Dialkylated

product in these cases is 2,2,6-trimethylcyclohexanone 12. When methylation was conducted with HSS-G (20%) and methyl iodide, reductive coupling of ketone 9 gave 2,2'-dimethylbicyclohexyl-1,1'-diol 13 which was isolated in very small amount by distillation. For 12: IR (neat) 1706 cm^{-1}; NMR (CCl_4) δ 0.96 (3H, d, J = 7 Hz), 1.0 (3H, s), 1.2 2.25 (6H, broad), 2.54 (1H, m); mass spectrum, m/e 140 (21%, parent). For 13: MP 138~140°; IR (CCl_4) 3620 (w), 3550 (w), 2940 (s), 1465 (m), 1390 (m), 1140 (m), 970 (m), 890 (w) cm^{-1}; NMR ($CDCl_3$) δ 1.14 (6H, d, J = 7 Hz), 1.25 2.3 (20H, broad); mass spectrum, m/e (rel. intensity) 226 (1.6), 198 (2.8), 190 (6.6), 175 (3.7), 133 (3.7), 123 (8), 113 (100), 95 (48).

5. Methylation of Enolate Mixture 14 and 15 in the Presence and Absence of Charcoal

An enolate mixture 14 and 15 was prepared from 2.8 g (0.025 mole) of 2-methylcyclohexanone and 0.025 mole of lithium diisopropylamide in 20 ml of dimethoxyethane (DME) at 0°C according to House's procedure.[12a] Predried charcoal (10 g) was then added and 3.6 g of methyl iodide in 5 ml of DME was added all at once. After stirring for 20 min, 20 ml each of $NaHCO_3$ solution and ether were added. The charcoal was filtered and the filtrate was extracted with ether. The organic layer was then washed successively with 5% HCl, sat. $NaHCO_3$ solution and dried (Na_2SO_4). The concentrated reaction mixture was analyzed by VPC (column A, at 145°C) to give the following composition: 9 (20.2%), 10 (29%), 11 (2.9%), 12 (12.2%).

When the same enolate mixture 14 and 15 (prepared as above) was methylated with methyl iodide in DME at 0°C directly, the reaction product analyzed by VPC (column A, 145°C) was found to have the following composition: 9 (2%), 11 (57.4%, both cis and trans isomers), 12 (24.4%).

6. Allylation of 2-Methylcyclohexanone

The procedure and workup were as described for the methylation of 2-methylcyclohexanone. Thus, 2-methylcyclohexanone (2.8 g, 0.025 mol) reacted with 15% HSS-C (3.88 g, 0.025 mol) and allyl bromide (3.02 g, 0.025 mol) in hexane for 4 hr to yield the following products (determined by VPC, column A, at 145°C): 2-methylcyclohexanol (11.5%), 2-methylcyclohexanone (11%), 2-allyl-2-methylcyclohexanone 16 (68%). For 16: IR (neat) 1700 (s), 1640 (m), cm^{-1}; NMR (CCl_4) δ 1.0 (3H, s), 1.2-1.95 (6H, broad), 1.95-2.5 (4H, broad), 4.8 (1H, m), 5.0 (1H, m), 5.58 (1H, m); mass spectrum, m/e (rel. intensity) 152 (19%, parent), 55 (100%).

7. Preparation of 2,2,6,6-Tetradeuterocyclohexanone 20

Cyclohexanone (9.8 g, 0.1 mol) was refluxed overnight with 8 g of D_2O and 1.5 g of potassium carbonate in a 100-ml flask equipped with a drying tube. Ether (8 ml) was added to the cooled reaction mixture. The organic layer was separated, dried (Na_2SO_4), and concentrated to give 8.6 g of deuterated cyclohexanone which according to NMR had 60% of the four α-hydrogens exchanged. The deuterium exchange reaction was then repeated several times. After the 4th exchange, 92% of deuterium exchange was a achieved and 6 g of the 2,2,6,6-tetradeuterocyclohexanone 20 was obtained. IR (neat) 1700 cm^{-1}; NMR (CCl_4) δ 1.80 (singlet); mass spectrum, m/e (rel. intensity) 102 (40), 56 (100).

8. Methylation of 2,2,6,6-Tetradeuterocyclohexanone 20

The procedure as described above for cyclohexanone was followed except at the point of workup where D_2O and CH_3OD were used to destroy the unreacted sodium, and tridecane was used as an internal standard for VPC analysis (column A, 140°C). Thus 5.1 g (0.05 mol) of 20 was methylated with 5.75 g of 20% HSS-C (0.05 mol) and 7.1 g of methyl iodide (0.05 mol) to give the following products: 1,2,2,6,6-pentadeuterocyclohexanol-O-d 21 (6.7%), 20 (12.4%), 2-methyl-2,6,6-trideuterocyclohexanone 22 (35.7%), 2,2-dimethyl-6,6-dideuterocyclohexanone 23 (6.3%), 2,6-dimethyl-2-6-dideuterocyclohexanone 24 (≈ 0.7%), 2,2,2',2',6,-6,6',6'-octadeuterobicyclohexyl-1,1'-diol-O-d_2 25 (17.3%). For 21: IR (neat) 3350 (s), 2920 (s), 2200 (w), 1450 (m) cm^{-1}; NMR (CCl_4) δ 1.0~1.9 (broad); mass spectrum, m/e 106 (parent). For 22: IR (neat) 1703 cm^{-1}; NMR (CCl_4) δ 0.98 (3H, s), 1.17~2.50 (6H, broad); mass spectrum, m/e 115 (parent). For 23: IR (neat) 1700 cm^{-1}; NMR (CCl_4) δ 1.06 (6H, s), 1.68 (6H, broad); mass spectrum, m/e 128 (parent). For 25: MP 123~125°C; IR (CCl_4) 3620 (w), 3570 (w), 2930 (s), 2200 (w), 2100 (w) cm^{-1}; NMR (CCl_4) δ 1.0~1.9 (broad); mass spectrum, m/e (rel. intensity) 188 (3%, M-20), 168 (6%, M-40), 149 (1.7), 131 (4), 114 (5), 103 (100); high resolution mass spectrum showed 208 (25), 207 (90), 206 (100), molecular formula $C_{12}H_{12}D_{10}O_2$.

When the quenching was done with H_2O and ethanol, the alcohol obtained was 1,2,2,6,6-pentadeuterocyclohexanol 26: IR (neat) 3340 (s), 2940 (s), 2200 (w), 2100 (w), 1450 (m) cm^{-1}; NMR (CCl_4) δ 1.0~2.0 (broad); mass spectrum, m/e 105 (parent). For recovered ketone 22: mass spectrum

showed 69% d_0, 25% d_1, 6% d_2. For 23: mass spectrum showed 19% d_0, 38% d_1, 31% d_2, 12% d_3.

9. Methylation of 4-t-Butylcyclohexanone 27

4-t-Butylcyclohexanone (7.5 g, 0.0487 mol) was methylated with 20% HSS-C (5.75 g, 0.05 mol) and methyl iodide (7.0 g, 0.049 mol) in hexane for 1.5 hr to give 8 g of crude product which was distilled at 60~65°C/0.5 mm Hg to yield 4.8 g of distillate and 2.0 g of solid residue. The distillate was analyzed by VPC (column B, at 170°C and column C at 150°C) to give the following products: 4-t-butylcyclohexanol 28 (8%), 4-t-butylcyclohexanone 27 (17.2%), cis-2-methyl-4-t-butylcyclohexanone 29 (32.5%), trans-2-methyl-4-t-butylcyclohexanone 30 (2.4%), 2,6-dimethyl-4-t-butylcyclohexanone 31 (4%). The solid residue was recrystallized from petroleum ether to give 4,4'-di-t-butylbicyclohexyl-1,1'-diol 32 (24.1%). For 28: IR (nujol) 3280 (m) cm^{-1}; NMR ($CDCl_3$) δ 0.82 (9H, s), 0.9 2.2 (10H, broad), 3.4 (1H, broad). For 29: IR (neat) 1710 cm^{-1}; NMR (CCl_4) δ 0.89 (9H, s), 1.0 (3H, d, J = 7 Hz), 1.20-2.60 (8H, broad); mass spectrum, m/e 168 (parent). For 30: IR (neat) 1710 cm^{-1}; NMR (CCl_4) δ 0.92 (9H, s), 1.13 (3H, d, J = 7 Hz), 1.25-2.65 (8H, broad); mass spectrum, m/e 168 (parent). For 31: NMR ($CDCl_3$) δ 0.90 (9H, s), 1.10 (6H, d, J = 7.5 Hz), 1.25-2.50 (7H, broad); mass spectrum, m/e 182 (parent). For 32: MP 252~253°C (sealed tube, sublimed); IR (nujol) 3500 (m), 2930 (s), 1460 (s), 1380 (m), 950 (w) cm^{-1}; NMR ($CDCl_3$) δ 0.86 (18H, s), 1.0 2.0 (20H, broad); mass spectrum, m/e 310 (0.5%, parent), 155 (100%, base).

10. Methylation of Cycloheptanone 34

Cycloheptanone (2.8 g, 0.025 mol) was methylated with 20% HSS-C (2.9 g, 0.025 mol) and methyl iodide (3.6 g, 0.025 mol) in hexane overnight to give after distillation (80~90°/20 mm) 2.3 g of distillate and 0.34 g of solid residue. The distillate was analyzed by VPC (column B, 175°C) and found to contain the following compounds: cycloheptanol 35 (6.5%), cycloheptanone 34 (21.8%), 2-methylcycloheptanone 36 (45.8%), 2,2-dimethylcycloheptanone 37 (3.8%). The solid residue was recrystallized from hexane to give bicycloheptyl-1,1'-diol 38 (12%). For 35: NMR (CCl_4) δ 2.10-0.90 (13H, broad), 3.65 (1H, broad). For 36: NMR (CCl_4) δ 1.02 (3H, d, J = 7 Hz), 1.68 (8H, broad), 2.40 (3H, broad). For 37: NMR (CCl_4) δ 1.02 (6H, s), 1.56 (8H, broad), 2.40 (2H, broad). For 38: MP 75.5°C; IR (CCl_4) 3620 (m), 3560 (m) cm^{-1}; NMR (CCl_4) δ 1.53 (broad); mass spectrum, m/e (rel. intensity) 226 (0.36), 208 (2.2), 190 (5.5), 151 (6), 133 (46), 113 (100), 95 (50).

11. Methylation of Cyclooctanone 39

Cyclooctanone (3.2 g, 0.025 mol) was methylated with 20% HSS-C (3.14 g, 0.028 mol) and methyl iodide (4.0 g) in hexane for 1.5 hr to give after distillation 3.0 g of distillate and 0.16 g of solid residue. The distillate was analyzed by VPC (column B, at 185°C) and contained the following compounds: cyclooctanone 39 (36.2%), 2-methylcyclooctanone 40 (41%), 2,2-dimethylcyclooctanone 41 (14%). The solid residue was recrystallized from hexane to give bicyclooctyl-1,1'-diol 42 (5%). For 40: NMR (CCl_4) δ 0.98 (3H, d, J = 7 Hz), 1.1-2.05 (10H, broad),

2.05-2.7 (3H, broad). For 41: NMR (CCl_4) δ 1.0 (6H, s), 1.1-2.0 (10H, broad), 2.0-2,5 (2H, broad). For 42: MP 86-88°C, IR (CCl_4) 3630 (w), 3560 (w) cm^{-1}; NMR (CCl_4) δ 1.3-2.0 (broad); mass spectrum, m/e (rel. intensity) 254 (1.5), 236 (2.2), 218 (2.2), 165 (6), 127 (100).

12. Methylation of Isophorone 52

Isophorone (3.5 g, 0.02536 mol), was methylated with 20% HSS-C (3.1 g, 0.028 mol) and methyl iodide (4.0 g, 0.028 mol) in hexane for 1.5 hr to give after distillation (64-69°C/1.5 mm Hg) 2 g of distillate and 1.33 g of residue. The distillate was found by VPC (column B, 185°C) to have the following compositon: 3,3,5-trimethylcyclohexanone 53 (10%), isophorone 52 (12.5%); 2-methylisophorone 54 (32.1%). The residue was recrystallized from petroleum ether to give 1,1',3,3,3',3'-hexamethyl-bicyclohexyl-5-5'-dione 55 (38.3%). For 53: IR (neat) 1715 (s) cm^{-1}; NMR (CCl_4) δ 0.95 (3H, d, J = 6 Hz), 1.02 (6H, s), 1.15-1.75 (3H, broad), 1.75-2.4 (4H, broad); mass spectrum, m/e (rel. intensity) 140 (23), 125 (13), 109 (5), 97 (7), 83 (100), 69 (57). For 54: IR (neat) 2950 (s), 1665 (s), 1380 (s), 1320 (s) cm^{-1}; UV (95%, ethanol) λ_{max} 252 nm (ε 6870); NMR (CCl_4) δ 0.98 (6H, s), 1.68 (3H, s), 1.83 (3H, s), 2.07 (4H, s); mass spectrum, m/e (rel. intensity) 152 (30), 137 (5), 109 (8), 96 (100), 83 (7), 68 (27). For 55: MP 156-157°C; IR (CCl_4) 2960 (s), 1710 (s), 1460 (w), 1395 (w), 1280 (m) cm^{-1}; NMR ($CDCl_3$) δ 1.05 (18H, s), 1.35-1.80 (4H, broad), 2.0-2.3 (8H, broad); mass spectrum, m/e (rel. intensity) 278 (0.2), 263 (0.7), 207 (1), 153 (11), 139 (100), 125 (33).

13. Methylation of Phenylacetonitrile 69

Phenylacetonitrile (5.85 g, 0.025 mol) was methylated with 20% HSS-C (5.75 g, 0.05 mol) and methyl iodide (7.1 g, 0.05 mol) in a solvent mixture of hexane and THF for 2 hr to give 5.6 g of product mixture which was analyzed by VPC (column C, 170°C) and contained the following products: phenylacetonitrile 69 (7.6%), 2-methylphenylacetonitrile 70 (74%), 2,2-dimethylphenylacetonitrile 71 (4.4%). For 70: NMR (CCl_4) δ 1.6 (3H, d, J = 7 Hz), 3.75 (1H, q, J = 7 Hz), 7.2 (5H, s); mass spectrum, m/e 131 (parent, 31%), 116 (100%). For 71: NMR (CCl_4) δ 1.67 (6H, s), 7.2 (5H, broad); mass spectrum, m/e 145 (parent, 27%), 130 (100%).

14. Reduction of Cyclohexanone with High Surface Sodium

The procedure and workup were essentially the same as that described for the methylation of cyclohexanone, except in these cases no methyl iodide was used. The results are summarized in Table 6.

15. Reductions of 2-Methylcyclohexanone with High Surface Sodium

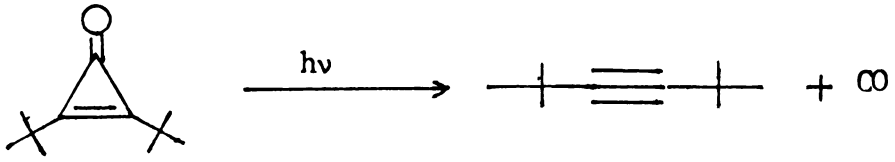
The procedure and workup were as described for the reductions of cyclohexanone and the results are summarized in Table 7.

PART II

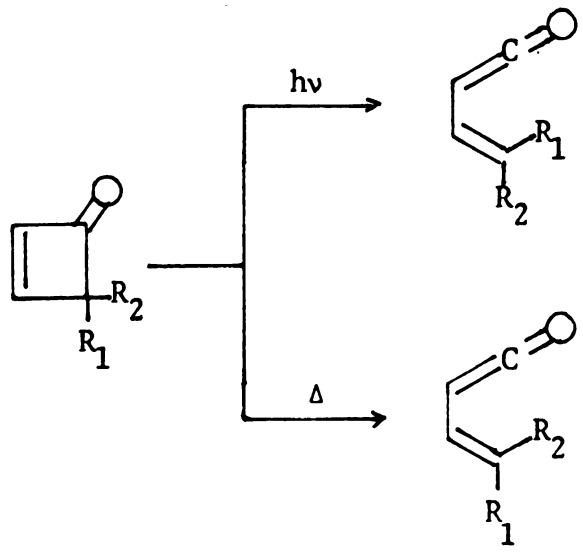
SYNTHESIS AND PHOTOCHEMISTRY OF SUBSTITUTED 2-CYCLOOCTENONES

INTRODUCTION

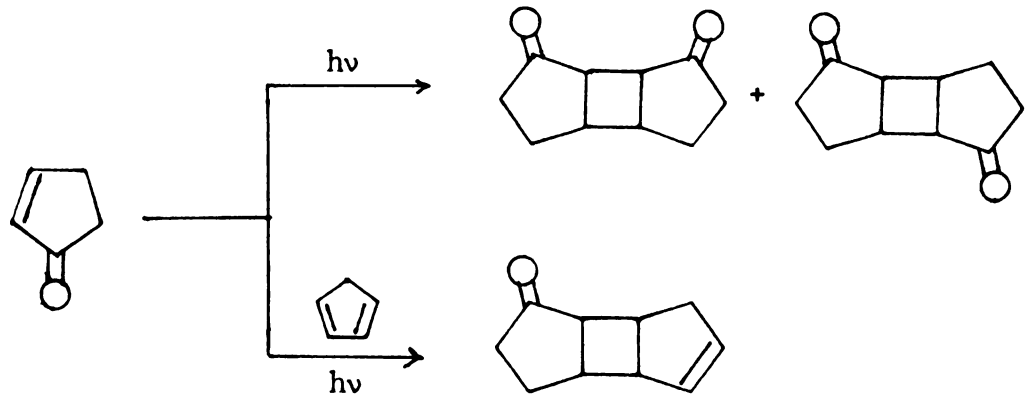
In recent decades the photochemistry of cyclic α,β-unsaturated ketones has received considerable attention.[25a] Particularly interesting is the fact that the reaction course is profoundly influenced by the ring size. The major photochemical reaction of cyclopropenones is the loss of carbon monoxide. For example, irradiation of a 3% solution of di-t-butylcyclopropenone at 2537Å results in the formation of di-t-butylacetylene;[25b] apparently, decarbonylation is sufficiently fast that other processes cannot compete.



Cyclobutenone derivatives open to vinyl ketenes thermally and photochemically,[26b] but the stereochemistry of the opening is different in the thermal and photochemical processes. The ketene from perchlorocyclobutenone has been observed spectroscopically.[26a]

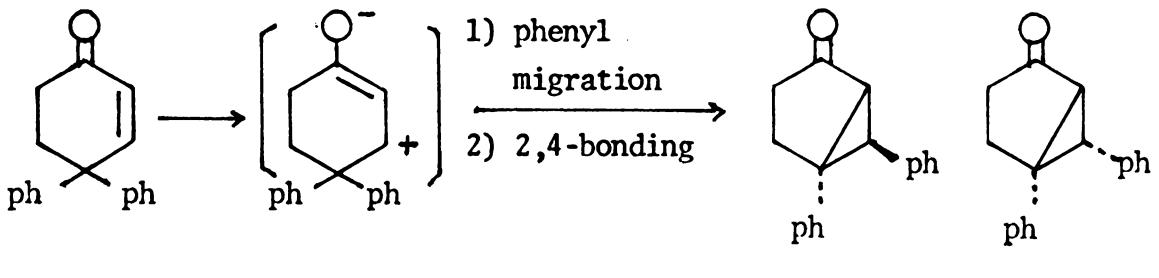


The five and six membered homologs can undergo intermolecular photoreactions.[27a] 2-Cyclopentenone, upon irradiation, leads to the cyclobutane dimers in good yield, while in the presence of excess cyclopentadiene (2 + 2) cross cycloaddition takes place.[27b]

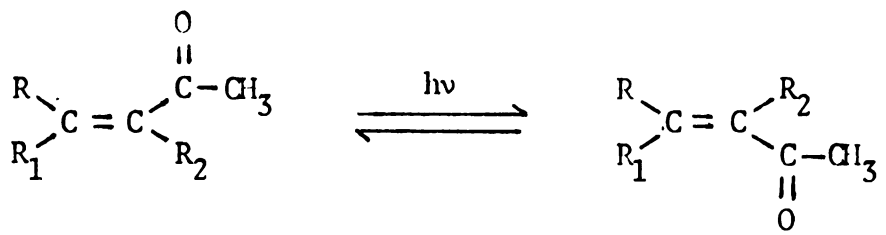


2-Cyclohexenone shows a reactivity qualitatively parallel to that of 2-cyclopentenone in cycloaddition. Certain 4,4-disubstituted 2-cyclohexenones are known to rearrange to the bicyclo[3.1.0]hexan-

2-ones with group migration. A dipolar species such as 72 has been suggested as an intermediate.[28] Although it is well known that the



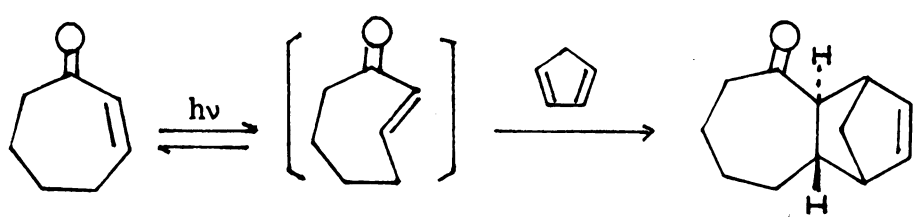
72



primary photochemical reaction of most acyclic enones is cis-trans isomerization about the double bond, no good evidence has yet been found for the cis-trans isomerization of a cyclopentenone or cyclohexenone. The process is probably not geometrically permissible.

It has been shown by Eaton[29a] and Corey[29b] that both cis-2-cycloheptenone and cis-2-cyclooctenone can be isomerized photochemically to their trans isomers, and IR spectra of these trans isomers were observed at low temperatures. Although dimerization and cycloaddition reactions do occur, these have been shown unequivocally to be reactions of trans-2-cycloheptenone and trans-2-cyclooctenone that occur readily in the dark.[30] Thus irradiation of a mixture of cis-2-cycloheptenone and cyclopentadiene at -50°C afforded a single 1 : 1 adduct which is

formulated as 73.[29b] Irradiation of the cis isomers in the presence of piperylene or cyclopentadiene leads neither to sensitized isomerization of piperylene nor to sensitized dimerization of cyclopentadiene, in contrast to the corresponding experiments with five and six membered cyclic enones. The intramolecular cis-trans isomerization of cycloheptenone and cyclooctenone, presumably via the triplet state, is very much faster than either intermolecular energy transfer or cycloadditions. What is notable is that this reaction dominates the photochemistry of medium-ring cycloalkenones and provides exceptionally easy access to compounds of great interest.



73(95%)

It is clear that the flexibility of the ring determines the photochemical behavior of simple cycloalkenones. Since the ethylenic portion of the triplet state of an α,β-unsaturated ketone can be treated in a useful simplification, rather like the triplet state of an unconjugated olefin, the relationship between the reactivity and ring size of cyclic enones can be inferred from the potential energy curves of the twisted olefins (Fig. 3).[30a,31a] The twist angle, ∅, indicates the deviation from the normal C (sp^2) = C (sp^2) plane. An electronically excited olefin (either S_1 or T_1) should prefer a rotation about the

C (sp^2) -C (sp^2) single bond to afford an orthogonal geometry ($\phi = 90^\circ$), thus minimizing the mutual repulsive interactions of the π and π^* electrons. Decay by either internal conversion or intersystem crossing leads to the cis or trans ground state, in which ϕ is 0° or 180° respectively.

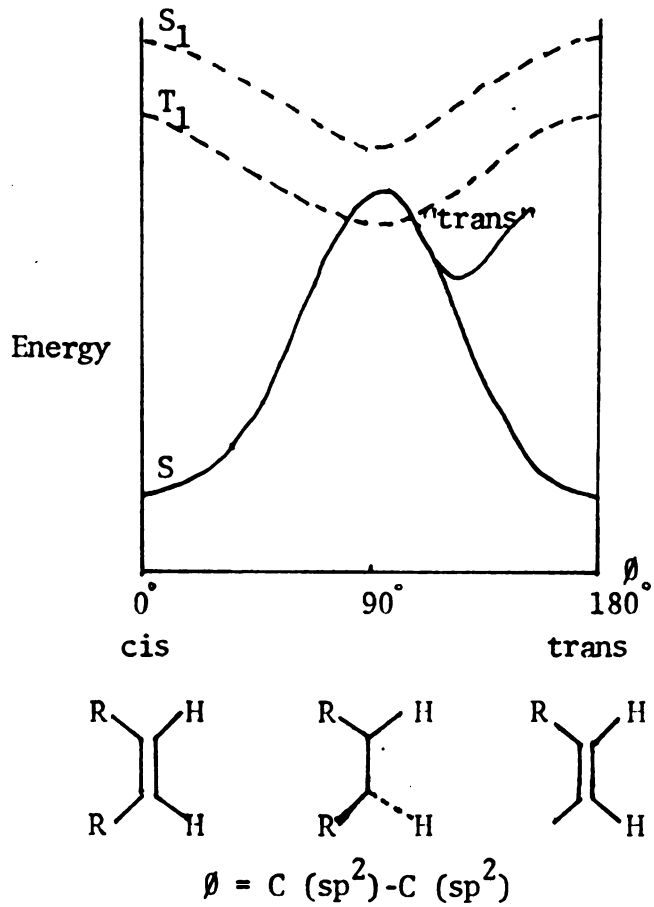


Figure 3. Energy for the Twisting of Various Electronic States of 1,2-Disubstituted Olefin.[30a]

With rather small ring olefins, however, a complete twisting ($\phi > 90^\circ$) is sterically impossible; consequently, their cis-trans isomerization is precluded. In contrast, open chain or sufficiently

large membered cyclic olefins undergo the geometrical isomerization readily. Seven and eight membered cyclic olefins are located intermediate between the two extremes. Obviously, a coplanar trans double bond ($\phi = 180^{\circ}$) can not be accommodated, but a 90° twisted conformation can be adopted and further twisting to a ground state isomer ($90^{\circ} < \phi < 180^{\circ}$) with minimized energy could occur. Such molecules are conventionally referred to as trans-isomers. The eight membered ring is the smallest cycle capable of incorporating a double bond of trans configuration, while trans-cycloheptene and trans-cyclohexene have both been proposed as fleeting intermediates.[31b] Models suggest that a rigid, planar trans double bond cannot be built into an eight-membered ring. In accordance with this, trans-cyclooctene has dipole moment of 0.8 D caused by out of plane bending and rehybridization of the strained π-bond.[32a]

Since trans-cycloalkenes cannot have a planar structures, it was been suggested that trans cyclic olefins of intermediate size should be capable of existence in stable enantiomorphic conformations (Fig. 4). The molecular asymmetry of the trans-cycloalkenes results from steric barriers to rotation of double bond substituents past the carbon chain. Trans-cyclooctene has been resolved by Cope et al,[33] whereas trans-cyclononene can be resolved only at low temperature and trans-cyclodecene has not yet been resolved.

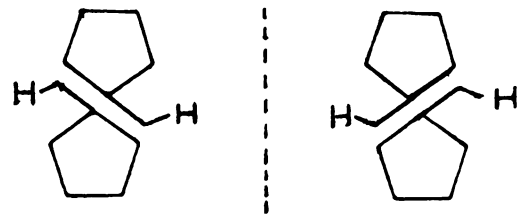
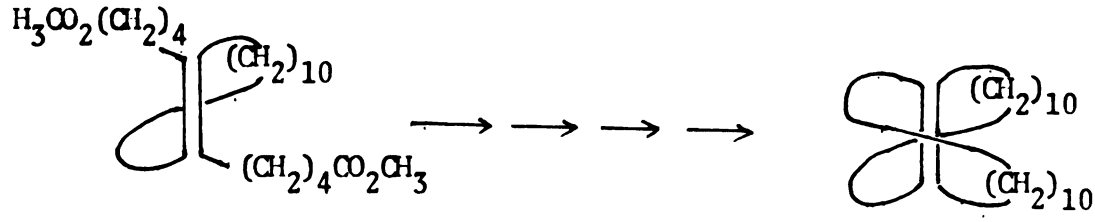
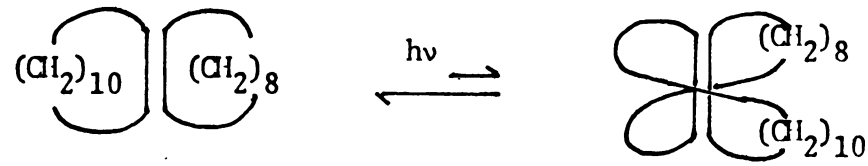


Figure 4. Enantiomorphic Trans-cyclooctenes

Interest in the properties of trans-cycloalkenes led to speculation on a novel and unknown class of bicyclic trans-cycloalkenes wherein the two rings share a common double bond. Such compounds have been named as (a,b)betweenanenes because the double bond is sandwiched between two alkyl chains. It was not until recently that the first known betweenanene, i.e. (10,10)betweenanene was prepared, by Marshall.[32a] In their elegant synthesis, they have sucessfully introduced a trans double bond bearing two ester substituents in a 12-membered ring olefin; subsequent reactions led to the (10,10)betweenanene (Eq. 15). While this work was in progress, another example of a betweenanene was reported by Nakazaki.[32b] They prepared (10,8)betweenanene by photochemical isomerization of its cis precursor (Eq. 16). Since it is known that medium ring cycloalkenones are capable of isomerization to their trans-isomers, it seems likely that if one could photochemically generate a stable trans-cycloalkenone bearing suitable substituents at the trans-double bond, trans-cycloalkenones might be key intermediates leading to the synthesis of betweenanenes. This was one objective of the present research.



(Eq. 15)



(Eq. 16)

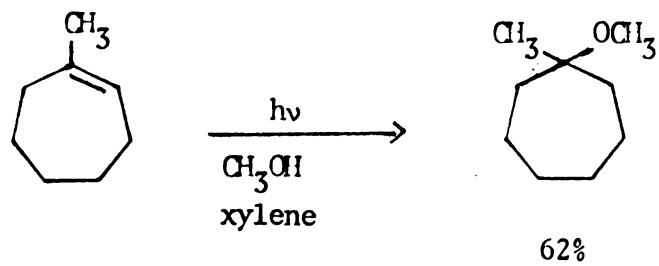
Table 8 Ir data of cis and trans-2-Cycloalkenones

2-Cycloalkenones	IR cm^{-1} -C-
cis-cycloheptenone	1669
trans-cycloheptenone	1715
cis-cyclooctenone	1664
trans-cyclooctenone	1715
cis-cyclononenone	1667
trans-cyclononenone	1692

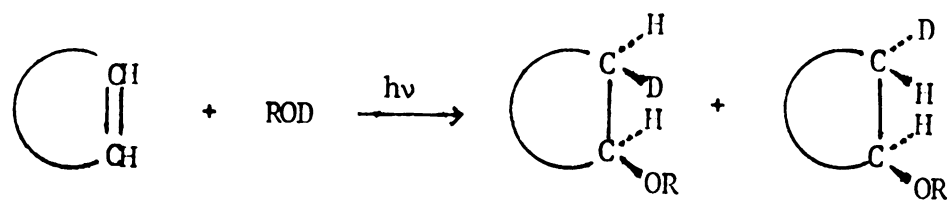
Table 8 compares the IR spectral data of certain cis and trans 2-cycloalkenones.[30a] The degree of conjugation of C = C bond with C = O group in the seven and eight-membered trans-2-cycloalkenones is markedly decreased as compared with that of the cis isomers. These trans double

bonds suffer enough torsional strain to provide effective strain releasing reactions. However, the IR spectrum shows that the trans-2-cyclononenone is sterically less strained, and in fact is stable enough to be isolated.[30a]

The photochemical polar addition of alcohols to cycloalkenes (C_6-C_8) has been extensively studied.[31] The reaction has been proposed to proceed by the following sequence: 1. a photochemical cis-trans isomerization of the olefins; 2. protonation of the strained trans-olefins to produce carbocations; 3. nucleophilic attack by the solvent. For instance irradiation of 1-methylcycloheptene in a mixture of methanol and xylene solution affords a 62% yield of an adduct (Eq. 17). These photoadditions are not stereospecific, since mixtures of cis and trans adducts are usually formed[13] (Eq. 18).

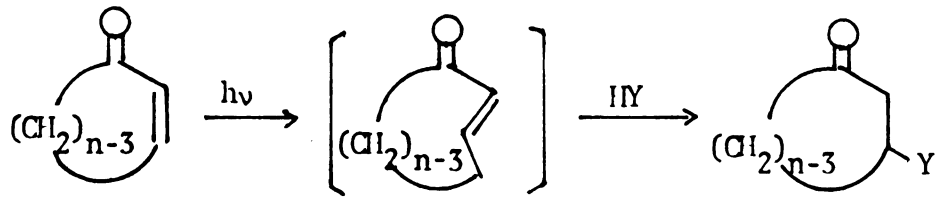


(Eq. 17)



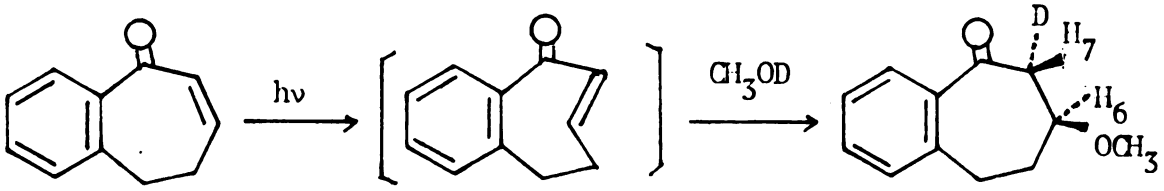
(Eq. 18)

Similarly, various examples of photochemical polar addition of protic solvents to α,β-unsaturated ketones have been reported. The irradiation of 2-cyclcheptenone and 2-cyclooctenone in various solvents (alcohols, acetic acid, water, diethylamine) results in the formation of Michael-type addition products. The mechanism of these reactions has been suggested to consist of a prior photochemical isomerization to the trans isomer and a subsequent thermal reaction with the nucleophilic solvents to give the adducts.[30] It is still not clear, however, if the addition of protic solvents across the trans double bond is a concerted or a stepwise process.

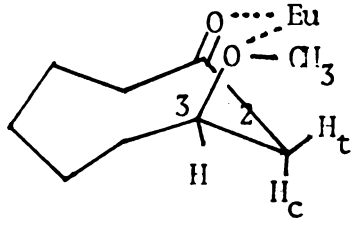


Recently, Hart and Dunkelblum[34] found that irradiation of 2,3-benzo-2,6-cycloheptadienone 74 in methanol-d give 6-methoxy-2,3-benzo-2-cycloheptenone 75 in which the methoxyl at C-6 and deuterium at C-7 are trans. The results are rationalized by a photoisomerization of 74 to the $\Delta^{6,7}$-trans isomer 74t which thermally adds methanol in a regio- and stereospecific syn manner to give a single adduct. Thus the addition of methanol to the trans double bond may be a concerted process. In connection with stereochemical studies on the photochemical addition of methanol to 2-cycloalkenones, Dunkelblum and Hart[45] have observed a dramatic conformational change between the free and europium

coordinated forms of these compounds when the rings were sufficiently large so that the substrate could act as a bidentate ligand toward the europium. Hence, Eu-complexed 76 has a sufficiently rigid structure that the gem coupling between the H_2 protons (12 Hz) was readily observed. This observation was useful in assigning the stereochemistry of the CH_3OD adducts.



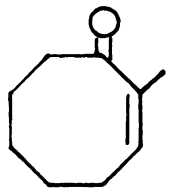
74 74t 75



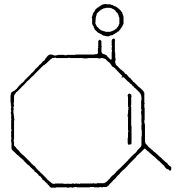
76

So far, there have been no studies done on the photochemical addition of methanol to a 2-cycloalkenone with substituents at the C-2 or C-3 positions. It is the purpose of this part of my thesis to further examine the generality of the photo-induced addition of methanol to substituted 2-cyclooctenones and to see if the substituents would have any effect to these photochemical reactions. Compounds that were

synthesized for this study are as follows: 2-methyl-2-cyclooctenone 93, 3-methyl-2-cyclooctenone 98, and 2,3-dimethyl-2-cyclooctenone 100.



93



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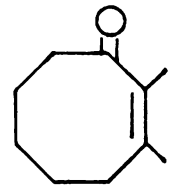
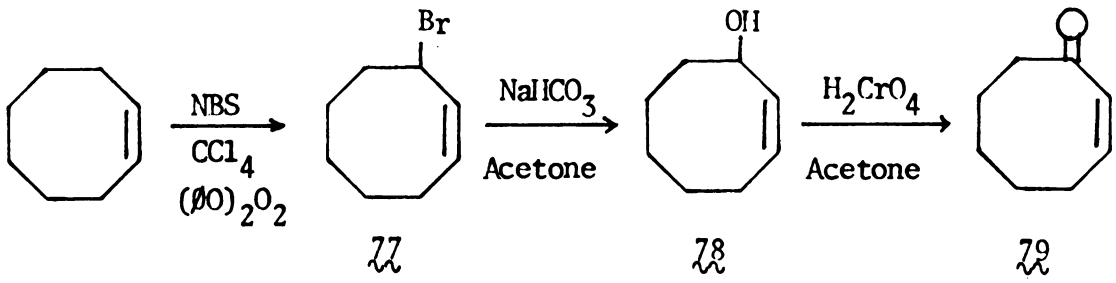


100

RESULTS AND DISCUSSION

1. Synthesis of 2-Methyl-2-cyclooctenone

Our initial approach to the synthesis of 2-methyl-2-cyclooctenone was essentially the one used by Whitham and Heap[35] for the synthesis of medium ring 2-cycloalkenones. For example, 2-cyclooctenone can be made according to Eq. 19. Allylic bromination of cyclooctene using N-bromosuccinimide gives 1-bromo-2-cyclooctene. Hydrolysis of allylic bromide 77 in aqueous acetone buffered with sodium bicarbonate produces allylic alcohol 78, and oxidation of the allylic alcohol with 6N chromic acid in acetone affords 2-cyclooctenone.

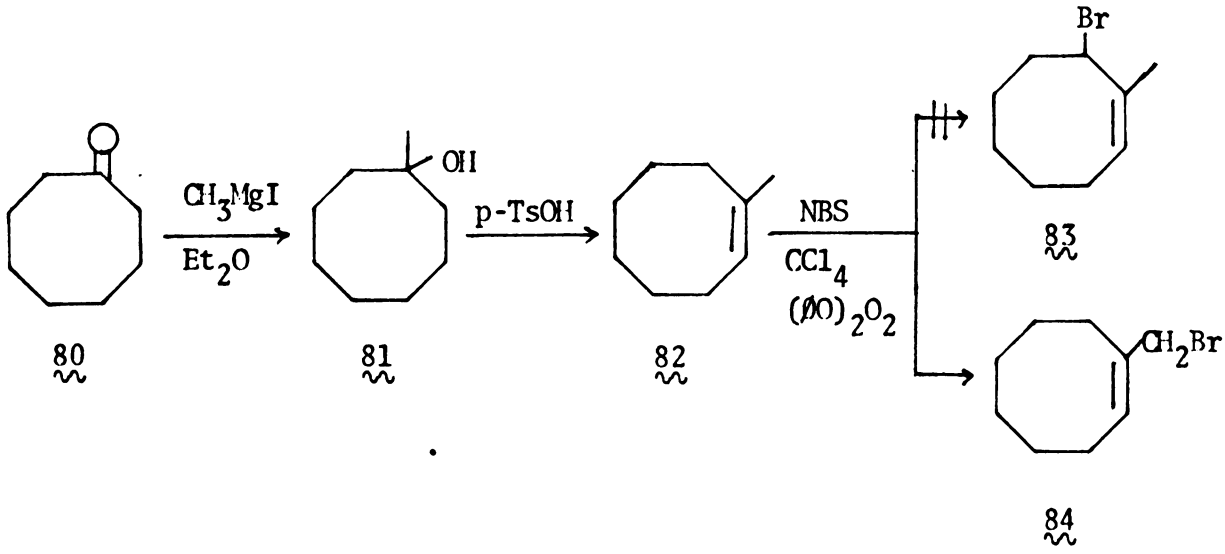


77 78 79

(Eq. 19)

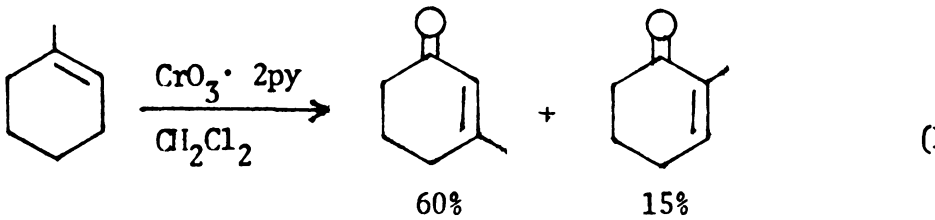
In order to synthesize 2-methyl-2-cyclooctenone employing the reaction sequence outlined in Eq. 19, we had to start with 1-methyl-cyclooctene. The procedure leading to the synthesis of 1-methylcyclooctene by Brown[36] was followed. Reaction of cyclooctanone with methyl-magnesium iodide and subsequent dehydration of the alcohol 81 with p-toluenesulfonic acid gave 1-methylcyclooctene 82 in 76% yield.

Bromination of 1-methylcyclooctene 82 with N-bromosuccinimide in carbon tetrachloride afforded in 44% yield, an allylic bromide which was identified as 1-bromomethylcyclooctene. Allylic bromide 84 was characterized through its NMR spectrum. Apparently, allylic bromination of 82 occurred at the side chain instead of in the ring. Therefore this approach to the synthesis of 2-methyl-2-cyclooctenone, by way of Eq. 19, is not feasible.

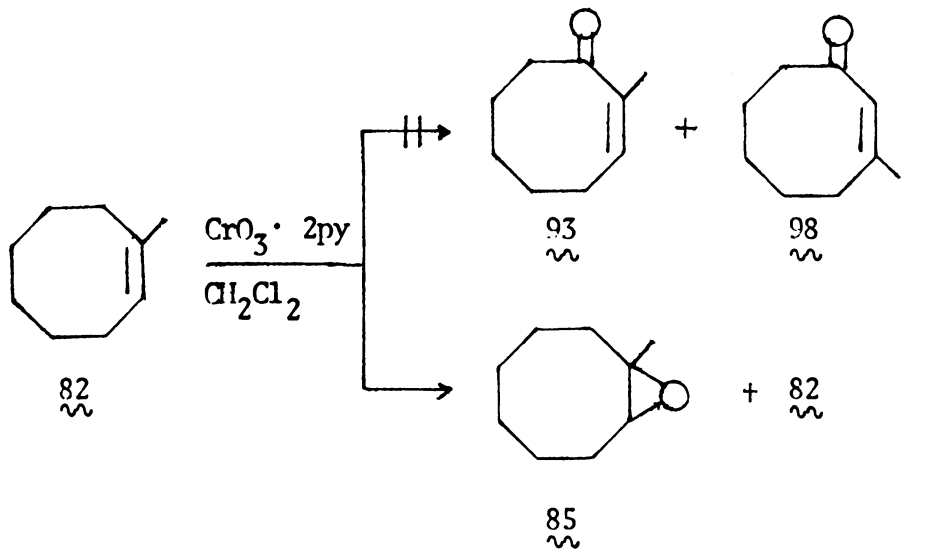


It has been shown by Dauben and Shaffer[37] that allylic oxidation of cyclic olefins with chromium trioxide-pyridine complex can give the α,β-unsaturated ketone in fairly good yield. For example 1-methylcyclohexene can be oxidized with chromium trioxide-pyridine complex in methylene chloride to afford 15% of 2-methyl-2-cyclohexenone and 60% of 3-methyl-2-cyclohexenone (Eq. 20). If 1-methylcyclohexene is replaced by 1-methylcyclooctene, a route similar to Eq. 20 could be used for the synthesis of substituted-2-cyclooctenones. However, when 1-methylcyclooctene was treated with chromium trioxide-pyridine complex in methylene chloride, the desired substituted 2-cyclooctenones

were not obtained. Instead, 1-methylcyclooctene oxide 85 was isolated along with some recovered starting olefin.

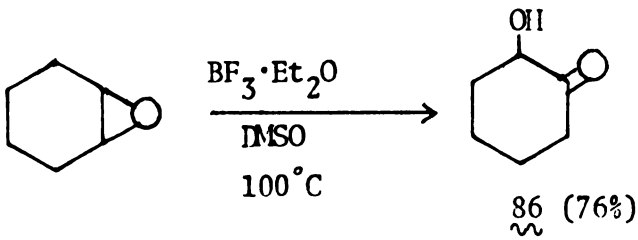


(Eq. 20)



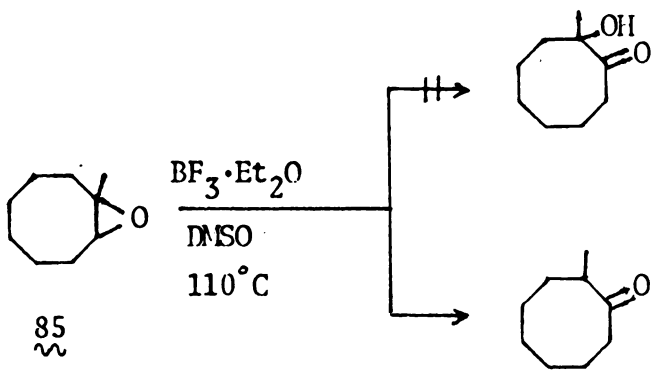
It has been reported by Cohen[38a] that epoxides can be oxidized by dimethyl sulfoxide to α-hydroxy ketones if catalytic amounts of boron trifluoride are present. For example, when cyclohexene oxide is heated with a catalytic amount of boron trifluoride etherate in dimethyl sulfoxide on a steam bath for 22 hr, 2-hydroxycyclohexanone 86 is isolated in 76% yield (Eq. 21). Thus, oxidation of epoxides by dimethyl sulfoxide to α-hydroxy ketones and subsequent dehydration of the α-hydroxy ketones might constitute a way of synthesizing 2-cyclooctenones. However, when a solution of 1-methylcyclooctene oxide 85 and a catalytic amount of boron trifluoride etherate in dimethyl sulfoxide was heated at

110°C for 20 hr, 2-methylcyclooctanone was isolated as the only major product (Eq. 22).



86 (76%)

(Eq. 21)



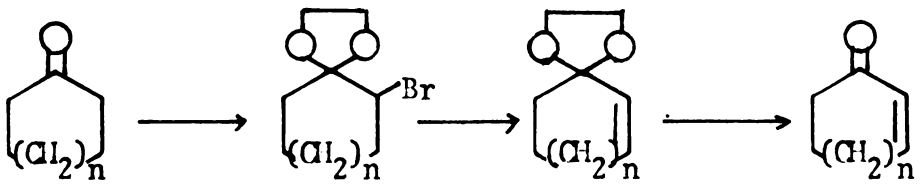
85

89

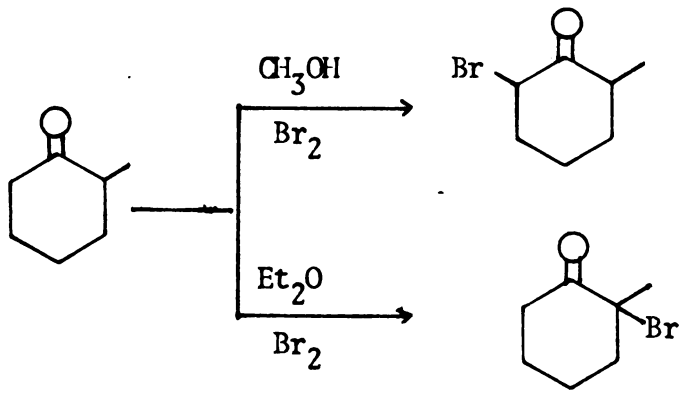
(Eq. 22)

It has been demonstrated by Garbisch[39] that a convenient and expedient synthesis of many 2-cycloalkenones may be accomplished by monobrominating the cyclic ketone in methanol or ethylene glycol followed by dehydrobromination and subsequent ketal hydrolysis (Eq. 23). However, the synthesis of 2-substituted-2-cycloalkenones from 2-substituted cyclic ketones by the same sequence of reactions has not been tried. Although Garbisch also found that monobromination of dimethyl or ethylene ketals of 2-alkylcyclohexanones occurs with predominant substitution at C-6, and brominations of 2-alkylcyclohexanones in ether lead to predominant substitution at C-2 (Eq. 24), dehydrobromination of 2-alkyl-2-bromocyclohexanones to 2-alkyl-2-cyclohexenones has not been effected.

Since 2-alkylcycloalkanones can be brominated selectively at the C-2 position in ether, bromination and subsequent dehydrobromination might provide a good route to 2-substituted-2-cycloalkenones.



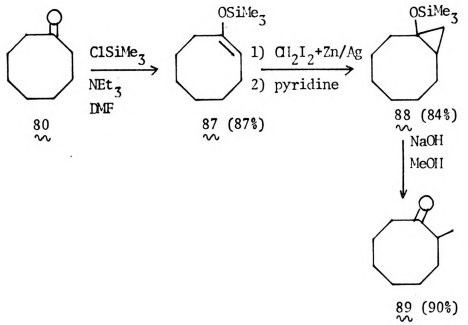
(Eq. 23)



(Eq. 24)

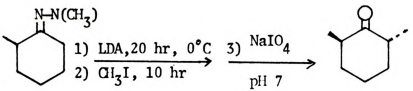
In order to prepare 2-methyl-2-cyclooctenone by this method, we would need 2-methylcyclooctanone. It has been known that direct alkylation of ketones using conventional bases gives a complex product mixture which is often difficult to separate. Literature search showed that to date the best way to synthesize 2-methylcyclooctanone was that developed by Conia.[40] Cyclooctanone is converted to the trimethyl silyl enol ether 87. Cyclopropanation of 87 by way of an improved Simmons-Smith reaction gives siloxycyclopropane compound 88 and hydrolysis of 88 with sodium hydroxide in methanol affords 2-methylcyclooctanone

(Eq. 25). However, the Simmons-Smith reaction seems to be not always reproducible and is quite dependent on the quality of the zinc-silver couple. Therefore we decided to look for a simple and better way of synthesizing 2-methylcyclooctanone.



80 87 (87%) 88 (84%) 89 (90%) (Eq. 25)

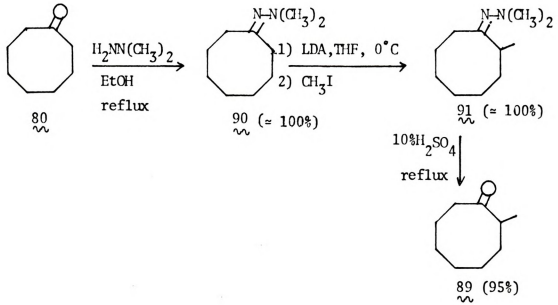
Recently, Corey[41a] found that N,N-dimethylhydrazone derivatives (i.e. DMH's) of enolizable aldehydes and ketones can be metallated cleanly by lithium diisopropylamide (LDA) in THF at 0°C, and that these α-lithiated DMH's can serve as equivalents of enolate ions in synthesis (e.g. alkylation). For instance, the DMH of 2-methylcyclohexanone can be methylated to give trans-2,6-dimethylcyclohexanone in 95% yield (Eq. 26). Since DMH's of ketones are easily available in quantitative yield from the corresponding carbonyl compound and N,N-dinethylhydrazine, methylation of cyclooctanone via its DMH derivative may constitute a simple and efficient method of preparing 2-methylcyclooctanone.



95%

(Eq. 26)

When cyclooctanone 80 was refluxed with N,N-dimethylhydrazine in absolute ethanol overnight, dimethylhydrazone 90 was obtained in quantitative yield. Methylation of the dimethylhydrazone 90 with lithium diisopropylamide and methyl iodide in THF at 0°C gave cleanly the monoalkylation product 91. Hydrolysis of dimethylhydrazone 91 with 10% sulfuric acid afforded after distillation a 95% yield of 2-methylcyclooctanone 89. The structure of 89 followed from its spectra. Clearly our overall yield of 2-methylcyclooctanone starting from cyclooctanone is much better than that obtained using Conia's method, and the procedure is simpler. Therefore, alkylation via the dimethylhydrazone derivative provides a very good method for the α-alkylation of medium ring cyclic ketones.



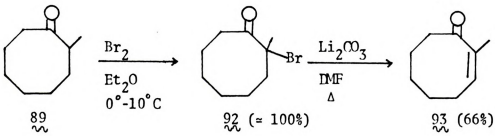
80

90 (≈ 100%)

91 (≈ 100%)

89 (95%)

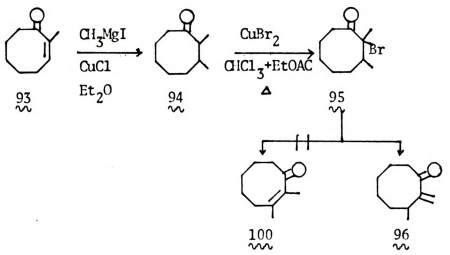
Bromination of 2-methylcyclooctanone in ether with bromine gave 2-bromo-2-methylcyclooctanone in quantitative yield. The bromoketone 92 was characterized by the appearance of a singlet methyl resonance at δ 1.75 in its NMR spectrum and the disappearance of the doublet methyl resonance corresponding to the starting ketone 89. Dehydrobromination of bromoketone 92 with refluxing methanolic sodium hydroxide yielded only rearranged product which was not identified. After several trials we finally arrived at the proper conditions for the dehydrobromination. Thus bromoketone 92 was dehydrobrominated with lithium carbonate in refluxing dimethyl formamide to give after column chromatography a 66% yield of 2-methyl-2-cyclooctenone 93. The structure of 93 was deduced from its spectra. The IR spectrum, with a strong band at 1660 cm^{-1} with a shoulder at 1685 cm^{-1}, and the UV maxima at 242 nm (6800) and 285 nm (750) support a conjugated enone structure. The NMR spectrum showed a doublet at δ 1.76 (J = 1.5 Hz) for the C-2 methyl, a region at δ 1.33-2.0 for six methylenic protons, a broad region at δ 2.0-2.66 for two allylic and two alpha protons, and a triplet of quartets (J = 1.5 and 7 Hz) at δ 5.67-6.07 for the C-3 vinylic proton. The molecular formula $C_9H_{14}O$ was confirmed by a mass spectrum (parent peak m/e 138) and elemental analysis.



89 92 (≈ 100%) 93 (66%)

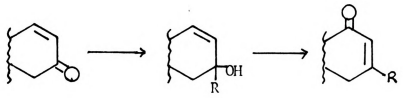
2. Synthesis of 3-Methyl- and 2,3-dimethyl-2-cyclooctenones

Scheme 3



Our first approach to the synthesis of 2,3-dimethyl-2-cyclooctenone 100 is shown in Scheme 3. 1,4-Addition of methylmagnesium iodide to 2-methyl-2-cyclooctenone 93 in the presence of cuprous chloride in ether produced an essentially quantitative yield of 2,3-dimethylcyclooctanone 94. Bromination of 94 with either bromine in ether or cupric bromide in refluxing chloroform and ethyl acetate gave bromoketone 95 in quantitative yield. Bromoketone 95 was characterized by a strong carbonyl band at 1710 cm^{-1}. Its NMR spectrum showed a methyl doublet at δ 1.28 (J = 7 Hz) and a methyl singlet at δ 1.6. Finally, dehydrobromination of bromoketone 95 with lithium carbonate (or lithium chloride) in refluxing DMF afforded only 2-methylene-3-methylcyclooctanone 96 in good yield. The structure of 96 was deduced from its spectra. The IR spectrum showed a carbonyl band at 1690 cm^{-1} which means that the conjugation is very weak. The NMR spectrum of 96 had a methyl doublet (J = 7 Hz) at δ 1.15, eight methylenic protons at δ 1.2-2.0, one allylic proton and two alpha protons at

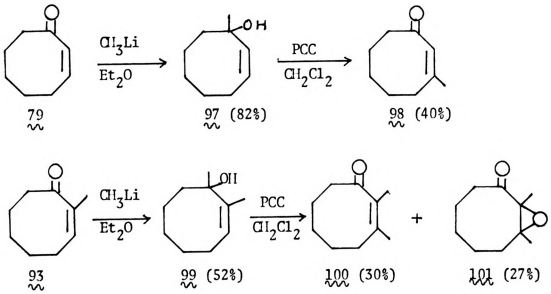
δ 2.0-3.0, and two-proton multiplets at δ 5.05 and 5.6 for the vinyl protons. Apparently the dehydrobromination of bromoketone 95 occurred at the side chain instead of in the ring.



(Eq. 27)

Dauben[43] recently developed a procedure by which tertiary allylic alcohols, generated by the 1,2-addition of an organometallic reagent to an α,β-unsaturated ketone, are converted with pyridinium chlorochromate (PCC) in a single step to a new, transposed β-alkyl-α,β-unsaturated ketones in good to excellent yield (Eq. 27). This method for alkylative 1,3-carbonyl transposition provided us a simple and effective way of synthesizing the desired cyclooctenones 98 and 100. Thus, 3-methyl and 2,3-dimethyl-2-cyclooctenones were synthesized according to Scheme 4.

Scheme 4

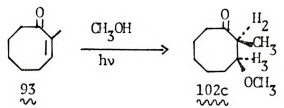


2-Cyclooctenone 79 was prepared as reported by Whitham.[35] 1,2-Addition of methyllithium to 2-cyclooctenone produced 1-methylcyclooct-2-en-1-ol (82%) which was oxidized with pyridinium chlorochromate in methylene chloride to give 3-methyl-2-cyclooctenone 98 in 40% yield after purification. Compound 98 was assigned the structure shown on the basis of the following spectral data. The molecular formula $C_9H_{14}O$ was confirmed by the high resolution mass spectrum (parent peak m/e 138). The IR absorption at 1650 cm^{-1} showed that there is conjugation between the carbonyl group and the carbon-carbon double bond. The UV spectrum showed a maximum at 245 nm (ε 7500) which indicates that compound 98 is an α,β-unsaturated ketone. Its NMR spectrum showed six methylenic protons at δ 1.3-2.1, a vinyl methyl doublet at δ 1.84 with a coupling constant of 1.5 Hz, a four proton broad region at δ 2.2-2.8 and a vinyl proton at δ 5.87.

Treatment of 2-methyl-2-cyclooctenone 93 with methyllithium in ether afforded 1,2-dimethylcyclooct-2-en-1-ol 99 in 52% yield. Oxidation of alcohol 99 with PCC in methylene chloride gave a 30% yield of 2,3-dimethyl-2-cyclooctenone 100 and 27% yield of epoxyketone 101. Compound 100 was assigned the structure shown on the basis of the following spectral properties. The molecular formula $C_{10}H_{16}O$ was confirmed by the high resolution mass spectrum (parent peak m/e 152). Its IR spectrum showed a strong absorption at 1685 cm^{-1} with a shoulder at 1650 cm^{-1}. The UV spectrum had maxima at 250 nm (ε 4360) and 206 nm (890) indicative of conjugation. Its NMR spectrum showed a slighten broadened singlet at δ 1.7 corresponding to two vinyl methyls, a six-methylenic proton resonance at δ 1.2-1.9, a four-proton resonance at δ 2.0-2.6 and no vinyl protons.

3. Photochemical Addition of Methanol to 2-Methyl-2-cyclooctenone 93

The photolysis of 2-methyl-2-cyclooctenone 93 in methanol through Pyrex was followed by analytic VPC. As the reaction proceeded, the peak due to 93 began to diminish while that corresponding to the major product 102c began to rise. The reaction was essentially complete with 90% conversion in 4 hr.



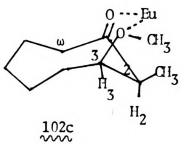
93 102c

The product 3-methoxy-2-methylcyclooctanone 102c was assigned the structure shown on the basis of its spectral properties. The molecular formula $C_{10}H_{18}O$ was confirmed by a mass spectrum (parent peak m/e 170) and elemental analysis. In the IR spectrum, absorption at 1705 cm^{-1} indicates that 102c must be a saturated cyclic ketone. The NMR spectrum (60 MHz) showed a methyl doublet at δ 0.98 (J = 7 Hz), a methyl singlet at δ 3.27 corresponding to the methoxyl group, a methine proton at δ 3.7-4.1, eight methylenic protons at δ 1.1-2.1 and three α-protons at δ 2.1-3.0.

To obtain stereochemical information about 102c, a 180 MHz proton spectrum was taken in $CDCl_3$. In this spectrum, the C-2 methyl appeared at δ 1.09 as a doublet (J = 7 Hz), H_2 was a quartet of doublets at δ 2.90 (J = 7 Hz and 3.5 Hz) which indicates that H_2 was split by the C-2 methyl into a quartet and each of these quartets was split further by

H_3 into a doublet. H_3 appeared as a multiplet at δ 4.04. Irradiation at δ 1.09 (C-2 methyl) caused the quartet of doublets at δ 2.90 to become a doublet with J = 3.5 Hz, and irradiation at δ 1.52 (C-4 methylene) caused the multiplet at δ 4.04 to become a doublet with J = 3.5 Hz. Thus the coupling constant between H_2 and H_3 is 3.5 Hz and H_2, H_3 are assigned as cis to each other based on the premise that $J_{trans} > J_{cis}$.[44] To obtain further support for this assignment, we studied the LIS spectra of compound 102c with Eu $(fod)_3$. The resulting chemical shift differences for compound 102c are summarized in Table 9.

Table 9 Lis Shift Data for Eu-complexed 102c



102c

Δ (ppm)					
H_2	H_3	CH_3	OCH_3	ω	J_{H_2,H_3} (Hz)
10.4	7.4	8.7	4.4	8.2	3.0

As we can see from Table 9 that there was only a very slight change in H_2-H_3 coupling constant when shift reagent was added. Therefore, there would be only a small change in dihedral angles for H_2-H_3 from free 102c to the Eu-complexed 102c. The coupling constant $J_{H_2H_3}$ of 3 Hz was reported for Eu-complexed 76 by Hart and Dunkelblum.[45] The fact that C-2 methyl has a large Δ value suggests that C-2 methyl is cis to the C-3 methoxyl. Also, the greater Δ value for H_2 than for the ω protons would be consistent with having europium coordinated between the carbonyl oxygen and the methoxyl oxygen, above the C-2 position. The stereochemistry of photoadduct 102c is thus certain with methyl and

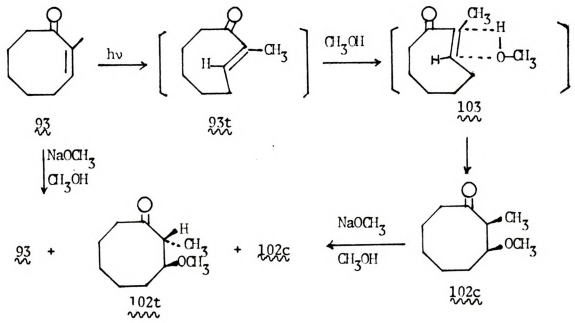
methoxyl cis to each other, and there is no appreciable conformational change in free 102c and Eu-complexed 102c.

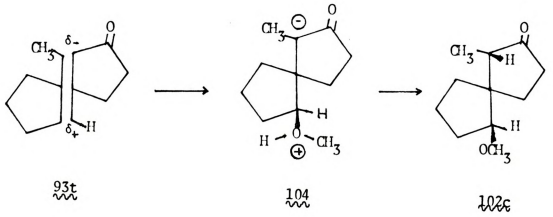
Although the photochemical addition of methanol (and other protic solvents) to cyclic enones has been suggested to proceed through a photochemical isomerization to the trans isomer which then adds methanol (or other protic solvent) thermally to give the products, little is known about the stereochemistry of the addition of methanol to the trans intermediate. Our stereochemical findings outlined above seem best accommodated by a mechanism as shown in Scheme 5; that is, compound 93 photoisomerizes to its trans isomer 93t which then adds methanol in a concerted, regio- and stereospecific syn manner to give adduct 102c.

The addition process deserves some consideration. A conventional Michael type addition mechanism is ruled out on the basis of the following observations. Treatment of 93 with 0.01 N methanolic sodium methoxide solution for 8 days gave a mixture of 93, 102t, and 102c in 45 : 35 : 20 ratio (only very small amount of 102t and 102c were formed in a shorter reaction time). Interestingly, when the photoadduct 102c was treated with 0.01 N methanolic sodium methoxide solution for 1 day, the same mixture of 93, 102t, and 102c was obtained. The stereochemistry of 102t (C-2 methyl and methoxyl groups are trans to each other) was confirmed from its NMR spectrum and europium shift study (see experimental section). These results indicate that the rate of base-catalyzed Michael addition of methanol to 93 is slower then that of the base-catalyzed exchange reaction of 102c, and that both the Michael addition and exchange reactions are stepwise processes involving the same intermediate (i.e.

carbanion). It is apparent that in the Michael type addition the enolate is not protonated stereospecifically.

Scheme 5

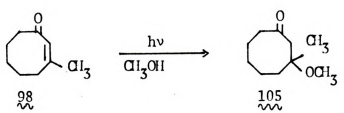




The carbon-carbon double bond in trans intermediate 93t is highly polarized by the electron-withdrawing carbonyl group, although it is not appreciably conjugated. Consequently, if methanol addition is stepwise, the intermediate carbanion would be formed with charge localized on the α-carbon (in 104), and a proton must be transferred to it before any conformational change necessary for charge delocalization can occur, to account for the formation of only the trans adduct. In the concerted addition process, methanol adds to the carbon-carbon double bond in trans intermediate 93t probably via a four center transition state (i.e. syn addition in 103) to give the trans adduct 102c.

4. Photochemistry of 3-Methyl and 2,3-dimethyl-2-cyclooctenones in Methanol

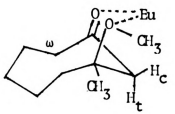
The irradiation of 3-methyl-2-cyclooctenone 98 in methanol through Pyrex with a Hanovia 450 W lamp afforded 3-methoxyl-3-methylcyclooctanone 105 in 72% yield after 5 hr. Compound 105 was assigned the structure shown on the basis of its spectral properties. It has a parent peak at m/e 170 and a peak at 138 corresponding to the loss of a methanol molecule in mass spectrum. The IR absorption at 1700 cm^{-1} showed that there is no conjugation within the molecule. The NMR spectrum showed two methyl singlets at δ 1.16 and 3.12, two broad regions at δ 1.2-2.0 (8H) and 2.2-2.4 (2H), two doublets at δ 2.24 (1H) and 2.7 (1H) respectively with a coupling constant of 11 Hz. LIS spectra of compound 105 with Eu $(fod)_3$ were also studied and the results are shown in Table 10.



98 105

Table 10 LIS Shift Data for 105

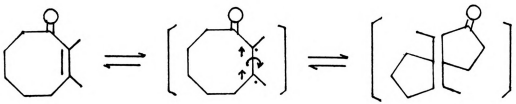
Δ (ppm)					
H_{2c}	H_{2t}	CH_3	OCH_3	ω	$J_{H_{2t}H_{2c}}$ (Hz)
17.4	12.3	6.9	11.6	8.3	12



105

The gem coupling constand $J_{H_{2t}H_{2c}}$ is essentially the same in both the free and complexed 105, indicating that there is no appreciable conformational difference between these two forms of compound 105. Free 105 already has a sufficiently rigid structure with the C-3 methyl in an equatorial position that the gem coupling between the C-2 protons (J = 11 Hz) is readily observed. The mechanism for the formation of 105 would be the same as that described for 102c.

When 2,3-dimethyl-2-cyclooctenone 100 was irradiated in methanol through Pyrex with a Hanovia 450 W lamp for 8 hr, only starting material was recovered. Prolonged irradiation did not give a methanol adduct and only resulted in more polymeric material. A possible explanation for this result is as follows. Since intramolecular cis-trans isomerization is considered to proceed vis the triplet state, the presence of methyl groups at both C-2 and C-3 positions would hinder the formation of trans isomer 100t from its triplet state due to the presence of steric crowing during the process of rotation around the C2-C3 single bond in the triplet state. In both 93 and 98, there is still one way open for the rotation about the C2-C3 single bond to occur readily to form the trans isomer. Thus the reason that no methanol adduct was found in the photolysis of 100 is probably because no trans isomer was formed during irradiation.



100 triplet state 100t

5. Summary

A method was found to prepare 2-methylcyclooctanone in quantitative yield, and 2-methyl-2-cyclooctenone 93 was synthesized by bromination-dehydrobromination of 2-methylcyclooctanone in good yield. 3-Methyl- and 2,3-dimethyl-2-cyclooctenones 98 and 100 were prepared by the oxidation (with PCC) of the tertiary allylic alcohols generated by the 1,2-addition of methyllithium to 2-cyclooctenone 79 and 2-methyl-2-cyclooctenone 93 respectively. Irradiation of 2-methyl- and 3-methyl-2-cyclooctenones 93 and 98 in methanol resulted in the formation of adducts 102c and 105, whereas no methanol adduct was found for the photolysis of 2,3-dimethyl-2-cyclooctenone 100. The addition of methanol to the trans intermediate of 93 is stereospecific.

EXPERIMENTAL

1. Gas Chromatography

VPC columns that were used in this section are as follows:

A. 5' x 0.25 in column, 6% SE30 on chromosorb W.

B. 5' x 0.25 in column, 10% SE30 on chromosorb W.

C. 5' x 0.125 in column, 5% SE30 on chromosorb G.

D. 5' x 0.25 in column, 10% FFAP on chromosorb W.

E. 5' x 0.125 in column, 5% FFAP on chomosorb W.

2. Preparation of 1-Methylcyclooctene

The procedure of Brown[36] was employed. A solution of 7.56 g (0.06 mol) of cyclooctanone in 70 ml of anhydrous ether was added slowly to a methylmagnesium iodide solution (prepared from 4.86 g of magnesium turnings in 20-ml ether and 28.4 g of methyl iodide in 30-ml ether) under nitrogen over about 20 min, followed by refluxing for 1.5 hr. The reaction mixture was then quenched carefully with 20 ml of saturated ammonium chloride solution, and 30 ml of ether was added. The ether layer was separated, washed with saturated sodium chloride solution, and dried over Na_2SO_4. Removal of the ether gave a light yellowish liquid which was the crude 1-methylcyclooctanol. An IR spectrum of the crude alcohol showed the disappearance of the carbonyl group and the presence of strong -OH absorption at 3440 cm^{-1}.

The crude alcohol 81 was refluxed with 2 g of p-toluenesulfonic acid in 100 ml of benzene for 2 hr using a Dean-Stark trap for continuous removal of water. The reaction mixture was cooled, and 40 ml each of ether and dilute NaCl solution was added. The organic layer was separated, washed with sat. Na_2CO_3 and NaCl solutions, and dried over Na_2SO_4. Removal of the solvent with an evaporator gave, after distillation (62°/25 mm), 5.7 g of pure 1-methylcyclooctene 82 (76% yield based on starting ketone): NMR (CCl_4) δ 1.44 (8H, s), 1.64 (3H, d, J = 1.5 Hz), 2.08 (4H, broad), 5.2 (1H, broad triplet, J = 7 Hz).

3. Bromination of 1-methylcyclooctene 82

A mixture of 5.6 g (0.045 mol) of 1-methylcyclooctene 82, 9.1 g of N-bromosuccininide and 0.04 g of benzoyl peroxide in 50 ml of CCl_4 was refluxed under nitrogen. The reaction was essentially complete in 20 min, with succinimide floating on the top. Succinimide was removed by filtration, the filtrate was washed with 20 ml of 5% $NaHCO_3$, 40 ml of water and dried over Na_2SO_4. The solvent was removed to give a crude product which upon distillation (93-96°/10 mm Hg) afforded 4.0 g of 1-bromomethylcyclooctene 84 (44% yield): IR (neat) 2950 (s), 1690 (w), 1655 (w), 1480 (s), 1460 (s), 1210 (s) cm^{-1}; NMR (CCl_4) δ 1.2-1.8 (8H, broad), 1.8-2.4 (4H, broad), 3.83 (2H, s), 5.7 (1H, t, J = 8 Hz).

4. Allylic Oxidation of 1-Methylcyclooctene

The procedure of Shaffer[37] for the allylic oxidation of olefins was used. Thus 7.4 g (0.06 mol) of 1-methylcyclooctene was oxidized with

chromiumtrioxide-pyridine comples (80 g of CrO_3 and 126.4 g of pyridine) in 800 ml of methylene chloride. The reaction mixture after workup and column chromatography (silica gel, ether : hexane = 1 : 1) gave 1.2 g of starting olefin and 2.4 g (29%) of 1-methylcyclooctene oxide 85:[38b] IR (neat) 2920 (s), 1470 (m), 1450 (m), 1380 (m), 910 (m), 830 (m) cm^{-1}; NMR (CCl_4) δ 1.22 (3H, s), 1.24-2.3 (12H, broad), 2.3-2.7 (1H, broad); mass spectra, m/e 140 (parent).

5. Acid-catalyzed Rearrangement of 1-Methylcyclooctene Oxide 85

A solution of 0.23 g (0.0016 mol) of epoxide 85 and 0.05 ml of boron-trifluoride etherate in 10-ml DMSO was heated at 110°C for 20 hr. The reaction mixture was poured into ice water and extracted with chloroform. The combined organic layers were washed with sat. $NaHCO_3$ and NaCl solutions, and dried over $MgSO_4$. Evaporation of solvent gave a brown liquid. Preparative VPC (column B, 135°C) gave 2-methylcyclooctanone as the major product which had the correct spectra data (see page 86).

6. Preparation of Cyclooctanone-N,N-dimethylhydrazone 90

A mixture of 50.4 g of cyclooctanone (0.4 mol) and 72 g of anhydrous N,N-dimethylhydrazine (1.2 mol) in 100-ml absolute ethanol was refluxed overnight. Excess dimethylhydrazine and ethanol were removed by distillation at aspirator pressure (25 mm Hg). The crude product was then distilled at 55°/0.5 mm Hg to give 67.6 g of pure 90 as a colorless liquid (quantitative yield): IR (neat) 2960 (s), 1630 (m, C = N-), 1475 (m), 1455 (m), 1030 (m), 980 (m) cm^{-1}; NMR (CCl_4) δ 1.2-2.0 (10H, broad),

2.26 (6H, s, dimethyl), 2.0-2.5 (4H, broad, allylic).

7. Methylation of Cyclooctanone-N,N-dimethylhydrazone 90

A solution of 67.2 g of cyclooctanone-N,N-dimethylhydrazone (0.4 mol) in 50-ml THF was added slowly to a lithium diisopropylamide (LDA) solution (prepared from 63 ml of diisopropylamine (0.45 mol) and 281 ml of 1.6 N n-butyllithium (0.45 mol) in 100-ml THF) at 0°C under nitrogen, resulting in a milky-pink solution. After the mixture was stirred for 4 hr, 59 g of methyl iodide (0.41 mol) in 50 ml of THF was added slowly at 0°C, and the reaction mixture was stirred overnight. Upon workup, 200 ml of water was added dropwise to destroy the unreacted diisopropyl amide. The organic layer was separated, and the aqueous layer was extracted with 200 ml of methylene chloride. The combined organic solutions were washed with sat. NaCl, and concentrated to give 92 g of crude 2-methyl-cyclooctanone-N,N-dimethylhydrazone 91 which was used directly for hydrolysis without further distillation (quantitative yield). Data for 91: IR (neat) 2960 (s), 1632 (m, C = N-), 1475 (m), 1455 (m), 1380 (w), 1030 (m), 970 (m) cm^{-1}; NMR (CCl_4) δ 0.93 (3H, d, J = 7 Hz, C-2 methyl), 1.1-2.0 (10H, broad), 2.0-2.4 (3H, broad, allylic), 2.25 (6H, s, $-N(CH_3)_2$).

8. Hydrolysis of 2-Methylcyclooctanone-N,N-dimethylhydrazone 91

A mixture of 92 g of crude 2-methylcyclooctanone-N,N-dimethylhydrazone 91 and 300 ml 10% sulfuric acid was refluxed overnight. The solution was cooled and the organic layer separated. The aqueous layer was extracted with 200 ml ether. The combined organic layers were washed with saturated $NaHCO_3$ and NaCl solution, and dried over Na_2SO_4. Removal of the solvent

gave 74.5 g of crude 89 which upon distillation (at 38°/0.4 mm Hg or 72°/5 mm Hg) afforded 53.3 g of pure 2-methylcyclooctanone 89 (95% yield) as a colorless liquid: IR (neat) 2950 (s), 1698 (s), 1470 (s), 1455 (m), 1380 (w) cm^{-1}; NMR (CCl_4) δ 0.98 (3H, d, J = 7 Hz, methyl), 1.1-2.05 (10H, broad), 2.05-2.7 (3H, broad).

9. Bromination of 2-Methylcyclooctanone 89

A solution of 19 g of 2-methylcyclooctanone (0.136 mol) in 100 ml of ether was placed in a 200-ml flask (equipped with a magnetic stirrer, thermometer, dropping funnel) and cooled in an ice bath. Bromine (22.4 g, 7.5 ml, 0.14 mol) was added dropwise. At the end of the addition, a faint bromine color persisted in the solution for several minutes (if not, a little additional bromine was added). After the reaction mixture was stirred for another 15 min, 20 ml each of sat. $NaHCO_3$ and Na_2SO_3 solution were added to remove the excess bromine and HBr produced. The reaction mixture was then extracted with 200 ml of ether. The organic layer was washed with saturated $NaHCO_3$ and NaCl solution, and dried over Na_2SO_4. Removal of the solvent gave 37.3 g (quantitative yield) of crude 2-bromo-2-methylcyclooctanone 92. Since the NMR spectrum of the crude product showed the disappearance of the doublet corresponding to methyl protons in 89 and the apperance of a singlet at δ 1.75 (C-2 methyl), the crude product was used for dehydrobromination without purification.

10. Dehydrobromination of 2-Bromo-2-methylcyclooctanone 92

A solution of 37.3 g (0.17 mol) of crude 2-bromo-2-methylcyclooctanone 92 and 70 g of lithium carbonate in 300 ml of dry DMF was refluxed overnight under nitrogen. After the mixture was cooled, 100 ml of water was added. The reaction mixture was then extracted with 300 ml of ether, and the organic layer was dried (Na_2SO_4) and concentrated to give crude product which upon distillation at 73°/2.75 mm Hg yielded 14 g distillate and 10 g residue. Column chromatography of the distillate on silica gel (chloroform / hexane = 3 : 1) gave 12.4 g of pure 2-methyl-2-cyclooctenon 93 (66%) as a yellowish liquid: IR (neat) 2940 (s), 1685 (m), 1660(s), 1450 (m), 1380 (m) cm^{-1}; UV (95% ethanol) λ_{max} 242 nm (ε 6800), 285 nm (750); NMR (CCl_4) δ 1.76 (3H, d, J = 1.5 Hz C-2 methyl), 1.33-2.0 (6H, broad), 2.0-2.66 (4H, broad), 5.67-6.07 (1H, triplet of quartets, J = 7 Hz, 1.5 Hz, vinyl proton); mass spectrum, m/e (rel. intensity) 138 (parent, 18), 123 (3), 110 (14), 96 (35), 95 (100), 81 (40), 67 (72), 54 (41).

Anal. Calcd. for $C_9H_{14}O$: C 78.21; H 10.21.

Found : C 78.06; H 10.10.

11. Preparation of 2,3-Dimethylcyclooctanone 94

A solution of 0.108 g (0.7 mmol) of 93 in 5-ml ether was added to a methylmagnesium iodide solution (prepared from 0.05 g of magnesium and 0.284 g of methyl iodide in 20 ml ether) with 0.05 g of cuprous chloride added as catalyst. After addition, the reaction mixture was stirred for 30 min and refluxed for 20 min. Workup involved addition of aqueous NH_4Cl solution and extraction with ether. The ether layer was separated, dried

(Na_2SO_4) and concentrated to give 0.1 g of crude product. Preparative VPC (column A, 155°C) gave 2,3-dimethylcyclooctanone 94 as the major product (quantitative yield). The crude product was used for bromination directly without further purification. For 94: IR (neat) 2950 (s), 1692 (s), 1385 (m) cm^{-1}; NMR (CCl_4) δ 0.94 (3H, d, J = 7 Hz), 1.00 (3H, d, J = 7 Hz), 1.1-2.0 (9H, broad), 2.0-3.0 (3H, broad); mass spectrum, m/e (rel. intensity) 154 (30), 139 (9), 125 (27), 112 (37), 98 (90), 83 (100).

12. Bromination of 2,3-Dimethylcyclooctanone 94

A solution of 0.694 g (4.5 mmol) of 94 in 50 ml of a mixture of chloroform and ethyl acetate was refluxed with 2.1 g (9 mmol) of cupric bromide for 3 hr. The reaction mixture became dark green with white cuprous bromide suspending in the solution. The cuprous bromide was filtered and the filtrate was washed with saturated $NaHCO_3$ and NaCl solution, and dried over Na_2SO_4. Removal of the solvent gave 1.2 g of crude 2-bromo-2,3-dimethylcyclooctanone 95 (quantitative yield). The crude bromo ketone 95 was used for dehydrobromination directly. Bromination of 94 with bromine in ether also gave the same result. For 95: IR (neat) 1710 cm^{-1}; NMR (CCl_4) δ 1.28 (3H, d, J = 7 Hz), 1.6 (3H, s), 0.7-2.0 (8H, broad), 2.0-3.1 (3H, broad).

13. Dehydrobromination of 2-Bromo-2,3-dimethylcyclooctanone 95

The procedure as described for the dehydrobromination of bromoketone 92 was followed. The crude bromoketone 95 (1.2 g) was dehydrobrominated with 1.0 g of lithium carbonate and 0.5 g lithium chloride in 15 ml of

DMF to give 0.3 g (44%) of the product which was identified as 2-methylene-3-methylcyclooctanone 96: IR (neat) 2940 (s), 1690 (s), 1615 (m), 1470 (m) cm^{-1}; NMR (CCl_4) δ 1.15 (3H, d, J = 7 Hz), 1.2-2.0 (8H, broad), 2.0-3.0 (3H, broad), 5.05 (1H, m), 5,6 (1H, m).

14. 1,2-Addition of Methyllithium to 2-Cyclooctenone 79

To a stirred solution of 2-cyclooctenone (2.5 g, 0.02 mol) in 50 ml of anhydrous ether at room temperature under nitrogen was added, dropwise, an ethereal solution of methyllithium (14 ml, 1.7 M ethereal solution). The resulting solution was stirred for 2 hr, refluxed 1 hr, and quenched by the dropwise addition of 20 ml water. The phases were separated and the aqueous layer was extracted with two 20-ml portions of ether. The combined organic layers were washed with 20 ml of saturated NaCl solution and dried over Na_2SO_4. The solvent was removed at reduced pressure to give a yellow liquid which after column chromatrography (neutral alumina, hexane : ether = 1 : 1) afforded 2.3 g of 1-methylcyclooct-2-en-1-ol 97 (82%) and 0.4 g of starting material (16%). Pure samples of 97 were collected via VPC (column D, 175°C) for identification: IR (neat) 3370 (s), 2940 (s), 1450 (m), 1375 (m), 1240 (w), 1040 (m), 920 (m), 895 (m), 805 (m), 735 (m) cm^{-1}; NMR (CCl_4) δ 1.08 (1H, s, -OH), 1.23 (3H, s, C-1 methyl), 1.3-2.0 (8H, broad), 2.0-2.9 (2H, broad), 5.4 (2H, m, vinyl proton); mass spectrum, m/e (rel. intensity) 140 (2.5), 122 (47), 107 (40), 93 (8), 81 (39), 79 (100), 77 (34), 67 (31).

15. 1,2-Addition of Methyllithium to 2-Methyl-2-cyclooctenone 93

The procedure and workup were the same as that described above for 79. Thus 2 g of 2-methyl-2-cyclooctenone (0.015 mol) in 50 ml ether reated with 10 ml of methyllithium to yield after column chromatography 1.2 g of 1,2-dimethylcyclooct-2-en-1-ol 99 (52%) and 0.7 g of starting material (35%). For 99: IR (neat) 3410 (s), 2930 (s), 1450 (s), 1375 (m), 1035 (m), 950 (m), 885 (m), 850 (m) cm^{-1}; NMR (CCl_4) δ 1.06 (1H, s, -OH), 1.23 (3H, s, C-1 methyl), 1.76 (3H, s, C-2 methyl), 1.2-2.6 (10H, broad), 5.12 (1H, m, vinyl proton); mass spectrum, m/e (rel. intensity) 154 (7), 136 (70), 121 (49), 107 (85), 93 (100), 91 (44), 79 (84), 67 (53).

16. Oxidation of 1-Methylcyclooct-2-en-1-ol 97

To a magnetically stirred slurry of pyridinium chlorochromate (PCC, 8.6 g, 0.04 mol) in 60 ml of dichloromethane was added in one portion a solution of 97 (2.3 g, 0.0164 mol) in 10 ml of dichloromethane at room temperature. The resulting dark red-black mixture was allowed to stir for 3 hr, and was diluted with 30 ml of ether. The ethereal solution was decanted from the black resinous polymer, which in turn was washed with three 20-ml portions of ether. The combined ethereal phases were washed successively with two 100-ml portions of 10% aqueous NaOH, 100 ml of 10% aqueous HCl, and two 50-ml portions of saturated $NaHCO_3$, and dried over $MgSO_4$. Removal of the solvent gave a yellow liquid which after chromatography (silica gel, hexane : ether = 1 : 1) yielded 0.9 g (40%) of 3-methyl-2-cyclooctenone 98. Pure samples of 98 were collected via VPC

(column D, at 165°C) for spectral data: IR (neat) 2940 (s), 1650 (s), 1450 (m), 1380 (m), 1340 (m), 1265 (m), 1145 (w), 1040 (w), 885 (w), 845 (w) cm^{-1}; UV (95% EtOH) λ_{max} 245 nm (ε 7500); NMR (CCl_4) δ 1.35-2.1 (6H, broad), 1.84 (3H, d, J = 1.5 Hz, C-3 methyl), 2.2-2.8 (4H, broad), 5.78 (1H, broad); mass spectrum, m/e (rel. intensity) 138 (20), 123 (7), 109 (6), 95 (100), 82 (34), 67 (34), 55 (18), 41 (23). High resolution mass spectrum mol wt. 138.10384 (calcd. for $C_9H_{14}O$, 138.10446).

17. Oxidation of 1,2-Dimethylcyclooct-2-en-1-ol 99

The procedure described above for the oxidation of 97 was followed. A solution of 1.2 g of 99 (0.0078 mol) in 10 ml of methylene chloride was oxidized with PCC (4.2 g, 0.0195 mol) in 40 ml of methylene chloride to give after chromatography (neutral alumina, hexane : ether = 1 : 1) 0.36 g (30%) of 2,3-dimethyl-2-cyclooctenone 100 and 0.36 g (27%) of 2,3-dimethyl-2,3-epoxycyclooctanone 101. Compounds 100 and 101 were also separable by VPC (column D, at 165°C). For compound 100: IR (neat) 2930 (s), 1685 (s), 1650 (m), 1450 (m), 1380 (w), 1275 (w) cm^{-1}; UV (95% EtOH) λ_{max} 206 nm (ε 890), 250 (4360); NMR (CCl_4) δ 1.7 (6H, s, C-2 and C-3 methyls), 1.2-1.9 (6H, broad), 2.0-2.6 (4H, broad); mass spectrum, m/e (rel. intensity) 152 (29), 147 (8), 137 (11), 123 (8), 109 (100), 96 (22), 81 (42), 67 (32). High resolution mass spectrum mol wt. 152.12029 (calcd. for $C_{10}H_{16}O$, 152.12012). For compound 101: IR (neat) 2940 (s), 1715 (s), 1465 (s), 1390 (m), 1110 (m), 1075 (m), 895 (m), 850 (m), 830 (m) cm^{-1}; NMR (CCl_4) δ 1.3 (3H, s, C-3 methyl), 1.43 (3H, s, C-2 methyl), 1.0-2.0 (8H, broad), 2.1-2.8 (2H, broad); mass spectrum, m/e (rel. intensity) 168 (11), 140 (10), 126 (83), 125 (100), 112 (22), 111 (62), 98 (23),

97 (63), 85 (39), 84 (57).

18. Irradiation of 2-Methyl-2-cyclooctenone 93 in Methanol

A solution of 0. 139 g (1 mmol) of 93 in 10 ml of methanol was placed in a Pyrex tube, flushed with nitrogen and irradiated externally using a 450 W Hanovia Mercury lamp at room temperature. The photolysis was followed by analytic VPC (column C, at 165°C). As the reaction proceeded, the peak with a retention time of 0.6 min (starting material) decreased in area and a major product peak appeared at 1.3 min. After 4 hr of irradiation, the conversion was about 90% (a longer reaction time gave more of other undesired products) and the major product 102c was formed in 80% yield (55% isolated yield). 3-Methoxy-2-methylcyclooctanone 102c was collected by preparative VPC (column A, at 165°C) and examined: IR (neat) 2940 (s), 1705 (s), 1470 (s), 1450 (s), 1384 (m), 1330 (m), 1095 (s), 950 (m), 910 (m) cm^{-1}; NMR (CCl_4) δ 0.98 (3H, d, J = 7 Hz, C-2 methyl), 1.1-2.1 (8H, broad), 2.1-3.0 (3H, broad), 3.27 (3H, s, methoxyl), 3.7-4.1 (1H, broad, C-3 methine); mass spectrum, m/e (rel. intensity) 170 (6), 138 (24), 123 (7), 109 (25), 98 (25), 81 (26), 71 (100), 57 (71).

Anal. Calcd. for $C_{10}H_{18}O_2$: C 70.54; H 10.66.
Found : C 70.57; H 10.57.

19. Europium Shift Study of 3-Methoxy-2-methylcyclooctanone 102c

LIS spectra were recorded by gradually adding weighed amounts of Eu $(fod)_3$ (Aldrich Chemical Company) to 14 mg of 102c in CCl_4. The LIS

chemical shifts were plotted against the weight of Eu $(fod)_3$ and Δ is the extrapolated value of the chemical shift difference in p.p.m. for a molar ratio 1 : 1 of shift reagent : substrate. Δ's: 4.4 (OCH_3), 7.4 (H_3), 8.7 (CH_3), 10.4 (H_2), 8.2 (ω proton).

20. Decoupling Experiment of 102c and Eu-complexed 102c

Proton spectra of 102c were measured in $CDCl_3$ with TMS as an internal standard using a 180 MHz Bruker spectrometer: 1.09 (3H, d, J = 7 Hz, C-2 methyl), 1.25-2.07 (8H, broad, C4-C7 methylenes), 2.24-2.76 (2H, m, C-8 methylene), 2.90 (1H, quartet of doublets, J = 7 Hz, 3.5 Hz, C-2 methine), 3.4 (3H, s, methoxyl), 4.04 (1H, m, C-3 methine). Irradiation at δ 1.09 (C-2 methyl) caused the quartet of doublets at δ 2.90 to become a doublet with J = 3.5 Hz. Irradiation at δ 1.52 (C-4 methylene) caused the multiplet at δ 4.04 to become a doublet with J = 3.5 Hz.

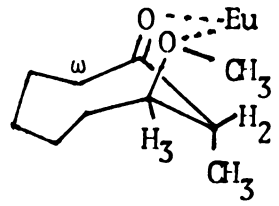
A solution of molar ratio of Eu $(fod)_3$: 102c = 0.71 in $CDCl_3$ (TMS as an internal standard) was placed in a 5-mm NMR tube which was in turn placed in a 10-mm NMR tube containing $CDCl_3$ solution for taking a 180 MHz spectrum. Shifted spectra ($CDCl_3$) 2.68-4.8 (6H, m, C5-C7 methylenes), 5.37-6.0 (2H, m, C-4 methylene), 6.1 (3H, d, J = 7 Hz, C-2 methyl), 6.33 (3H, s, methoxyl), 6.6-7.22 (2H, m, C-8 methylene), 8.83 (1H, m, C-3 methine), 9.28 (1H, m, C-2 methine). Irradiation at δ 6.1 (C-2 methyl) caused the multiplet at δ 9.28 to become a doublet, J = 3.0 Hz.

21. Base-catalyzed Addition of Methanol to 93

A solution of 76 mg of 93 in 15 ml of 0.01 N methanolic sodium methoxide was stirred at room temperature and the reaction course was followed by VPC (column C at 170° C). The reaction rate was quite slow; only very small amount of the adduct was formed after 1 day. The maximum yield of adduct was obtained after stirring for 8 days and VPC showed the composition of the reaction mixture (equilibrium mixture) to be 93 : 102t : 102c = 45 : 35 : 20. This ratio remained about the same for a prolonged reaction time (2 weeks). For 102t: IR (CCl_4) 2940 (s), 1705 (s), 1465 (m), 1100 (s); NMR ($CDCl_3$) δ 1.14 (3H, d, J = 6 Hz), 1.25-2.2 (8H, broad), 2.35 (2H, broad), 2.95 (2H, broad), 3.28 (3H, s); mass spectrum, m/e (rel. intensity) 170 (5), 138 (31), 123 (6), 109 (23), 98 (21), 81 (29), 71 (100).

LIS shift data were obtained (as that described for 102c) with 4.5 mg of 102t in $CDCl_3$ solution to give the following results.

Molar Ratio 102t : Eu (fod)$_3$	Δ (ppm)				
1 : 1	H_ω	H_2+H_3	CH_3	OCH_3	
	4.9	4.6	3.2	1.4	
1 : 2	H_2	H_ω	H_3	CH_3	OCH_3
	7.14	6.87	6.70	4.80	2.16



102t

LIS shifted spectrum (180 MHz, 4.5 mg of 102t and 54.8 mg Eu (fod)$_3$ in $CDCl_3$ solution): δ 3.3-5.16 (8H, C4-C7 methylene), 5.26 (3H, s), 5.47

(3H, d, J = 6.5 Hz), 8.48 (2H, C-8 methylene), 8.9 (1H, C-3 methine), 9.29 (1H, C-2 methine); irradiation at δ 9.29 caused the doublet at δ 5.47 to become a singlet. These results indicated that C-2 and C-3 methine protons in 102t are trans to each other.

22. Base-catalyzed Exchange Reaction of 102c in Methanol

A solution of 25 mg of 102c in 5 ml of 0.01 N methanolic sodium methoxide was stirred at room temperature and the reaction course was sollowed by VPC (column C, 170°C). After 1 day, VPC showed the composition of the reaction mixture to be 93 : 102t : 102c = 45 : 35 : 20. This ratio remained about the same for a few days.

23. Irradiation of 3-Methyl-2-cyclooctenone 98 in Methanol

A degassed solution containing 70 mg of 98 in 10 ml of methanol in a Pyrex tube was irradiated with a 450 W Hanovia lamp. The photolysis was followed by analytical VPC (column E, 180°C). The reaction was essentially complete in about 5 hr. VPC showed that the major product 105 was formed in 72% yield (retention time 7 min). Preparative VPC (column D, 175°C) gave pure 3-methoxy-3-methylcyclooctanone 105: IR (neat) 2940 (s), 1700 (s), 1470 (m), 1380 (w), 1310 (m), 1280 (w), 1220 (w), 1130 (m), 1080 (m) cm^{-1}; NMR (CCl_4) δ 1.16 (3H, s, C-3 methyl), 1.2-2.0 (8H, broad), 2.0-2.4 (2H, broad, C-8 methylene), 2.24 (1H, d, J = 11 Hz, H_t), 2.7 (1H, d, J = 11 Hz, H_c), 3.12 (3H, s, methoxyl); mass spectrum, m/e (rel. intensity) 170 (3), 155 (5), 140 (7), 138 (7), 123 (3), 114 (18), 99 (22), 95 (31), 85 (77), 72 (100), 55 (45).

24. Europium Shift Study of 3-Methoxy-3-methylcyclooctanone 105

The procedure was the same as that described for 102. The chemical shift differences found for a molar ratio 1 : 1 of shift reagent to substrate are as follows: Δ's in ppm, 6.9 (C-3 methyl), 11.6 (OCH_3), 12.3 (H_t), 17.4 (H_c), 8.3 (H_ω).

25. Irradiation of 2,3-Dimethyl-2-cyclooctenone 100 in Methanol

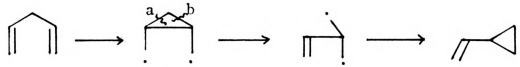
In a Pyrex test tube, 46 mg of 100 was dissolved in 10 ml of methanol. After being deoxygenated for 15 min with a stream of nitrogen, the solution was irradiated with a Hanovia 450 W lamp. The course of the reaction was followed by VPC (column E, 180°C). After 8 hr, VPC showed that the peak corresponding to starting material remained and the intensity decreased only a little bit. The solvent was removed under reduced pressure. Preparative VPC (column C, 175°C) gave only the starting material.

PART III

SYNTHESIS AND PHOTOCHEMISTRY OF

1,5-DIMETHYL-4-METHYLENEBICYCLO[3.3.0]OCTADIENES

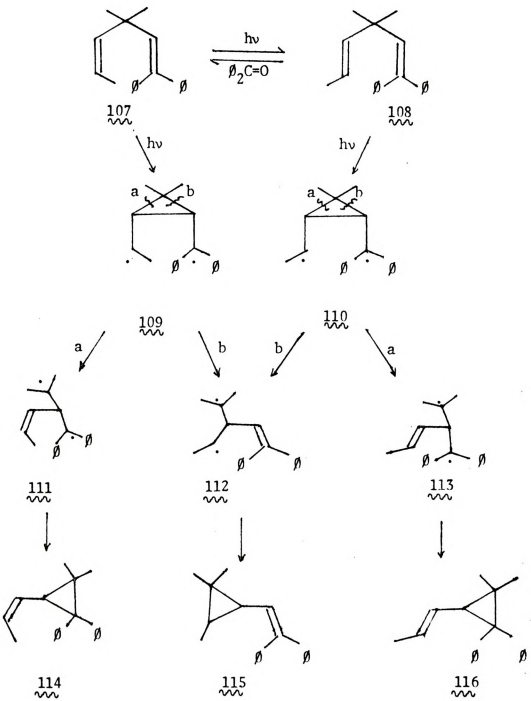
It was first noted by Zimmerman and coworkers[46] that molecules having the di-π-methane moiety, (i.e. having two π-systems bonded to a single sp^3 carbon) undergo a general photochemical transformation to vinylcyclopropanes. This reaction has been termed the di-π-methane rearrangement. This rearrangement can be accounted for by the gross mechanism shown below, which involves vinyl-vinyl bridging to give diradical 106, cleavage of the cyclopropane ring at either bond a or bond b and subsequent ring closure of the radical to afford the vinylcyclopropane.



106

Zimmerman's[47] study of the photochemistry of cis- and trans-1,1-dipheny1-3,3-dimethyl-1,4-hexadienes 107 and 108 constitutes an example of a di-π-methane rearrangement which occurs from a singlet excited state. Upon direct irradiation, rearrangement of the cis and trans isomers (107 and 108) occurred with extreme regiospecificity and striking stereospecificity. The cis isomer 107 yielded exclusively the cis-propenyl product 114, and the trans isomer 108 only the trans-propenyl product 116. No product 115 was formed in either case. However, when 107 and 108 were separately irradiated in a solution containing benzophenone as a sensitizer, no vinylcyclopropanes were produced but the cis-trans isomerization interconverting 107 and 108 was observed. Hence

the triplet excited states of 107 and 108 do not undergo the di-π-methane rearrangement.

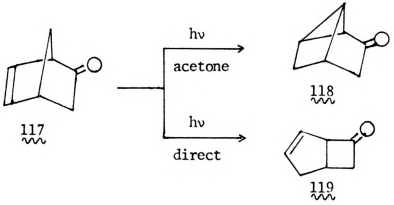


The selectivity in the opening of cyclopropane intermediates 109 and 110 by the cleavage of only bond a in each case indicates that the reaction proceeds by the route which allows maximum odd-electron delocalization. Routes b lead to loss of benzhydryl delocalization while routes a do not. Hence, 112 would be expected to be a higher energy intermediate than either 111 or 113 which afford the observed products. It has been proposed that the di-π-methane rearrangement, especially from the singlet excited state, can best be rationalized by a concerted mechanism.[46] Therefore, intermediates like 109 - 113 may not be discrete species and should be considered only as working models of the system.

It has been generally observed that nonconstrained acyclic and methylene monocyclic di-π-methane systems undergo the di-π-methane rearrangement exclusively from singlet excited states, whereas constrained bicyclic systems undergo the rearrangement from triplet excited states. The rationale for this observation is that bicyclic or constrained triplets are unable to dissipate their excitation energy by rotation about a double bond and thus undergo the di-π-methane rearrangement. Alternatively, triplet states of acyclic systems such as 107 or 108 do not have this constraint, and cis-trans isomerization is observed.

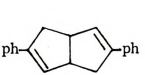
The di-π-methane rearrangement was further generalized by Givens[49a] in 1969 when he noted that a carbon-oxygen π-bond (in β,γ-unsaturated ketones) can also participate in the same manner as a carbon-carbon double bond. Dauben[49b] termed this the oxa-di-π-methane rearrangement. In constrast to the di-π-methane rearrangement which has been found to occur from both singlet and triplet states, the oxa-di-π-methane

rearrangement appears to take place solely from the triplet state. The singlet photochemistry observed under direct photolysis of β,γ-unsaturated ketones consists mainly of 1,3-acyl migration and/or decarbonylation, although other processes are sometimes also observed. For example, sensitized irradiation of bicyclo[2.2.1]hepta-5-ene-2-one 117[48] yields the oxa-di-π-methane product 118, whereas direct irradiation of 117 affords an isomeric β,γ-unsaturated ketone 119.

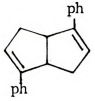


117 118 119

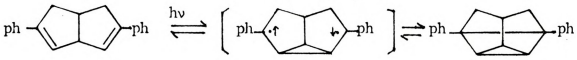
The [π2 + π2] cycloaddition is one of the most widely observed photochemical reactions, with numerous examples reported in the literature.[50] Although intramolecular [π2 + π2] cycloadditions are photochemically allowed, factors such as bond distance and orbital dihedral angle may make these cycloadditions unfavorable. For example, compounds 120 and 121 whose double bonds are separated by about 3.5Å do not undergo intramolecular cycloaddition on irradiation. In contrast, compound 122 upon irradiation (acetonitrile, Pyrex) affords compound 123.[51]



120

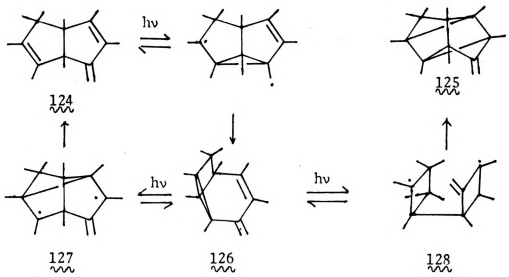


121



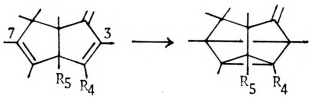
122 123

Recently, however, Hart and Kuzuya[52] found that 124 on irradiation (ether, vycor) gave an essentially quantitative yield of the crystalline isomer 125, whose structure corresponds to that of a cycloaddition of the two endocyclic π-bonds. The structural feature present in 124 but absent in 120 and 121 is the di-π-methane moiety. This reaction which on the surface corresponds to an intramolecular [π2 + π2] cycloaddition has been proposed to proceed in two steps, involving initial di-π-methane rearrangement to 126 and subsequent [σ2 + π2] cycloaddition to give 125 as shown below.



124 125 127 126 128

Another example of a reaction which appears to be a [π2 + π2] cycloaddition but which probably involves two steps is the conversion of 129 to 130 examined by Hart and Kuzuya.[52] Under conditions where

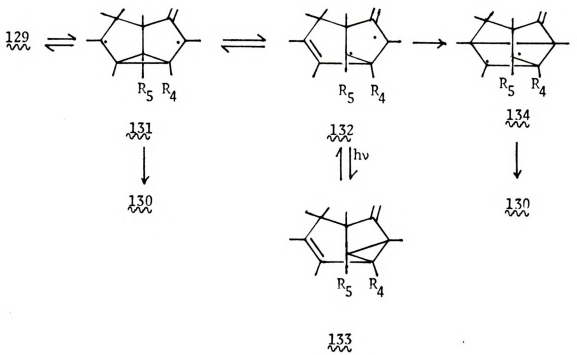


129 130

a: $R_4 = R_5 = CH_3$
b: $R_4 = H$, $R_5 = CH_3$
c: $R_4 = CH_3$, $R_5 = H$

photoisomerization of 129a and 129b were complete only 30% of 129c was converted to 130c. If the conversion of 129 to 130 were a direct [π2 + π2] process, there is no obvious reason why substitution of H for CH_3 at C5 would diminish the reaction efficiency; this observation can be best understood if a bond to C5 is broken during the reaction. The following mechanism has been suggested. The initial step is a di-π-methane rearrangement with cleavage of the cyclopropane ring at the site of higher

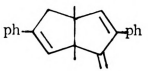
odd electron density (3° vs allylic). Direct ring closure from diradical 131 (to give 130) as has been suggested[51] seems rather unlikely in view of the large distance between C-3 and C-7 (ca. 3.8Å in 129, 3.1Å in 131) and the poorly oriented dihedral angle of the pertinent orbitals. The geometry of 132 is much more conducive to formation of C3 - C7 bond than is that of 131; in 134, the orbitals are close and properly oriented for the final bond-forming step to give 130. The di-π-methane intermediate 133 might be a discrete intermediate. This mechanism explains why 129c reacts more slowly than 129a and 129b. Therefore, it is important to consider multistep mechanisms for intramolecular [π2 + π2] cycloaddition if the substrate also contains a di-π-methane moiety.



The purpose of this part of the thesis was to synthesize bicyclo-[3.3.0] compounds containing a di-π-methane moiety with the hope that evidence might be found in these systems to support the two-step mechanism for the intramolecular [π2 + π2] photocycloaddition; that is a di-π-methane rearrangement followed by a [σ2 + π2] cycloaddition. In particular, it was hoped that the product of the first step might in some cases be isolated. Compounds that were selected for study, and were synthesized are 148, 150, and 163.

148

150



163

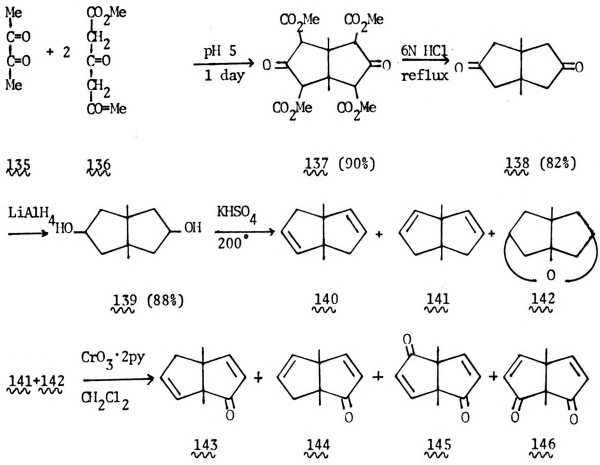
RESULTS AND DISCUSSION

1. Synthesis of 1,5-Dimethyl-4-methylenebicycl[3.3.0]octa-2,6 and 2,7-dienes 148 and 150

The synthesis of 148 and 150 was accomplished as outlined in Scheme 6. The method of Weiss[53] was followed to prepare dione 138. Reaction of dimethyl β-ketoglutarate and 2,3-butanedione at pH 5 for 1 day gave tetraester 137 in 90% yield. The peak at δ 10.4 (two enolic hydrogens) in the NMR spectrum of 137 indicated that 137 in $CDCl_3$ or CCl_4 solution is 100% enolized at both keto groups. A plausible mechanism[54] for the formation of 138 is shown in Scheme 7. Aldol condensation of 135 and 136 in equimolar amounts would produce the adduct 151 which is dehydrated to intermediate 152; intramolecular aldol condensation of 152 then generates the cyclopentenone 153. Michael addition of a second molecule of 136 to 153 would afford the intermediate 154 which, as a β-hydroxy ketone, would readily eliminate water to form the α,β-unsaturated ketone 155. A second Michael addition (intramolecular) would lead to the product 137.

Decarboxylation of 137 in aqueous hydrochloric acid gave cis-1,5-dimethylbicyclo[3.3.0]octa-3,7-dione 138 in 82% yield. The stereochemistry of the ring juncture is based on europium shift data as shown in the structure below. The two methyls at δ 1.2 which showed the least europium shift, are assigned as cis to each other,

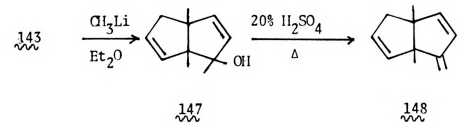
Scheme 6



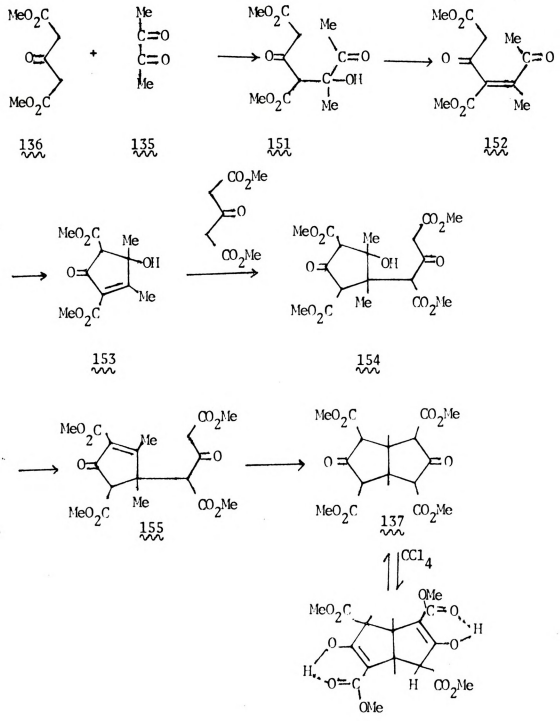
135 136 137 (90%) 138 (82%)

139 (88%) 140 141 142

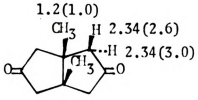
141+142 → 143 + 144 + 145 + 146



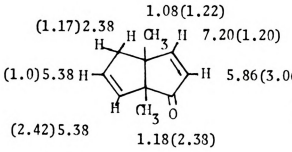
Scheme 7


MeO2C
Me
C=O
C=O
Me
MeO2C
136
135
151
152
153
154
155
137
CO2Me
OH
CCl4
OMe
H
enol form

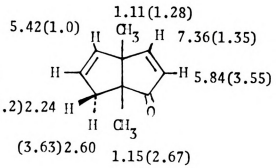
and the methylene protons at δ 2.34 was well resolved into two doublets with J = 19 Hz.



Reduction of diketone 138 with lithium aluminum hydride in ether yielded 88% of diol 139 which upon dehydration with potassium bisulfate gave the isomeric dienes 140 and 141 in only 30% yield, along with cyclic ether 142 as a major undesired product (50% yield). Dienes 140 and 141 were separated by VPC in 55 : 45 ratio. Allylic oxidation of the mixture of 141 and 142 with chromium trioxide-pyridine complex resulted in a complicated mixture of α,β-unsaturated ketones which was first separated into three fractions by preparative TLC (with 143 and 144 being in the first fraction, and 145 and 146 constituting the second and third fractions respectively). The mixture of 143 and 144 was further separated by VPC to give each compound pure. Compounds 143 and 144 were distinguished on the bases of different chemical shifts and europium ahift slopes of the methylene protons. This signal is most affected by shift reagent when the methylene protons are at C-6 (i.e. in 144). The IR ($\nu_{C=O}$ 1720 cm^{-1}) and UV spectra (λ_{max} 238 nm, ε 1740 for 143; 241 nm, 1600 for 144) support the presence of a cyclopentenone moiety in each isomer. The NMR spectrum of each isomer showed two bridge-head methyls, four vinyl protons, and two methylene protons. The mass spectra of 143 and 144 were nearly identical, and they both had a correct elemental analysis.

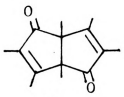


143



144

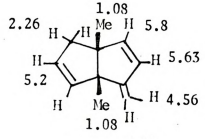
The distinction between 145 and 146 is based on their IR and NMR spectra. The IR spectrum of 145 showed one carbonyl absorption at 1700 cm^{-1}, whereas that of 146 showed two absorptions at 1720 and 1680 cm^{-1}. An infrared absorption at 1700 cm^{-1} was reported for 156 by Shih.[57] The structure of 145 was also suggested by the presence of two equivalent methyls at δ 1.30 (6H, s) in the NMR spectrum as compared to the two different methyl singlets at δ 1.28 and 1.35 for 146. Both 145 and 146 had parent peaks at m/e 162 in their mass spectra.



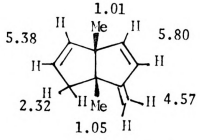
156

Compounds 143 and 144 were finally converted to the desired trienes 148 and 150 respectively in good yield upon treatment with methyllithium followed by dehydration with dilute sulfuric acid. Compounds 148 and

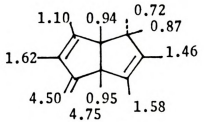
150 were assigned structures on the basis of their spectral data. The IR absorptions at 1635 cm^{-1} for both compounds indicated the presence of conjugated diene moiety. The UV spectrum of 148 at λ_{max} 234 nm (ϵ 14800, cyclohexane) and of 150 at 238 nm (12620) also support the presence of a conjugated diene moiety. The mass spectra of both 148 and 150 showed a parent peak at m/e 146. The NMR spectrum of 148 showed a singlet for the two bridgehead methyls at δ 1.08 (6H), two methylene protons at δ 2.26 (2H), two exo-methylene protons at δ 4.56 (1H, s) and 4.72 (1H, s), four vinyl protons at δ 5.2 (2H), 5.63 (1H, d, J = 6 Hz), and 5.8 (1H, d, J = 6 Hz). The NMR spectrum of 150 showed the expected resonances: two methyl singlets at δ 1.05 and 1.10, two methylene protons at δ 2.32 (2H), two exo-methylene protons at δ 4.57 (1H, s) and 4.72 (1H, s), four vinyl protons at δ 5.38 (2H, m) and 5.80 (2H, m). All of the spectra of 148 and 150 resemble closely the published spectra of 157 and 158 by Hart and Kuzuya.[58]



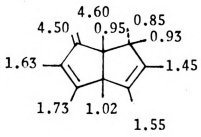
148



150



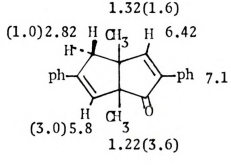
157



158

2. Synthesis of 1,5-Dimethyl-3,7-diphenyl-4-methylenebicyclo[3.3.0]-octa-2,6-diene 163

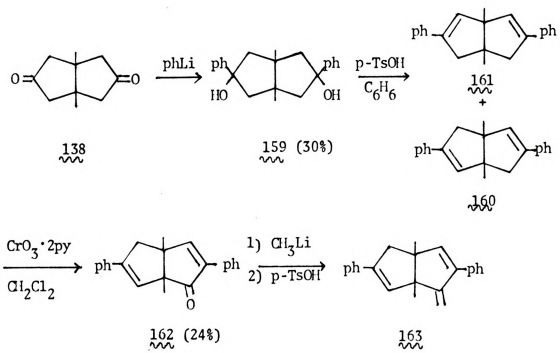
The synthesis of 163 was accomplished according to Scheme 8. Treatment of diketone 138 with phenyllithium or phenylmagnesium bromide in ether gave diol 159 in 30% yield. Dehydration of diol 159 with refluxing p-toluenesulfonic acid in benzene afforded a mixture of dienes 160 and 161 (in a 75 : 25 ratio, calculated from NMR) in 46% yield. Allylic oxidation of the diene mixture 160 and 161 with chromium trioxide-pyridine complex in methylene chloride produced after chromatography on alumina, a 24% yield of an α,β-unsaturated ketone 162 which was assigned the structure shown on the basis of its spectral data. The molecular formula $C_{22}H_{20}O$ was confirmed by its mass spectrum (parent



162

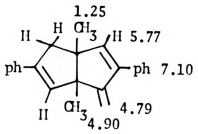
peak m/e 300) and elemental analysis. Compound 162 showed infrared bands at 1695, 705, and 770 cm^{-1} which are indicative of the presence of cyclopentenone moiety and a monosubstituted phenyl group. The UV spectrum showed λ_{max} 223 (ε 15550) and 258 nm (18550) consistent with extended conjugation between the phenyl ring and the α,β-unsaturated carbonyl chromophore. The NMR spectrum showed two methyl signals at δ 1.22 and 1.32, two methylene protons at δ 2.82 (2H), two vinyl protons at δ 5.80 (1H) and 6.42 (1H), and ten phenyl protons centered at δ 7.1.

Scheme 8



138 159 (30%) 161 + 160 162 (24%) 163

Compound 162, on treatment with methyllithium followed by dehydration with p-toluenesulfonic acid in benzene gave the desired triene 163 in quantitative yield. Compound 163 was assigned the structure shown. The molecular formula $C_{23}H_{22}$ was confirmed by a mass spectrum (parent peak m/e 298) and elemental analysis. The IR absorptions at 1630, 765

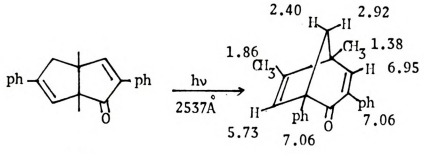


163

and 706 cm^{-1} are consistent with the conjugated olefin and the presence of a phenyl ring; UV maxima at 222 nm (ε 7950) and 255 nm (7000) indicated the presence of conjugation within the molecule. The NMR spectrum showed the two bridgehead methyls at δ 1.25 (6H), methylene protons at 2.73 (2H), exo-methylene protons at δ 4.79 (1H) and 4.90 (1H), two vinyl protons at δ 5.77, and ten phenyl protons at δ 7.10.

3. Photolysis of 1,5-Dimethyl-3,7-diphenylbicyclo[3.3.0]octa-2,6-dien-4-one 162

The irradiation of 162 in ether with 2537 Å light resulted in the formation of 164, which is the product of a 1,3 acyl migration. Compound 164 was assigned the structure shown on the basis of the following spectral data. The molecular formula $C_{22}H_{20}O$ confirmed by a mass spectrum (parent peak m/e 300) and elemental analysis. IR absorption at 1690 cm^{-1} and a UV maximum at 225 nm (ε 15600) are consistent with the conjugated structure shown. In its NMR spectrum, irradiation at δ 5.73 caused the doublet at δ 1.86 to become a singlet indicating that it is due to a vinyl methyl group.

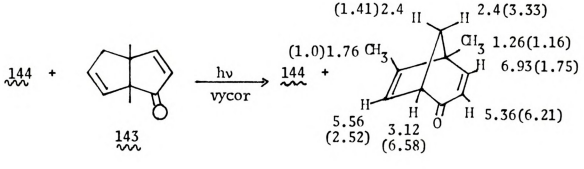


162

164 (37%)

4. Photolysis of 1,5-Dimethylbicyclo[3.3.0]octa-2,6-dien-4-one 143

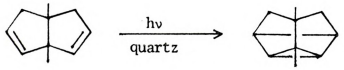
When the mixture of α,β-unsaturated ketones 143 and 144 was irradiated in ether through a vycor filter for 14 hr, compound 144 was recovered and 143 underwent 1,3 acyl migration to give compound 165. The structure of 165 followed from its spectral data. The molecular formula $C_{10}H_{12}O$ was confirmed by a mass spectrum (parent peak m/e 148) and elemental analysis. Infrared absorption at 1685 cm^{-1} and UV maxima at 244 nm (ε 2570) and 281 (1230) are consistent with the conjugated cyclic enone. The NMR spectrum and europium shift data are also consistent with the structure shown.



165

5. Photolysis of 1,5-Dimethylbicyclo[3.3.0]octa-2,7-diene 141

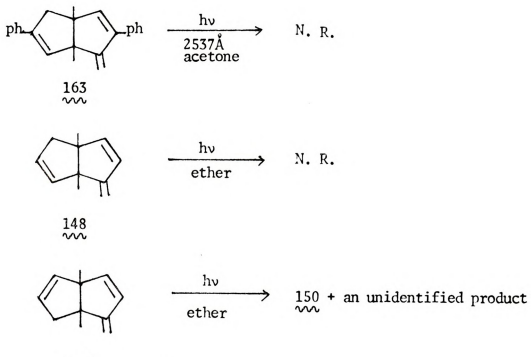
When the diene mixture of 140 and 141 was irradiated (ether, quartz, followed by VPC) for 38 hr, diene 140 remained unchanged, whereas a new product 1,5-dimethyl[3.3.$0^{1,5}$.$0^{2,8}$.$0^{3,7}$]quadricyclooctane 166 was formed from diene 141. This result was further confirmed by the irradiation of diene 141 alone under identical condition to give the same product 166 in 10% isolated yield. Hence, diene 140 did not undergo intramolecular photocycloaddition due presumably to the unfavorable bond distance between the two double bonds. The formation of 166 from 141 is similar to what was observed by Kaupp[51] (see introduction). Compound 166 was assigned the structure shown on the basis of the following spectral data. The absence of infrared bands in the region of 1500-1680 cm^{-1} together with the absence of signals corresponding to vinyl protons in the NMR spectrum indicated that 166 must be a saturated compound. The mass spectrum showed a parent peak at m/e 134 and a base peak at m/e 119 corresponding to a loss of CH_3. The NMR spectrum showed two methyl singlets at δ 1.06 and 1.32, four methine protons at δ 0.95 (2H, d, J = 9.5 Hz) and 1.24 (2H, d, J = 9.5 Hz) and four methylene protons at δ 1.8 (2H) and 2.28 (2H).



141 166

6. Photolysis of 1,5-Dimethyl-3,7-diphenyl-4-methylenebicyclo[3.3.0]-octa-2,6-diene 163 and 1,5-Dimethyl-4-methylenebicyclo[3.3.0]octa-2,6 and 2,7-dienes 148 and 150

Compound 148, 150, and 163 all contain di-π-methane moieties, and would theoretically be capable of undergoing the di-π-methane rearrangement. However, when compound 163 was irradiated in acetone with 2537 Å light and the reaction was followed by VPC for 22 hr, no detectable new product was formed. Irradiation of 148 in ether through a vycor filter for 29.5 hr only resulted in recovery of starting material. Photolysis of 150 under identical conditions gave some recovered starting triene 150 and an unidentified product, according to VPC and NMR analysis. All three of the above compounds may have suffered significant



polymerization because substantial amounts of starting materials were lost and some polymeric material was found in each case. The failure of these compounds to undergo the di-π-methane rearrangement is probably because the polymerization and other energy dissipation processes (involving no chemical change) of the excited trienes are more efficient than the di-π-methane rearrangement.

In summary, compounds 148, 150, and 163 containing the di-π-methane moiety have been successfully synthesized. However, these compounds on irradiation did not give detectable amount of di-π-methane rearrangement product or the product corresponding to cycloaddition of the two endocyclic double bonds.

EXPERIMENTAL

1. Gas Chromatography

VPC columns that were used in this section are as follows:

A: 10' x 0.25 in column, 21% β,β'oxydipropionitrile on firebrick.

B: 5' x 0.25 in column, 20% FFAP on chromosorb W.

C: 5' x 0.25 in column, 5% SE30 on chromosorb W.

D: 5' x 0.125 in column, 5% SE30 on chromosorb W.

2. 1,5-Dimethyl-2,4,6,8-tetramethoxycarbonylbicyclo[3.3.0]octan-3,7-dione 137[53]

Reaction of dimethyl β-ketoglutarate 136 (59.12 g, 0.34 mol) and 2,3-butanedione 135 (14.62 g, 0.17 mol) at room temperature in 300 ml of aqueous buffer (pH 5) for 1 day afforded tetraester 137 in 90% yield, MP 155-159° (sublimed), recrystallized from methanol. It is 100% enolized in $CDCl_3$ and CCl_4 solution as shown by NMR. NMR ($CDCl_3$ + CCl_4) δ 1.25 (6H, s), 3.68 (6H, s), 3.8 (4H, s), 10.4 (2H, s, enol). IR ($CDCl_3$) 1730 (s), 1665 (s), 1630 (s) cm^{-1}; mass spectrum, m/e 398 (parent).

3. 1,5-Dimethylbicyclo[3.3.0]octan-3,7-dione 138[53]

Hydrolysis of 137 (139.3 g, 0.35 mol) in 600 ml of 6 N HCl at reflux for 1 day resulted in an 82% yield of 138 (after recrystallization

from ethanol), MP 166- 167° (sealed tube). IR ($CDCl_3$) 1738 cm^{-1}; NMR ($CDCl_3$) δ 1.2 (6H, s), 2.34 (8H, s); Eu $(fod)_3$ shift reagent resolved the peak at δ 2.34 into two doublets with J = 19 Hz; for europium shift slopes see its structure in the text.

4. 1,5-Dimethylbicyclo[3.3.0]octan-3,7-diol 139

A solution of diketone 138 (9.96 g, 0.06 mol) in 150 ml ether was added under nitrogen over 40 min to a stirred refluxing solution of $LiAlH_4$ (2.6 g, 0.068 mol) in 75 ml ether. After addition, the reaction mixture was stirred at reflux for 4 hr, then cooled and quenched through the sequential addition of 2.4 ml H_2O, 2.4 ml 1.5% NaOH, and 7 ml H_2O. The precipitate was filtered, and filtrate was dried over Na_2SO_4. Concentration of the filtrate gave 8.5 g of a white powder. Extraction of the salts precipitated through the quenching sequence with ether led to an additional 0.5 g of diol. Recrystallization from chloroform gave a white crystalline solid in 88% yield, MP 148-151° (sublimed); IR (KBr) 3300 cm^{-1}; mass spectrum, m/e 170 (parent).

5. 1,5-Dimethylbicyclo[3.3.0]octa-2,6 and 2,7-dienes 140 and 141[53b]

A mixture of 6.8 g (0.04 mol) of diol 139 and 6 g of fused $KHSO_4$ was placed in a 100-ml round-bottomed flask equipped with a distillation apparatus. The mixture was heated to 200°C for 2 hr. The dehydrated product was condensed in the condenser as a semisolid material which is mostly diene. The residue left in the flask was then cooled, dissolved in 30 ml of water, extracted several times with ether. Ether layer was

washed with saturated $NaHCO_3$ and NaCl solution, dried over $MgSO_4$ and decolorized with Norit A. The ether extract was then combined with the distillate and concentrated to give about 20 ml of crude product which upon distillation at 85-90°C/120 mm Hg gave 1.64 g of colorless liquid (30% yield) consisting of dienes 140 and 141 in 55 : 45 ratio (judged by VPC). The residue (3 g, 50% yield) left behind in the flask contained mainly cyclic ether 142. The mixture of 140 and 141 was further separated by VPC (column A, 80°C). For 140: retention time 10 min; NMR (CCl_4) δ 1.02 (6H, s), 2.18 (4H, s), 5.29 (4H, s); mass spectrum, m/e 134 (40%, parent), 119 (100%). For 141: retention time 12.5 min; NMR (CCl_4) δ 0.95 (3H, s), 0.97 (3H, s), 2.18 (4H, s), 5.35 (4H, s); mass spectrum, m/e 134 (45%), 119 (100%). For 142: MP 140-142°C; IR (CCl_4) 2950 (s), 1460 (s), 1320 (s), 1190 (m), 1160 (s), 1130 (m) cm^{-1}; NMR (CCl_4) δ 1.07 (6H, s), 1.2-1.7 (8H, m), 4.12 (2H, broad); mass spectrum, m/e 152 (14%, parent), 95 (100%). High resolution mass spectrum mol wt 152.11969 (calcd. for $C_{10}H_{16}O$, 152.12012).

6. Allylic Oxidation of Dienes 140 and 141

The procedure of Shaffer and Pesaro[37b] was followed. Thus 0.373 g (2.8 mmol) of diene mixture 140 and 141 was oxidized by chromium trioxide-pyridine complex (6.7 g pyridine and 4.18 g CrO_3) in 70 ml methylene chloride. The reaction mixture after workup and preparative TLC (silica gel, hexane : ether = 1 : 1) gave 0.168 g of a mixture of 1,5-dimethylbicyclo[3.3.0]octa-2,6-dien-4-one 143 and 2,7-dien-4-one 144, 0.0117 g of 1,5-dimethylbicyclo[3.3.0]octa-2,6-dien-4,8-dione 145 and 0.0077 g of 1,5-dimethylbicyclo[3.3.0]octa-2,7-dien-4,6-dione 146. The mixture of

143 and 144 was further separated by VPC (column B, 105°C). Therefore, the yields for these compounds are as follows: 143 : 144 : 145 : 146 = 20% : 20% : 2.6% : 1.8%. Spectroscopic data for compound 143: IR (neat) 1702 cm^{-1}; UV (95% EtOH) λ_{max} 238 (ε 1740); NMR ($CDCl_3$) δ 1.08 (3H, s), 1.18 (3H, s), 2.38 (2H, s), 5.38 (2H, s), 5.86 (1H, d, J = 6 Hz), 7.20 (1H, d, J = 6 Hz); for Europium shift data see structure 143; mass spectrum, m/e (rel. intensity) 148 (59), 133 (57), 120 (23), 105 (100), 91 (26), 79 (29).

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16.
Found: C, 80.78; H, 8.05.

For compound 144: IR (neat) 1702 cm^{-1}; UV (95% EtOH) λ_{max} 241 (ε 1600); NMR ($CDCl_3$) δ 1.11 (3H, s), 1.15 (3H, s), 2.24 (1H, d, J = 18 Hz), 2.60 (1H, d, J = 18 Hz), 5.42 (2H, broad), 5.84 (1H, d, J = 6 Hz), 7.36 (1H, d, J = 6 Hz); for Europium shift data see structure 144; mass spectrum, m/e (rel. intensity) 148 (71), 133 (61), 120 (17), 105 (100), 91 (27), 79 (30).

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16.
Found: C, 81.09; H, 8.14.

For compound 145: MP 161-162°C (sublimed); IR (KBr) 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (6H, s), 5.88 (2H, d, J = 6 Hz), 7.30 (2H, d, J = 6 Hz); mass spectrum, m/e (rel. intensity) 162 (48), 147 (35), 134 (44), 119 (8), 106 (24), 91 (100). For compound 146: MP 170°C (sublimed); IR (KBr) 1720 (s), 1680 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.28 (3H, s), 1.35 (3H, s), 5.74 (2H, d, J = 6 Hz), 7.40 (2H, d, J = 6 Hz); mass spectrum, m/e (rel. intensity) 162 (50), 147 (38), 134 (56), 119 (11), 105 (26), 91 (100).

7. Synthesis of 1,5-Dimethyl-4-methylenebicyclo[3.3.0]octa-2,6-diene 148

To a solution of 0.567 g (3.8 mmol) of 142 in 30 ml ether was added 5 ml of methyllithium (1.8 M in ether) with a syringe at 0°C under nitrogen. The mixture was then refluxed for 2 hr. After cooling, the reaction mixture was poured into an ice-NH_4Cl solution (≈ 100 ml) and extracted with 150 ml ether. The ether layer was concentrated to give 0.63 g of crude alcohol 147 which showed hydroxyl absorption at 3460 cm^{-1} and no carbonyl absorption. The crude alcohol 147 was refluxed with 30 ml of 20% sulfuric acid for 1 hr. The reaction mixture was extracted with 50 ml of ether, the ether layer washed with saturated $NaHCO_3$ and NaCl solution, and dried over $MgSO_4$. Removal of the solvent left 0.56 g of crude diene 148 as a yellow liquid. A pure sample of compound 148 was collected in 50% yield by VPC (column B, 130°C, retention time 3.1 min). IR (CCl_4) 2980 (s), 1635 (s), 1380 (s), 880 (s) cm^{-1}; UV (cyclohexane) λ_{max} 234 nm (ε 14800); NMR (CCl_4) δ 1.08 (6H, s), 2.26 (2H, s), 4.56 (1H, s), 4.72 (1H, s), 5.2 (2H, m), 5.63 (1H, d, J = 6 Hz), 5.8 (1H, d, J = 6 Hz); mass spectrum, m/e (rel. intensity) 146 (31), 131 (100), 116 (19), 105 (9), 91 (38), 77 (9). High resolution mass spectrum mol wt. 146.10854 (calcd. for $C_{11}H_{14}$, 146.10954).

8. Synthesis of 1,5-Dimethyl-4-methylenebicyclo[3.3.0]octa-2,7-diene 150

The procedure and workup were as described for diene 148. From 0.64 g of 144 there was obtained 0.7 g of crude alcohol 149, and dehydration of the crude alcohol 149 gave 0.58 g of crude diene 150. A pure sample was collected by VPC (same conditions as for 148, except

retention time = 2.8 min) in 40% yield. IR (CCl_4) 2980 (s), 1635 (s), 1380 (s), 880 (s) cm^{-1}; UV (cyclohexane) λ_{max} 238 nm (ε 12620); NMR (CCl_4) δ 1.05 (3H, s), 1.10 (3H, s), 2.32 (2H, m), 4.57 (1H, s), 4.72 (1H, s), 5.38 (2H, m), 5.80 (2H, m); mass spectrum, m/e (rel. intensity) 146 (35), 131 (100), 116 (16), 105 (7), 91 (35), 77 (12). High resolution mass spectrum mol wt. 146.10881 (calcd. for $C_{11}H_{14}$, 146.10954).

9. 1,5-Dimethyl-3,7-diphenylbicyclo[3.3.0]octan-3,7-diol 159

A solution of 0.83 g of (5 mmol) of diketone 138 in 50 ml THF was added solwly at 0°C under nitrogen to a solution of 8 ml of 2.0 M phenyllithium (16mmol) in 20 ml THF. The reaction mixture was refluxed for 2 hr, then cooled and quenched with 50 ml ice water. Ether (100 ml) was used to extract the diol. The organic layer was dried over Na_2SO_4 and the solvent was stripped to give crude diol 159. Recrystallization from methanol gave colorless needle-like crystals (0.5 g, 30% yield), MP 155-157°: IR (KBr) 3250 (s), 2950 (s), 1600 (m), 760 (s), 700 (s) cm^{-1}. Compound 159 was also obtained from diketone 138 and phenylmagnesium bromide in a similar yield.

10. 1,5-Dimethyl-3,7-diphenylbicyclo[3.3.0]octa-2,6 and 2,7-diene 160 and 161[56]

A mixture of 17.6 g of (55 mmol) of diol 159 and 12 g of p-toluenesulfonic acid in 350 ml benzene was refluxed for 2 hr with continous removal of water. The reaction mixture was then cooled, neutralized with 350 ml 5% $NaHCO_3$, and extracted with 200 ml benzene. The benzene

layer was washed with water and dried ($MgSO_4$). Removal of solvent and column chromatography (neutral alumina, cyclohexane) gave 7.2 g (46% yield, recrystallized from petroleum ether) of colorless crystals which was a mixture of dienes 160 and 161 in a 75 : 25 ratio (calculated from NMR), MP 64-65°; IR (KBr) 2920 (s), 1500 (s), 1450 (s), 760 (s), 700 (s) cm^{-1}; UV (cyclohexane) λ_{max} 220 nm (ε 1770), 247 (21200), 253 (23100), 258 (24200), 263 (24200); NMR (CCl_4) δ 1.2 (6H, m), 2.5 (4H, broad), 5.8 (2H, broad), 7.1 (10H, broad).

11. 1,5-Dimethyl-3,7-diphenylbicyclo[3.3.0]octa-dien-4-one 162

The procedure as described for making 143 and 144 was followed. A diene mixture of 160 and 161 (75 : 25 ratio, 8 g, 28 mmol) was oxidized by chromium trioxide-pyridine complex (72 g pyridine, 45 g CrO_3) in 1000 ml methylene chloride. Product 162 was separated on alumina (hexane : ether = 1 : 4 initially, then 1 : 1) in 24% yield: MP 94-95°C; IR (KBr) 2950 (m), 1695 (s), 1500 (m), 145- (m), 770 (s), 705 (s) cm^{-1}; UV (95% EtOH) λ_{max} 223 nm (ε 15550), 258 (18550); NMR (CCl_4) δ 1.22 (3H, s), 1.32 (3H, d, J = 2 Hz), 2.82 (2H, m), 5.80 (1H, m), 6.42 (1H, m), 7.1 (10H, broad); mass spectrum, m/e (rel. intensity) 300 (100), 238 (20), 272 (20), 257 (23), 183 (58), 170 (64).

Anal. Calcd. for $C_{22}H_{20}O$: C, 87.96; H, 6.71.
Found: C, 87.91; H, 6.78.

12. 1,5-Dimethyl-3,7-diphenyl-4-methylenebicyclo[3.3.0]octa-2,6-diene 163

The procedure described for making compound 148 was followed except

that p-toluensulfonic acid was used for the dehydration in this case. Thus compound 163 was obtained in quantitative yield from 162 (0.3 g, 1 mmol) by treatment with methyllithium (1.5 ml, 1.8 M in ether) followed by dehydration with p-toluenesulfonic acid (0.24 g) in 150 ml benzene. A sample of pure 163 was obtained by VPC (column C, 225°) or TLC (silica gel, ether + hexane). IR (neat) 3000 (m), 1630 (m), 1505 (m), 1455 (m), 765 (s), 706 (s) cm^{-1}; UV (cyclohexane) λ_{max} 223 nm (ε 7950), 255 (7000); NMR (CCl_4) δ 1.25 (6H, singlet with side peak), 2.73 (2H, broad), 4.79 (1H, s), 4.90 (1H, s), 5.77 (2H, broad), 7.10 (10H, broad); mass spectrum, m/e (rel. intensity) 298 (100), 283 (61), 268 (16), 252 (12), 205 (25), 195 (55), 165 (53).

Anal. Calcd. for $C_{23}H_{22}$: C, 92.62; H, 7.83.
Found: C, 92.70; H, 7.71.

13. Photolysis of 1,5-Dimethyl-3,7-Diphenylbicyclo[3.3.0]octa-2,6-dien-4-one 162

A degassed solution containing 100 mg of 162 in 12 ml ether was irradiated with 2537 Å light in a Rayonet photochemical reaction apparatus for 18 hr. The photolysis was followed by VPC. A major product 164 was separated by VPC (column C, 215°) in 37% yield. Data for 164: IR (CCl_4) 2980 (m), 1690 (s), 1510 (m), 1455 (m), 705 (s) cm^{-1}; UV (95% EtOH) λ_{max} 225 nm (ε 15600); NMR (CCl_4) δ 1.38 (3H, s), 1.86 (3H, d, J = 2 Hz), 2.40 (1H, d, J = 10 Hz), 2.92 (1H, d, J = 10 Hz), 5.73 (1H, broad), 6.95 (1H, broad), 7.06 (10H, s); irradiation at δ 5.73 caused the doublet at δ 1.86 to become a singlet: mass spectrum, m/e (rel. intensity) 300 (95), 285 (20), 262 (19), 257 (27), 170 (100),

155 (56).

Anal. Calcd. for $C_{22}H_{20}O$: C, 87.96; H, 6.71.
Found: C, 88.02; H, 6.76.

14. Photolysis of 1,5-Dimethylbicyclo[3.3.0]octa-2,6-dien-4-one 143

A quartz tube containing 100 mg of the mixture of 143 and 144 (1 : 1 ratio) was flushed with nitrogen and irradiated for 14 hr with a Hanovia 450 watt lamp using a vycor filter. Compound 144 was recovered, whereas compound 143 (50% conversion) gave a new product 165 which was collected in 12% yield by VPC (column B, 130°). Data for 165: IR (neat) 2980 (m), 1685 (s) cm^{-1}; UV (95% EtOH) λ_{max} 244 nm (ε 2570), 281 (1230); NMR ($CDCl_3$) δ 1.26 (3H, s), 1.76 (3H, d, J = 2 Hz), 2.4 (2H, broad), 3.12 (1H, broad), 5.36 (1H, d x d, J = 10 Hz, 2 Hz), 5.56 (1H, broad), 6.93 (1H, d x d, J = 10 Hz, 2 Hz); Europium shift data see structure 165; mass spectrum, m/e (rel. intensity) 148 (59), 133 (51), 120 (19), 105 (100), 91 (28).

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16.
Found: C, 81.13; H, 8.07.

15. Photolysis of 1,5-Dimethylbicyclo[3.3.0]octa-2,7-diene 141

A quartz tube containing 41 mg of diene 141 in 12 ml ether was degassed and irradiated with a Hanovia 450 watt lamp (no filter used) for 46 hr. The progress of the photolysis was followed by VPC (column A, 80°C). The new product 1,5-dimethyl[3.3.$0^{1,5}$.$0^{2,8}$.$0^{2,7}$]quadricyclooctane 166 was formed with retention time of 5.4 min in 45% yield

(10% isolated yield from VPC). IR (CCl_4) 2960 (s), 1460 (m), 1315 (m) cm^{-1}; NMR (CCl_4) δ 0.95 (2H, d, J = 9.5 Hz), 1.06 (3H, s), 1.24 (2H, d, J = 9.5 Hz), 1.32 (3H, s), 1.8 (2H, broad), 2.28 (2H, broad); mass spectrum, m/e (rel. intensity) 134 (16), 119 (100), 105 (22), 91 (71), 77 (27). Photolysis of a mixture of 140 and 141 under the same conditions gave recovered 140 and product 166 in the same yield.

16. Photolysis of 1,5-Dimethyl-3,7-diphenyl-4-methylenebicyclo[3.3.0]-octa-2,6-diene 163

A quartz tube containing 55 mg of 163 in 10 ml of acetone was degassed and irradiated with 2537 Å light. The photolysis was followed by VPC (column D, 200°). After irradiation for 22 hr, VPC showed that starting material remained there with no detectable volatile new product formed. Preparative VPC gave only starting material. Prolonged irradiation produced only polymeric material.

17. Photolysis of 1,5-Dimethyl-4-methylenebicyclo[3.3.0]octa-2,6-diene 148 and 2,7-diene 150

A degassed solution containing 97.5 mg of 148 in 12 ml ether was irradiated through vycor filter with a 450 watt lamp. VPC (column D, 85°) showed no reaction even after irradiation for 29.5 hr. Preparative VPC gave only the starting diene 148.

Diene 150 (91 mg in 12 ml ether) was irradiated under identical condition. VPC showed a new peak corresponding to the new product in

12 hr; however, the ratio of the new product to diene 150 was small and did not change even after irradiation for 29.5 hr. After removal of solvent, there was left a light brown viscous liquid (containing polymeric material). Preparative VPC gave some starting diene 150 and a very small amount of an unidentified new product.

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