THE STRUCTURE AND REACTIVITY OF ENOLATE ANIONS

by

Barry Martin Trost

B.A., University of Pennsylvania
(1962)

Submitted in Partial Fulfillment
of the Requirements for the
Degree of Doctor of Philosophy

at the

Massachusetts Institute of Technology
April 20, 1965

Signature of Author ______________________________
Department of Chemistry, April 20, 1965

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Thesis Supervisor

Accepted by ______________________________
Chairman, Department Committee on Graduate Students

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ABSTRACTS

Part I: Potassium and Lithium Enolates Derived from Cyclic Ketones:

The compositions of the enolate anion mixtures derived from 2-methylcyclopentanone, 1-decalone, trans-2-decalone and cis-2-decalone have been studied. Equilibration among the isomeric enolate anions derived from each ketone did not occur unless an excess of the free ketone was present. This was particularly true for the lithium enolate anions where a substantial excess of unionized ketone was required before rapid equilibration was observed. The lithium enolates of 2-methyl-3-pentanone and 2-heptanone were reinvestigated. The previous results with the pentanone were found to be correct; whereas, the previously obtained results with 2-heptanone were found to represent kinetic controlled enolate formation. As a consequence, it is possible to prepare different enolate anion mixtures from an unsymmetrical ketone reflecting either kinetic or thermodynamic control by the appropriate choice of reaction conditions and quantities of reactants.

Part II: Selective Alkylation of Unsymmetrical Ketones

Solutions of enolate anions which retain their structural and stereochemical integrity can be prepared by reaction of the corresponding enol acetates with two equivalents of methyllithium in 1,2-dimethoxyethane. By use of this procedure, it is possible to effect the selective alkylation of unsymmetrical ketones at either the more or less highly substituted alpha position utilizing the appropriate enol acetate derivatives of the ketone. Selective alkylations of 2-heptanone, 2-methylcyclopentanone, 2-methylcyclohexanone, and 1-decalone are described. The portion of cis-fused 9-methyl-1-decalone obtained from alkylation of 1-decalone can be significantly enhanced by use of the very reactive alkylating agent, trimethyloxonium 2,4,6-trinitrobenzenesulfonate. The relative rates of reaction of the enolate of 1-decalone with methyl iodide, dimethyl sulfate, and methyl *p*-toluenesulfonate were determined. The reaction of *β,β*-dimethylacrylic acid with *n*-amyllithium is reported.

Part III: The Mannich Reaction of 2-Methylcyclopentanone and 2-Methylcyclohexanone:

The Mannich reaction of dimethylamine and formaldehyde with 2-methylcyclopentanone yielded 2-dimethylaminomethyl-2-methylcyclopentanone (15). The corresponding reaction with 2-methylcyclohexanone yielded a mixture of structurally isomeric amino ketones 5 and 16 in which 2-dimethylaminomethyl-2-methylcyclohexanone (16) is the predominant product. These orientations are contrary to what has previously been reported for the Mannich condensation with these ketones.

Part IV: By-Products in the Robinson Annelation Reaction:

Reaction of the pyrrolidine enamine of cyclohexanone with methyl vinyl ketone was found to yield, in addition to the expected enamines of $\Delta^{1,9}$-octal-2-one, the saturated diketone 5. Syntheses for 2,6-bis-(3-keto-1-butyl)-cyclohexanone, a precursor for diketone 5, and 2,5-bis-(3-keto-1-butyl)-cyclopentanone are described. Each of these compounds was treated with pyrrolidine in benzene to effect dehydration.

Appendix: The Michael Reaction of 2-Methylcyclopentanone:

The reaction of 2-methylcyclopentanone with methyl and ethyl acrylate has been found to yield 2-methyl-2-(*β*-carbomethoxyethyl)-1-cyclopentanone and 2-methyl-2-(*β*-carboethoxyethyl)-1-cyclopentanone respectively. None of the isomeric 2-methyl-5-(β-carbomethoxyethyl)-1-cyclopentanone was detected. The synthesis of this latter material by the Michael reaction of 2-methyl-5-carboethoxy-1-cyclopentanone is reported.

Thesis Supervisor: Herbert O. House

Title: Professor of Chemistry

This Doctoral Thesis has been examined by a committee of the Department of Chemistry as follows:

Professor George H. Büchi___
(Chairman)

Professor Herbert O. House__
(Thesis Supervisor)

Professor Arthur C. Cope____

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The author wishes to express his sincere appreciation and gratitude to Professor Herbert O. House for his guidance and many fruitful discussions during the course of this work. Professor House's intense interest in and thorough knowledge of organic chemistry has had a profound influence on the author.

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To my Parents

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Part I

Lithium and Potassium Enolates Derived
Cyclic Ketones

In earlier studies of enolate anion equilibria,[1] methods were developed for the preparation and analysis of equilibrium mixtures of ketone enolate anions. For analysis of these mixtures, the solution of enolate anions was quenched either in buffered deuterium oxide to form mixtures of monodeuterated ketones or in acetic anhydride to form mixtures of enol acetates. The latter procedure has fewer analytical complications, particularly for cyclic ketones, and has been the method employed in our subsequent work. Since our previous studies dealt primarily with equilibrium mixtures of the potassium enolates of acyclic ketones, we have now extended these studies to include preparations and analyses of both the potassium and lithium enolates derived from cyclic ketones.

In other recent studies,[2] ketone enolate anions which have been generated in the absence of either a relatively acidic proton-donating solvent or an excess of the ketone appeared not to lead to equilibrium mixtures of enolate anions. This failure to equilibrate seemed to be espeically true when lithium enolates were involved. To explore these

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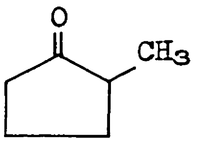
(1) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963).

(2) (a) G. Stork, P. Rosen and N. L. Goldman, *J. Am. Chem. Soc.*, **83**, 2965 (1961). ; (b) R. E. Schaub and M. J. Weiss, *Chemistry and Industry*, 2003 (1961); (c) M. J. Weiss, R. E. Schaub, J. F. Poletto, G. R. Allen, Jr. and C. J. Coscia, *ibid.*, 118 (1963); (d) M. J. Weiss and co-workers, *Tetrahedron*, **20**, 357 (1964); (e) D. Caine, *J. Org. Chem.*, **29**, 1868 (1964).

phenomena further, we have examined the ease of equilibration of enolate anions formed under various conditions.

The cyclic ketones employed in this study are shown in the accompanying formulas **1** - **4**. Each of these compounds was converted to



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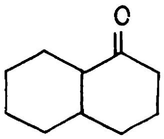

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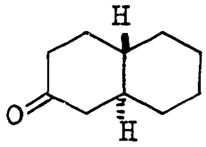

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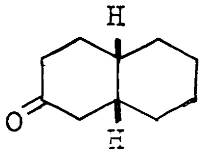
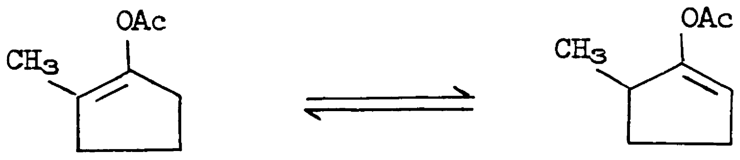


4

a mixture of the corresponding enol acetates **5** - **13** by previously described procedures[1,3] and the enol acetates were separated and characterized. The n.m.r. spectra (see *Experimental*) of the pure enol acetates served to define their structures. The stereochemistry of enol acetates **8** and **9** was established by conversion of each ester to the corresponding *cis* or *trans* 1-decalone. The various enol acetates



5 (98%) **6** (2%)

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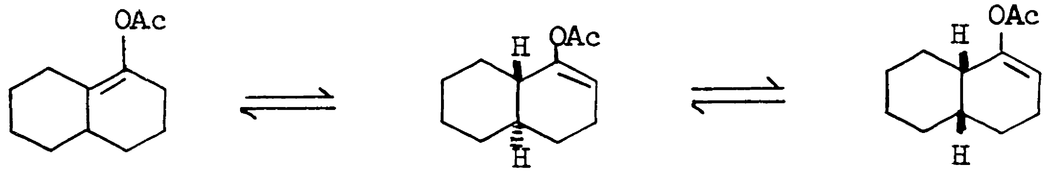
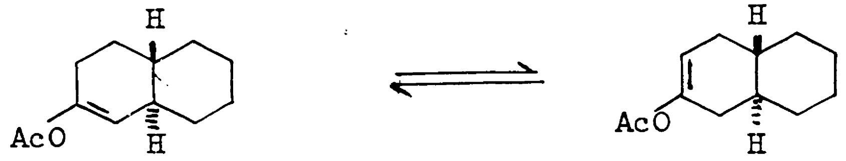
(3) (a) H. O. House and H. W. Thompson, *J. Org. Chem.*, **26**, 3729 (1961); (b) M. Mousseron, F. Winternitz, R. Granger, J. Claret and M. Trinquier, *Bull. soc. chim. France*, 598 (1947).



7 (93.8%) 8 (4.7%) 9 (1.5%)



10 (28%) 11 (72%)

12 (60%) 13 (40%)

were equilibrated at 100° in the presence of *p*-toluenesulfonic acid to give equilibrium mixtures having the compositions indicated in the accompanying equations. The positions of equilibrium for the 2-decalone derivatives 10 - 13 are of interest since the preference for a 2,3-double bond in the *trans* series (*i.e.* 11) and a 1,2-double bond in the *cis* series (*i.e.* 12) is much less[4] than appears to be the case for enol derivatives of 3-keto steroids.[5] Calculations[6] have shown

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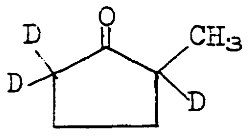
(4) Cf. H. Favre and A. J. Liston, *Cand. J. Chem.*, 42, 268 (1964).

(5) L. R. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N.Y., 1959, pp. 276-279.

that the specificity obtained in the octalin system depends upon the interactions of the axial substituent at the bridgehead carbon with the other axial or pseudoaxial substituents. Thus, a large group, such as methyl, at the bridgehead position should cause an appreciable energy difference between the $\Delta^{1,2}$- and $\Delta^{2,3}$-octalins, the greater stability depending on the ring fusion; whereas, a small group, such as hydrogen, should lower this energy difference considerably. The results obtained in this study and other studies[4,7] bear out this prediction very well.

Of initial concern in this study was the question of what conditions are required to achieve equilibration of the various enolate anions derivable from ketones **1** - **4**. To provide an unambiguous answer we chose to follow a previously described procedure[1] in which each ketone **1** - **4** was mixed with an equimolar portion of its polydeuterated analog **15** - **18**; this mixture of non-deuterated and polydeuterated ke-



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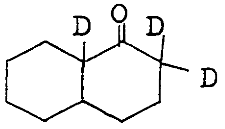

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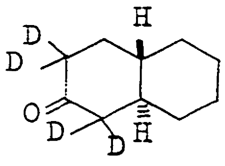

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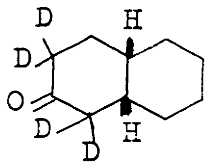

18

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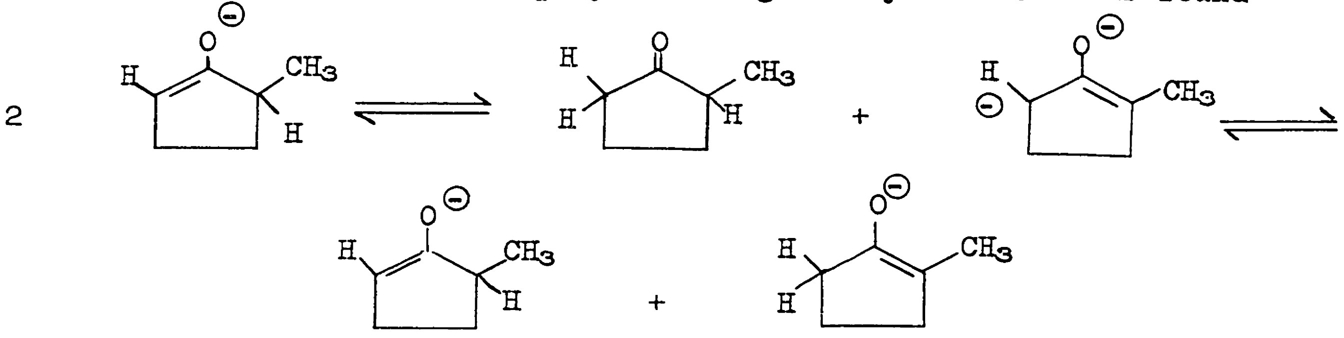
(6) R. Bucourt, Bull. soc. chim. France, 1262, 1983 (1963).

(7) (a) R. Villotti, H. J. Ringold, and C. Djerassi, J. Am. Chem. Soc., 82, 5695 (1960); (b) M. P. Hartshorn and E. R. H. Jones, J. Chem. Soc., 1312 (1962).

tones was converted to the corresponding enolate anions by reaction with either triphenylmethyllithium or triphenylmethylpotassium in 1,2-dimethoxyethane. After the resulting mixture of enolate anions had been quenched in acetic anhydride or in an aqueous buffer, the products (enol acetates and/or ketones) were analyzed by mass spectrometry. If the products were mixtures of non-deuterated and polydeuterated material, no equilibration had occurred; whereas, mixtures of partially deuterated material with an approximately statistical distribution of deuterium at the *α*-carbon atoms of the ketone (or corresponding positions of the enol acetates) indicated complete equilibration. The results of these experiments (see *Experimental*) indicated that little equilibration occurred over a period of an hour at 25° with either potassium or lithium enolates when no free ketone was present in the reaction medium. In other words, both equilibria of the type illustrated in the following equation and intramolecular 1,3-proton transfers must occur very slowly under the usual conditions employed in organic synthesis.[8] As found



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[8] Presumably these considerations are applicable only to solutions of enolates in non-protonic solvents since the presence of a proton-donating solvent would offer a mechanistic pathway for exchange

previously with the potassium enolates of several acyclic ketones,[1] the presence of only 2-10 mole % excess of the ketone 1 in solution with its potassium enolates permitted rapid equilibration among the enolates, the equilibration being complete in less than 30 min. at room temperature. Since the potassium enolates of all three decalones 2, 3 and 4 were only slightly soluble in 1,2-dimethoxyethane, we were able only to examine suspensions of these potassium enolates. As might be expected with these suspensions, equilibration of the enolate anions occurred very slowly even when excess ketone was present.

Solutions of the lithium enolates of all four ketones 1 - 4 were found to equilibrate very slowly when only a slight excess (5 mole % or less) of the free ketone was present in the solution and rapid equilibration among these lithium enolates was achieved only when a substantial excess (25 to 100 mole %) of the free ketone was present in the solution. Thus, it is clear that equilibration of potassium enolates is much more rapid than equilibration of lithium enolates in the presence of a small amount of excess ketone as previous product studies have suggested.[2] This rate difference is presumably a reflection of the fact that the lithium-oxygen bond is more nearly covalent (or is a much tighter ion pair) than the potassium-oxygen bond.

These data caused us to question the validity of the earlier, preliminary examination[1] of the equilibrium position of the lithium

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which need not involve a dianion intermediate or an intramolecular proton transfer.

enolates derived from the acyclic ketones 19 and 20 since these measurements had been made with solutions of lithium enolates containing only a slight excess of the free ketone. Accordingly we have reexamined these two cases and found that the equilibrium values reported

$(CH_3)_2CH\text{-}CO\text{-}CH_2CH_3$ 19

n-$C_4H_9\text{-}CH_2\text{-}COCH_3$ 20

for ketone 19 are correct but the values reported for ketone 20 do not correspond to an equilibrium mixture but rather to the mixture of enolate anions formed in a kinetically controlled process.

The compositions of the mixtures of potassium and lithium enolate anions obtained in this study are summarized in Table I. The data include both enolate anion mixtures obtained from the ketones under approaching kinetic control and mixtures obtained under thermodynamically controlled conditions. From reference to Table I, it is apparent that *when equilibrium has been established*, the concentration of the more highly substituted enolate is usually slightly greater with the lithium enolate mixture than it is with the potassium enolate mixture. This conclusion, which is contrary to what the preliminary data[1] on lithium enolates had suggested, would appear to be explicable in terms of the greater covalent character of the lithium - oxygen bond. In other words, the negative charge of lithium enolates is more nearly localized on oxygen than is the negative charge of potassium enolates.

TABLE I

COMPOSITION OF MIXTURES OF ENOLATE ANIONS GENERATED IN 1,2-DIMETHOXYETHANE

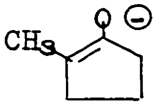
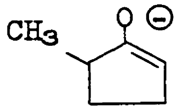
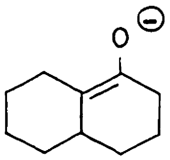
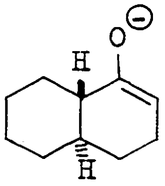
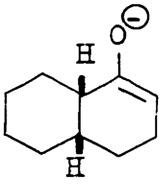
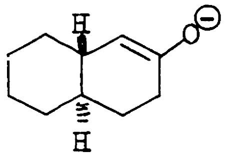
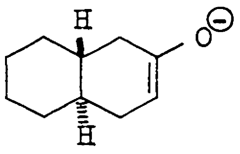
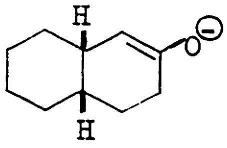
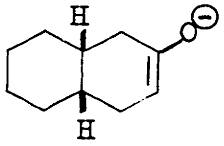
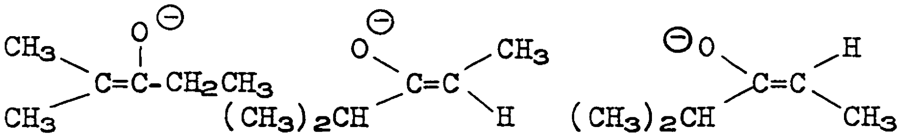
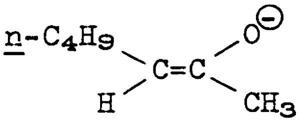
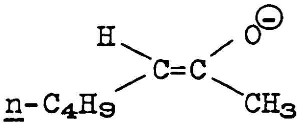
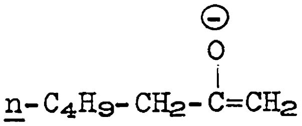
Ketone and reaction conditions	enolate anion composition, %[a]		
1			
Ph_3CK (apparent kinetic control[b])	55	45	
Ph_3CK (equilibrium)	78	22	
Ph_3CLi (kinetic control)	28	72	
Ph_3CLi (equilibrium)	94	6	
2			
Ph_3CK (apparent kinetic control, enolate not in solution)	29	58	13
Ph_3CLi (kinetic control)	10	68	22
Ph_3CLi (equilibrium)	66	21	13
3			
Ph_3CK (apparent kinetic control, enolate not in solution)[c]	52	48	
Ph_3CLi (kinetic control)	12	88	
Ph_3CLi (equilibrium)	53	47	

TABLE I (continued)

Ketone and reaction conditions	enolate anion composition, %[a]		
4			
Ph_3CK (apparent kinetic control, enolate not in solution)[c]	60	40	
Ph_3CLi (kinetic control)	67	33	
Ph_3CLi (equilibrium)	68	32	
19			
Ph_3CK (equilibrium, ref. 3)	12	74	14
Ph_3CLi (equilibrium, ref. 3 and this study)	< 1	> 98	< 1
20			
Ph_3CK (apparent kinetic control)	37	9	54
Ph_3CK (equilibrium)	39	10	51
Ph_3CLi (kinetic control, ref. 1 and this study)	25 or less	5 or less	70-88
Ph_3CLi (equilibrium)[d]	ca. 65	ca. 22	ca. 13

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[a] Unless otherwise noted, the compositions listed are average values from analyses of two or more different reactions; the individual values differed from these average values by 3% or less except as noted in footnote d. [b] These values are based on a single reaction. The deuterium distribution obtained in this case (Table II) suggests that partial equilibration may have occurred. [c] Although the reaction conditions employed for these reactions (Table III) are expected to give kinetic control, the use of deuterium labelling to establish kinetic control was not done in this case. [d] The measurements of these enolate anions in the presence of a large excess of ketone was complicated by a competing aldol condensation and may not represent true equilibrium values (see Experimental).

As a result, the carbon-carbon double bond of the lithium enolate resembles more closely an olefinic carbon-carbon double bond. Although the reason is perhaps debatable, it is clear experimentally that an olefinic double bond is stabilized by alkyl substitution. This stabilizing effect may be seen from the equilibrium positions for various enol acetates such as **5** - **13** and earlier examples.[1]

Two features of importance in synthetic chemistry arise from these findings. First, it will be noted that the mixtures obtained by adding one equivalent of an unsymmetrical ketone to one equivalent of a strong base in the absence of a proton-donating solvent may not be equilibrium mixtures of enolate anions especially in cases where a lithium cation is involved. Since there is a kinetic preference for abstracting a proton from the less highly substituted *α*-carbon atom,[1,2e] this kinetically-controlled generation of enolate anions will usually lead to mixtures of enolate anions in which the less highly substituted enolate predominates. On the other hand, conversion of a ketone to its mixture of enolate anions under circumstances which permit equilibration (*e.g.* the addition of 1.05 equiv. of a ketone to a solution containing 1.0 equiv. triphenylmethylpotassium) may lead to an enolate anion mixture of rather different composition. This is especially true with five- and six-membered cyclic ketones where the more highly substituted enolate is favored at equilibrium. However, it will be noted that irrespective of whether one employs reaction conditions permitting generation of enolate anions with kinetic control or thermodynamic control, many ketones still yield mixtures containing substantial amounts of both structurally isomeric enolates and, consequently, mixtures of products are to be expected from further reaction.

Of more importance is the demonstration that enolate anions produced in the absence of excess ketone and in the absence of proton-donating solvents do not undergo appreciable equilibration during periods of an hour or longer. This finding clearly indicates that a single enolate anion could be generated and stored for at least limited periods of time. The generation of specific enolate anions by reduction[2] of α,β-unsaturated ketones, α-halo ketones and α-chloromercuriketones with metals illustrates the possibility. The production of a specific enolate anion can also be accomplished by the reaction of one equivalent of the corresponding enol acetate with two equivalents of methyllithium in 1,2-dimethoxyethane solution. A description and discussion of this procedure will be presented in Part II of this thesis.

EXPERIMENTAL[9]

Preparation of Starting Materials.-- The sources or preparations of ketones **1**, **2**, **19** and **20** have been cited previously.[1,3] The *trans*-1-decalone (**2**) employed was an equilibrium mixture containing about 95% of the *trans*-isomer **2** and 5% of the *cis*-isomer. Reaction of 1-(1-pyrrolidino)-cyclohexene with methyl vinyl ketone as previously described[10] produced a mixture of unsaturated ketones[10,11] containing[12] $\Delta^{1,9}$-octal-2-one (*ca.* 90%, second eluted) and $\Delta^{9,10}$-octal-2-one (*ca.* 10%, first eluted). Catalytic hydrogenation of the octalone mixture over a 5% palladium-on-carbon catalyst in acidic ethanol[13] yielded a

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[9] All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin Elmer, Model 237, infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The n.m.r. spectra were determined at 60 mc. with a Varian, Model A-60, n.m.r. spectrometer. The mass spectra were obtained with a CEC, Model 21-130, mass spectrometer. The microanalyses were performed by the Scandinavian Microanalytical Laboratory.

(10) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

(11) (a) R. L. Augustine and H. V. Cortez, *Chemistry and Industry*, 490 (1963); (b) D. J. Baisted and J. S. Whitehurst, *J. Chem. Soc.*, 4089 (1961).

(12) A gas chromatography column packed with Ucon Polar suspended on Chromosorb P was employed.

mixture[12] of *cis*-2-decalone (**4**, *ca*. 91%, second eluted) and *trans*-2-decalone (**3**, *ca*. 9%, first eluted) from which the pure *cis*-isomer **4** was collected.[14] Reduction of the octalone mixture with lithium in liquid ammonia as previously described[13] gave a sample of *trans*-2-decalone (**3**, *ca*. 90%, first eluted) contaminated with about 10% of the starting 2-octalones (eluted second and third). The pure *trans*-2-decalone, b.p. 109-110° (8 mm.), $n^{14}\mathrm{D}$ 1.4855 [lit.[15] b.p. 100-102° (12 mm.), $n^{20}\mathrm{D}$ 1.4818], could be separated by fractional distillation of this mixture through a 40-cm. spinning band column. A better separation procedure consisted of refluxing a solution of the crude reduction product (from 0.0611 mole) of the octalones in 90 ml. of ether with 4.5 g. (0.0635 mole) of pyrrolidine for 48 hr. The resulting solution was washed with aqueous hydrochloric acid to remove the pyrrolidine adduct of the unsaturated ketone and then washed with aqueous sodium chloride, dried, concentrated and distilled. The

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(13) R. L. Augustine, *J. Org. Chem.*, **23**, 1853 (1958); see also E. E. van Tamelen and W. C. Proost, Jr., *J. Am. Chem. Soc.*, **76**, 3632 (1954).

(14) A gas chromatography column packed with Carbowax 20M suspended on Chromosorb P was employed.

(15) W. Hückel, W. Egerer and F. Mössner, *Ann.*, **645**, 162 (1961).

distillate, b.p. 62-64° (0.4 mm.), n^{26}D 1.4812 [lit.[13] b.p. 127-128° (28 mm.), n^{23}D 1.4820] was the pure[12] *trans*-2-decalone.

The solutions of triphenylmethylpotassium in 1,2-dimethoxyethane were prepared and standardized as previously described.[1,16] Solutions which were approximately 1M triphenylmethyllithium were prepared by the following procedure.[17] The solvent was removed from 15 ml. (15 mmoles) of a 1 *M* ethereal methyllithium solution under reduced pressure and the residual white solid was dissolved in 15 ml. of 1,2-dimethoxyethane. A 4.4760-g. (18.3-mmole) portion of triphenylmethane was added and the resulting solution was stirred under a nitrogen atmosphere until a negative Gilman color test for methyllithium was obtained (usually 2-3 hr.). A 0.50-ml. aliquot of the solution was titrated with pure 2-heptanone, 50.6 mg. (0.452 moles or 90% of the theoretical amount) of the ketone being required to just discharge the red color.

Preparation of the Polydeuterated Ketones.-- The procedure illustrated by the following example was found most convenient for the preparation of samples of the polydeuterated ketones **15** - **18**. The previously described[1] samples of 2,4,4-trideuterio-2-methyl-3-pentanone

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(16) H. O. House and V. Kramar, *J. Org. Chem*., **27**, 4146 (1962).

(17) A similar procedure has been described by H. Gilman and B. J. Gaj, *J. Org. Chem*., **28**, 1725 (1963).

(90% d_3 species, 10% d_2 species) and 1,1,1,3,3-pentadeuterio-2-heptanone (86% d_5 species, 14% d_4 species) were used. A solution of 1.8908 g. (12.4 mmoles) of trans-2-decalone (3) and 38 mg. (0.36 mmole) of sodium carbonate in 6 ml. of deuterium oxide and 20 ml. of 1,2-dimethoxyethane was refluxed for 18 hr. and then concentrated under reduced pressure. The ketone was recovered by extraction with ether followed by drying and concentrating the ethereal extract. A total of seven such equilibrations were performed. The final recovered ketone 17 (403 mg. or 22%) was analyzed by mass spectrometry and found to contain 95% d_4 species and 5% d_3 species. The n.m.r. spectrum[18] of the sample lacks absorption present at 2.05-2.4 δ in the spectrum of the non-deuterated ketone 3 attributable to the protons alpha to the carbonyl group. The infrared spectrum[18] of the deuterated ketone 17 differs from the spectrum of the non-deuterated material in having additional peaks at 2140 (shoulder) and 2190 cm.$^{-1}$ (C-D stretching), in lacking absorption at 1410-1420 cm.$^{-1}$ (CH_2-CO) and in several other bands in the fingerprint region.

Comparable exchange experiments with the cis-ketone 4 gave a sample of the deuterated ketone 18 containing 99% d_4 species and 1% d_3 species. The sample lacks infrared (1410 cm.$^{-1}$) and n.m.r. absorption[18] attributable to protons alpha to the carbonyl group and has

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(18) Determined as a solution in carbon tetrachloride.

peaks at 2120, 2150, and 2220 cm.$^{-1}$ (C-D stretch). The deuterio ketone **16**,[19] obtained by exchange of 1-decalone with methanol-d_1 in the presence of sodium methoxide, contained 86% d_3 species and 14% d_2 species. This sample also lacks infrared absorption[18] at 1410 cm.$^{-1}$ attributable to a $-CH_2-CO-$ grouping and has much diminished n.m.r. absorption[18] in the region 2.1-2.5 δ where the spectrum of *trans*-1-decalone (**2**) has a complex multiplet attributable to the protons *alpha* to the carbonyl function. The sample has infrared bands at 2110, 2150, 2200 and 2220 cm.$^{-1}$ (C-D stretching). The deuterated ketone **15**, obtained by exchange with sodium carbonate and deuterium oxide, contained 99% d_3 species and 1% d_2 species. The n.m.r. spectra[18] of the deuterated (**15**) and non-deuterated (**1**) ketones differ in the absence of absorption in the region 1.9-2.0 δ (protons *alpha* to the carbonyl function) for the deuterated ketone. Also the doublet (J = 6.5 c.p.s.) at 1.05 δ in the spectrum of ketone **1** is a triplet (J = 1 c.p.s. for deuterium-hydrogen coupling) in the spectrum of ketone **15**. The infrared spectrum[18] of the deuterated ketone **15** lacks absorption at 1410 cm.$^{-1}$ ($-CH_2-CO-$) and has peaks at 2120 (shoulder), 2140, 2200 (shoulder) and 2230 cm.$^{-1}$ (C-D stretching).

Preparation of the Enol Acetates.-- Reaction of 1-decalone with isopropenyl acetate and *p*-toluenesulfonic acid as previously described[3]

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(19) E. Lund, H. Budzikiewicz, J. M. Wilson and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 941 (1963).

produced (in 79% yield) a liquid, b.p. 56-58° (0.15 mm.), which contained[14] the enol acetate **7** (43%, first eluted), the enol acetate **8** (40%, second eluted) and the enol acetate **9** (17%, third eluted). The first two samples **7** and **8** were collected[14] and identified with the previously characterized samples by comparison of retention times and infrared spectra. A collected sample of the ester **9** was redistilled in a short path still. This material has infrared absorption[18] at 1760 (ester C=O) and 1680 cm.^{-1} (C=C) with n.m.r. peaks at 5.39 δ (1H triplet, J = 3.5 c.p.s., vinyl C-H) and at 2.13 δ (singlet, CH_3-CO-O-) as well as broad absorption in the regions 1.9-2.5 δ and 1.2-1.8 δ.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34; mol. wt., 194. Found: C, 74.31; H, 9.39; mol. wt., 194 (mass spectrum).

Samples (from 0.23 to 0.15 mmole) of each of the pure enol acetates **7**, **8** and **9** was mixed with 0.5 mg. (0.003 mole) of dry p-toluenesulfonic acid and each of the mixtures was heated to 100° in a sealed tube for 96 hr. The resulting solutions were diluted with pentane and then washed with aqueous sodium bicarbonate, dried, concentrated and analyzed.[14] Each of the mixtures contained, in addition to a small amount of 1-decalone, a mixture of the three enol acetates the average composition of which was **7** (93.8%), **8** (4.7%) and **9** (1.5%). None of the values obtained in the individual runs differed from these average values by more than ± 0.6%.

Since earlier reports[3,20] of the 1-decalone enol acetates had not provided rigorous evidence for the stereochemistry of pure compounds **8** and **9**, the following transformations were effected. To a solution of 0.6 mmole of methyllithium in 1 ml. of 1,2-dimethoxyethane containing a few milligrams of triphenylmethane (as an indicator) was added the cis-enol acetate **9** (46.9 mg. or 0.242 mmole) at which point the solution still retained the red color of the triphenylmethyl anion. The solution was stirred for 1 hr. and then a 0.5 ml. aliquot was quenched in dilute, aqueous acetic acid. The remaining 0.5 ml. aliquot of the reaction solution was quenched in a mixture of deuterium oxide and deuterioacetic acid. After each of the resulting mixtures had been extracted with ether, the ethereal solutions were washed with aqueous sodium bicarbonate, dried and concentrated. The non-deuterated sample exhibited two peaks on gas chromatography[14,21] corresponding to trans-1-decalone (22%, first eluted) and cis-1-decalone (78%, second eluted). A sample of the cis-ketone was collected and shown to have infrared peaks characteristic[20] of cis-1-decalone. Treatment of the sample with dilute, aqueous acid isomerized the material to a mixture of decalones containing[14] more than 95% of trans-1-decalone. Because of the fact that the preheater (and/or columns) employed in our gas

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(20) C. Djerassi and J. Staunton, J. Am. Chem. Soc., **83**, 736 (1961).

(21) A gas chromatography column packed with Silicone Fluid No. 710 suspended on diatomaceous earth was employed.

chromatographic separations caused partial isomerization of cis-1-decalone to trans-1-decalone, the degree of stereoselectivity in conversion of the cis-enol acetate 9 to cis-1-decalone is probably a good deal better than the above analysis would indicate. The cis-1-decalone was collected[21] from the deuterated sample and found to contain 88% d_1 species and 12% d_0 species. This monodeuterated sample has infrared absorption[18] at 2150 and 2205 (more intense) $cm.^{-1}$ (C-D stretching).

The same procedure was used with 111.4 mg. (0.575 mmole) of the trans-enol acetate 8 employing 1.2 mmoles of methyllithium and 1 ml. of 1,2-dimethoxyethane. The non-deuterated sample contained[14] 97% of trans-1-decalone and 3% of cis-1-decalone. The infrared spectrum of a collected sample of the major product was identical with the spectrum of an authentic sample of trans-1-decalone. The trans-1-decalone was collected from the deuterated sample and found to contain 91% d_1 species and 9% d_0 species. This material has infrared absorption at 2150 (more intense) and 2190 $cm.^{-1}$ (C-D stretching).

Reaction of 2.0 g. (0.013 mole) of cis-2-decalone (4) with excess isopropenyl acetate in the presence of p-toluenesulfonic acid as previously described[1,3] yielded 2.24 g. (88%) of a mixture of enol acetates, b.p. 67° (0.2 mm.), containing[22] 12 (ca. 40%, first eluted)

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(22) A gas chromatography column packed with Silicone Fluid, No. 550, suspended on Chromosorb P was employed.

and 13 (*ca*. 60%, second eluted). Each pure enol acetate was collected from the gas chromatograph. The enol acetate 12 has infrared absorption[18] at 1750 (ester C=O) and 1675 (C=C) cm.$^{-1}$ with an n.m.r. singlet[18] at 2.03 δ (3H, CH_3-CO-O-) as well as broad absorption within the region 1.2-2.4 δ and a doublet (J = 3.5 c.p.s.) of triplets (J = 1 c.p.s.) centered at 5.15 δ (1 vinyl CH in the environment $>$CH-CH=C(OAc)-CH_2- The isomeric enol acetate 13 has infrared absorption[18] at 1760 (ester C=O) and 1685 (C=C) cm.$^{-1}$ with an n.m.r.[18] singlet at 2.04 δ (3H, CH_3-CO-O-) as well as broad absorption in the region 1.2-2.4 δ and a broad, unresolved peak centered at 5.22 δ (1H, vinyl C-H).

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34; mol. wt., 194. Found for 12: C, 74.08; H, 9.26; mol. wt., 194 (mass spectrum). Found for 13: C, 74.02; H, 9.30; mol. wt., 194 (mass spectrum).

Samples (40 mg.) of each of the pure enol acetates 12 and 13 were equilibrated at 100° in the presence of 0.7 mg. of *p*-toluenesulfonic acid as previously described. In each case the equilibrated mixture contained[14] 60% of acetate 12 and 40% of acetate 13.

A 2.0-g. (0.013-mole) sample of *trans*-2-decalone (3) was allowed to react with excess isopropenyl acetate in the presence of *p*-toluenesulfonic acid in the usual manner. The resulting product [2.20 g. or 86%, b.p. 68-69° (0.2 mm.) lit.[3b] b.p. 110-112° (15 mm.), $n^{25}D$ 1.4825 for a mixture of 10 and 11] contained[22] enol acetate 11 (*ca*. 40%, first eluted) and enol acetate 10 (*ca*. 60%, second eluted). Each pure ester was collected[22] from the gas chromatograph. The acetate

11 has infrared absorption[18] at 1755 (ester C=O) and 1685 (C=C) cm.$^{-1}$ with an n.m.r.[18] singlet at 2.02 δ (3H, CH_3-CO-O-) as well as broad absorption in the region 1.0-2.3 δ and a broad, unresolved peak at 5.07 δ (1H, vinyl C-H). The isomeric acetate **10** has infrared peaks[18] at 1760 (ester C=O) and 1685 (C=C) cm.$^{-1}$ with an n.m.r.[18] singlet at 2.01 δ (3H, CH_3-CO-O-), broad absorption in the region 1.0-2.3 δ and a doublet (J = 3.5 c.p.s.) of triplets (J = 1 c.p.s.) centered at 5.22 δ (1 vinyl C-H in the environment $>$CH-CH=C(OAc)-CH_2-).

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34; mol. wt., 194.
Found for **11**: C, 74.10; H, 9.29; mol. wt., 194 (mass spectrum).
Found for **10**: C, 74.03; H, 9.32; mol. wt., 194 (mass spectrum).

Samples (40 mg.) of each of the pure enol acetates **10** and **11** were equilibrated at 100° in the presence of 0.5 mg. of p-toluenesulfonic acid as previously described. Each equilibrated mixture contained[14] 28% of the acetate **10** and 72% of the acetate **11**.

Experiments to Establish the Presence or Absence of Equilibration Among Enolate Anions.-- Unless otherwise noted, equimolar mixtures of the ketones **1** - **4**, **19** and **20** and their previously described polydeuterated derivatives were added to standardized solutions of either triphenylmethyllithium or triphenylmethylpotassium in 1,2-dimethoxyethane. The quantities employed are given in Table II. After the resulting solutions (or suspension with the potassium enolate of ketone **2**) had been stirred for the specified times, aliquots were removed and quenched in acetic anhydride and in acetic acid-water mixtures of such concen-

TABLE II

THE PREPARATION OF ENOLATE ANIONS FROM MIXTURES OF NONDEUTERATED AND POLYDEUTERATED KETONES

Ketone (total mmoles of non- and poly-deuterated ketone added)	Base (mmoles)	Solvent, ml.	Reaction time, hr.	Deuterium distribution in ketone from HOAc-H_2O quenching, %						Composition of enol acetate mixture from Ac_2O quenching
				d_0	d_1	d_2	d_3	d_4	d_5	
1 (1.03)	Ph_3CLi(1.26)	2.1	0.5	49	8	42	1	--	--	5 (28%), 6 (72%)[a]
1 (3.04)	Ph_3CLi(2.4)	4.0	0.5	34	39	24	3	--	--	5 (94%), 6 (6%)[b]
			1.0	32	44	22	2	--	--	5 (94%), 6 (6%)[c]
1 (0.93)	Ph_3CK(0.98)	1.5	0.5	41	15	43	1	--	--	5 (55%), 6 (45%)[d]
1 (1.35)	Ph_3CK(0.98)	1.5	0.5	27	47	25	1	--	--	5 (78%), 6 (22%)[e]
1 (1.65)	Ph_3CK(1.63)	2.1	0.5	27	47	24	2	--	--	5 (77%), 6 (23%)[f]
2 (1.65)	Ph_3CLi(1.59)	2.0	1.0	45	17	34	2	--	--	7 (10%), 8 (68%), 9 (22%)[g]
2 (1.14)	Ph_3CLi(1.05)	1.5	1.0	43	16	38	3	--	--	7 (11%), 8 (67%), 9 (22%)[h]
2 (1.17)	Ph_3CLi(0.58)	1.0	1.0	23	32	31	14	--	--	7 (65%), 8 (22%), 9 (13%)[i]
2 (0.92)	Ph_3CLi(0.45)	1.0	1.0	23	26	33	18	--	--	7 (67%), 8 (20%), 9 (13%)[j]
2 (1.10)	Ph_3CK(1.03)	1.5[k]	0.5	45	12	43	--	--	--	7 (29%), 8 (58%), 9 (13%)[l]
3 (1.14)	Ph_3CLi(1.10)	2.0	1.0	38	6	12	41	3	--	10 (12%), 11 (88%)[m]
3 (1.03)	Ph_3CLi(0.50)	1.0	1.0	8	21	35	28	8	--	10 (54%), 11 (46%)[n]
3 (0.91)[o]	Ph_3CLi (0.56)	1.0	1.0	15	32	33	16	4	--	10 (52%), 11 (48%)[p]

TABLE II (continued)

Ketone (total mmoles of non- and poly-deuterated ketone added)	Base (mmoles)	Solvent, ml.	Reaction time, hr.	Deuterium distribution in ketone from HOAc-H_2O quenching, %						Composition of enol acetate mixture from Ac_2O quenching
				d_0	d_1	d_2	d_3	d_4	d_5	
4 (1.14)	Ph_3CLi(1.10)	2.0	1.0	42	5	9	43	1	--	12 (67%), 13 (33%)[q]
4 (1.15)	Ph_3CLi(0.55)	1.0	1.0	8	23	36	26	7	--	12 (67%), 13 (33%)[r]
4 (1.19)	Ph_3CLi(0.60)	1.0	1.0	11	25	33	24	7	--	12 (68%), 13 (32%)[s]
19 (1.36)	Ph_3CLi (1.36)	2.0	0.5	32	45	21	2	--	--	25 (98%)[t]
20 (1.03)	Ph_3CLi(0.92)	1.5	1.0	23	26	21	15	9	6	26(69%), 27 (18%), 28 (13%)[u]

[a] The calculated yields were 1 (4%), 5 (12%) and 6 (31%). The deuterium contents of these products were: 1, 51% d_0, 10% d_1, 34% d_2, 5% d_3; 5, 53% d_0, 7% d_1, 39% d_2, 1% d_3; 6, 46% d_0, 9% d_1, 45% d_2 and 1% d_3.

[b] The calculated yields were 1 (12%), 5 (40%), and 6 (3%). The deuterium contents of these products were: 1, 19% d_0, 36% d_1, 34% d_2, 11% d_3; 5, 36% d_0, 41% d_1, 23% d_2.

[c] The calculated yields were 1 (13%), 5 (37%) and 6 (3%). The deuterium contents of these products were: 1, 22% d_0, 40% d_1, 30% d_2, 8% d_3; 5, 32% d_0, 46% d_1, 22% d_2.

[d] The calculated yields were 1 (2%), 5 (40%) and 6 (33%). The deuterium contents of these products were: 5, 42% d_0, 16% d_1, 40% d_2, 2% d_3; 6, 32% d_0, 12% d_1, 54% d_2, 2% d_3.

[e] The calculated yields were 1 (15%), 5 (63%), and 6 (18%). The deuterium contents of these products were: 5, 24% d_0, 49% d_1, 26% d_2, 1% d_3; 6, 24% d_0, 48% d_1, 26% d_2, 2% d_3.

[f] The calculated yields were 1 (15%), 5 (65%) and 6 (19%). The deuterium contents of these products were: 5, 29% d_0, 47% d_1, 23% d_2, 1% d_3; 6, 28% d_0, 48% d_1, 22% d_2, 2% d_3.

[g] The calculated yields were 2 (10%), 7 (5%), 8 (36%) and 9 (12%).

[h] The calculated yields were 2 (33%), 7 (6%), 8 (36%) and 9 (12%).

[i] The calculated yields of enol acetates were 7 (48%), 8 (16%) and 9 (10%).

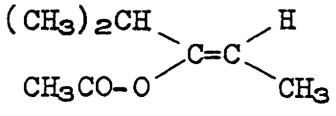
[j] The calculated yields of enol acetates were 7 (47%), 8 (14%) and 9 (9%).

[k] Since this potassium

TABLE II (continued)

enolate was only slightly soluble, the reaction mixture was a suspension. [l] The calculated yields were 2 (12%), 7 (21%), 8 (42%) and 9 (10%). [m] The calculated yields were 3 (18%), 10 (8%) and 11 (57%). [n] The calculated yields of enol acetates were 10 (29%) and 11 (26%). [o] In this experiment a 1.7:1 mole ratio of the non-deuterated to the polydeuterated ketone was employed. [p] The calculated yields of enol acetates were 10 (27%) and 11 (25%). [q] The calculated yields were 4 (6%), 12 (44%) and 13 (21%). [r] The calculated yields of enol acetates were 12 (34%) and 13 (17%). [s] The calculated yields of enol acetates were 12 (36%) and 13 (16%). [t] The calculated yields were 19 (12%) and 25 (43%). [u] The calculated yields were 20 (36%), 26 (35%), 27 (9%) and 28 (7%).

tration that the pH of the final solution was 5-6. As described previously,[1] the mixtures from the acetic anhydride quenching procedure were stirred with mixtures of pentane and aqueous sodium bicarbonate after which the pentane solution was dried and a weighed amount of an internal standard (m-diisopropylbenzene for ketone 1, acenaphthene for ketones 2, 3 and 4, anisole for ketones 19 and 20) was added. The pentane solution was then concentrated and analyzed by gas chromatography,[14,22] response factors being determined from independent calibration curves. In certain cases, samples of enol acetates and ketones from these mixtures were collected and analyzed for deuterium content by mass spectrometry. The mixtures from the aqueous acetic acid quenching procedures were extracted with ether within 10 min. after quenching and the ethereal extracts were dried and concentrated. The pure ketone was collected from a gas chromatograph and analyzed for deuterium content by mass spectrometry. In all cases, appropriate control experiments were employed to demonstrate the lack of hydrogen-deuterium exchange either in the quenching medium or on the gas chromatography column used for collecting the samples. The results of these experiments are summarized in Table II. The enol acetates 25, 26, 27 and 28 obtained from ketones 19 and 20, were collected from quenching experiments employing non-deuterated



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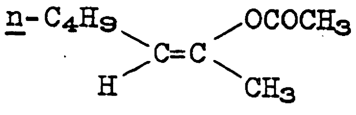

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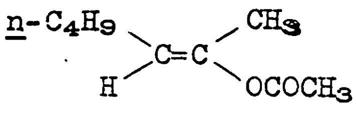

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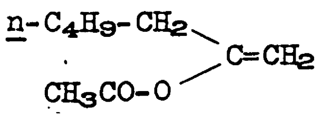

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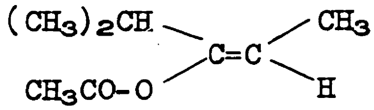

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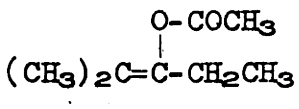

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samples of ketones 19 and 20 and shown to be identical with previously described samples[1] by comparison of retention times and infrared spectra.

Since the statistical deuterium distribution observed (Table II) in experiments with 2-methyl-3-pentanone (19) could be considered to indicate that exchange was occurring only between the C-4 positions of the deuterated and non-deuterated ketones 19 without concurrent exchange at the C-2 positions, the following additional experiment was performed. The ketone 19 was converted as previously described[1] to a mixture of enol acetates containing[14] 52% of 25, 7% of 29 and 41% of 30. A mixture of 129.1 mg. (0.911 mmole) of this enolate acetate mixture and 50 mg. (0.50 mmole) of the ketone 19 was added to a solution of 2.0 mmoles of methyllithium in 2 ml. of 1,2-dimethoxyethane. The addition served to consume all of the methyllithium (as judged from the disappearance of the color of the triphenylmethyl anion indicator) and provide about 0.3 mmole of excess ketone. The resulting solution was stirred for 1 hr. at room temperature and then quenched in excess acetic anhydride; the product was isolated and analyzed in the usual way. The enol acetate portion of product contained[14] more than 98% of the enol acetate 25, the calculated yield of which was approximately

90%. (The *t*-butyl acetate peak in the gas chromatogram interfered sufficiently to prevent a more accurate yield calculation.) A comparable experiment was done with 0.885 mmole of the enol acetate mixture and 2.0 mmoles of methyllithium so that no excess ketone **19** was present. After the resulting solution had been stirred for 1 hr. and then quenched in acetic anhydride, the recovered enol acetate mixture contained approximately 52% of **25**, 5% of **29** and 42% of **30**. Thus, equilibration among all three enolates derivable from the ketone **19** is occurring when excess ketone is present.

Formation and Analysis of Mixtures of Enolate Anions.-- As in previous experiments, measured quantities of ketones **1** - **4**, **19** and **20** were added to standardized solutions of triphenylmethylpotassium, or triphenylmethyllithium in 1,2-dimethoxyethane. The resulting solutions (or suspensions with the potassium enolates of ketones **2**, **3** and **4**) were stirred for the specified period of time and then aliquots were quenched in acetic anhydride. The enol acetate mixtures were separated and analyzed[14,22] by previously described procedures. The internal standards and column calibrations described in the previous experiment were employed. The reaction products were shown to be identical with authentic samples by comparison of retention times and by comparison of the infrared spectra of collected samples. The experimental results are summarized in Table III. In the case of the ketone **20**, certain of the analyses of enolate anion mixtures were also obtained by quenching aliquots of the solutions in deuterium oxide containing sufficient deuterioacetic acid so that the pH of the final solution was 5 to 6. The

TABLE III

THE PREPARATION AND COMPOSITION OF MIXTURES OF ENOLATE ANIONS

Ketone (mmoles)	Base (mmoles)	Solvent, ml	Reaction time, hr.	Composition of enol acetate mixture	Calculated yields from Ac_2O quenching experiment
1 (2.36)	Ph_3CLi(2.36)	5.0	0.5	5 (27%), 6 (73%)	1 (9%), 5 (13%), 6 (34%)
			1.0	5 (29%), 6 (71%)	1 (8%), 5 (13%), 6 (33%)
1 (6.38)	Ph_3CK(6.38)	8.0	0.5	5 (81%), 6 (19%)	1 (16%), 5 (57%), 6 (14%)
1 (3.22)	Ph_3CK(3.22)	10.0	0.5	5 (78%), 6 (22%)	1 (13%), 5 (54%), 6 (16%)
1 (3.69)	Ph_3CK(3.69)	10.0	0.5	5 (75%), 6 (25%)	1 (15%), 5 (56%), 6 (19%)
2 (4.70)	Ph_3CK(4.70)	7.5[a]	0.5	7(29%), 8(58%), 9(13%)	2(15%), 7(20%), 8(40%), 9(9%)
2 (4.90)	Ph_3CK(4.90)	7.8[a]	0.5	7(29%), 8(58%), 9(13%)	2(12%), 7(21%), 8(41%), 9(9%)
3 (1.06)	Ph_3CLi(1.06)	2.8	0.5	10 (13%), 11 (87%)	3 (18%), 10 (8%), 11 (55%)
3 (1.10)	Ph_3CLi(1.10)	1.5	0.5	10 (13%), 11 (87%)	3 (14%), 10 (9%), 11 (56%)
3 (1.84)	Ph_3CK(1.80)	4.5[a]	0.5	10 (52%), 11 (48%)	3 (7%), 10 (39%), 11 (36%)
3 (1.94)	Ph_3CK(1.92)	4.8[a]	1.0	10 (51%), 11 (49%)	3 (8%), 10 (39%), 11 (38%)
4 (1.07)	Ph_3CLi(1.07)	2.9	0.5	12 (69%), 13 (31%)	4 (16%), 12 (49%), 13 (22%)
4 (1.13)	Ph_3CLi (1.11)	1.5	0.5	12 (69%), 13 (31%)	4 (16%), 12 (52%), 13 (24%)
4 (3.58)[b]	Ph_3CK(2.04)	10.0[a]	0.5	12 (60%), 13 (40%)	4 (49%), 12 (25%), 13 (17%)
4 (1.56)[b]	Ph_3CK(0.80)	4.0[a]	0.5	12 (57%), 13 (43%)	4 (47%), 12 (18%), 13 (14%)
4 (1.60)[b]	Ph_3CK(0.80)	4.0[a]	1.0	12 (61%), 13 (39%)	4 (47%), 12 (23%), 13 (15%)
19 (1.26)	Ph_3CLi(1.26)	2.0	0.5	25 (> 98%)	19 (3%), 25 (57%)
19 (2.45)	Ph_3CLi(1.26)	2.0	1.0	25 (> 98%)	25 (60%)
20 (1.17)[c]	Ph_3CLi(1.16)	2.0	0.5	26(25%), 27(5%), 28(70%)	20(38%), 26(9%), 27(2%), 28(25%)
20 (1.45)	Ph_3CLi(1.19)	2.2	1.0	26(61%), 27(26%), 28(13%)	20(48%), 26(34%), 27(15%), 28(7%)
20 (0.97)	Ph_3CK(1.14)	1.5	0.5	26(37%), 27(11%), 28(52%)	20(3%), 26(34%), 27(10%), 28(48%)

TABLE III (continued)

Ketone (mmoles)	Base (mmoles)	Solvent, ml.	Reaction time, hr.	Composition of enol acetate mixture	Calculated yields from Ac_2O quenching experiment
20 (1.60)	Ph_3CK (1.90)	2.0	< 0.02	**26**(37%), **27**(10%), **28**(53%)	
			0.5	**26**(37%), **27**(9%), **28**(54%)	
20 (0.81)	Ph_3CK (0.76)	1.0	0.5	**26**(46%), **27**(12%), **28**(42%)	**20**(8%), **26**(41%), **27**(11%), **28**(37%)
20 (1.16)	Ph_3CK (1.14)	1.2	0.5	**26**(45%), **27**(13%), **28**(42%)	

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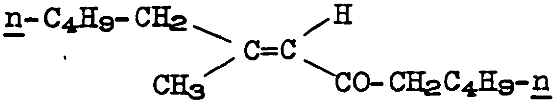
[a] Since the potassium enolate was only slightly soluble, the reaction mixture was a suspension. [b] In this titration, it was necessary to add excess cis-2-decalone in order to discharge the red color of the triphenylmethyl anion. Apparently, the precipitate of potassium enolate incorporates an additional equivalent of the ketone in this case. [c] In two comparable experiments, the solution of enolate anions was quenched in a mixture of deuterium oxide and deuterioacetic acid. From each reaction the recovered ketone contained 24% d_0, 70% d_1 and 6% d_2 species. The deuterium distribution in the monodeuterated ketones (see Ref. 3) was approximately 26% n-C_4H_9-CHD-CO-CH_3 (corresponding to enol acetates **26** and **27**) and 74% n-C_4H_9-CH_2-CO-CH_2D (corresponding to enol acetate **28**).

resulting mixtures of monodeuterated ketones were isolated and analyzed by mass spectrometry as described previously.[1]

A solution of 25.5 mmoles of triphenylmethyllithium in 23 ml. of 1,2-dimethoxyethane was treated with a slight excess (2.565 g. or 26.2 mmoles) of 2-methylcyclopentanone (**1**) and then 1-ml. aliquots were removed from the reaction solution after 1, 5 and 40 min. Each of the aliquots was quenched in acetic anhydride and the enol acetate mixtures were separated and analyzed in the usual way. In each case a mixture of 33% of enol acetate **5** and 67% of enol acetate **6** was obtained. The reaction mixture remaining after 40 min. was added to 54 g. (0.51 mole) of acetic anhydride and then subjected to the usual isolation procedure. Distillation separated 1.57 g. (42.8%) of the mixture of enol acetates **5** and **6**. The residue from this distillation was separated into material soluble in cyclohexane, from which only triphenylmethane was isolated, and 0.43 g. of a cyclohexane-insoluble fraction which was identified as *α*-methylglutaric acid apparently formed by an oxidation of one of the enolate anions. The acid was identified by esterification with ethereal diazomethane to form dimethyl *α*-methylglutarate whose infrared and ultraviolet spectra were compared with the spectra of an authentic sample. Thus, no materials were isolated corresponding to aldol condensation products.

The *α*-methylglutaric acid was apparently formed in this experiment by the unintentional air oxidation of the enolate anion corresponding to enol acetate **6**. We believe it unlikely that unavoided air oxidation led to significant errors in quantitative experiments listed in Tables I, II, and III for two reasons. In all cases the reactions were conducted under a nitrogen atmosphere and all transfers were made with nitrogen filled syringes inserted through "no-air" stoppers to minimize contact with oxygen and atmospheric moisture. However, more significant is the fact that all of the enol acetate composition data could be reproduced to within 3% except when competing aldol condensation was occurring. In the case of the reactions of 2-methylcyclopentanone (**1**) with triphenylmethyllithium under kinetically controlled conditions, at least fifteen different quantitative runs have been made under various conditions, all of which gave enol acetate compositions corresponding to the values listed in Tables I, II, III. This reproducibility in the various quantitative runs leads us to believe that no serious errors are being introduced either from adventitious air oxidation or from partial equilibration in the kinetically controlled runs.

To a solution of 11.7 mmoles triphenylmethyllithium in 20 ml. of 1,2-dimethoxyethane was added 1.686 g. (14.8 mmoles) of 2-heptanone. The resulting solution was stirred for 1 hr. and then poured into 50 ml. of aqueous 10% hydrochloric acid. The organic components, extracted with ether, were dried and distilled to separate 631 mg. (37%) of 2-heptanone, b.p. 145-150°. The residue was triturated with methanol and the methanol extract was concentrated and distilled to separate 701 mg. of liquid, b.p. 120-130° (0.05 mm.), $\underline{n}^{20}\underline{\underline{D}}$ 1.4580, exhibiting two peaks on gas chromatography.[14] These two peaks, **A** (*ca.* 45%, first eluted) and B (ca. 55%, second eluted), were collected. The material in peak A has infrared absorption[18] 1720, 1690, 1645 (shoulder) and 1620 cm.$^{-1}$ suggestive of a mixture of conjugated and non-conjugated unsaturated ketones while the sample in peak B has infrared absorption[18] at 1690 (conj. C=O) and 1620 (conj. C=C). The mass spectrum of material collected from each gas chromatographic peak has a molecular ion peak at



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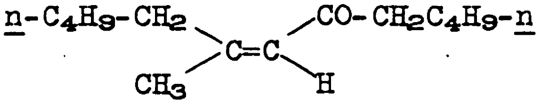

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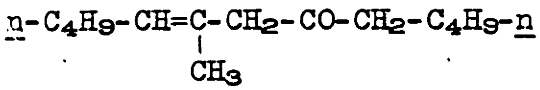

$$\underline{n}-C_4H_9-CH=\underset{CH_3}{\underset{|}{C}}-CH_2-CO-CH_2-C_4H_9-\underline{n}$$

33

m/e 210 with fragment peaks at m/e 154 ($C_5H_{11}-\overset{CH_3}{\overset{|}{C}}=CH-\overset{OH}{\overset{|}{C}}=CH_2^{\oplus}$), 139 ($C_5H_{11}-\overset{CH_3}{\overset{|}{C}}=CH-C\equiv O^{\oplus}$) and 99 ($C_5H_{11}-C\equiv O^{\oplus}$). These data suggest that the high-boiling products are aldol condensation products having structures such as 31, 32 or 33. Since the rate of formation of these aldol products appears to be slower than the rate of equilibration of the lithium enolate anions derived from 2-heptanone (20), the compositions of the mixtures of enolate anions reported (Tables I, II and III) are believed to represent equilibrium concentrations. However, lacking accurate values for the relative rates of aldol condensation and enolate equilibration, we cannot exclude the possibility that the compositions reported are steady-state concentrations rather than equilibrium concentrations.

Several experiments were performed to examine the use of lithium dimethylamide as a base for generating lithium enolate anions. The following procedure is illustrative. The ether was removed from 1 ml. of an approximately 1 M ethereal solution of methyllithium under reduced pressure and the residual lithium reagent, under a nitrogen atmosphere, was treated with 1.4 ml. of 1,2-dimethoxyethane containing 1.33 mmoles of dimethylamine. In other comparable experiments, it was shown that one mole of methane is rapidly evolved for each mole of methyllithium employed. Several milligrams of triphenylmethane (as an indicator) was added to the solution of lithium dimethylamide[22] and 2-methylcyclopentanone (105.4 mg. or 1.08 mmoles) was added until the red color of the triphenylmethyl anion was discharged. The resulting solution was concentrated under reduced pressure to remove dimethylamine, and then diluted with 1 ml. of 1,2-dimethoxyethane and the concentration and dilution process repeated. At this time no dimethylamine could be detected (moist litmus paper) in a stream of nitrogen which had been passed through the solution. The solution was then added to 2.26 g. (22.2 mmoles) of acetic anhydride and the enol acetates were

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(22) Other experiments performed by Mr. Ben Tefertiller in our laboratories have demonstrated that lithium dimethylamide attacks the solvent, 1,2-dimethoxyethane relatively rapidly so that it is not practical to store these solutions for more than an hour. Thus, these solutions are distinctly less stable than solutions of triphenylmethylpotassium (ref. 16).

isolated from the mixture and analyzed in the usual way. The composition of the enol acetate mixture was 30% of enol acetate **5** and 70% of enol acetate **6** with the calculated yields being 28% of **1**, 12% of **5** and 29% of **6**. Comparable yields and enol acetate compositions were obtained in two additional experiments. Thus, the conditions employed correspond to kinetically controlled enolate formation with triphenylmethyllithium.

Part II

Selective Alkylation of Unsymmetrical Ketones

Because the alkylation of unsymmetrical ketones[1] usually leads to mixtures of structurally isomeric alkylated products, methods have been developed for selective alkylation which involve either blocking one *alpha* position[2] or adding an activating group at one *alpha* position.[1,3] In some cases, conversion of the ketone to an enamine[4] or imine[5] derivative prior to alkylation has been reported to give predominantly one structural isomer of the product. An alternative solution to the problem of selectively alkylating an unsymmetrical ketone would be the con-

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(1) (a) J. M. Conia, *Rec. Chem. Progress*, **24**, 43 (1963); (b) J. M. Conia, Bull. soc. chim. France, 1040 (1956); (c) J. M. Conia, *ibid*., 1392 (1956); (d) J. M. Conia and P. Gosselin, *ibid*., 836 (1961).

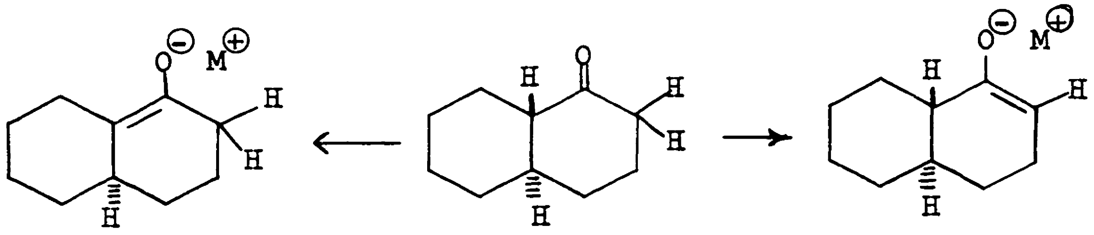
(2) (a) A. J. Birch and R. Robinson, *J. Chem. Soc*., 501 (1944); (b) W. S. Johnson and H. Posvic, *J. Am. Chem. Soc*., **69**, 1361 (1947); (c) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives and R. B. Kelly, *J. Chem. Soc*., 1131 (1957); (d) R. E. Ireland and J. A. Marshall, *J. Org. Chem*., **27**, 1615, 1620 (1962); (e) S. Boatman, T. M. Harris and C. R. Hauser, *J. Am. Chem. Soc*., **87**, 82 (1965).

(3) (a) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *J. Am. Chem. Soc*., **74**, 4223 (1952); (b) Y. Mazur and F. Sondheimer, *J. Am. Chem. Soc*., **80**, 5220, 6296 (1958).

(4) (a) G. Stork, A. Brizzolara, H. Landeman, J. Szmuszkovicz and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963); (b) J. Szmuszkovicz in R. A. Raphael, E. C. Taylor and H. Wynberg, Ed., *Advances in Chemistry, Methods and Results*, Vol. 4, Interscience Publishers, New York, N.Y., 1963, pp. 1-113.

(5) G. Stork and S. R. Dowd, *J. Am. Chem. Soc*., **85**, 2178 (1963).

version of the ketone (*e.g.* 1) to one of the structurally isomeric enolate anions (*e.g.* 2) with reaction conditions which do not permit subsequent interconversion of the isomeric enolate anions (*e.g.* $2 \rightleftharpoons 3$).



2 1 3

Previously,[6] we provided direct experimental evidence for the for the hypothesis that solutions of structurally isomeric enolate anions such as 2 and 3 are interconverted rapidly only when a proton-donating material, such as a protonic solvent or the unionized ketone 1, is present in the solution. In particular, solutions of lithium enolate anions in 1,2-dimethoxyethane (DME) were found not to interconvert over periods of several hours at room temperature unless a substantial amount (10-100 mole %) of unionized ketone was present in the solution to serve as a proton donor. Evidence supporting this hypothesis is also derived from selective alkylation experiments in which solutions of particular enolate anions, apparently free of structural isomers, have been generated by reductions, with alkali metals in liquid ammonia, of *α,β*-unsaturated ketones,[7] of *α*-halo or *α*-acyloxy ketones,[8]

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(6) Part I of this thesis.

or of *α*-chloromercuric ketones.[9,10] The reaction of *α*-bromo ketones with methyl Grignard reagents has also been reported to form an enolate which gives a single alkylated product.[11] Enol acetates have served as intermediates for the introduction of a single alkyl group at the *alpha* position.[12] The method involved bromination of the enol acetate

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(7) G. Stork, P. Rosen, N. Goldman, R. V. Coombs and J. Tsuji, *J. Am. Chem. Soc.*, **87**, 275 (1965).

(8) M. J. Weiss and co-workers, *Tetrahedron*, **20**, 357 (1964).

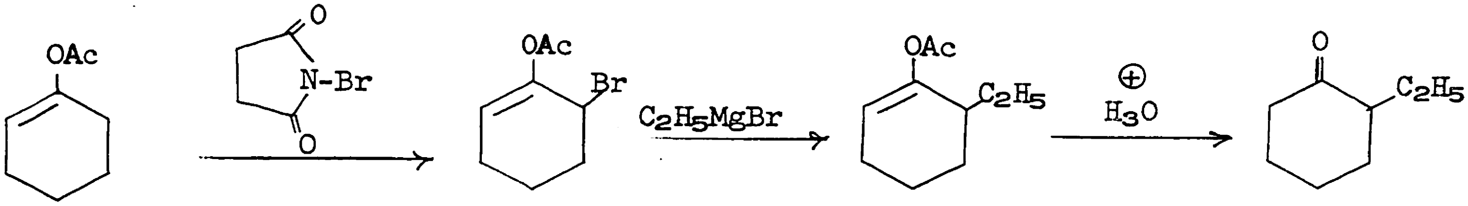
(9) D. Caine, *J. Org. Chem.*, **29**, 1868 (1964).

(10) To examine the question of whether *α*-chloromercuric ketones possess a C-Hg bond or an O-Hg bond, Mr. W. Larry Respess in our laboratories prepared a pure sample of *α*-chloromercuriacetone, m.p. 102-103° [A. N. Nesmeyanov, I. F. Lutsenko and Z. M. Termanova, *Isvest. Akad. Nauk. S.S.S.R., Otdel Khim Nauk.*, 601 (1949), report m.p. 103-104°]. The sample has infrared absorption (Nujol mull) at 1650 cm.$^{-1}$ (C=O) with n.m.r. (solution in perdeuteriodimethylformamide) singlets at 2.80 δ (2H, Hg-CH$_2$-CO-) and 2.17 δ (3H, CH$_3$-CO-). In the fraction of the molecules containing the ^{199}Hg isotope, each of these n.m.r. peaks appears as doublet with $J_{^{199}\text{Hg-H}}$ values of 317 and 14 c.p.s., respectively. Consequently, we conclude that this derivative has a C-Hg bond.

(11) (a) R. E. Beyler, F. Hoffman, L. H. Sarett, and M. Tishler, *J. Org. Chem.*, **26**, 2426 (1961); (b) S. Binns, J. S. G. Cox, E. R. H. Jones, and B. G. Ketcheson, *J. Chem. Soc.*, 1161 (1964).

(12) I. V. Machinskaya and V. A. Barkhash, *J. Gen. Chem. U.S.S.R.*, **29**, 2750 (1959).

with N-bromosuccinimide and subsequently coupling this allylic bromide with a Grignard reagent. The intermediate alkylated enol acetate was



isolated in this reaction. It is curious that the coupling reaction appears to be much more rapid than the addition of the Grignard reagent to the carbonyl even though this latter process is known to be extremely rapid.[13]

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(13) H. O. House and D. D. Traficante, J. Org. Chem., 28, 355 (1963).

We examined the use of enol acetates (e.g. 4) as precursors for specific lithium enolate anions (e.g. 5) because earlier work[6,14] in-

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(14) (a) C. W. Marshall, T. H. Kritchevsky, S. Lieberman, and T. F. Gallagher, J. Am. Chem. Soc, 70, 1837 (1948); (b) A. H. Soloway, W. J. Considine, D. K. Fukushima, and T. F. Gallagher, ibid., 76, 2941 (1954); (c) H. O. House and H. W. Thompson, J. Org. Chem., 26, 3729 (1961); (d) H. O. House and V. Kramar, ibid., 28, 3362 (1963); (e) F. Bohlman, C. Arndt and J. Starnick, Tetrahedron Letters, No. 24, 1605 (1963).

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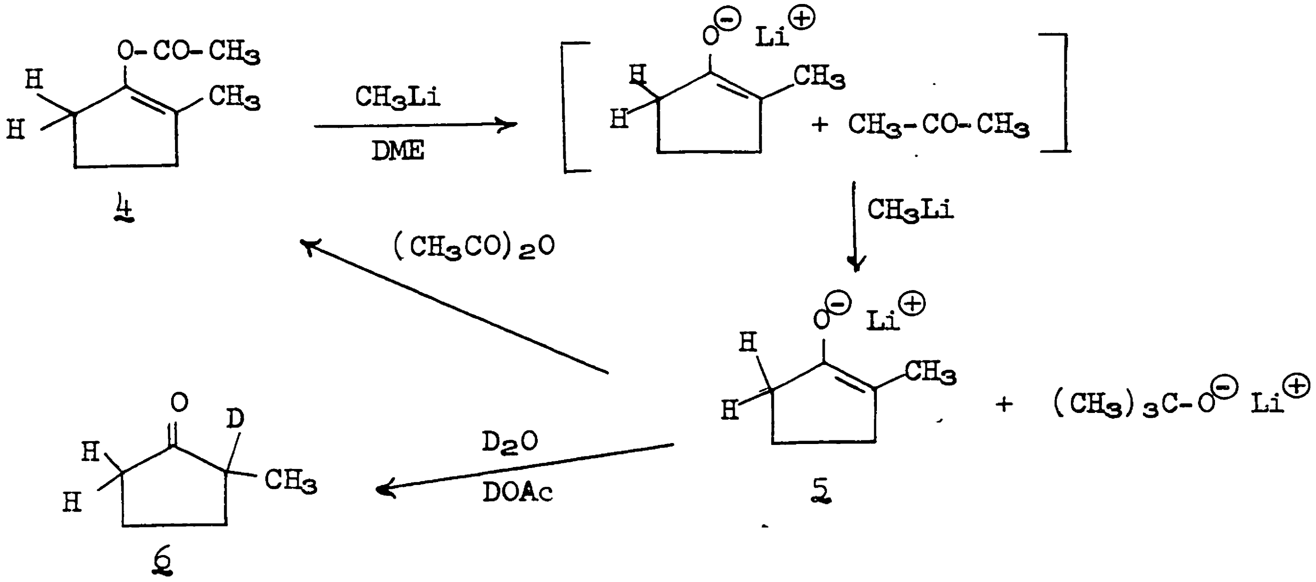
dicated that each of the possible structural and stereochemical enol acetate isomers could be readily prepared and the structure of each isomer could be established by simple physical measurements. In practice, addition of 1 equiv. of the enol acetate (e.g. 4) to a solution of methyllithium in 1,2-dimethoxyethane resulted in the immediate consumption of 2 equiv. of the organolithium reagent as indicated in the accompanying equations. By the use of a few milligrams of triphenylmethane (present in the organolithium solution as the red triphenylmethyllithium) as an indicator, the addition of the enol acetate could be performed as a titration, the addition being stopped when the solution was a pale pink color. In this way the absence of excess ketone (or other proton donating materials) in the reaction solution could be insured. The presence of a single enolate ion (*e.g.* 5) in the reaction solution was demonstrated^{6,14d} by quenching the anion either in excess acetic anhydride to form a single enol acetate (*e.g.* 4) or in buffered deuterium oxide to form a monodeuterio ketone (*e.g.* 6). By use of this procedure we have been able to convert each of the cyclic enol acetates 7 - 10 to the corresponding lithium enolate anions 11 - 14.^{15}



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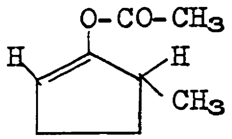
(15) The conversions 9 $\rightleftharpoons$ 13 and 10 $\rightleftharpoons$ 14 were described in Part I of this thesis.



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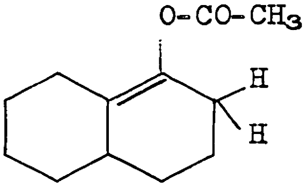

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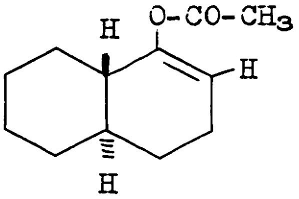

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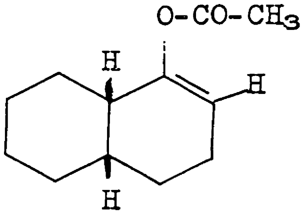

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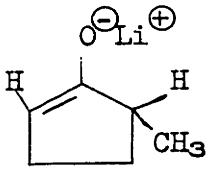

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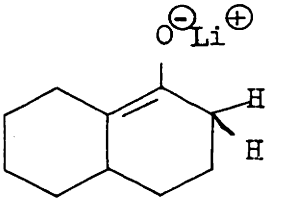

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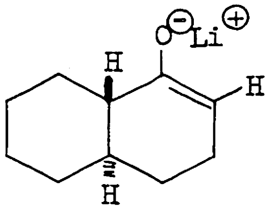

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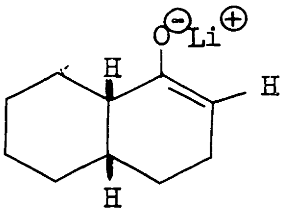

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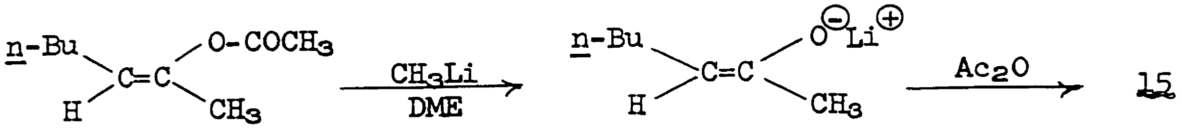
Interestingly, each of the stereoisomeric, acyclic enol acetates 15 or 16 could be converted to the corresponding lithium enolate 17 or 18 without loss of either structural or stereochemical integrity. In fact, solutions of each of the enolate anions 17 and 18 could be heated to 73° for 40 min. without detecting interconversion of the two



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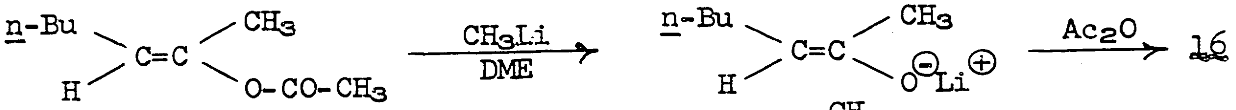

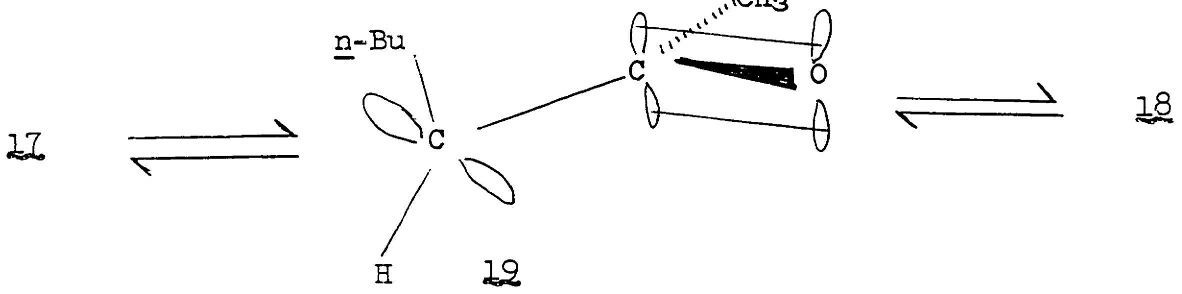

anions. These results indicate that the activation energy for interconversion (*e.g.* by rotation about the enolate C-C bond as in structure **19**) of the two lithium enolate anions must be substantial.[16] It is not clear how much of this activation energy is to be attributed to loss of the resonance stabilization in the free enolate anion (as in structure **19**)[17] rather than to the presence of a partially covalent lithium-oxygen bond which would enhance the double bond character of the carbon-carbon bond in the lithium enolate. Our efforts to prepare stereoisomeric enolate anions with counterions other than lithium have, thus far, given equivocal results.

With a procedure for the conversion of an enol acetate to the corresponding lithium enolate anion in hand, we were prompted to consider the procedures for preparing a single enol acetate from an

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(16) We were unable to explore more vigorous reaction conditions in a meaningful way because attack of methyllithium or triphenylmethyllithium on the solvent destroyed the excess base when longer reaction times (and presumably higher temperatures) were employed. However, it would appear that the free energy of activation for this isomerization is in excess of 20 kcal/mole. See A. A. Frost and R. G. Pearson, "*Kinetics and Mechanism*," 2nd. Ed., John Wiley and Sons, Inc., New York, N.Y., 1961.

(17) (a) Previous arguments based on kinetic data have indicated a substantial barrier to the interconversion of stereoisomeric allyl carbanions. D. H. Hunter and D. J. Cram, *J. Am. Chem. Soc.*, **86**, 5478 (1964); (b) The products of free radical substitution reactions indicate a substantial barrier to rotation also exists for the allyl free radical. C. Walling and W. Thaler, *J. Am. Chem. Soc.*, **83**, 3877 (1961).

unsymmetrical ketone. Previous experiments have indicated that reaction of an unsymmetrical ketone with acetic anhydride in the presence of p-toluenesulfonic acid[6,14] or perchloric acid[18] usually leads to an equilibrium mixture of enol acetates in which the more highly substituted isomer predominates. This is especially true when long reaction times and an excess of the acid catalyst are employed. Reaction of an unsymmetrical ketone with isopropenyl acetate in the presence of a catalytic amount of p-toluenesulfonic acid[14] frequently yields a mixture of enol acetates in which the less highly substituted isomer is the more abundant component. This result reflects the fact that acid-catalyzed equilibration of the enol acetates occurs relatively slowly under the conditions of the isopropenyl acetate procedure; the mixture of enol acetates obtained approaches the composition to be expected from the kinetically controlled formation of enols from the ketone. Depending on which structurally isomeric enol acetate is desired, the problem becomes either to separate the pure more highly substituted enol acetate from a small amount of the less highly substituted isomer or to separate the less highly substituted enol acetate from an approximately equal quantity of the more highly substituted isomer.

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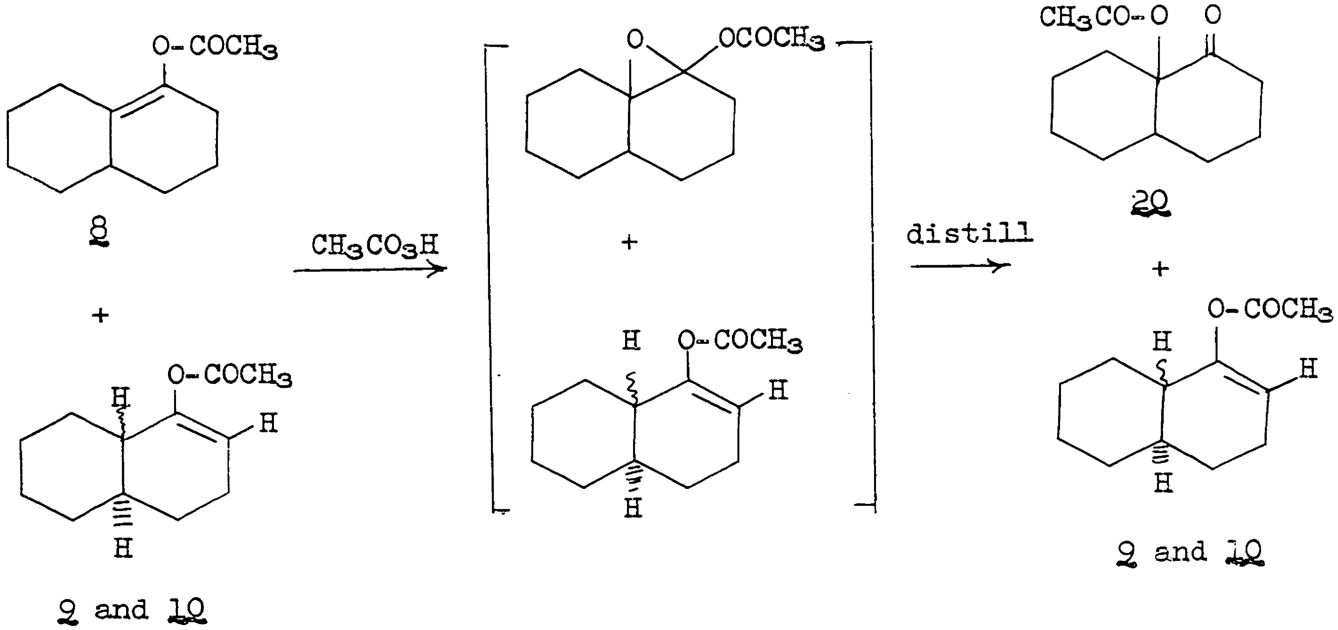
(18) (a) D. H. R. Barton, R. M. Evans, J. C. Hamlet, P. G. Jones and T. Walker, J. Chem. Soc., 747 (1954); (b) R. Villoti, H. J. Ringold, and C. Djerassi, J. Am. Chem. Soc., **82**, 5693 (1960); (c) M. P. Hartshorn and E. R. H. Jones, J. Chem. Soc., 1312 (1962); (d) B. Berkoz, E. P. Chavez, and C. Djerassi, ibid., 1323 (1962); (e) D. K. Banerjee, V. Paul, S. K. Balasubramanian, and P. S. Murphy, Tetrahedron, **20**, 2487 (1964).

Although several standard physical methods[14] can be applied to these separations, these methods may become tedious on a preparative scale especially for the isolation of the pure less highly substituted enol acetate. After examination of several chemical procedures, we found that the more highly substituted enol acetate **8** could be selectively epoxidized[19] in the presence of the less highly substituted isomers **9** and **10** to yield a mixture from which the enol acetates **9** and **10** were readily separable by distillation. Alternatively, small amounts of the less highly substituted enol acetate **21** could be removed from



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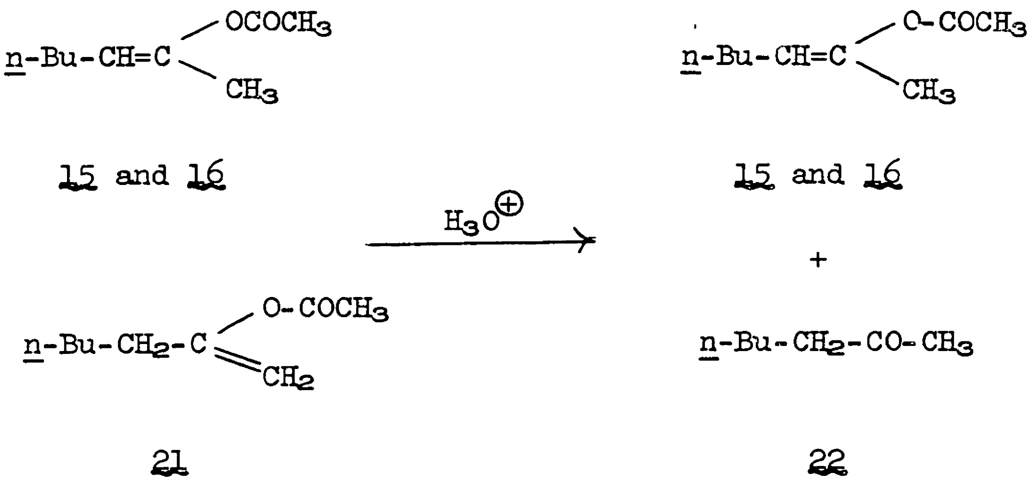
(19) This selectivity is to be expected from the facts that reaction of a peracid with an olefin is not seriously retarded by steric hindrance and is markedly accelerated by the presence of electron-donating substituents. D. Swern, *Chem. Rev.*, **45**, 1 (1949); D. Swern, *Org. Reactions*, **7**, 378 (1953).



the more highly substituted isomers **15** and **16** by partial hydrolysis with aqueous acid. Consequently, it appears that an appropriate choice from among the above procedures will, in general, permit the preparation of either structurally isomeric enol acetate from an unsymmetrical ketone.

Returning to our original objective, the selective alkylation of unsymmetrical ketones, we examined the reactions of each of the enolate ions **5**, **12** and **13** with methylating agents as well as the reaction of a mixture of stereoisomeric anions **17** and **18** with *n*-butyl iodide and the reaction of the enolate mixture **23** and **24**[20] with methyl bromoacetate.

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(20) As noted earlier (refs. 9 and 14d), we have been unable to separate the mixture of enol acetates from 2-methylcyclohexanone by gas chromatography and were forced to determine the approximate composition of the enol acetate mixture from its n.m.r. spectrum. For this reason, a mixture of enolate anions **23** and **24** was generated; the composition of the product mixture corresponded to the enol acetate composition indicating the absence of equilibration among the enolate anions during alkylation.

The results, summarized in the accompanying equations, indicate that selective alkylations can be accomplished without concurrent isomerization of the starting enolate anion. In particular, the methylated products from anions **5**, **12** and **13** were shown to be free of methylated products **27**, **28** and **30**, respectively, demonstrating the lack of significant equilibration (*e.g.* **12** $\rightleftharpoons$ **13**) prior to and during the alkylation reaction.[21]

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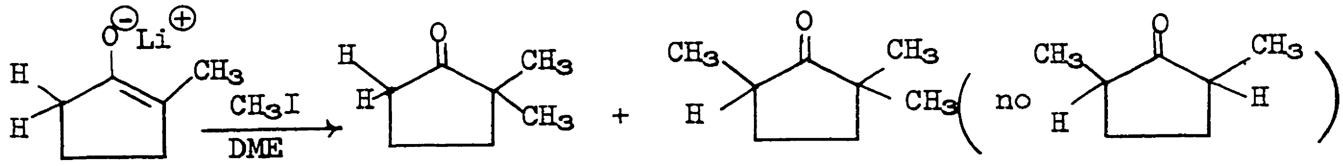
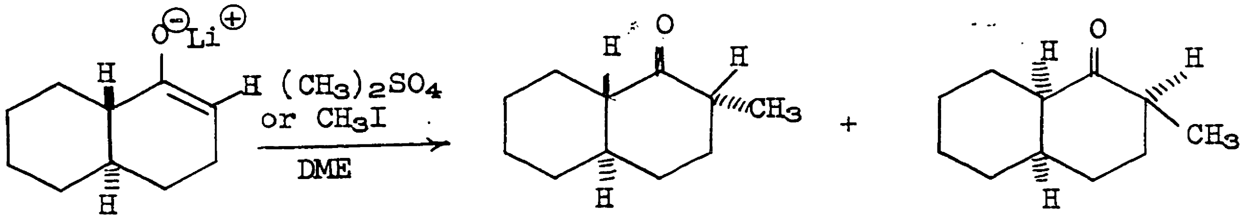
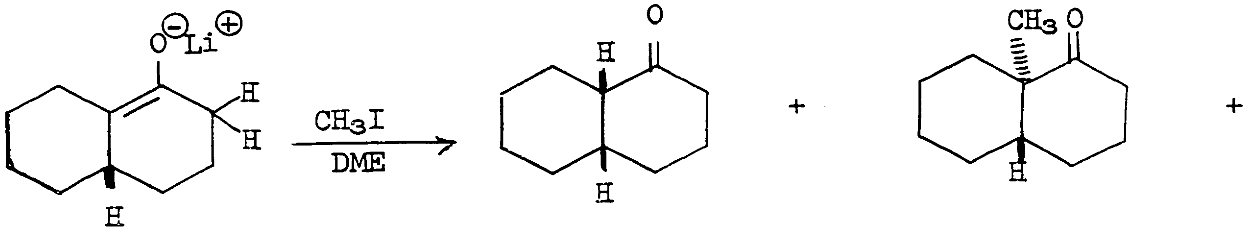
(21) The same degree of structural specificity has been observed in several unrelated alkylation reactions performed in our laboratory by this procedure.



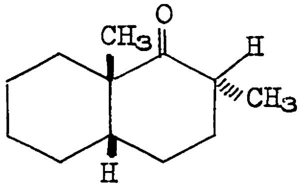
5 **25** **26** **27**



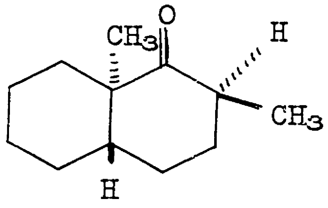
13 **28** **29**



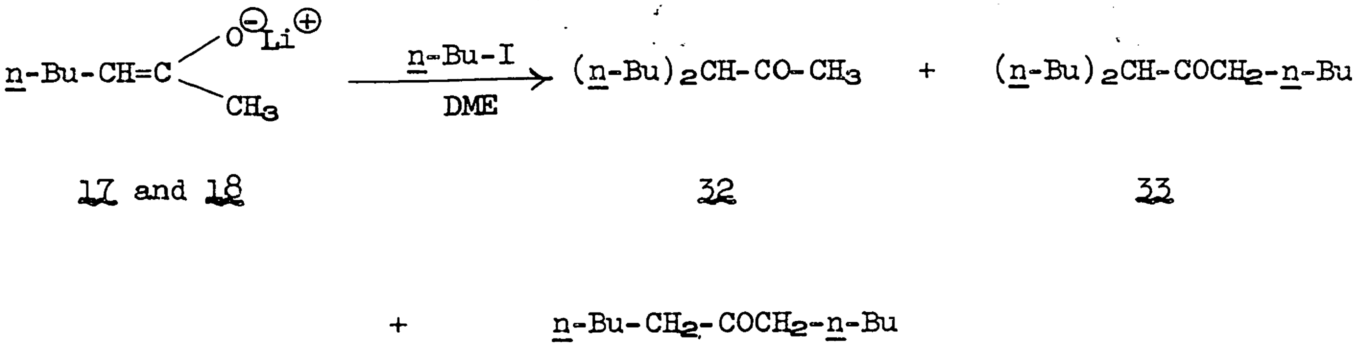
12 **30** **31**



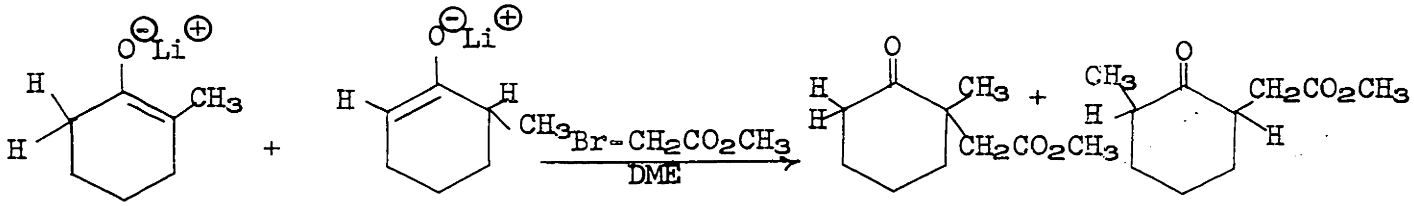
37a



37b



17 and 18 32 33 34



23 (ca. 90% of mixture)

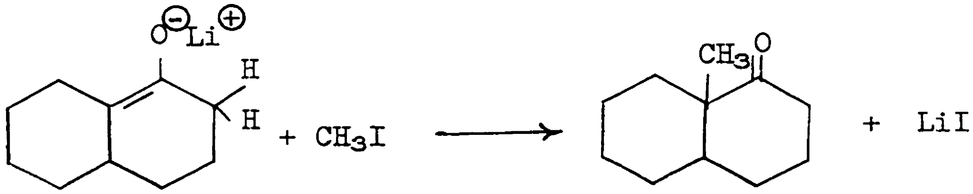
24 (ca. 10% of mixture)

35 (ca. 90% of mixture)

36 (ca. 10% of mixture)

Although the previously cited data provide ample reason to expect no isomerization of enolate anions prior to alkylation, the observed lack of isomerization during the alkylation reaction is by no means inevitable. The accompanying equations A - G illustrate the fact that during alkylation of a particular enolate anion 12, a proton-donating product 30 + 31 is formed which can enter into equilibria (Equations C, D and E) forming two new enolate anions 13 + 14 and 39 and, subsequently, two new alkylated products 28 and 37. The alkylation reactions A and B are relatively rapid having half-lives, under our reaction conditions, of about 1 min. and 20 min., respectively. Both our product studies

(A)

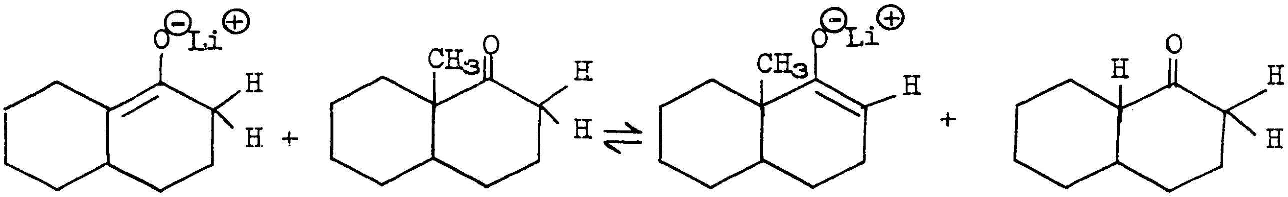


12 30 + 31

(B) $(CH_3)_3C\text{-}O^{\ominus}Li^{\oplus} + CH_3I \longrightarrow (CH_3)_3C\text{-}O\text{-}CH_3 + LiI$

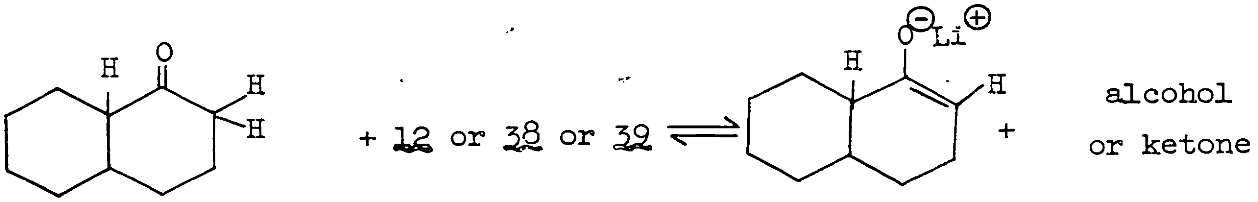
38

(C)



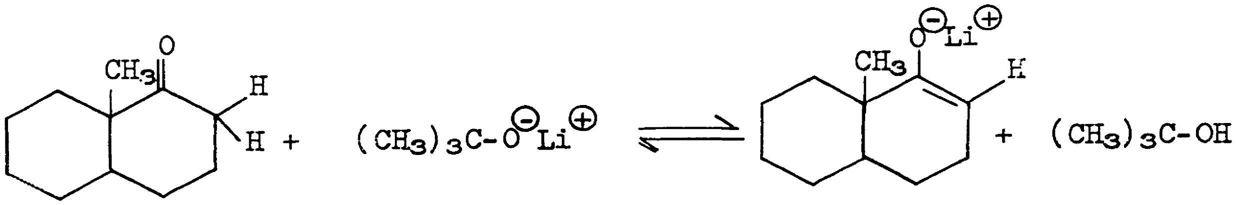
12 30 + 31 39

(D)



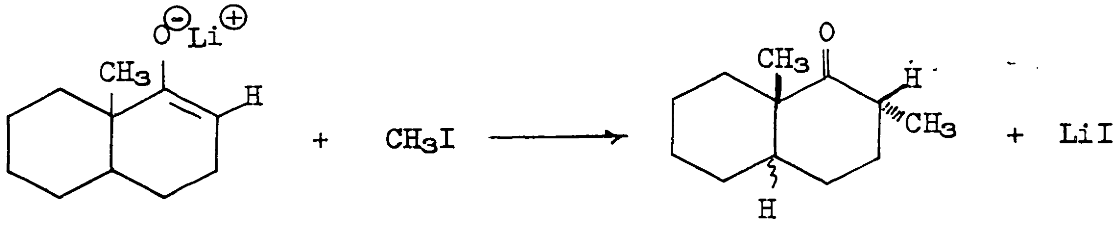
13 + 14

(E)



30 + **31** **32**

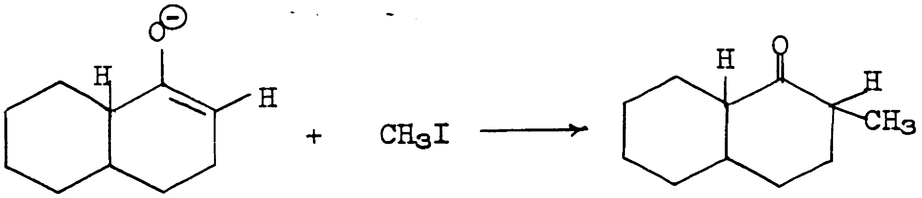
(F)



32

37 **a**, *cis*-ring fusion
b, *trans*-ring fusion

(G)



13 + **14** **28**

(*i.e.* no dialkylated product from the alkylation of **13** with methyl iodide) and earlier kinetic measurements[1,22] suggest that, at comparable concentrations, alkylation of the less highly substituted enolate anions **13** + **14** (Eq. **G**) and **32** (Eq. **F**) will be at least as rapid as reaction **A**. Consequently, our failure to find alkylated product **28** in this

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(22) H. Zook and W. L. Rellahan, *J. Am. Chem. Soc.*, **79**, 881 (1957).

reaction indicates that no appreciable concentration of enolate anions **13** or **14** was produced and, accordingly, that the rate of the forward reaction in equilibrium **C** and/or **D** must be slower than alkylation.

An approximate measure of the rate of reaction **D** was obtained by determining the rate of hydrogen-deuterium scrambling when a mixture of 1-decalone and 2,2,9-trideuterio-1-decalone was added to a solution of lithium *t*-butoxide in 1,2-dimethoxyethane. At comparable concentrations of reactants, reaction **A** is about four times as rapid as reaction **D**. Consequently, it is primarily the slow rate of the ketone-enolate anion equilibration (Eq. **C**) which accounts for the failure to find any significant quantity of the wrong alkylated product, ketone **28**.

At relatively high enolate anion concentrations (0.5 M or greater), the dialkylation product **37** (Eq. **F**) becomes a significant by-product of the alkylation of the enolate anion **12** in agreement with the fact that the rate of reaction **D** is greater than the rate of consumption of the lithium *t*-butoxide (Eq. **B**). The presence of equimolar concentrations of the enolate anion (*e.g.* **12**) and lithium *t*-butoxide (**35**) in our reaction mixtures is, of course, an undesirable but necessary consequence of the reaction used to form the enolate anion. In any event, this dialkylation side reaction (Eq. **E** and **F**) can be effectively minimized by use of short reaction times and solutions in which the concentration of enolate anion and *t*-butoxide anion are in the range 0.1-0.2 *M* as is illustrated in Table I.[23]

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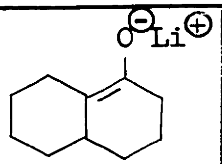
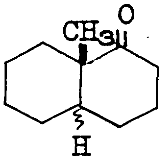
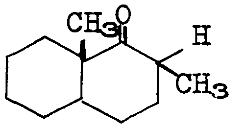
(23) This ability to decrease the proportion of dialkylation by lowering the initial enolate ion 12 (and *t*-butoxide anion 38) concentration is to be expected if the reactions C and E are relatively slow since the rates of the initial alkylation reactions A and B are proportional to the first power of the concentrations of anions 12 and 38 whereas the formation of the dialkylation precursor 39 is indirectly dependent on the square of the concentration of one or both of the anions 12 and 38. Of course, this concentration effect also serves to repress the formation of the unwanted monoalkylated product 28 for the same reasons.

Table I

Concentration Dependence in the Alkylation of 1-Decalone

Reactants, molar conc.		Reaction time, min.	Products, % Yield	
 12	CH_3I		 30 + 31	 37 + 1-decalone (1)
0.155	0.47	5.0	86	7
0.145	0.46	10.0	54	39
0.467	1.40	10.0	38	59
0.37	1.84	*ca.* 0.5	51	15

As part of our study of the alkylation of the 1-decalone enolate 12, we examined the effect of the alkylating agent reactivity on the proportions of *cis*(30)- and *trans*(31)-alkylated products (Table II).

Table II

Stereochemical Outcome of the Alkylation of 1-Decalone

Methylating agent	Approximate half-life for reaction min.	Composition of 9-methyl-1-decalone	
		cis (**30**), %	*trans* (**31**), %
CH_3-O-Ts	30	*ca.* 87[a]	*ca.* 13[a]
CH_3-I	1	93	17
$CH_3\text{-}O\text{-}SO_2OCH_3$	< 0.5	86	14
$CH_3\text{-}\overset{\oplus}{O}(CH_3)_2\ ArSO_3^{\ominus}$	< 0.5	> 95	< 5

[a] Because of the low percentage of reaction, these values are only approximate

The proportion of the *cis*-isomer **30** was generally found to increase as the reactivity of the alkylating agent increased,[24] and was parti-

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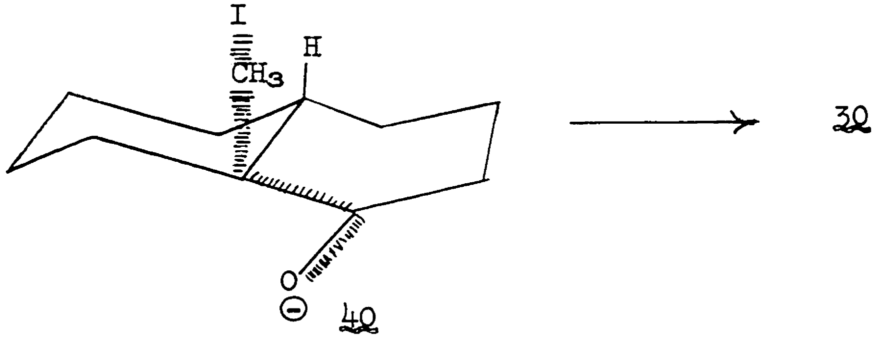
(24) J. M. Conia [*Bull. soc. chim. France*, 533 (1950)] reported the relative reactivities of methyl iodide, methyl benzenesulfonate and methyl sulfate to be 1, 4 and 60, respectively, for reaction with a solution prepared from sodium *t*-amylate, 2-methylcyclohexanone and toluene. Similar studies with ethyl benzenesulfonate and ethyl *p*-toluenesulfonate indicated that the benzenesulfonate esters should be about twice as reactive as the *p*-toluenesulfonate esters suggesting that methyl *p*-toluenesulfonate would be more reactive than methyl iodide. However, it is clear that for the reaction system we are studying, methyl iodide reacts more rapidly than methyl *p*-toluenesulfonate.

ticularly striking when the trimethyloxonium salt was used. These results may be interpreted in terms of the transition state for alkylation resembling the starting materials (*e.g.* 40 in which steric factors favor the approach of the alkylating agent to give the *cis*-product 30) rather than the products (*e.g.* 41 in which thermodynamic and stereoelectronic factors favor the *trans*-product 31).[25] If one accepts this idea, the prediction follows that increasing the reactivity of the



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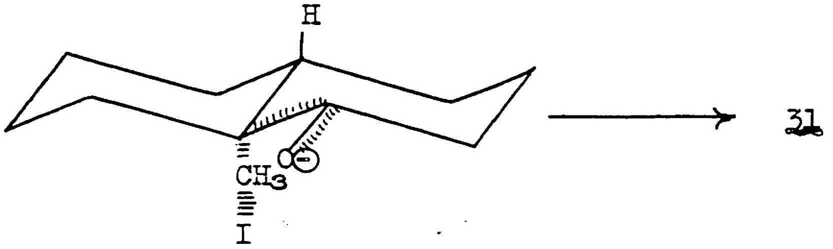

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(25) For recent discussions of the stereochemistry of alkylation of cyclohexanone derivatives, see ref. 2a and (a) W. S. Johnson, D. S. Allen, Jr., R. R. Hindersinn, G. N. Sausen and R. Pappo, *J. Am. Chem. Soc.*, 84, 2181 (1962); (b) C. Djerassi, J. Osiecki and E. J. Eisenbraun, *ibid.*, 83, 4433 (1961); (c) F. J. McQuillin and P. L. Simpson, *J. Chem. Soc.*, 4726 (1963); (d) J. M. Conia and P. Briet, *Tetrahedron Letters*, No. 39, 2797 (1964).

alkylating agent would cause the transition state to resemble the reactants[26] even more closely and would enhance the proportion of the *cis*-product **30**. Unfortunately, it does not appear practical to utilize the reverse strategy in which an alkylating agent of sufficiently low reactivity is employed that the *trans*-ketone **31** (from **41**) will become the major product.

From the foregoing discussion of the relative rates of the various competing processes in the alkylating reaction mixtures, it will be apparent that use of a less reactive alkylating agent will retard the rate of consumption of the initial enolate and the lithium *t*-butoxide (Cf. Eq. **A** and **B**) with the result that both dialkylation and equilibration of initial enolate anion prior to reaction (Cf. Eq. **C** - **G**) can be expected to become a serious problem. We found that this difficulty began to become apparent in the reaction of the 2-heptanone enolate anions **17** and **18** with *n*-butyl iodide, an alkylating agent which would appear to be about 50-100 times less reactive than methyl iodide.[1] In this case, reaction conditions which produced 50-55% of the expected monoalkylated ketone **32** also yielded 12-14% of dialkylated product **33** and 6-10% of the structurally isomeric monoalkylated ketone **34**. For comparison, the alkylation of 2-heptanone was effected by treatment of the ketone with *n*-butyl iodide and potassium *t*-butoxide

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(26) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

in *t*-butyl alcohol. The yields of the monoalkylated ketones **32** and **34** were 11% and 6%, respectively; other products included unchanged 2-heptanone, the dialkylated ketone **33**, and a large amount of less volatile material, believed to have resulted from an aldol condensation of 2-heptanone with itself.[6] This result, which is hardly in agreement with Conia's generalization[1] that ketones of the type $R-CH_2-CO-CH_3$ are alkylated very largely if not exclusively at the methylene position, leads us to conclude that our alkylation procedure is advantageous even for alkylation with relatively sluggish alkylating agents where complete structural specificity is not maintained. It is also of interest that the only dialkylated product present in sufficient amount to characterize was 2-*n*-butylundecan-2-one (**33**) and not 3,3-di-*n*-butyl-2-heptanone. This fact is also contrary to Conia's generalization[1] that ketones of the general formula $R_2CHCOCH_3$ alkylate at the methinyl carbon not at the methyl group, but is in agreement with out findings that the kinetically and thermodynamically favored enolate is the less highly substituted one.[6,14d]

A feature of incidental interest was noted in certain alkylation reactions with dimethyl sulfate. With solutions of either lithium *t*-butoxide (**38**) alone or equimolar mixtures of the alkoxide **38** and the 1-decalone enolate **12**, in 1,2-dimethoxyethane, reaction with dimethyl sulfate was very rapid (half lives of approximately 30 sec.) until one-half of the total base was consumed at which time the reaction rate dropped markedly. In reactions with the alkoxide, a precipitate separated from the reaction solution in less than a minute whereas in t-butyl alcohol. The yields of the monoalkylated ketones 32 and 34 were 11% and 6%, respectively; other products included unchanged 2-heptanone, the dialkylated ketone 33, and a large amount of less volatile material, believed to have resulted from an aldol condensation of 2-heptanone with itself.[6] This result, which is hardly in agreement with Conia's generalization[1] that ketones of the type R-CH$_2$-CO-CH$_3$ are alkylated very largely if not exclusively at the methylene position, leads us to conclude that our alkylation procedure is advantageous even for alkylation with relatively sluggish alkylating agents where complete structural specificity is not maintained. It is also of interest that the only dialkylated product present in sufficient amount to characterize was 2-n-butylundecan-2-one (33) and not 3,3-di-n-butyl-2-heptanone. This fact is also contrary to Conia's generalization[1] that ketones of the general formula $R_2CHCOCH_3$ alkylate at the methinyl carbon not at the methyl group, but is in agreement with out findings that the kinetically and thermodynamically favored enolate is the less highly substituted one.[6,14d]

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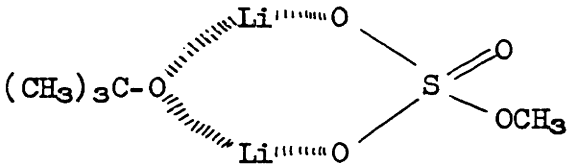

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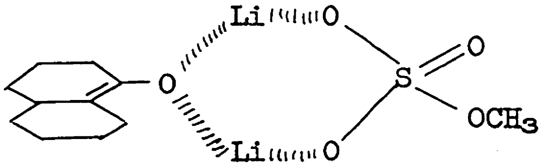

43

EXPERIMENTAL[27]

Preparation of Starting Materials.-- The preparation of trans-1-decalone, 2-methylcyclopentanone, 2-methylcyclohexanone, 2-heptanone and the preparation and characterization of the corresponding enol acetates have been described previously.[6,14c,14d] Two additional methods were used to obtain the enol acetates of 1-decalone. To a solution of 147 mg. (0.968 mmole) of trans-1-decalone (**1**) and 1.0 g. (9.8 mmoles) of acetic anhydride in 3 ml. of carbon tetrachloride was added 0.005 ml. of 70% aqueous perchloric acid.[18,28] The resulting mixture was stirred for 15 min. at room temperature and then diluted with ether, washed with aqueous sodium bicarbonate, dried and concentrated. The residual liquid contained,[29] in order of elution, trans-

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(27) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin Elmer, Model 237, infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The n.m.r. spectra were determined at 60 mc. with a Varian, Model A-60, n.m.r. spectrometer. The mass spectra were obtained with a CEC, Model 21-130, mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

(28) The use of larger quantities of perchloric acid led to the formation of high-molecular weight by-products.

1-decalone (**1**, 5%), the $\Delta^{1,9}$-enol acetate **8** (78%), the *trans*-$\Delta^{1,2}$-enol acetate **9** (13%) and the *cis*-$\Delta^{1,2}$-enol acetate **10** (4%). From a comparable reaction employing 0.895 mmole of 1-decalone, 9.8 mmoles of acetic anhydride, 0.005 ml. of 70% aqueous perchloric acid and 3 ml. of carbon tetrachloride in which a reaction period of 24 hr. at room temperature was employed, the composition[29] of the enol acetate mixture was 98% of **8** and 2% of **9**. The calculated[30] yield of the enol acetate mixture was 78%, 5% of 1-decalone also being recovered.

A mixture of enol acetates (40% of **8**, 42% of **9** and 18% of **10**),[29] b.p. 66-69° (0.2 mm.), was obtained in 82% yield from the reaction of 5.225 g. (34.4 mmoles) of *trans*-1-decalone with 6.948 g. (69.5 mmoles) of isopropenyl acetate containing a few milligrams of *p*-toluenesulfonic acid at 110° for 6 hr. as previously described.[14c,31] A solution of 2.25 g. (11.7 mmoles) of this enol acetate mixture in 250 ml. of petroleum ether (b.p. 30-60°) was stirred at room temperature for 48 hr.

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(29) A gas chromatography column packed with Carbowax 20M suspended on Chromosorb P was employed.

(30) A weighed quantity of acenaphthene was added to the crude product and the yield was determined by gas chromatography (Ref. 29).

(31) No reaction was observed when the *p*-toluenesulfonic acid was omitted.

with a mixture of 2.5 g. of sodium acetate, 3.75 ml. of water and 6.0 g. of an acetic acid solution containing 23.6 mmoles of peracetic acid.[32] The resulting reaction mixture was stirred with excess solid sodium bisulfite for 1 hr. and then the organic layer was separated, dried and concentrated. The residual pale yellow liquid, which no longer contained[29] the enol acetate 8, was distilled through a 30-cm. spinning band column to separate 1.008 g. (75% recovery) of the $\Delta^{1,2}$-enol acetates (70% of 9 and 30% of 10), b.p. 58-61° (0.2 mm.) and 1.221 g. of 9-acetoxy-1-decalone (20), b.p. 65-70° (0.2 mm.). The latter product 20 (presumably a mixture of <u>cis</u> and <u>trans</u> isomers) was identified with a previously described[14c] sample by comparison of infrared spectra.

The reaction of 28.0 g. (0.245 mole) of 2-heptanone, 50.5 g. (0.505 mole) of isopropenyl acetate and 200 mg. of <u>p</u>-toluenesulfonic acid at reflux with continuous distillation of acetone yielded, after the previously described isolation,[14d] 35.2 g. (93%) of a mixture of 2-heptanone (6%), the <u>trans</u>-$\Delta^{2,3}$-enol acetate 15 (47%), the $\Delta^{1,2}$-enol acetate 21 (28%), and the <u>cis</u>-$\Delta^{2,3}$-enol acetate 16 (19%), b.p. 155-163°. A solution of 2.50 g. (16.4 mmoles) of this mixture in 30 ml. of carbon tetrachloride was added to a solution of 0.020 ml. of 70% aqueous perchloric acid in 5.0 g. of acetic anhydride. The resulting mixture

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(32) The use of less peracetic acid for a shorter reaction time resulted in incomplete oxidation of the enol acetate 8.

was stirred for 6 hr. and then diluted with ether and washed with aqeuous sodium bicarbonate. After the organic layer had been dried, concentrated and distilled, the distillate (2.50 g., b.p. 145-170°, containing 21% of 2-heptanone, 59% of **15** and 20% of **16**) was fractionally distilled through a 40-cm. spinning-band column to separate 1.95 g. (78% recovery) of a mixture, b.p. 160-165°, containing 2% of 2-heptanone, 73% of **15** and 25% of **16**.

Ethereal solutions of methyllithium were prepared from lithium and either methyl bromide or methyl iodide in the usual way. The methyllithium solutions were standardized either by use of a double acid-base titration employing ethylene dibromide or by reaction with chlorodimethylphenylsilane and subsequent gas chromatographic analysis.[33]

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(33) (a) H. Gilman and F. K. Cartledge, J. Organomet. Chem., **2**, 447 (1964); (b) H. O. House and W. L. Respess, ibid., **00**, 0000 (1965).

1,2-Dimethoxyethane was purified by refluxing over sodium or potassium followed by distillation from lithium aluminum hydride. All organometallic and enolate anion reactions were carried out under a nitrogen atmosphere and either siphons, nitrogen filled pipettes or nitrogen-filled syringes were used for all transfers. All alkylating agents except the trimethyloxonium salt were distilled immediately before use. Trimethyloxonium 2,4,6-trinitrobenzensulfonate, m.p. 110-125° dec. resolidifies and melts at 181-183° (lit.[34] 115-125° dec., then melts

181-183°), was prepared as previously described.[34]

Preparation of the Enolate Anions. A. From 2-Methylcyclopentanone.-- After an ethereal solution containing 1.5 mmoles of methyllithium had been concentrated to dryness under reduced pressure, 1.5 ml. of 1,2-dimethoxyethane containing a few milligrams of triphenylmethane was added.[35] To the resulting red solution was added, dropwise and with stirring, 98 mg. (0.70 mole) of 1-acetoxy-2-methylcyclopentene (**4**) at which point the reaction solution retained a light red color. This solution was stirred for 0.75 hr. and then a 1.0-ml. aliquot was added to deuterium oxide containing sufficient acetic acid-d_1 that the final solution had a pH of 5. This solution was stirred for 5 min. and then partitioned between ether and aqueous sodium carbonate. After the organic layer had been dried and concentrated, the monodeuterated ketone **6** was collected[29] from the residual liquid (which contained[29] no enol acetate **4** or **7**) and found to contain 3% d_0 species, 96% d_1

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(34) D. J. Pettit and G. K. Helmkamp, *J. Org. Chem.*, **29**, 2702 (1964).

(35) We found it impractical to prepare a stock solution of methyllithium in 1,2-dimethoxyethane because this solvent is attacked by the organolithium reagent at a significant rate. Consequently, solutions of methyllithium in 1,2-dimethoxyethane were always prepared immediately before use. The removal of ether from the ethereal methyllithium solution was necessary because several of the lithium enolates were found to be soluble in 1,2-dimethoxyethane but insoluble in mixtures of ether and 1,2-dimethoxyethane.

species and 1% d_2 species. The mass spectrum of the monodeuterated ketone **6** has abundant peaks at m/e 99, 84, 71, 70, 69, 56, 55, 43, 42, 41, 40 and 39; the corresponding peaks in the non-deuterated ketone are at m/e 98, 83, 70, 69, 55, 42 and 39. The infrared spectrum[36] of the monodeuterio ketone **6** differs from the spectrum of 2-methylcyclopentanone in having a band at 2110 cm.$^{-1}$ (C-D) and in several bands in the fingerprint region.

A comparable solution, prepared from 1.0 mmole of methyllithium and 0.498 mmole of the enol acetate **4** in 1.0 ml. of 1,2-dimethoxyethane, was stirred for 30 min. at room temperature and then poured into 2.0 g. (13.2 mmoles) of acetic anhydride. The resulting mixture was stirred for 30 min. and then diluted with pentane and aqueous sodium carbonate. The organic layer was separated, combined with a pentane extract of the aqueous phase and then dried, concentrated and mixed with 44.8 mg. of an internal standard.[37] The crude product contained[38] the enol acetate **4** in which none of the isomeric ester **7** was detected; the calculated yield of **4** was 86%. The product from a corresponding experiment was identified with an authentic sample[14d] of the enol acetate **4**

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(36) Determined as a solution in carbon tetrachloride.

(37) m-Diisopropylbenzene was employed as an internal standard for this experiment.

(38) A gas chromatography column packed with Silicone Fluid, No. 710, suspended on Chromosorb P was employed.

by comparison of retention times and infrared spectra.

Similarly, an enolate solution prepared from 2.0 mmoles of methyllithium and 127.7 mg. (0.911 mmoles) of the enol acetate **7** in 2.0 ml. of 1,2-dimethoxyethane was stirred at 25° for 1 hr. and then quenched in 3.0 g. (29.5 mmoles) of acetic anhydride. The crude enol acetate, recovered as in the previous case, contained[38] the enol acetate **7** but none of the isomer **4** was observed. The calculated[37] yield of the ester **7** was 86%.

B. From 1-Decalone.-- A solution of the enolate anion **13**, prepared from 0.55 mmole of methyllithium and 33.7 mg. (0.174 mmole) of the trans-$\Delta^{1,2}$-enol acetate **9** in 1.0 ml. of 1,2-dimethoxyethane was stirred for 1 hr. at 25° and then quenched in excess acetic anhydride and processed as in previous cases. The crude product contained[29] the enol acetate **9** (calculated yield[30] was quantitative) but neither of the enol acetates **8** or **10** were detected.

Similarly, the enolate solution obtained from 1.0 mmole of methyllithium and 89.9 mg. (0.464 mmoles) of the $\Delta^{1,9}$-enol acetate **8** in 1.0 ml. of 1,2-dimethoxyethane was stirred for 1 hr. and then added to 3.0 g. (29.5 mmoles) of acetic anhydride. The crude product contained[29] the enol acetate **8** but neither of the isomers **9** or **10** was detected.

C. From 2-Heptanone.-- A solution of the enolate anion **18**, prepared from 1.0 mmole of methyllithium and 30.0 mg. (0.192 mmole) of the enol acetate **16** in 1.0 ml. of 1,2-dimethoxyethane was heated to

73° for 45 min. at which time the solution no longer retained the red color of the triphenylmethyl anion. After the reaction mixture had been poured into acetic anhydride and the crude product had been separated in the usual way, the crude product contained[29] the *cis*-enol acetate **16** (calculated[39] yield 76%) but none of the isomeric enol acetate **15** was detected. A collected sample of the product **16** was identified with an authentic sample[6,14d] by comparison of retention times and infrared spectra.

Similarly a solution of the enolate anion **17**, from 1.0 mmole of methyllithium and 43.0 mg. (0.276 mmole) of the enol acetate **15**, in 1.0 ml. of 1,2-dimethoxyethane was heated to 73° for 40 min. and then subjected to the usual quenching and isolation procedure. The crude product contained[29] the *trans*-enol acetate **15** (calculated[39] yield 99%) but the stereoisomer **16** was not detected.

Preparation of Alkylated Products. A. The Polymethylcyclopentanones.-- Following previously described procedures,[44] a solution of sodium *t*-amylate [from 176 g. (2.00 moles) of *t*-amyl alcohol, 46 g. (2.0 g.-atoms) of sodium and 824 ml. of benzene] was added, dropwise

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(39) Anisole was employed as an internal standard for this experiment.

(44) (a) J. M. Conia, *Bull. soc. chim. France*, 537 (1950); (b) J. M. Conia, *ibid.*, 1064 (1957); (c) M. Muhlstadt, *Chem. Ber.*, **93**, 2638 (1960).

and with stirring over an 8-hr. period, to a cold (0°) solution of 84 g. (1.0 mole) of cyclopentanone and 2.77 g. (2.20 moles) of dimethyl sulfate in 2.0 l. of ether. The resulting mixture was refluxed for 2 hr., allowed to stand overnight and then washed with water. The ether layer was separated, washed with aqueous potassium hydroxide until the washings remained basic, and then washed with water, dried and concentrated. Distillation of the residue afforded 52.06 g. of colorless liquid, b.p. 120-145°, which was stirred with excess aqueous sodium bisulfite to remove the cyclopentanone and 2-methylcyclopentanone. An ether solution of the organic phase was dried, concentrated, mixed with 57 g. (0.77 mole) of ethyl formate and added, dropwise over a 2.5-hr. period, to a suspension of 2.70 moles of sodium methoxide in 375 ml. of benzene. The resulting slurry was stirred overnight under a nitrogen atmosphere and then mixed with 500 g. of ice. The resulting aqueous, alkaline phase was separated, washed with benzene and acidified at 0° with aqueous hydrochloric acid. The ether extract of this mixture was dried and concentrated to leave the crude 2-formyl-5,5-dimethylcyclopentanone which was treated with refluxing 5% aqueous potassium hydroxide for 2 hr. The mixture was extracted with ether; the extract was dried, concentrated and distilled to separate 17.59 g. of pure[29] **2,2-dimethylcyclopentanone** (**25**), b.p. 142-144°, $\underline{n}^{25}$ $\underline{D}$ 1.4317 (lit.[44] b.p. 143°; $\underline{n}^{20}$ $\underline{D}$ 1.4332), $\bar{\nu}_{max}$[36] 1740 (C=0) and 1355 and 1375 cm.$^{-1}$ [$C(CH_3)_2$]. The product has an n.m.r.[36] singlet at 1.02 δ (6H, CH_3-C) with a multiplet in the region 1.6-2.4 δ (6H, aliphatic CH_2) and abundant peaks in the mass spectrum at m/e 112 (molecular ion), 97, 79, 69, 56, 41 and 39.

The benzene solution remaining after separation of the formyl derivative was concentrated and the residual yellow oil (19.2 g.) was heated on a steam bath with 20 g. of semicarbazide hydrochloride and 25 g. of sodium acetate in aqueous ethanol for 15 min. The resulting mixture was extracted with ether and the extract was concentrated. Successive recrystallization of the residue from water and from aqueous ethanol afforded 10.0 g. of the crude semicarbazide of 2,2,5-trimethylcyclopentanone, m.p. 131-135°. A 3.38-g. portion of this derivative was heated under reflux with 26 g. of oxalic acid in 124 ml. of water for 3 hr. and then extracted with ether. The ethereal extract was washed successively with 5% aqueous sodium hydroxide and aqueous sodium chloride and then concentrated and distilled to separate 937 mg. of a colorless liquid, b.p. 149° (lit.[44] b.p. 151°), containing[29] *ca.* 90% of **2,2,5-trimethylcyclopentanone** (**26**). A collected[29] sample of the pure ketone **26**, n^{24}_{D} 1.4275, has infrared absorption[36] at 1735 (C=O) and at 1360 and 1380 cm.$^{-1}$ [$C(CH_3)_2$] with n.m.r.[36] singlets at 0.97 and 1.04 δ (6H, $C-CH_3$), a doublet (J = 6.5 c.p.s.) at 1.07 δ (3H, methyl group of CH_3-CH) and a multiplet in the region 1.4-2.4 δ (5H, aliphatic C-H). The mass spectrum of this product has abundant peaks at m/e 126 (molecular ion), 111, 83, 69, 56, 41 and 39.

A mixture of 980 mg. (10 mmoles) of 2-methylcyclopentanone and 4.02 g. (54.3 mmoles) of ethyl formate was added, dropwise and with stirring, to a slurry of 5.95 g. (52.2 mmoles) of sodium methoxide in 62 ml. of benzene. The resulting slurry was stirred overnight and then mixed with 100 g. of ice. After the benzene layer had been separated, the aqueous phase was washed with benzene, cooled, acidified with hydrochloric acid and extracted with ether. Concentration of the ethereal solution left 1.85 g. of crude 2-formyl-5-methylcyclopentanone as a yellow oil which was taken up in 70 ml. of methanol containing 2 ml. of 10% aqueous hydrochloric acid and hydrogenated at 25° and atmospheric pressure over 1.25 g. of a 5% palladium-on-carbon catalyst. The hydrogen uptake (370 ml. or 1.49 mmoles) ceased after two days, the first half of the hydrogen uptake being relatively rapid. The mixture was filtered, concentrated, and taken up in ether. The ethereal solution was washed successively with 5% aqueous potassium hydroxide and water and then dried and concentrated. Distillation of the residue afforded 577 mg. (51.5%) of **2,5-dimethylcyclopentanone** (**27**) as a colorless liquid, b.p. 149-153°, n^{25} *D* 1.4292 (lit.[44] b.p. 149-149.5°, n^{20} *D* 1.4310. The product **27**, a mixture of *cis*- and *trans*-isomers was only partially resolved on our gas chromatograph.[29] This mixture has infrared absorption[36] at 1740 cm.$^{-1}$ (C=O) with abundant peaks in the mass spectrum at m/e 112 (molecular ion), 97, 69, 55, 42, 41 and 39. The n.m.r. spectrum[36] of the mixture has a broad multiplet in the region 1.2-2.4 δ (6H, aliphatic C-H) as well as a multiplet in the region 0.9-1.2 δ (6H, CH_3). The latter multiplet appears to consist of a doublet (J = 6 c.p.s.) at 1.07 δ and a less intense doublet (J = 6.5 c.p.s.)

at 1.02 δ.

B. Preparation of 2-Methyl-1-decalone.-- A mixture of 1.52 g. (10.0 mmoles) of *trans*-1-decalone and 4.02 g. (54.3 mmoles) of ethyl formate was added, dropwise and with stirring at 25°, to a suspension of 5.95 g. (50.5 mmoles) of sodium methoxide in 62 ml. of benzene. The resulting slurry was stirred for 15 hr. and then mixed with ice. The resulting aqueous phase was separated, washed with benzene, acidified with hydrochloric acid at 0° and then extracted with ether. After the ethereal extract had been dried and concentrated, the remaining crude 2-formyl-1-decalone, a yellow liquid, was taken up in 70 ml. of methanol containing 2 ml. of 10% aqueous hydrochloric acid and hydrogenated at 25° and atmospheric pressure over 1.25 g. of a 5% palladium-on-carbon catalyst. After the hydrogen uptake (465 ml., 19.0 mmoles) ceased, the mixture was filtered, concentrated and taken up in ether. The ethereal extract was washed with aqueous sodium carbonate, dried and concentrated. Distillation of the residual yellow oil (1.173 g.) separated 1.165 g. (70%) of *2-methyl-1-decalone* (**28**), b.p. 93-95° (2 mm.), n^{16}D 1.4832 [lit. b.p. 96-99° (4 mm.),[45a] $n^{17.7}$D 1.4812[45b]]. This product is an equilibrium mixture of epimers exhibiting two peaks on gas chromatography.[29] The larger peak (94% of area, first eluted) is believed

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(45) (a) W. J. Bailey and M. Madoff, *J. Am. Chem. Soc.*, **76**, 2707 (1954); (b) J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 817 (1937).

to be the most stable epimer **28** with a trans-ring fusion and an equatorial methyl group while the peak eluted second (6% of area) is tentatively assigned the configuration **29** with an equatorial methyl group and a cis-ring fusion. The material has infrared absorption[36] at 1715 cm.$^{-1}$ (C=O) but lacks absorption attributable to a -CH$_2$-CO- function at 1400-1420 cm.$^{-1}$. The n.m.r. spectrum[36] has a doublet (J = 6 c.p.s.) at 0.93 δ (3H, methyl group of CH$_3$-CH) as well as complex absorption in the region 1.0-2.5 δ (15 H, aliphatic C-H). The mass spectrum has abundant peaks at m/e 166 (molecular ion), 124, 109, 81, 67, 55, 41 and 39.

Alkylation of 2-Methylcyclopentanone.-- As described previously and summarized in Table III, the enol acetate **4** was added to a solution of methyllithium in 1,2-dimethoxyethane until the red color of the indicator (triphenylmethyllithium) was just discharged. The resulting solution of the enolate anion **5** was mixed with methyl iodide (or dimethylsulfate); after the mixture had been stirred for the specified time, it was poured into dilute, aqueous hydrochloric acid and extracted with ether. The ethereal solution was washed with aqueous sodium carbonate, dried, concentrated and analyzed by gas chromatography.[29,38] In certain cases, a weighed amount of an internal standard[37] was added prior to analysis to permit calculation of yields. Samples of the alkylated products **25** and **26** as well as 2-methylcyclopentanone were collected[38] from certain of the reactions and identified with previously described samples by comparison of retention times, infrared and mass

Table III

Methylation of the Enolate Anion 5 From 2-Methylcyclopentanone

nol acetate 4, mg. mmoles)	1,2-Dimethoxyethane ml.	Methyl iodide mg. (mmoles)	Reaction temp., °C	Reaction time, min.	Composition of methylated cyclopentanone mixture, %			
					2-methyl	2,2-dimethyl	2,2,5-trimethyl	2,2,5,5-tetramethyl
13.5 (0.81)	2.0	116.1 (0.81)	0°	< 0.5[a]	55	45	--	--
6.7 (0.69)	2.0	336.6 (2.40)	0°	< 0.5[a]	--	70	30	--
48.4 (1.06)	1.6	565.1 (3.95)	-5°	2.0[b]	3	53	28	16
63.2 (1.17)	2.0	1303.1 (9.12)	25°	< 0.5[b]	--	10	30	60
41.8 (1.01)	2.2	6850 (48.2)	25°	5.0[a,c]	--	31	69	--
23.7 (0.88)	2.-	8900 (62.6)	25°	120[a]	--	--	48	52
52.0 (1.08)	2.0	283.5[d] (2.25)	25°	2.0[b,d]	17	63	16	4

The enolate anion solution was added to the alkylating agent. [b] The alkylating agent as added to the enolate anion solution. [c] The calculated material balance (Ref. 37) n this case was 64%. [d] Dimethyl sulfate was the alkylating agent for this experiment. he calculated (Ref. 37) material balance was 99%.

spectra. The product, 2,2,5,5-tetramethylcyclopentanone [lit.[44a] b.p. 154-155°, n^{20}D 1.4280], was formed in certain of the alkylation reactions. A collected[38] sample of this product has infrared absorption[36] at 1780 (weak) and 1740 (strong) cm.$^{-1}$ (C=O in a 5-membered ring; the doublet appears to arise from Fermi resonance with the overtone of a peak at 880 cm.$^{-1}$) with abundant peaks in its mass spectrum at m/e 140 (molecular ion), 72, 69, 57, 56, 41 and 39. The sample has two n.m.r.[36] singlets at 1.73 δ (4H, CH_2) and 1.02 δ (12 H, CH_3). To obtain the analytical data summarized in Table III, calibration curves were prepared from known mixtures of authentic samples. The retention times of the products on our silicone oil column[38] were: 2-methylcyclopentanone, 6.2 min.; 2,2-dimethylcyclopentanone (25), 7.7 min.; 2,2,5-trimethylcyclopentanone (26), 8.7 min.; 2,2,5,5-tetramethylcyclopentanone, 11.4 min.; 2,5-dimethylcyclopentanone (27, both isomers), 11.8 min. The corresponding values on our Carbowax column[29] were 2,2,5,5-tetramethylcyclopentanone, 31.2 min.; 2,2,5-trimethylcyclopentanone (26), 36.6 min., 2,2-dimethylcyclopentanone (25), 39.2 min.; 2-methylcyclopentanone, 43.2 min. and 2,5-dimethylcyclopentanone (27), 48.0 min. In no case was 2,5-dimethylcyclopentanone (27) detected in the product mixtures.

Alkylation of 1-Decalone. A. At Position 2.-- To a solution of the enolate anions 13 and 14, prepared from 1.50 mmoles of methyllithium and 149.1 mg. (0.777 mmole) of the mixture of stereoisomeric

$\Delta^{1,2}$-enol acetates 9 and 10 in 2.0 ml. of 1,2-dimethoxyethane, was added in one portion with stirring, 307.7 g. (2.16 mmoles) of methyl iodide. The reaction was immediately (reaction time < 30 sec.) quenched by the addition of 5 ml. of dilute, aqueous hydrochloric acid and the resulting mixture was extracted with ether. After the resulting mixture had been washed with aqueous sodium carbonate, mixed with a known amount of internal standard,[39] dried and concentrated, the residual oil contained[29] 98% of the more stable 2-methyl-1-decalone 28 and 2% of the less stable epimer believed to be 29. The calculated yield was 93% of 28 and 2% of 29.

In a second experiment the enolate anion solution from 1.90 mmoles of methyllithium and 189.4 mg. (0.976 mmoles) of the enol acetates 9 and 10 in 2.0 ml. of 1,2-dimethoxyethane was treated with 330 mg. (2.62 mmoles) of dimethyl sulfate after which the reaction and isolation procedure described above was followed. The crude product contained[29] 91% of 28, 2% of 29 and 7% of a dialkylated product believed to be 2,2-dimethyl-*trans*-1-decalone; the calculated yields were 84% of 28, 2% of 29 and 6% of the dialkylated product. The major alkylation product was identified with the previously described sample of 2-methyl-1-decalone 28 by comparison of retention times and infrared and mass spectra. A collected[29] sample of the dialkylated product, thought to be 2,2-dimethyl-*trans*-1-decalone, has infrared absorption[36] at 1710 (C=O) and 1385 and 1365 cm.$^{-1}$ $[\gt C(CH_3)_2]$ but lacks absorption in the region 1400-1420 (-CH$_2$-CO-). The mass spectrum of the product has abundant peaks at m/e 180 (molecular ion), 109, 82, 67, 55, 41 and 39. Neither of the 9-methyl-1-decalones **30** or **31** was detected in these reaction mixtures. The retention times of the various decalone derivatives on our gas chromatography column[29] were: 2,2-dimethyl-1-decalone, 24.1 min.; 2-methyl-1-decalone **28**, 27.0 min.; 2-methyl-1-decalone **29**, 29.3 min.; *trans*-1-decalone, 38.2 min.; 2,9-dimethyl-*cis*-1-decalone (**37a**), 38.2 min. (not resolved from *trans*-1-decalone); 9-methyl-*cis*-1-decalone (**30**), 42.5 min.; a dialkylation product believed to be 2,9-dimethyl-*trans*-1-decalone (**37b**), 46.3 min.; 9-methyl-*trans*-1-decalone (**31**), 50.3 min.

B. At Position 9.-- Solutions of the enolate anion **12** were prepared from the $\Delta^{1,9}$-enol acetate **8** employing the quantities of reactants listed in Table IV. The resulting solutions were mixed with the methylating agents listed and the crude products were separated by adding dilute, aqueous hydrochloric acid to the reaction mixture and subsequent extraction with ether. The ethereal extracts were washed with aqueous sodium carbonate, dried, concentrated and analyzed.[29] In certain reactions an internal standard[39] was added to permit yield calculations. A calibration curve for 1-decalone and its monomethylated derivatives was prepared from known amounts of authentic samples. The gas chromatographic retention times[29] for the various decalone derivatives are given in the previous experiment. Collected[29] samples of *trans*-1-decalone (**1**) and the *cis*(**30**)- and *trans*(**31**)-9-methyl derivatives were identified with authentic samples.[46]

Table IV

Methylation of the Enolate Anion 12 from 1-Decalone

Enol acetate 8, mg. (mmoles)	1,2-Dimethoxyethane, ml.	Methylating agent, mg., (mmoles)	Reaction temp., °C	Reaction time, min.	Composition of Product Mixture, %[a]				Yield %[b]
					decalone 1 + 2,9-dimethyl 37a	cis-9-methyl 30	trans-9-methyl 31	2,9-dimethyl 37b	
301 (1.55)	10.0	CH_3I 635 (4.46)	28°	5.0	8	77	15	--	93
142 (0.73)	5.0	CH_3I 330 (2.32)	25°	10.0	32	44	14	10	93
451 (2.34)	5.0	CH_3I 996 (7.02)	25°	10.0	47	23	16	14	97
158 (0.82)	1.0	CH_3I 228 (1.61)	25°	< 0.5	52	40	8	--	97
1447 (7.46)	20.0	CH_3I 5267 (36.8)	0°	ca. 0.5	14	66	13	7	69[c]
147 (0.76)	1.0	CH_3OTs 158 (0.85)	25°	2.0	64	31	5	--	96
156 (0.80)	1.0	CH_3OTs 588 (3.15)	25°	< 0.5	78	19	3	--	98
301 (1.55)	10.0	$(CH_3)_2SO_4$ 571 (4.53)	28°	5.0	60	35	5	--	96
124 (0.64)	1.0	$(CH_3)_2SO_4$ 157 (1.24)	25°	5.0	45	43	12	--	--
211 (1.08)	2.0	$(CH_3)_2SO_4$ 545 (4.33)	25°	< 0.5	51	42	7	--	91
170 (0.88)	1.1	$(CH_3)_2SO_4$ 229 (1.82)	25°	30	38	49	10	3	94
208 (1.07)	7.0	$(CH_3)_3O^{\oplus}$[d] 1165 (3.30)	25°	< 0.5	3	97	--	--	68[e]

[a] These compositions were determined by gas chromatography (Ref. 29). Since our column did not resolve 1-decalone (**1**) and 2,9-dimethyl-*cis*-1-decalone (**37a**) the combined percentage of these two substances is listed. [b] The total calculated yields of products including 1-decalone. These values were obtained from gas chromatograms in which anisole was employed as an internal standard unless otherwise noted. [c] This yield was determined by the isolation of 866 mg. of product, b.p. 65-67° (0.35 mm.), which has the composition indicated. [d] In this experiment the solution of the enolate anion was added to a slurry of trimethyloxonium 2,4,6-trinitrobenzenesulfonate in 1,2-dimethoxyethane. [e] In addition to the products listed approximately 10% of other unidentified materials were present. The possibility that one of these unidentified products is the O-methyl derivative is being investigated.

by comparison of retention times and infrared and mass spectra. In addition, reaction of 200 mg. of one of the alkylation product mixtures (containing^{29} 79% of the *cis*-isomer **30** and 21% of the *trans*-isomer **31**) with excess hydroxylamine in aqueous ethanol yielded, after purification, 145.1 g. of the oxime of 9-methyl-*cis*-1-decalone as colorless plates from aqueous methanol, m.p. 108-110° (lit.^{2b} 109-110°). The n.m.r. spectrum^{36} of the *cis*-isomer **30** has broad absorption in the region 1.2-2.5 δ (aliphatic C-H) with a singlet at 1.18 δ (CH_3); the *trans* isomer **31** has broad absorption^{36} in the region 1.2-2.5 δ (aliphatic C-H) with a singlet at 1.08 δ (CH_3). The fact that the n.m.r. peak for the axial methyl group of the *trans* isomer **31** is at 0.10 p.p.m. (6 c.p.s.) higher field than the methyl group of the

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(46) (a) W. S. Johnson, S. L. Gray, J. K. Crandall and D. M. Bailey, J. Am. Chem. Soc., **86**, 1966 (1964); (b) We are indebted to Professor W. S. Johnson who supplied authentic samples of the *cis*- and *trans*-9-methyl ketones **30** and **31**.

cis-isomer **30** was confirmed by measuring the spectrum of a mixture of the two isomers.[47] The ratio of *cis*-isomer **30** to *trans*-isomer **31** was measured for methyl iodide in five separate reactions in which the amount of dialkylation was small; the average value of this ratio for methyl iodide was: *cis*/*trans* = 5.0 ± 0.2. Similarly, for eight different reactions with dimethyl sulfate, the average value was: *cis*/*trans* = 6.2 ± 0.2. Because of the low yields of alkylated products, a reliable value was not obtained for methyl *p*-toluenesulfonate; the value obtained was *cis*/*trans* ~ 7. Although a reliable value was also not obtained for alkylation with the trimethyloxonium salt, it is clear that the ratio, *cis*/*trans*, is greater than 20.

In order to obtain samples of the dialkylated products, a mixture of 295 mg. of the crude product from an alkylation experiment (third entry in Table IV) with 0.55 g. (7.4 mmoles) of ethyl formate was added to a suspension of 1.00 g. (18.5 mmoles) of sodium methoxide in 2.0 ml. of benzene. After this mixture had been stirred for 15 hr. at 25°, it was diluted with ice water. The benzene layer was separated, combined with the benzene extract of the aqueous phase, dried

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(47) This chemical shift difference is in agreement with the previous generalization of J. I. Musher [*J. Am. Chem. Soc.*, **83**, 1146 (1961)] that the 9-methyl group of a *trans*-fused decalin derivative has an n.m.r. peak at 0.14 p.p.m. higher field than the corresponding *cis*-fused isomer. Our results suggest that this generalization remains valid for decalin systems which contain a 1-keto group unlike the reversal observed for the axial and equatorial protons of α-halo ketones. A. Nickon, M. A. Castle, R. Harada, C. E. Berkoff and R. O. Williams, *J. Am. Chem. Soc.*, **85**, 2185 (1963).

and concentrated. The residual liquid, which contained[29] one major component (**37a**) and two minor constituents, was dissolved in 10 ml. of *t*-butyl alcohol containing 50 mg. of potassium *t*-butoxide and the resulting solution was stirred for 2 hr. at room temperature to epimerize any unstable stereoisomers present. After this solution had been diluted with water and extracted with ether, the organic extract was dried and concentrated. The residual liquid contained[29] the 2,9-dimethyl-*cis*-ketone **37a** (79%) and a component believed to be the *trans*-isomer **37b** (21%). A collected[29] sample of the *cis*-isomer **37a**[46a] has infrared absorption[36] at 1710 cm.$^{-1}$ (C=O) with a molecular ion peak in the mass spectrum at m/e 180 as well as abundant fragment peaks at m/e 125, 109, 95, 81, 68, 67, 55, 41, and 39. A 20-mg. sample of the ketone **37a** was treated with 75 mg. of hydroxylamine hydrochloride in a refluxing mixture of 0.25 ml. of ethanol and 0.25 ml. of pyridine for 2.5 hr. The crude product was recrystallized from an ether-petroleum ether mixture to separate 10 mg. of the **oxime of the cis-ketone 37a** as white needles, m.p. 173-175° (lit.[46a] m.p. 175-176°). A collected[29] sample of the second product, believed to be the *trans*-ketone **37b**,[46a] has infrared absorption[36] at 1710 cm.$^{-1}$ (C=O) with a molecular ion peak in the mass spectrum at m/e 180 as well as abundant fragment peaks at m/e 95, 82, 68, 67, 55, 41 and 39. The mass spectrum also has low intensity peaks at m/e 194 and 178 attributable to contaminants in this sample. A collected sample[29] of this same gas chromatographic peak from a reaction (fifth entry, Table IV) where less dialkylation was observed has a very similar mass spectrum but lacks peaks at m/e 194 and 178. The peak at m/e 194 is presumably attributable to one of the stereoisomeric 2,2,9-trimethyl-1-decalones as a contaminant; the nature of the contaminant responsible for the peak at m/e 178 is unknown.

C. Rates of Reaction.-- A 1,2-dimethoxyethane solution of the enolate anion 12 and lithium t-butoxide was prepared from the enol acetate 8 in the usual way. Aliquots (10.00 ml.) were held at 28.0° under a nitrogen atmosphere and the alkylating agents listed in Table V were added in one portion to each reaction vessel. Aliquots (1.00 ml.) of each reaction mixture were removed after the time periods indicated, quenched in 5.00 ml. of 0.101 M aqueous hydrochloric acid and titrated to a phenolphthalein end point with standard sodium hydroxide. Duplicate runs were made for each alkylating agent. The average percentage of total base (enolate anion and t-butoxide anion) consumed are summarized in Table V. The reaction with dimethyl sulfate became turbid after 20-30 min.

To learn what fractions of the above reactions were attributable to reaction of the alkoxide with the methylating agents, a solution of lithium t-butoxide was prepared by the addition of t-butyl alcohol to a solution of methyllithium in 1,2-dimethoxyethane until the color of the triphenylmethyllithium indicator was just discharged. Aliquots of the solution were held at 28.0° and the methylating agents indicated in Table V were added. Aliquots (1.00 or 2.00 ml.) of the

Table V

Reaction of the Enolate Anion 12 and Lithium t-Butoxide with Methylating Agents in 1,2-Dimethoxyethane at 28°

Enolate anion conc., M	Lithium t-butoxide conc., M	Methylating agent, conc., M	Amount of base consumed after various times (in minutes), %[a]						
			0.5[b]	2.0[b]	5.0	15.0	30.0	60.0	90.0
0.173	0.173	CH_3I[c] (0.518)	28[b]	45	60	73	77	82	85
--	0.181	CH_3I (0.543)	4	13	21	39	58	70	76
0.173	0.173	CH_3OTs[c] (0.518)	5	11	19	33	42	47	52
--	0.181	CH_3OTs (0.543)	14	18	20	26	36	40	48
0.173	0.173	$(CH_3)_2SO_4$[c] (0.518)	46	48	49	50	53	59	59
--	0.181	$(CH_3)_2SO_4$ (0.543)	32	36	42	44	46	47	48
	0.181	$(CH_3)_2SO_4$[d] (0.543)	15	39	42	44	47	50	50

[a] The numbers refer to the percentage of the total base consumed. Consequently, complete consumption of only the enolate anion 12 would give a value of 50%. [b] Since no special provisions were made for instant mixing, the numbers in these columns are only approximate. [c] The data listed are average values from duplicate runs. [d] In this run the dimethylsulfate was mixed with an equimolar quantity of trans-1-decalone and the mixture was added.

reaction mixtures were removed after the specified times, quenched in 5.0 ml. of water and titrated to a phenolphthalein end point with standard hydrochloric acid. The percentages of base consumed are indicated in Table V. The reaction with methyl p-toluenesulfonate became turbid after approximately 30 min.; in both reactions with dimethyl sulfate, a precipitate formed in less than 30 sec. A mixture of 1.69 mmoles of lithium t-butoxide and 5.12 mmoles of dimethyl sulfate in 10 ml. of 1,2-dimethoxyethane was allowed to stand for 0.5 min. and then centrifuged for 15 min. to separate the precipitate from the supernatant liquid. The supernatant liquid was neutral. The precipitate was washed with 1,2-dimethoxyethane; the n.m.r. spectrum of a solution of the strongly basic residue in deuterium oxide exhibited single peaks at 3.72 δ (CH_3-O-SO_2-) and 1.25 δ (CH_3 of the t-butyl alcohol).

To examine the product distributions, 10.00 ml. aliquots of a 1,2-dimethoxyethane solution which was 0.155 M in the enolate anion **12** and 0.155 M in lithium t-butoxide (0.311 M in total base by titration) were held at 28° and treated with 570.7 mg. (4.53 mmoles) of dimethyl sulfate or 634.9 mg. (4.46 mmoles) of methyl iodide. After the solutions had been stirred for 5.0 min., 1.00 ml. aliquots were quenched in excess standard acid and back titrated with base and the remaining 9.0 ml. of solution was quenched with dilute aqueous hydrochloric acid and the crude product was separated and analyzed[29] as described previously. In the dimethylsulfate reaction 49% of the total base had been consumed and the calculated yields of products were: 1-decalone (1), 57%; 9-methyl-*cis*-1-decalone (30), 34%; 9-methyl-*trans*-1-decalone (31), 5%. In the methyl iodide reaction, 54% of the total base had been consumed and the calculated yields were: 1-decalone (1), 7%; 9-methyl-*cis*-1-decalone (30), 72%; 9-methyl-*trans*-1-decalone (31), 14%.

It is apparent from the foregoing data that the initial rates of reaction of dimethyl sulfate with both the enolate anion 12 and lithium *t*-butoxide are very rapid. More than 50% of the enolate anion 12 had reacted in less than 0.5 min. However, both reactions became very slow after approximately 50% of the bases had been consumed, presumably because of complex formation and/or precipitation of mixtures of the bases and the lithium salt of methyl hydrogen sulfate. It is not clear whether similar complex formation retards the reaction with methyl *p*-toluenesulfonate but in any case the reaction is relatively slow. About 80 min. was required for the consumption of 50% of the total base and approximately 30 min. for consumption of 50% of the enolate anion 12. The corresponding half-life for the reaction of methyl iodide with a mixture of the enolate anion 12 and the *t*-butoxide anion was about 2.5 min. and the separate half-lives for the reaction of methyl iodide with the enolate anion 12 and with lithium *t*-butoxide are estimated to be 1 min. and 22 min., respectively.

To obtain a measure of how rapidly a solution of lithium *t*-butoxide reacts with 1-decalone, a solution containing 1.69 mmoles of lithium *t*-butoxide in 10 ml. of 1,2-dimethoxyethane was treated with a mixture of 130.9 mg. (0.861 mmole) of *trans*-1-decalone and 138.6 mg. (0.894 mmole) of 2,2,9-trideuterio-*trans*-1-decalone (86% d_3 species and 14% d_2 species).[6] The resulting solution, which was 0.169 *M* in lithium *t*-butoxide and 0.176 *M* in *trans*-1-decalone (mixture of deuterated and non-deuterated), was stirred under a nitrogen atmosphere at 25° and 2.00 ml. aliquots were removed after the times specified (Table VI) and quenched in aqueous acetic acid (final pH 5). After the resulting mixtures had been extracted with ether, the extracts were washed with aqueous sodium bicarbonate, dried and concentrated. The samples of *trans*-1-decalone were collected[29] and analyzed for deuterium content by mass spectrometry to give the data summarized in Table VI. From these data we estimate the half-life for equilibration of the non-deuterated and deuterated 1-decalones to be about 4 min. at the concentrations used.

Table VI

Equilibration of 1-Decalone-d_0 (0.0861 *M*) and 1-Decalone-d_3 (0.0894 *M*) in a 0.169 *M* Solution of Lithium *t*-Butoxide in 1,2-Dimethoxyethane

Reaction time, min.	Deuterium distribution, %			
	d_0	d_1	d_2	d_3
0	49	0	7	44
0.5	41	3	15	41
5.0	31	20	28	21
15.0	23	35	30	12
60.0	19	41	32	8

Alkylation of 2-Methylcyclohexanone.-- Reaction of 2-methylcyclohexanone with acetic anhydride and p-toluenesulfonic acid as previously described[14d] afforded a mixture of enol acetates 23 and 24, b.p. 80° (10 mm.). Although we were unsuccessful in resolving this mixture by gas chromatography, the n.m.r. spectrum[36] of the mixture allowed us to estimate[14d] the composition as 90% of 23 and 10% of 24. The addition of 2.4112 g. (15.45 mmoles) of this enol acetate mixture to 31.0 mmoles of methyllithium in 30 ml. of 1,2-dimethoxyethane just discharged the color of the indicator to give a yellow, slightly cloudy solution of the enolate anion. The solution was cooled to 0° and 5.107 g. (33.4 mmoles) of methyl bromoacetate was added in one portion with swirling. After 30 sec. dilute, aqueous hydrochloric acid was added and the mixture was extracted with ether. This extract was washed with aqueous sodium carbonate, dried, concentrated and distilled to separate 1.73 g. (60%) of a mixture of ketones 35 and 36, b.p. 59-61° (0.10 mm.). A collected[48] sample of this mixture, n^{26}_{D} 1.4643, exhibits a single peak on gas chromatography.[29,38,48] The infrared

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(48) A gas chromatography column packed with LAC, No. 728, liquid phase suspended on Chromosorb P was employed.

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spectrum[36] of this material has peaks at 1740 (ester C=O) and 1715 cm.$^{-1}$ (C=O); the mass spectrum exhibits a weak molecular ion peak at m/e 184 with abundant fragment peaks at 153, 152, 140, 112, 96, 95, 82, 81, 74, 69, 68, 67, 59, 55, 43 and 41. The n.m.r. spectrum[36] of the product has a large singlet at 3.58 δ (CH_3O of **35**) as well as two weak singlets at 3.73 and 3.76 δ (CH_3O of the two diastereoisomers of **36**). From the relative areas of these peaks, we estimate the composition of the mixture to be 90% of **35** and 10% of **36**. The spectrum also has broad absorption in the region 1.5-2.6 δ (aliphatic C-H) upon which are superimposed two doublets (J = 15 c.p.s.) centered at 2.32 and 2.53 δ (AB pattern for $-\overset{|}{\underset{|}{C}}-CH_2-CO_2R$ of **35**) as well as a singlet at 1.16 δ ($C-CH_3$ of **35**) and a weak doublet (J = 6 c.p.s.) at 0.96 δ ($C-CH_3$ of **36**).

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.93; H, 8.77.

Alkylation of 2-Heptanone.-- A mixture of $\Delta^{2,3}$-enol acetates (74% of **15** and 26% of **16**) was employed and the solutions of enolate anions **17** and **18** in 1,2-dimethoxyethane were generated in the usual way employing the quantities specified in Table VII. After the *n*-butyl iodide had been added in one portion, the reaction mixtures were stirred at 25° for the specified times and then diluted with aqueous hydrochloric acid and extracted with ether. The ethereal extracts were washed with aqueous sodium bicarbonate, dried, concentrated, mixed with a known weight of anisole (an internal standard) and analyzed.[29] Collected[29] samples of alkylated ketones **32** and **33** were used to prepare a calibration curve. Because of the large differences in retention times, a column temperature of 120° was used

Table VII

Alkylation of the Enolate Anions 17 and 18 From 2-Heptanone

Enol acetates 15 and 16, mg. (mmoles)	n-Butyl iodide, mg. (mmoles)	1,2-Dimethoxyethane, ml.	Reaction time, min.	Yield of products, %[a]			
				2-heptanone	32	33	34
120.2 (0.78)	420.2 (2.26)	3.0	30	50	33	--	6
191.0 (1.23)	675.0 (3.63)	5.0	120[b]	20	55	12	6

[a] Unless otherwise noted, the yields listed have been calculated from the gas chromatographs of mixtures of the products and a known amount of internal standard. [b] In a duplicate run, the yields were 20% of 2-heptanone, 51% of 32, 14% of 33 and 10% of 34.

to elute 2-heptanone (first eluted), the ketone 32 (second eluted), an unknown component (eluted third), and the ketone 34 (eluted fourth), after which the column temperature was raised to 150° to elute the dialkylated product 33. At 150° the retention times[29] of the products were: 32, 9.0 min.; the unknown component, 10.8 min.; 34, 12.6 min.; 33, 32.4 min. A collected[29] sample of the ketone 32 has infrared absorption[36] at 1715 cm.$^{-1}$ (C=O) with peaks in its mass spectrum at m/e 170 (very weak molecular ion), and at 127 (weak, M-COCH$_3$), as well as abundant peaks at m/e 114, 71, 58, 57 and 43. A 12-mg. sample of the collected ketone 32 was allowed to react with excess semicarbazide in boiling aqueous ethanol. Recrystallization of the crude product from aqueous ethanol afforded 8 mg. of the semicarbazone of 3-butyl-2-heptanone, m.p. 108-109° (lit.[49] 109°). The n.m.r. spectrum[38] of our ketone

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(49) W. B. Renfrow, Jr., J. Am. Chem. Soc., 66, 144 (1944).

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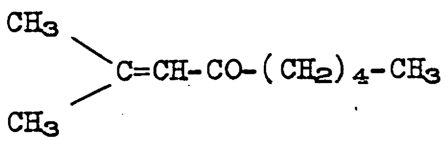
32 has a multiplet centered at 2.27 δ (1H, CH-CO), a singlet at 2.00 δ (3H, CH_3CO), a multiplet in the region 1.0-1.6 δ (12H, aliphatic CH_2) and a multiplet in the region 0.8-1.0 δ (6H, CH_3).

In a preparative run, a solution of 78 mmoles of methyllithium in 200 ml. of 1,2-dimethoxyethane was treated with 6.053 g. (38.8 mmoles) of the mixture of enol acetates 15 and 16. Sufficient heat was generated during the addition to cause the solution to reflux. Titration of a 2.00-ml. aliquot of the enolate solution with standard acid indicated that the total amount of base present was 77.6 mmoles. n-Butyl iodide (21.50 g., 13.3 ml. or 118 mmoles) was added and the mixture was stirred at room temperature. Aliquots (2.00 ml.) were removed at 30-min. intervals and titrated; after 30 min. (when 19% of the total base present had been consumed) a white precipitate began to separate from the reaction mixture. A total reaction time of 2.5 hr. was employed at which time 35% of the total base present had been consumed. The crude product, separated as in the previous cases, was distilled to separate the following fractions: (1) b.p. 135-160°, containing 2-heptanone and other low-boiling components; (2) 3.250 g. (49%) of a fraction [b.p. 90-105° (8 mm.)] containing[29] 2-heptanone (4%), the ketone 32 (85%) [lit.[49] b.p. 104-107° (22 mm.)], an unknown component (5%) and the ketone 34 (6%); (3) 1.496 g. (17%) of a fraction [b.p. 130-138° (8 mm.)] containing[29] the ketone 32 (4%), the ketone 34 (4%), the dialkylated ketone 33 (67%) and 21% of at least three other high-boiling components of unknown constitution.

Samples of the ketone 34 collected[29] from both this reaction and a small-scale reaction were identified with a commercial[50] sample of the ketone 34. A collected[29] sample of the dialkylated ketone 33 has infrared absorption[36] at 1715 cm.$^{-1}$ (C=O) with a very weak molecular ion peak at m/e 226 and abundant fragment peaks at m/e 99, 71, 57 and 43. The sample has n.m.r. multiplets[36] in the regions 2.0-2.5 δ (3H, $-CH_2-CO-CH<$) and 0.8-1.9 δ (27H, aliphatic C-H).

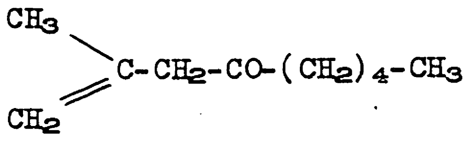
Anal. Calcd. for $C_{15}H_{30}O$; C, 79.57; H, 13.36. Found: C, 79.41; H, 13.31.

A collected[29] sample of the minor unknown component, eluted just after ketone 32, was identified with a subsequently described sample of the unsaturated ketone 44 by comparison of retention times and infrared and mass spectra.



$\genfrac{}{}{0pt}{}{CH_3}{CH_3}\!>C{=}CH{-}CO{-}(CH_2)_4{-}CH_3$

44



$\genfrac{}{}{0pt}{}{CH_3}{CH_2}\!>C{-}CH_2{-}CO{-}(CH_2)_4{-}CH_3$

45

An ethereal solution of n-amyllithium was prepared as previously described[51] and found to be 1.2 M by a double titration

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(50) Aldrich Chemical Company, Inc., Milwaukee, Wisconsin.

procedure[33a] employing ethylene dibromide. A 50-ml. (60-mmole) portion of this *n*-amyllithium solution was added, dropwise and with stirring and external cooling (ice bath), to a solution of 2.0 g. (20 mmoles) of *β,β*-dimethylacrylic acid in 5 ml. of ether. The resulting mixture was stirred for 3.5 hr. and then poured into cold, dilute, aqueous hydrochloric acid, and extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate, dried, concentrated and distilled to separate 2.55 g. (83%) of a yellow liquid, b.p. 80-84° (8 mm.). This product contained[29] 30% of the unconjugated isomer **45** (first eluted) and 70% of the conjugated ketone **44** (second eluted). A collected sample[29] of the **conjugated ketone 44** has infrared absorption[36] at 1690 (conj. C=O) and 1625 cm.$^{-1}$ (conj. C=C) with an ultraviolet maximum[52] at 237 mμ (ϵ 12,500) and an n.m.r.[36] multiplet at 6.02 δ (1H, vinyl C-H) as well as two doublets (J = 1 c.p.s. for each) at 2.10 and 1.85 δ (6H, $C=C(CH_3)_2$] superimposed on complex absorption in the region 1.8-2.5 δ (11 H, aliphatic C-H).

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.86; H, 11.76; mol. wt., 154. Found: C, 78.08; H, 12.09; mol. wt., 154 (mass spectrum).

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(51) H. W. Gilman, F. W. Moore and D. Baine, *J. Am. Chem. Soc.*, **63**, 2479 (1941).

(52) Determined as a solution in 95% ethanol.

A collected sample[29] of the unconjugated isomer **45** has infrared absorption[36] at 1720 (C=O), 1650 (C=C) and 895 cm.$^{-1}$ ($\rangle$C=CH$_2$) with an ultraviolet maximum[52] at 287 mμ (ϵ 96) and ϵ 1780 at 210 mμ. The sample has n.m.r. multiplets[36] at 4.81 and 4.90 δ (2 H, vinyl C-H) with a peak (no splitting resolved) at 3.02 δ (2 H, C=C-CH$_2$-CO-) and a partially resolved multiplet at 1.74 δ (3 H, CH$_3$-C=C) superimposed on complex absorption in the region 1.8-2.5 δ (11 H, aliphatic C-H).

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.86; H, 11.76; mol. wt., 154. Found: C, 77.98; H, 11.97; mol. wt., 154 (mass spectrum).

To learn the product distribution in a direct alkylation of 2-heptanone, a solution of 570 mg. (5.00 mmoles) of 2-heptanone and 1.00 g. (5.43 mmoles) of *n*-butyl iodide in 10 ml. of *t*-butyl alcohol containing 5.00 mmoles of potassium *t*-butoxide was stirred at 25° under a nitrogen atmosphere for 7 hr. A white precipitate began to separate from the reaction mixture after approximately 30 min. After the 7-hr. reaction period, the mixture, which was still basic, was diluted with aqueous hydrochloric acid and extracted with ether. The ether extract was washed with aqueous sodium carbonate, dried, concentrated, mixed with an internal standard[39] and analyzed. The calculated yields were: 2-heptanone, 11%; the monoalkylated ketone **32**, 11%; the monoalkylated ketone **34**, 6%; the dialkylated ketone **33**, 1%. In addition, the crude product contained several minor components (estimated yield *ca*. 1%) with retention times similar to the dialkylated ketone and two (or more) components (estimated yield *ca*. 60%)

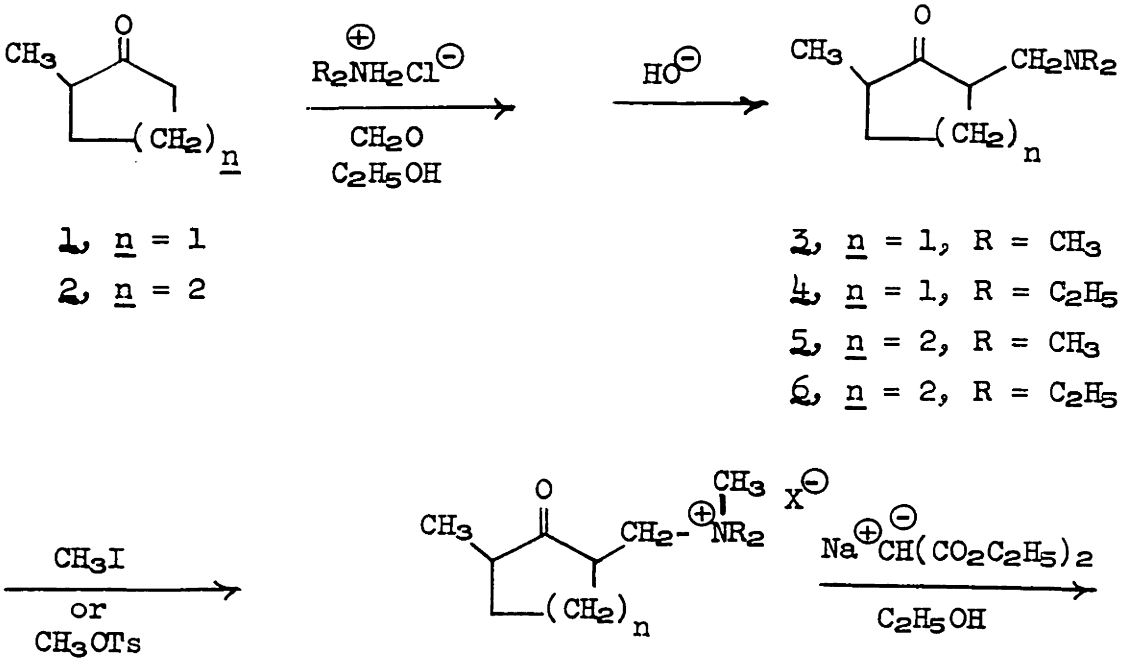
with longer retention times which are believed to arise from aldol condensation of 2-heptanone with itself (Cf. ref. 6).

Part III

Mannich Reaction with 2-Methylcyclopentanone and 2-Methylcyclohexanone

As part of a study of the Michael reaction, we wished to prepare an authentic sample of 2-(2-carboxyethyl)-5-methylcyclopentanone (**12**) and elected to follow a synthetic path (see Chart I) analogous to that previously employed[1] for the corresponding cyclohexanone derivative

Chart I



1, $\underline{n} = 1$
2, $\underline{n} = 2$

3, $\underline{n} = 1$, R = CH_3
4, $\underline{n} = 1$, R = C_2H_5
5, $\underline{n} = 2$, R = CH_3
6, $\underline{n} = 2$, R = C_2H_5

7, $\underline{n} = 1$, R = CH_3, X = I
8, $\underline{n} = 1$, R = C_2H_5, X = I
9, $\underline{n} = 2$, R = CH_3, X = I
10, $\underline{n} = 2$, R = CH_3, X = ETs
11, $\underline{n} = 2$, R = C_2H_5, X = I

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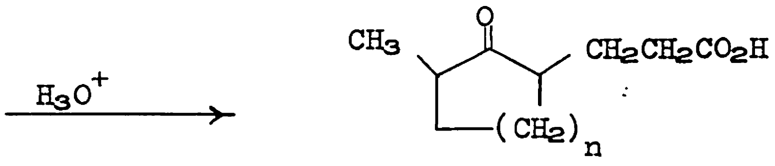
(1) (a) R. L. Frank and R. C. Pierle, J. Am. Chem. Soc., **73**, 724 (1951); (b) H. O. House and M. Schellenbaum, J. Org. Chem., **28**, 34 (1963).



12, n = 1
13, n = 2

13. Both of these preparative procedures were intended to make use of the reported[2] Mannich condensations of 2-methylcyclopentanone (**1**) and 2-methylcyclohexanone (**2**) at the less highly substituted position to form Mannich bases **4** and **6**. Although the reported orientation in these two Mannich condensations has been widely accepted as correct,[1,3] the current view that Mannich reactions in slightly acidic media involve an electrophilic attack of an imminium salt such as **14** on the enol form of the ketone[4] is difficult to reconcile with the reported[2]

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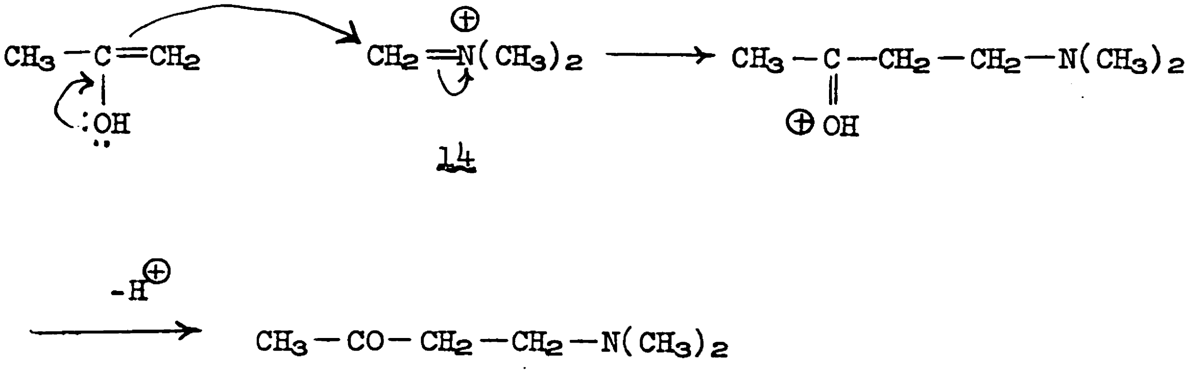
(2) E. C. du Feu, F. J. McQuillin and R. Robinson, J. Chem. Soc., 53 (1937).

(3) (a) F. F. Blicker, Org. Reactions, **1**, 303 (1942); (b) B. Reichert, "Die Mannich Reaktion", Springer Verlag, Berlin, 1959; (c) R. Jacquier, M. Mousseron and S. Boyer, Bull. soc. chim. France, 1653 (1956).

(4) (a) H. Hellmann and G. Opitz, Angew. Chem., **68**, 265 (1956); (b) T. F. Cummings and J. R. Shelton, J. Org. Chem., **25**, 419 (1960).



$$CH_3-\underset{\underset{:\ddot{O}H}{|}}{C}=CH_2 \quad \overset{\oplus}{CH_2=N}(CH_3)_2 \longrightarrow CH_3-\underset{\underset{\oplus OH}{\|}}{C}-CH_2-CH_2-N(CH_3)_2$$

14

$$\xrightarrow{-H^{\oplus}} CH_3-CO-CH_2-CH_2-N(CH_3)_2$$

orientation since the more highly substituted enols of 2-methylcyclopentanone and 2-methylcyclohexanone are expected to be the more stable.[5,6]

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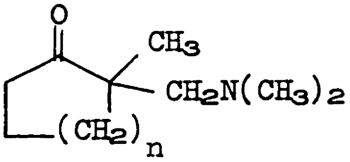
(5) H. O. House and V. Kramar, J. Org. Chem., 29, 0000 (1964).

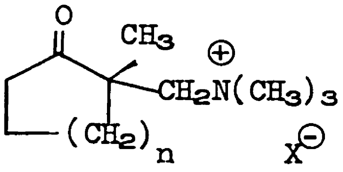
(6) Part I of this thesis.

Our initial attempt to prepare the acid 12 utilized the previously described[2] Mannich base derived from 2-methylcyclopentanone (1), diethylamine hydrochloride and formaldehyde. Neither the previous investigators nor we were able to obtain the base (reported to be 4) or its methiodide (reported to be 8) as crystalline solids. From the reaction of this crude methiodide with diethyl sodiomalonate as previously described[1] we were unable to isolate any of the desired keto acid 12, only a small amount of methylmalonic acid being recovered.

The Mannich reaction was therefore repeated with dimethylamine hydrobromide to form a Mannich base which readily yielded a crystalline methiodide in an overall yield of 89%. However, the n.m.r. spectrum (see Experimental) of this crystalline product left no doubt that it was not the methiodide **7** but rather had structure **17**. The

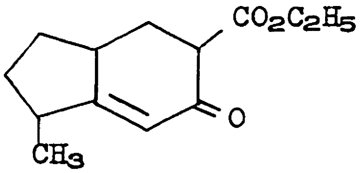


15, *n* = 1
16, *n* = 2



17, *n* = 1, X = I
18, *n* = 2, X = I
19, *n* = 2, X = TsO

n.m.r. spectrum of the original Mannich base indicated that at least 80% of this material had structure **15** and not **3**. Thus, our earlier failure to prepare the keto acid **12** was not surprising. The previous experimental data[1] which had led to the assignment of structure **4** to the Mannich condensation product consisted of the conversion of the crude methiodide (reported to be **8**) to a liquid product, thought to be **20**, in 18% yield. Further transformation of this liquid product



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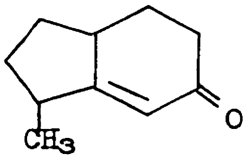

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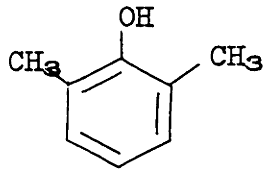
led to a mixture of materials from which a crystalline semicarbazone and a crystalline 2,4-dinitrophenylhydrazone were isolated in unstated yield. These crystalline materials were believed to be derivatives of the unsaturated ketone **21**. Thus, even if one accepts the fact that the liquid product was pure and had structure **20**, these earlier data require that 18% of the Mannich base have the assigned structure 4.

This finding made the corresponding report[1] that the Mannich condensation of 2-methylcyclohexanone (2) with diethylamine and formaldehyde yields 6 open to suspicion in spite of the fact that this report has been accepted by others.[1,3] Repetition of this reaction with dimethylamine hydrochloride produced, in 58% yield, a Mannich base whose n.m.r. spectrum (see *Experimental*) indicates the presence of approximately 30% of the Mannich base 5 and 70% of the Mannich base 16. In previous studies[1] the crude methiodide or methotosylate of this Mannich base had been used for the preparation of the keto acid 13; the yield of the crude ester (a mixture of the ethyl ester of the keto acid 13 and the corresponding malonic ester) corresponded to a yield of less than 42%.[1a] Partial separation of the mixture of methiodides obtained from the Mannich base afforded fractions, m.p. 190-192° dec. and 160-163° dec. which were thought[1b] to be the crude diastereoisomers of structure 9. We have now measured the n.m.r. spectra of these samples and find the fraction, m.p. 190-192° dec., to be the pure methiodide 18 while the fraction, m.p. 160-163° dec., is a mixture of methiodide 9 and 18. The crude Mannich base from 2-methylcyclohexanone (2) had also been converted[1b] to a mixture of crude methotosylates from which a small sample of a pure isomer, m.p. 141-142°, thought to be one of the diastereoisomers of structure 10 was isolated. The n.m.r. spectrum (see *Experimental*) of this material has established that this sample has the structure 19.

The experimental evidence[1] which had previously led to the assignments of structures 6 and 11 to the Mannich base and the corresponding methiodide derived from 2-methylcyclohexanone (2) consisted of the conversion of the crude Mannich base to 2,6-dimethylphenol (22) in unstated yield and the conversion of the crude methiodide to a liquid product, assigned structure 23, in 60% yield. This liquid product was converted to several crystalline derivatives but again no yields were stated. Consequently, no data permitting a reliable estimate of the homogeneity of this initial liquid product 23 are available.



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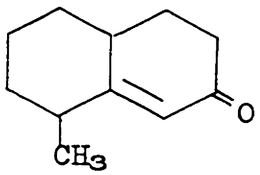

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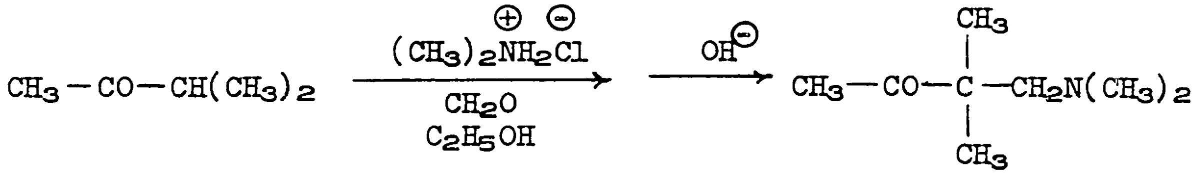
Since the mechanism of the Mannich reaction has been suggested[4b] to change for reactions carried out in neutral or basic solution rather than the usual acidic conditions, we have also examined the reaction of 2-methylcyclohexanone with formaldehyde and free dimethylamine. The n.m.r. spectrum of the resulting Mannich base, indicates the presence of about 65% of 16 and 35% of 5. Thus, at least for the ketone 2, the proportion of structurally isomeric bases obtained in the Mannich reaction do not differ appreciably when the free amine is employed rather than the amine hydrochloride.

Consequently, we conclude that both 2-methylcyclohexanone (**2**) and 2-methylcyclopentanone undergo predominant Mannich condensation at the most highly substituted position contrary to previous claims in the literature but in accord with the result to be expected on mechanistic grounds. It is also appropriate to note that 3-methyl-2-butanone (**24**), contrary to an earlier report,[3c] has also been found[7] to yield primarily, if not exclusively, the more highly substituted Mannich base **25**. These results suggest that certain previous reports[3] that Mannich reactions with unsymmetrical ketones occur at the less highly substituted position should be viewed with suspicion until rigorous structural evidence is provided.



$$CH_3-CO-CH(CH_3)_2 \xrightarrow[\substack{CH_2O \\ C_2H_5OH}]{\overset{\oplus\ \ \ominus}{(CH_3)_2NH_2Cl}} \xrightarrow{OH^{\ominus}} CH_3-CO-\overset{\overset{\large CH_3}{|}}{\underset{\underset{\large CH_3}{|}}{C}}-CH_2N(CH_3)_2$$

24 **25**

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[7] M. Brown and W. S. Johnson, J. Org. Chem., **27**, 4702 (1962).

Experimental[8]

Mannich Reaction of 2-Methylcyclopentanone (**1**).--- A mixture of 7.89 g. (0.0805 g. mole) of 2-methylcyclopentanone, 3.22 g. (0.107 mole of formaldehyde) of paraformaldehyde, 10.00 g. (0.0795 mole) of dimethylamine hydrobromide and 5 ml. of ethanol was heated on a steam bath overnight and then cooled. The resulting semisolid mixture was made basic by the addition of cold (0°) aqueous sodium hydroxide and then extracted with ether. After the ethereal solution had been dried and concentrated, 11.12 g. (90%) of the crude Mannich base **15** remained as a yellow liquid. To a solution of 9.72 g. (0.063 mole) of this crude amino ketone in 50 ml. of benzene was added, dropwise and with stirring, 9.50 g. (0.067 mole) of methyl iodide. After the resulting mixture had been allowed to stand in the refrigerator for three days, the crude methiodide **17** was collected and recrystallized from an ethanol-petroleum ether mixture to separate 18.2 g. (89% based on the starting dimethylamine) of the pure methiodide **17** as white

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[8] All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with either a Baird, Model B, or a Perkin Elmer, Model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The n.m.r. spectra were determined at 60 mc. with a Varian, Model A-60, n.m.r. spectrometer. The mass spectra were obtained with a CEC, Model 21-130, mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

needles, m.p. 196-196.5° dec. The product has infrared absorption[9] at 1730 cm.$^{-1}$ (cyclopentanone C=O) and n.m.r.[10] singlets at 3.74 δ (2H, $-\overset{|}{\underset{|}{C}}-CH_2-\overset{|}{\underset{|}{N}}-^{\oplus}$), at 3.36 δ (9 H, $CH_3-\overset{|}{\underset{|}{N}}-^{\oplus}$) and at 1.30 δ (3 H, $CH_3-\overset{|}{\underset{|}{C}}-$) as well as complex absorption attributable to three methylene groups in the region 2.1-3.1 δ.

Anal. Calcd. for $C_{10}H_{20}INO$: C, 40.40; H, 6.79; I, 42.73. Found: C, 40.25; H, 6.72; I, 42.74.

From a comparable reaction employing 3.99 g. (0.041 mole) of 2-methylcyclopentanone, 1.61 g. (0.054 mole of formaldehyde) of paraformaldehyde, 5.00 g. (0.040 mole) of dimethylamine hydrobromide and 5 ml. of ethanol, distillation of the crude basic product separated 4.5 g. (73%) of the Mannich base **15**, b.p. 43-45° (0.3 mm.), n^{23}_{D} 1.4562. The mass spectrum of the product exhibits a molecular ion peak at m/e 155; the sample has infrared absorption[11] at 1730 cm.$^{-1}$ (cyclopentanone C=O). The n.m.r. spectrum[11] of this sample has a singlet at 2.13 δ ($N-CH_3$) superimposed on a complex series of peaks in the region 1.5-2.5 δ and a singlet at 0.83 δ ($CH_3-\overset{|}{\underset{|}{C}}-$). A broadening

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(9) Determined as a suspension in a potassium bromide pellet.

(10) Determined as a solution in deuterium oxide.

(11) Determined as a solution in carbon tetrachloride.

at the base of the last mentioned singlet and several very small peaks in the region of 0.9-1.2 δ suggests that the major product 15 may be contaminated by a small amount (less than 20%) of one or both of the stereoisomeric Mannich bases 3, containing a $CH_3-CH<$ function, whose n.m.r. C-methyl signals could appear as a pair of doublets. A solution of the Mannich base 15 in deuterium oxide containing 20% deuterium chloride exhibited n.m.r. peaks at 3.39 δ (2 H singlet, $-\overset{|}{\underset{|}{C}}-CH_2-\overset{\oplus}{N}D<$) and at 1.22 δ (3 H singlet, $CH_3-\overset{|}{\underset{|}{C}}-$) with complex absorption in the region 1.6-2.8 δ and two peaks at 2.92 and 2.98 δ (6H, $CH_3-\overset{\oplus}{N}D<$). The presence of two peaks for the N-methyl signal in the salt suggests that the dimethylammonium grouping exists in a preferred conformation with respect to the asymmetric C-2 position of the cyclopentanone ring. As was the case for the n.m.r. spectrum of the free base 15, the n.m.r. singlet at 1.22 δ attributable to the C-methyl group has a slight broadening at the base suggesting the presence of a small amount of the salt of one or both of the amino ketones 3.

Mannich Reaction of 2-Methylcyclohexanone (2). A. With Dimethylamine Hydrochloride.-- A mixture of 9.0 g. (0.080 mole) of 2-methylcyclohexanone, 3.42 g. of an aqueous solution containing 37% (0.040 mole) of formaldehyde and 3.26 g. (0.040 mole) of dimethylamine hydrochloride was refluxed for 15 min. and then diluted with water and saturated with sodium chloride. After the resulting mixture had been extracted with ether, it was made basic with potassium hydroxide and extracted with ether. The resulting basic extract was dried, concentrated and distilled to separate 3.95 g. (59%) of the Mannich base (a mixture of 5 and 16), b.p. 48-50° (0.15 min.), n^{23} D 1.4638 [lit. 71° (1.3 mm.),[1a] 62-63° (0.7 mm.),[1b] n^{20} D 1.4650,[1a] n^{25} D 1.4639[1b]]. The mass spectrum of the product exhibits a molecular ion peak at m/e 169; the material has infrared absorption[11] at 1710 cm.$^{-1}$ (C=O). The n.m.r. spectrum of a solution of this Mannich base in deuterium oxide containing 20% deuterium chloride exhibits, apart from complex absorption in the region 1.7-2.7 δ, a singlet at 3.33 δ $(-\overset{|}{\underset{|}{C}}-CH_2-\overset{\oplus}{N}D\langle\ )$, a singlet at 2.98 δ $(CH_3-\overset{\oplus}{N}D\langle)$ and a singlet at 1.39 δ $(CH_3-\overset{|}{\underset{|}{C}}-)$ attributable to the salt of the amino ketone 16. In addition there is a small peak at 2.87 δ $(CH_3-\overset{\oplus}{N}D\langle)$ and two doublets centered at 0.98 δ (J = 6.5 c.p.s.) and 1.22 δ (J = 7 c.p.s.) corresponding to the C-methyl signal from the $CH_3-CH\langle$ grouping in the two stereoisomeric salts derived from the amino ketones 5. From the relative areas under these C-methyl peaks, we estimate the Mannich base to contain approximately 70% of the amino ketone 16 and 30% of the amino ketones 5. The n.m.r. spectrum[11] of the free base has single peaks at 2.36 δ $(-\overset{|}{\underset{|}{C}}-CH_2-N\langle)$, at 2.13 δ $(CH_3-N\langle)$ and at 0.97 δ $(CH_3-\overset{|}{\underset{|}{C}}-)$. In the n.m.r. spectrum of the free base, the singlet C-methyl peak at 0.97 δ partially obscures the small C-methyl doublets in the region 0.85-1.0 δ.

B. *With Dimethylamine*.-- Into a mixture of 6.0 g. (0.053 mole) of 2-methylcyclohexanone and 2.16 g. of an aqueous solution containing 37% (0.027 mole) of formaldehyde was distilled 1.22 g. (0.027 mole) of dimethylamine. An exothermic reaction occurred as the amine was added. The resulting mixture was refluxed for 10 min. and then cooled, poured into dilute aqueous hydrochloric acid and extracted with ether. The aqueous layer was made basic with potassium hydroxide and again extracted with ether. After the basic, ethereal extract had been dried and concentrated, distillation of the residue separated 2.7 g. (59%) of the Mannich base (a mixture of 5 and 16), b.p. 50-52° (0.2 mm.), $\underline{n}^{26}\underline{D}$ 1.4645. This sample, which has infrared absorption practically identical with the infrared absorption of the previous sample, has comparable n.m.r. absorption except that the C-methyl doublets are slightly more intense. From the areas under the C-methyl peaks we estimate that the sample contains about 35% of 5 and 65% of 16.

N.M.R. Spectra of the Quaternary Salts Derived From the Mannich Base of 2-Methylcyclohexanone.-- The previously described[1] methiodide, m.p. 190-192°,[1b] exhibits three n.m.r.[12] singlets at 3.81 δ (2 H, $-\underset{|}{\overset{|}{C}}-CH_2-\underset{|}{\overset{|}{N}}-^{\oplus}$), at 3.22 δ (9 H, $CH_3-\underset{|}{\overset{|}{N}}-^{\oplus}$) and at 1.42 δ (3 H, $CH_3-\underset{|}{\overset{|}{C}}-$) as well as complex absorption in the region 1.7-2.9 δ and should be assigned structure 18 rather than the previously[1] assigned structure 9. The methiodide sample, m.p. 160-163°,[1b] is apparently a mixture of approximately equal amounts of 18 and one of the diastereoisomers of

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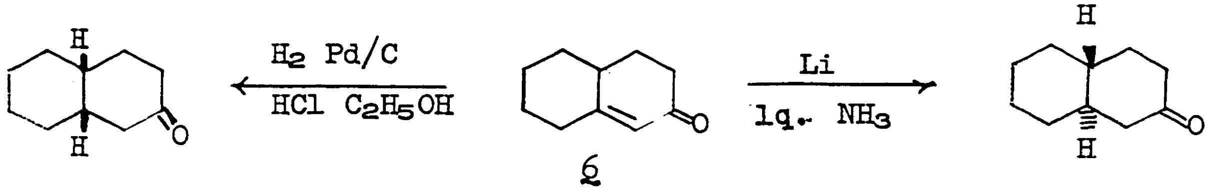
(12) Determined as a solution in deuterium oxide.

structure **9** since the n.m.r.[12] C-methyl absorption consists of a singlet at 1.42 δ and a doublet (J = 6.5 c.p.s.) centered at 0.99 δ. The previously described[1b] crude methotosylate, m.p. 120-145°, has C-methyl peaks in the n.m.r.[12] indicating the presence of **19** (about 65%, singlet at 1.32 δ) and one of the diastereoisomers of **10** (about 35%, doublet, J = 6.5 c.p.s., centered at 0.97 δ). The one pure isomer, m.p. 141-142°,[1b] isolated from the mixture has the structure **19** rather than the previously assigned structure **10**. The n.m.r. spectrum[12] has two doublets (J = 9 c.p.s. for each) centered at 7.37 and 7.74 δ (4 H, aryl C-H) as well as singlets at 3.69 δ (2 H, $-\overset{|}{\underset{|}{C}}-CH_2-\overset{|}{\underset{|}{N}}{}^{\oplus}-$), at 3.12 δ (9H, $CH_3-\overset{|}{\underset{|}{N}}{}^{\oplus}-$), at 2.38 δ (3 H, aryl CH_3) and at 1.32 δ (3H, $CH_3-\overset{|}{\underset{|}{C}}-$) and complex absorption in the region 1.5-2.8 δ.

Part IV

By-products of the Robinson Annelation Reaction

The Robinson annelation reaction[1] may yield, in addition to the expected cyclohexenone derivatives, bridged bicyclic compounds;[2] the presence of or absence of these by-products is often dependent on the reaction conditions. In conjunction with the study of the equilibria of enolates derived from unsymmetrical ketones,[3] samples of *cis*- and *trans*-2-decalones were required. A common intermediate for both of these compounds is $\Delta^{1,9}$-octal-2-one.[4] Many variations of the Robinson



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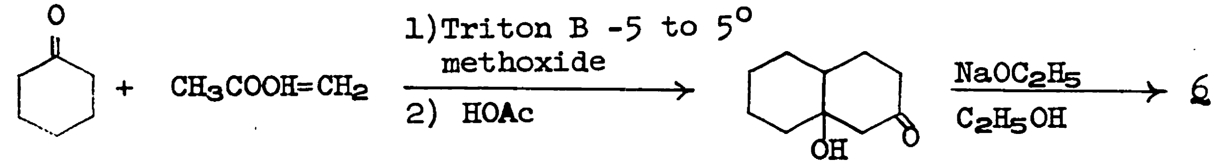
(1) (a) E. C. duFeu, F. J. McQuillin and R. Robinson, *J. Chem. Soc.*, 4060 (1937); (b) J. H. Brewster and E. L. Eliel, *Org. Reactions*, **8**, 99 (1953).

(2) (a) M. S. Julia, *Bull. soc. chim. France*, 780 (1954); (b) W. S. Johnson, J. J. Korst, R. A. Clement and J. Dutta, *J. Am. Chem. Soc.*, **82**, 614 (1960); (c) W. G. Dauben and J. W. McFarland, *Ibid.*, **82**, 4245 (1960); (d) T. A. Spencer, K. K. Schmiegel and R. L. Williamson, *ibid.*, **85**, 3785 (1963); (e) R. D. Sands, *J. Org. Chem.*, **28**, 1710 (1963).

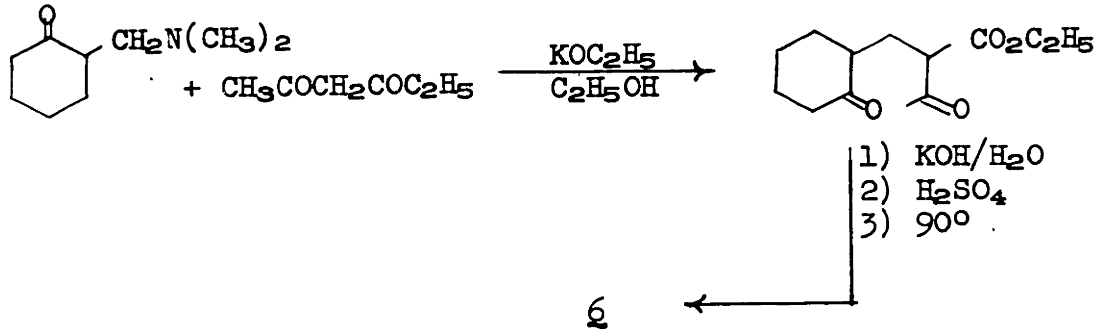
(3) Part I of this thesis.

(4) (a) R. L. Augustine, *J. Org. Chem.*, **23**, 1853 (1958); (b) E. E. van Tamelen and W. C. Proost, Jr., *J. Am. Chem. Soc.*, **76**, 3632 (1954).

procedure have been employed for the synthesis of this octalone (6) some of which are listed below.



Ref. 2b



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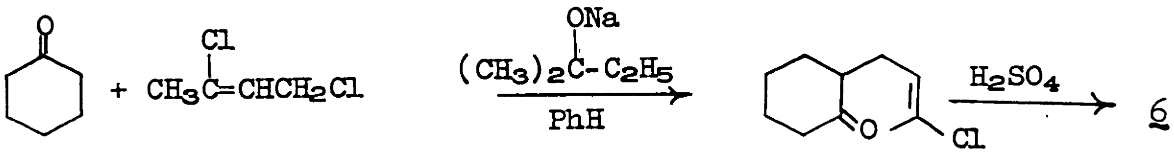

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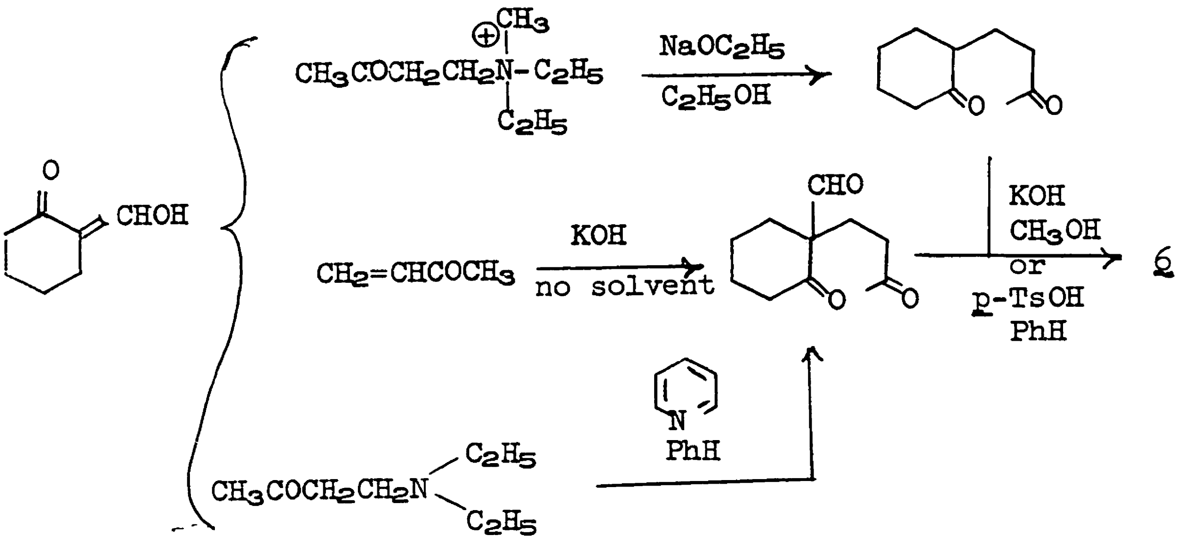

Ref. 6

From a modification of this annelation reaction in which an enamine[7] serves as the active methylene component, the product mixture from the enamine 1 and methyl vinyl ketone was found[8] to contain both the expected octalones 6 and 7 and other products including a ketol and both stereoisomeric 2-decalones. The latter saturated ketones were believed[8] to arise from disproportionation of the intermediate enamine which has been suggested[7a] to have structure 3.[9]

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(5) C. Mannich, W. Kochand, and F. Barkowsky, Chem. Ber., 70, 355 (1937).

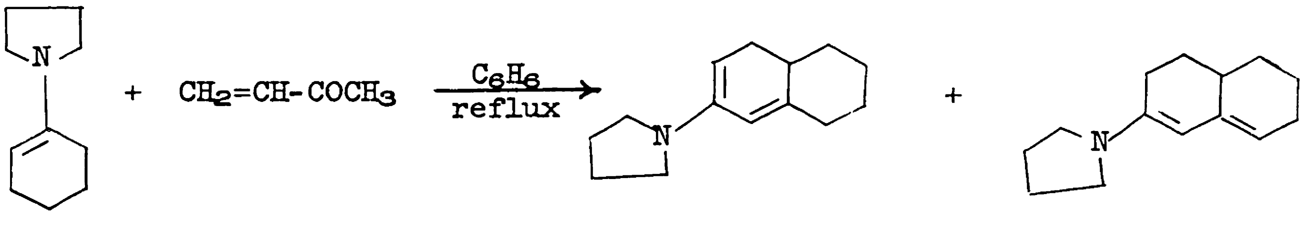
(6) D. J. Baisted and J. S. Whitehurst, J. Chem. Soc., 4089 (1961). See also D. K. Banerjee, S. Chatterjee, and S. P. Bhattacharya, J. Am. Chem. Soc., 77, 408 (1955).

(7) (a) G. Stork, A. Brizzolara, H. Landeman, J. Szmuszkovicz and R. Terrell, J. Am. Chem. Soc., 85, 207 (1963); (b) J. Szmuszkovicz in R. A. Raphael, E. C. Taylor and H. Wynberg, Ed., "Advances in Organic Chemistry, Methods and Results," Vol. 4, Interscience Publishers, Inc., New York, N.Y., 1964, p. 1.

(8) R. L. Augustine and H. V. Cortez, Chemistry and Industry, 490 (1963); also see T. A. Spencer and K. K. Schmiegel, ibid., 1765 (1963).

(9) G. A. Berchtold and J. Ciabattoni have observed the formation of 2,3,4,5-tetraphenylcyclopent-2-en-3-one in the reaction of 1 with 2,3,4,5-tetraphenylcyclopentadienone which must arise from a reduction of the dienone by the enamine.

From the previously described[7a,8] reactions of 1-(1-pyrrolidino)-cyclohexene (1) with methyl vinyl ketone, the enamine product separated by distillation had n.m.r. absorption (see *Experimental*) indicative of at least three types of vinyl protons. Hence, it is clear that this product is a mixture of isomeric enamines rather than the single isomer 3 previously suggested.[7a] The positions and areas of the n.m.r. peaks



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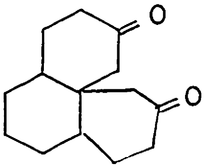

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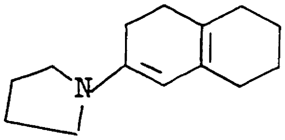

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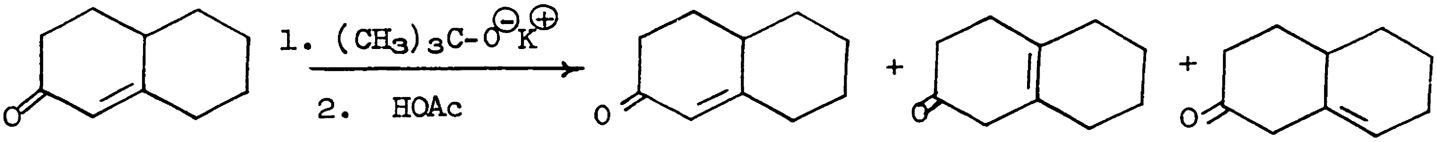
suggest that the mixture contains about 30% of enamine 2 and 65-70% of the isomer 3; it is possible that 5-10% of the isomer 4 may also be present. When this crude reaction mixture was hydrolyzed prior to isolation, the previously reported mixture[6,7a,8] of the $\Delta^{1,9}$-octalone 6 (ca. 90%) and the $\Delta^{9,10}$-isomer 7 (ca. 10%) was obtained. Treatment of this octalone mixture with acid resulted in partial isomerization of the $\Delta^{9,10}$-isomer 7 to the conjugated ketone 6 (97% of the mixture after isomerization). The $\Delta^{8,9}$-octalone 8 was not detected by n.m.r. measurements on any of these unsaturated ketone mixtures.



6 **6** **7** **8**

In an ancillary experiment, the octalone **6** was converted to its enolate anion and then quenched in acetic acid[10] to yield a mixture of octalones **6** - **8**. From the n.m.r. absorption (see Experimental) of the mixture, we estimate its approximate composition to be: **6** (15%); **7** (30%); **8** (55%). Thus, in agreement with other product studies,[11] it would appear that the hexahydronaphthalene system of either an enolate anion or an enamine derived from a 2-ketone (i.e. **6**) is most stable with the double bonds in the 1,2 and 8,9 positions (as in **3**) but other structural isomers are also present. The octalone mixture **6** - **8** was observed to

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(10) The procedure of H. J. Ringold and S. K. Malhotra, J. Am. Chem. Soc., **85**, 1538 (1963); H. J. Ringold and S. K. Malhotra, Tetrahedron Letters, **No. 15**, 669 (1962).

(11) (a) R. Bucourt, J. Tessier and G. No Nomine, Bull. soc. chim. France, 1923 (1963); (b) G. Just and F. E. Shortland, Can. J. Chem., **42**, 470 (1964); (c) B. E. Edwards and P. N. Rao, Angew. Chem., **76**, 795 (1964); (d) R. E. Ireland and L. N. Mander, Tetrahedron Letters, **No. 46**, 3453 (1964); (e) R. Sciaky and F. Mancini, Tetrahedron Letters, **No. 2**, 137 (1965).

isomerize on standing to a mixture in which only isomer 6 and 7 were detected suggesting that unconjugated ketone 8 is less stable than its $\Delta^{9,10}$-isomer 7.

In no case did we isolate from the reaction of the enamine 1 with methyl vinyl ketone either the previously reported[8a] disproportionation product, 2-decalone, or the other expected disproportionation product, 6-(1-pyrrolidino)-1,2,3,4-tetrahydronaphthalene. The reason for these differing results is not apparent to us. In seeking possible by-products formed during the preparation of enamines 2 - 4, we isolated from the distillation residue, after hydrolysis, a crystalline compound, m.p. 161-162°, which was subsequently shown to have structure 5. The yield of this diketone 5 could be increased to above 50% if the reaction of the enamine 1 with methyl vinyl ketone was effected either in ethanol solution or in the absence of a solvent.

The spectral properties of the product 5 established the presence of one or more saturated carbonyl functions and the absence of carbon-carbon double bonds and methyl groups. A negative tetranitromethane test and failure to absorb hydrogen over a platinum catalyst also attest to the absence of carbon-carbon double bonds. Treatment of either the enamine mixture 2 - 4 or the unsaturated ketone 6 with methyl vinyl ketone under a variety of conditions failed to yield the diketone 5 indicating that compounds 2 - 4 and 6 were not precursors of the by-product. Consideration of probable reaction paths for the reactants suggested the likelihood of the diketone structure 5 for this by-product as illustrated in Chart I.[12] The enhanced yield in ethanol is in agreement with such a pathway since use of this solvent is known to promote the formation of 2,6- and 2,5-disubstituted Michael products from cyclohexanone and cyclopentanone enamines.[8a,13]

To establish the correctness of this carbon skeleton, we elected to synthesize the diketone 5 from the triketone 13 whose preparation is illustrated in Chart II. The same synthetic procedure was also used for the cyclopentanone derivative 18. Although the usual ketalization conditions (ethylene glycol and p-toluenesulfonic acid in refluxing benzene) failed to form ketals 12 and 17 from the hindered ketones 10 and 15, the alternative procedure[14] employing boron trifluoride etherate in excess ethylene glycol was very effective. Reaction of the nitriles 12 and 17 with methylmagnesium bromide led to rather complex mixtures, possibly

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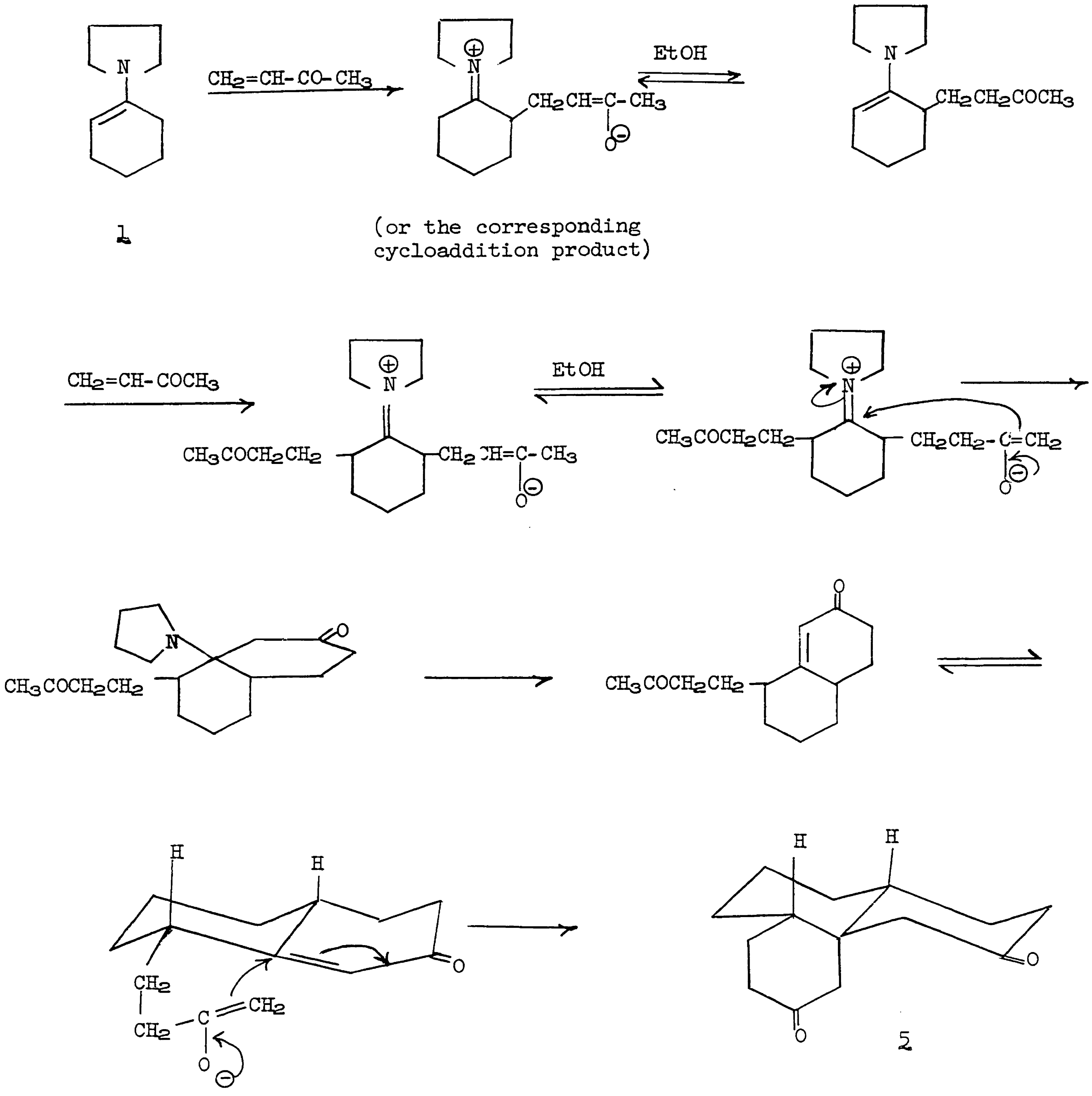
(12) Similar ring systems have been formed in heterocyclic series: (a) H. J. Backer and G. L. Wiggerink, Rec. trav. chim., 60, 453 (1941); (b) I. N. Nazarov, G. A. Shvekhgeimer and V. A. Rudenko, Zhur. Obshchei. Khim., 24, 319 (1954); Chem. Abstr., 49, 4652 (1955).

(13) (a) T. L. Westman, R. Paredes and W. S. Berg., J. Org. Chem., 28, 3512 (1963); (b) T. L. Westman and A. E. Kober, ibid., 29, 2448 (1964); (c) L. Mandell, B. A. Hall and K. P. Singh, ibid., 29, 3067 (1964).

(14) (a) W. J. Adams, D. N. Kirk, D. K. Patel, V. Petrow, and J. A. Stewart-Webb, J. Chem. Soc., 2298 (1954); (b) D. N. Kirk, D. K. Patel and V. Petrow, ibid., 1046 (1957).

Chart I

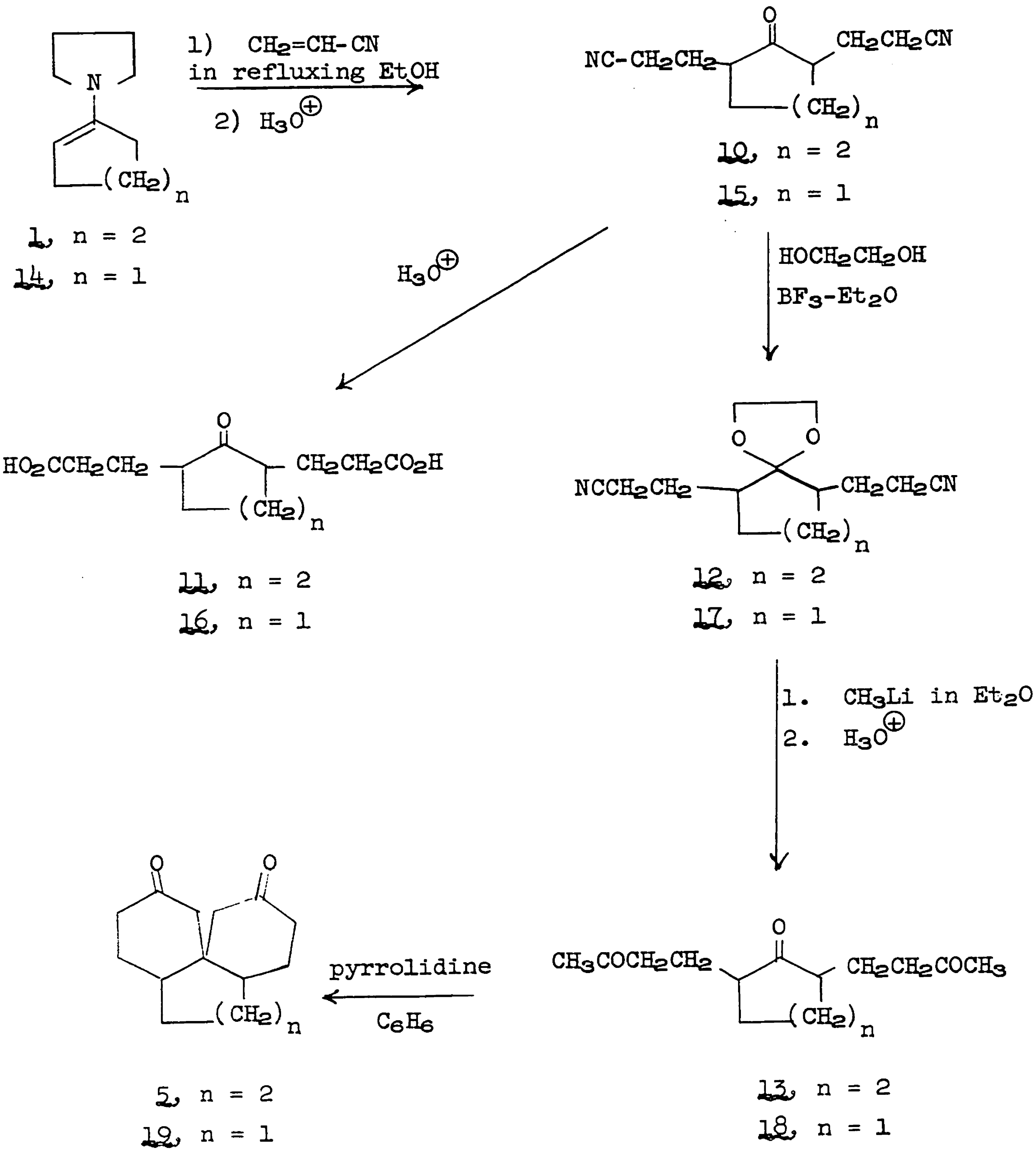


1

(or the corresponding cycloaddition product)

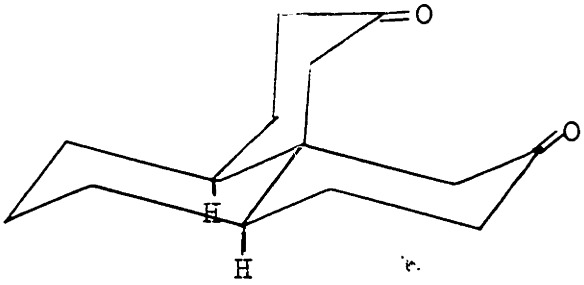
5

Chart II

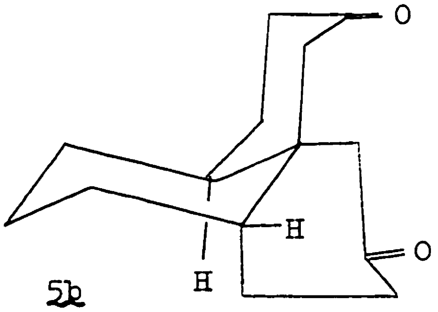

1) CH2=CH-CN in refluxing EtOH
2) H3O⊕
1, n = 2
14, n = 1
NC-CH2CH2
CH2CH2CN
(CH2)n
10, n = 2
15, n = 1
H3O⊕
HOCH2CH2OH
BF3-Et2O
HO2CCH2CH2
CH2CH2CO2H
11, n = 2
16, n = 1
NCCH2CH2
CH2CH2CN
12, n = 2
17, n = 1
1. CH3Li in Et2O
2. H3O⊕
pyrrolidine
C6H6
CH3COCH2CH2
CH2CH2COCH3
5, n = 2
19, n = 1
13, n = 2
18, n = 1

because precipitation of insoluble intermediates prevented complete reaction. However, reaction with methyllithium followed by acid hydrolysis of the intermediate ketal diimines produced the triketones 13 and 18 in good yield. Reaction of the triketone 13 with pyrrolidine in refluxing benzene produced the diketone 5 in 97% yield.

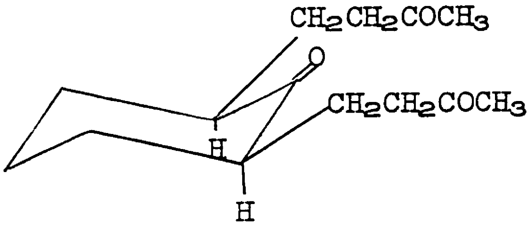
Three stereochemical arrangements are possible for the diketone 5, namely, the isomer 5a with one *cis* and one *trans* ring fusion, the isomer 5b with two *cis* ring fusions, and the isomer 5c with two *trans* ring fusions. Although isomers 5a and 5b can both adopt the relatively stable all-chair conformations indicated, the *trans,trans* isomer 5c can only be



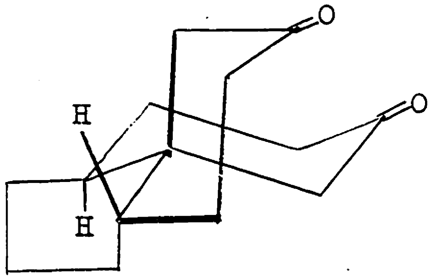
5a



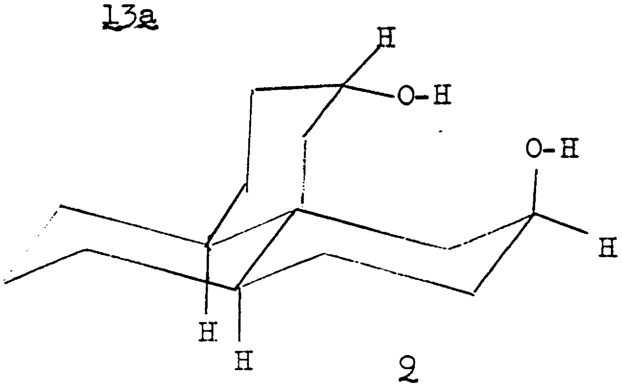
5b



13a



5c



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formed with the introduction of substantial strain. The ease with which diketone **5** is formed *via* presumably reversible reactions therefore argues against stereoisomer **5c**. Furthermore, it would seem reasonable to suppose that the more stable diequatorial epimer **13a** of the triketone **13** serves as the precursor of **5** and, hence, should lead to isomer **5a** rather than **5b** or **5c**. Finally, the last step in the formation of **5** is believed to be the intramolecular Michael reaction indicated in Chart I in which the enolate anion would be expected[15] to add to the conjugated system from an axial direction to form isomer **5a**. Further evidence indicating the correctness of the stereochemistry **5a** was obtained by reduction of the diketone with sodium borohydride. The resulting diol, believed to be **9** resulting from the reduction of each of the carbonyl groups in **5a** from the less hindered side, has infrared absorption (see **Experimental**) establishing the presence of an *intramolecular* hydrogen bond. This observation clearly excludes isomer **5b** since the oxygen functions of the corresponding diol are too far apart to permit intramolecular hydrogen bonding. Although we are unable to exclude rigorously the stereochemistry **5c** for the diketone, we believe the foregoing arguments make the stereochemistry **5a** for the diketone very probable.

In exploring preparative routes for the tetrahydroindanone **21**,[16]

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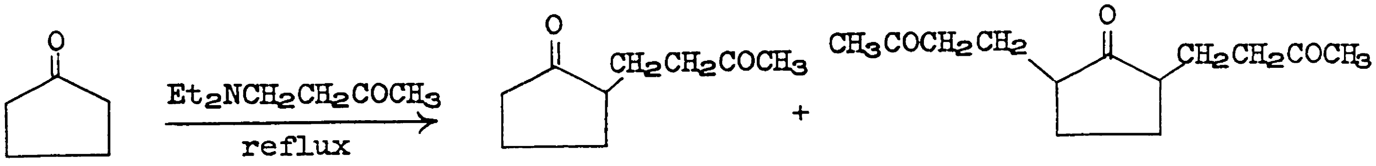
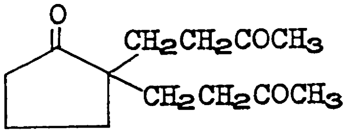
(15) (a) D. H. R. Barton, A. D. S. Campos-Neves and A. I. Scott, *J. Chem. Soc.*, 2698 (1957); (b) W. S. Johnson, S. Shulman, K. L. Williamson and R. Pappo, *J. Org. Chem.*, **27**, 2015 (1962).

it was found[17] that refluxing a mixture of cyclopentanone and 1-diethylamino-3-butanone yielded a mixture of the diketone **20**[18] and a triketone. The structure of this triketone was established as **18** and not the alternative **21** by the synthesis outlined in Chart II, n = 1. This



20 **18**



21

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(16) For previous preparations of this ketone, see (a) Ref. 7a; (b) V. Prelog and M. Zimmerman, *Helv. Chim. Acta*, **32**, 2360 (1949); (c) E. D. Bergmann and R. Corett, *J. Org. Chem.*, **23**, 1507 (1958).

(17) R. G. Carlson, Ph. D. Thesis, M.I.T. (1963).

(18) For previous preparations of this diketone see (a) N. S. Gill, K. B. James, F. Lions and K. T. Patts, *J. Am. Chem. Soc.*, **74**, 4923 (1952); (b) N. C. Ross and R. Levine, *J. Org. Chem.*, **29**, 2341 (1964).

material arises presumably from formation and reaction of the diethylamino enamine of cyclopentanone with methyl vinyl ketone in the reaction vessel. If it simply involved a base catalyzed Michael condensation of the diketone **20** with methyl vinyl ketone, the expected product would be **21**, since it is known[19] that Michael condensation of an unsymmetrical ketone normally occurs at the more highly substituted position. Reaction of the diketone **20** with pyrrolidine in refluxing benzene yielded a mixture of the unsaturated ketones containing **21** (_ca_. 95%) and **22** (_ca_. 5%). Reaction of the triketone **18** with pyrrolidine in refluxing benzene afforded an unstable liquid product believed to be one or more of the stereoisomers of diketone **19**; however, we were unable to isolate a pure product.

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(19) (a) The appendix of this thesis; (b) E. D. Bergman, D. Ginsberg, and R. Pappo, _Org. Reactions_, **10**, 183 (1959).

EXPERIMENTAL[20]

Reaction of 1-(1-Pyrrolidino)-cyclohexene (1) with Methyl Vinyl Ketone.-- Methyl vinyl ketone (21 g. or 0.30 mole) was added, with stirring under a nitrogen atmosphere, to a solution of 48 g. (0.32 mole) of the pyrrolidine enamine 1[7a] in 200 ml. of benzene. After the initial, vigorous reaction had subsided, the solution was refluxed overnight and then concentrated under reduced pressure. Distillation of the residual yellow-brown liquid afforded 47.58 g. (78.2%) of fractions containing mixtures of enamines 2 - 4; (1) 3.63 g., b.p. 120-130° (3 mm.); (2) 3.85 g. b.p. 130-138° (3 mm.); (3) 40.10 g., b.p. 138-140° (3 mm.) [lit.[7a] b.p. 146-150° (0.3 mm.) is reported for a comparable product assigned structure 3]. Redistillation of the latter fraction afforded a pale yellow liquid, n^{22}_{D} 1.5808, which solidified when cooled below room temperature. This product has infrared absorption[21] at 1710 (weak, C=C or C=O impurity) and at

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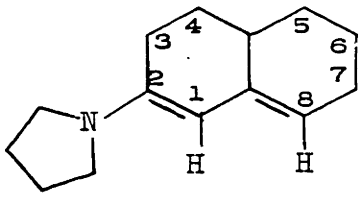
(20) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin Elmer, Model 237, infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The n.m.r. spectra were determined at 60 mc. with a Varian, Model A-60, n.m.r. spectrometer. The mass spectra were obtained with a CEC, Model 21-130, mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

(21) Determined as a solution in chloroform.

1655 (weak), 1630 and 1595 cm.$^{-1}$ (C=C, lit.[7a] 1630 and 1600 cm.$^{-1}$). The mass spectrum of the material has weak peaks at m/e 205, 204, 203 and 202 (the molecular ion from enamines 2 - 4 should be at m/e 203) with abundant peaks at m/3 201, 200, 173, 145, 91, 79, 51, 43, 41 and 39 suggesting that the sample has undergone substantial disproportionation and/or dehydrogenation in the heated inlet system. In agreement with this idea, the spectrum was found to change with time. The n.m.r. spectrum[22] has a broad peak (half-band width, 8.5 c.p.s.) at 5.07 δ, a peak (half-band with 2.5 c.p.s.) at 4.83 δ and a peak (half-band width 3 c.p.s.) at 4.29 δ as well as complex multiplets in the regions 2.9-3.3 δ and 1.1-2.5 δ. The area of peaks at 5.07, 4.83 and 4.29 δ are in the ratio 0.67:1.0:0.30 (average values from two runs). The relatively sharp peak at 4.83 δ is believed attributable to the proton



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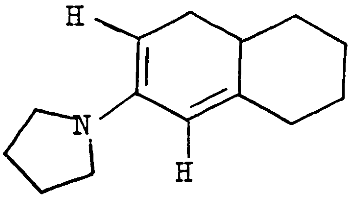

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at C-1 in any of the enamine isomers 2 - 4. The higher field peak at 4.29 δ is tentatively assigned to the proton at C-3[23] in isomer 2

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[22] Determined as a solution in deuteriochloroform.

and the peak at 5.07 δ is tentatively assigned to the proton at C-8 in isomer **3**.[24] Thus, the product is clearly a mixture of isomeric enamines and would appear to contain 65-70% of the isomer **3**, *ca*. 30% of the isomer **2** and possibly a small amount of the isomer **4**.

From a comparable preparation where the crude product was hydrolyzed with an acetate buffer[25] prior to isolation, a mixture of octalones **6** and **7** (74% yield) was obtained as a colorless liquid, b.p. 85-86° (1 mm.), $n_{D}^{24.5}$ 1.5232 [lit.[7a] b.p. 135-138° (15 mm.)]. This mixture contained[26] the conjugated octalone **6** (*ca*. 90%, second eluted) and the unconjugated isomer **7** (*ca*. 10%, first eluted). The n.m.r.

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(23) The C-2 proton in 6-methyl-1-(1-pyrrolidino)-cyclohexene is found at 4.21 δ; H. O. House and M. Schellenbaum, *J. Org. Chem*., **28**, 34 (1963).

(24) The n.m.r. signals for the C-2 and C-4 vinyl protons of 1-diethylamino-1,3-butadiene are found in the region 4.2-5.2 δ whereas the vinyl protons at C-1 and C-3 give rise to n.m.r. peaks in the region 5.8-6.2 δ. G. A. Berchtold and J. Ciabattoni, Unpublished work.

(25) The proportions used in this solution were 25 ml. of water, 25 ml. of acetic acid and 12.5 g. of sodium acetate.

(26) A gas chromatography column packed with Ucon Polar suspended on Chromosorb P was employed.

spectrum[27] of this mixture has a peak (half-band width 4 c.p.s.) at 5.60 δ (*ca.* 90% of 1 H, vinyl C-H of octalone 6) with complex absorption in the region 1.0-3.0 δ (aliphatic C-H) but lacks absorption at 5.36 δ attributable to the vinyl proton of the subsequently discussed octalone 8. When a solution of this octalone mixture (6 and 7) in ethanol containing 5% aqueous hydrochloric acid was stirred at room temperature, it was rapidly isomerized to a mixture containing[26] 97% of the conjugated ketone 6 and 3% of the unconjugated isomer 7.

The residue remaining after the initial distillation of the above enamines was dissolved in a mixture[25] of water, acetic acid and sodium acetate and the resulting mixture was refluxed for 4 hr. After the reaction mixture had been cooled, acidified with hydrochloric acid and extracted with ether, the ethereal extract was dried and concentrated. An ethanol solution of the residue deposited 1.5 g. of the diketone 5 as white needles, m.p. 161-162°. An additional 1.1 g. of the same diketone 5, m.p. 156-159°, was recovered from the mother liquors. No other pure substances were isolated from the various neutral and basic fractions of the hydrolyzed residue.

The diketone 5 has infrared absorption[21] at 1712 cm.$^{-1}$ (C=O) with no absorption in the 3μ region attributable to a hydroxyl function; the material has ultraviolet maxima[28] at 243 mμ (ε 32) and

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(27) Determined as a solution in carbon tetrachloride.

287 mμ (ϵ 45) with ϵ 122 at 210 mμ. The n.m.r. spectrum[27] of the material consists of a complex multiplet in the region 1.1-2.7 δ with no evidence for either a C-methyl group or a vinyl C-H. An ethanol solution of the diketone 5 over the catalyst from platinum oxide absorbed no hydrogen.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15; mol. wt., 220. Found: C, 76.08; H, 9.07; mol. wt., 212 (vapor pressure in benzene), 220 (mass spectrum).

No evidence for the formation of the diketone 5 was found from reaction of the enamines 2 - 4 with methyl vinyl ketone in refluxing benzene, from the reaction of cyclohexanone with methyl vinyl ketone and potassium t-butoxide in 1,2-dimethoxyethane, or from the reaction of $\Delta^{1,9}$-octal-2-one (6) with methyl vinyl ketone and pyrrolidine in refluxing benzene. However, the yield of the diketone 5 could be increased substantially by use of one of the following procedures. The enamine 1 (3.0 g. or 2.0 mmoles) was added, dropwise and with stirring under a nitrogen atmosphere, to 2.8 g. (4.0 mmoles) of pure methyl vinyl ketone. After the initial vigorous reaction subsided, the mixture was heated to 90° for 1 hr. and then diluted with 6 ml. of benzene and refluxed overnight. After 5 ml. of aqueous acetate buffer[25] had been added, the resulting mixture was refluxed for 4 hr. The organic layer was separated, dried and concentrated. Recrystalliza-

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(28) Determined as a solution in 95% ethanol.

tion of the residue from isopropyl alcohol afforded 2.2 g. (51%) of the diketone 5, m.p. 160-162°, identified with the previous sample by comparison of infrared spectra.

A solution of 15.1 g. (0.10 mole) of the enamine 1 and 18.0 g. (0.30 mole) of methyl vinyl ketone in 35 ml. of absolute ethanol was refluxed for 4 hr., mixed with 15 ml. of acetate buffer[25] and refluxed for an additional 2 hr. The resulting mixture was concentrated under reduced pressure, diluted with water and extracted with ether. After this ethereal solution had been dried and concentrated, recrystallization of the residue from isopropyl alcohol afforded 11.5 g. (52%) of the diketone 5, m.p. 159-162°.

Deconjugation of $\Delta^{1,9}$-Octal-2-one.-- To a solution of potassium *t*-butoxide, prepared from 8.27 g. (0.221 g.-atom) of potassium and 170 ml. of *t*-butyl alcohol, was added 3.00 g. (0.020 mole) of the octalone 6 (containing *ca*. 10% of the isomer 7). The mixture was stirred for 1.5 hr. and then poured into 750 ml. of cold (0°) 10% aqueous acetic acid.[10] The resulting mixture was partially neutralized with sodium bicarbonate and then extracted with ether. The ethereal extract was concentrated, neutralized with excess aqueous sodium bicarbonate, taken up in ether, dried and concentrated. Distillation of the residue afforded 1.901 g. (63.3% recovery) of fractions, b.p. 55-60° (0.3 mm.). The distillate has infrared absorption[27] at 1720 (unconj. C=O), 1675 (conj. C=O) and 1615 cm.$^{-1}$ (conj. C=C) with n.m.r. peaks[27] at 5.60 δ (half-band width 4 c.p.s.) and at 5.36 δ (half-band width 9 c.p.s.) as well as a multiplet in the region 2.7-3.0 δ and a complex multiplet in the region 1.0-2.7 δ. The following assignments appear to be appropriate: C-1 vinyl proton of **6**, 5.60 δ; C-8 vinyl proton of **8**, 5.36 δ; C-1 methylene group of **7** and **8**, 2.7-3.0 multiplet. If these assignments are correct, the composition of the mixture can be estimated to be 15% of **6**, 30% of **7**, and 55% of **8** from the areas under the various peaks.

Preparation of the Diol 9.-- A solution of 1.00 g. (4.55 mmoles) of the diketone **5** and 555 mg. (14.5 mmoles) of sodium borohydride in 2.5 ml. of 1,2-dimethoxyethane was refluxed for 20 hr.[29] and then cooled and mixed with dilute aqueous hydrochloric acid. The precipitated solid (950 mg. or 95%) melted at 162-163° with softening at 158° after recrystallization from benzene. A 100-mg. portion of the product was chromatographed on 5.0 g. of Alcoa alumina (mesh 20-200). The product, 89 mg. eluted with 10% ethyl acetate in benzene, was recrystallized from benzene to separate the pure **diol 9** as colorless needles, m.p. 170.5-171°. The product has infrared bands[21] at 3595 and 3450 (broad) cm.$^{-1}$ (unassoc. and assoc. O-H) with no absorption in the 6μ region attributable to a carbonyl

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(29) When a reaction time of only 2 hr. was employed, the reaction was incomplete as judged by the presence of infrared absorption attributable to a carbonyl function in the spectrum of the crude product.

function. The infrared absorption in the 3μ region was examined[30] in the concentration range 0.0016 *M* to 0.0129 *M*; as the solution was diluted, the intensity of the band at 3620 cm.$^{-1}$ (unassociated O-H) decreased more rapidly than the intensity of the band at 3527 cm.$^{-1}$ (intramolecularly assoc. O-H) and a broad band at 3375 cm.$^{-1}$ (intermolecularly assoc. O-H) disappeared in the most dilute solution. The n.m.r. spectrum[22] of the diol has broad peaks at 4.17 δ (2H, $\rangle$CH-O) and at 3.29 δ (2H, shifted by the addition of pyridine, O-H) with a complex multiplet in the region 0.9-3.2 δ (20 H, aliphatic C-H).

Anal. Calcd. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.79; H, 10.63.

Preparation of the Ethylene Ketal 12.-- Reaction of 10.0 g. (66.3 mmoles) of the enamine **1** with 20.0 g. (377 mmoles) of acrylonitrile in 50 ml. of ethanol as previously described[7a] afforded 12.3 g. (91%) of the **keto dinitrile 10** as a pale yellow oil, b.p. 165-167° (0.05 mm.) [lit.[7a] 178-180° (0.4 mm.)], $\bar{\nu}_{max}^{21}$ 2250 (C≡N) and 1710 cm.$^{-1}$ (C=O). This product has complex n.m.r. multiplets[22] in the regions 2.2-2.9 δ (6H) and 1.1-2.2 δ (10 H). Hydrolysis of a 1.00-g. (4.95-mmole) sample of the dinitrile **10** with refluxing aqueous hydrochloric acid for 3 hr. yielded 444 mg. (32%) of the **keto diacid 11** as white needles from an ethyl acetate-pentane mixture, m.p. 142-143°

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[30] A solution in carbon disulfide was employed.

[lit.[7a] m.p. 142-143°]. To a solution of 2.04 g. (10.0 mmoles) of the keto dinitrile 10 in 33 g. (30 ml., 0.53 mole) of ethylene glycol was added, dropwise and with stirring, 6.0 ml. of boron trifluoride etherate. After the mixture had been stirred at 25° for 96 hr., it was poured into dilute, aqueous potassium hydroxide and extracted with ether. The ether extract was dried and concentrated; recrystallization of the residual solid from ethyl acetate separated 1.89 g. (77%) of the ketal 12 as white needles, m.p. 95-96°. An additional recrystallization raised the melting point to 97-98°. This product has infrared absorption[21] at 2250 cm.$^{-1}$ (C≡N) with an n.m.r. peak[22] at 4.05 δ (4H, CH_2-O) as well as a complex multiplet in the region 1.0-2.6 δ (16 H).

Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12. Found: C, 67.49; H, 8.11.

Preparation of the Ethylene Ketal 17.-- Reaction of 55 g. (0.40 mole) of 1-(1-pyrrolidino)-cyclopentene [b.p. 88-90° (15 mm.), lit.[7a] b.p. 88-92° (15 mm.)] with 100 g. (1.89 moles) of acrylonitrile in 250 ml. of absolute ethanol as previously described[13b] yielded 35.6 g. (47%) of the crude dinitrile 15 as colorless plates from aqueous ethanol, m.p. 55-60°. An additional recrystallization separated the pure keto dinitrile 15, m.p. 64-65° (lit.[13b] m.p. 63-65°), with $\bar{\nu}_{max}$[21] 2250 (C≡N) and 1740 cm.$^{-1}$ (cyclopentanone C=O), a molecular ion peak at m/e 190 and a complex n.m.r. multiplet[21] in the region 1.1-2.8 δ with no absorption at lower field. The viscous liquid remaining after concentration of the mother liquors of the above crystallization was distilled to separate a fraction, b.p. 40-43° (0.4 mm.), whose spectra identify it as 3-ethoxypropionitrile.[31] This material has infrared absorption[27] at 2255 cm.$^{-1}$ ($C\equiv N$)with n.m.r. triplets[27] at 2.56 δ (2 H, J = 6.5 c.p.s., $-CH_2-C\equiv N$) and at 1.20 δ (3H, J = 7 c.p.s., CH_3-) as well as an overlapping triplet (J = 6.5 c.p.s.) at 3.64 δ and a quadruplet (J = 7 c.p.s.) at 3.58 δ attributable to the $-CH_2-O-CH_2-$ grouping. A 1.00-g. (5.31-mmole) sample of the keto dinitrile **15** was hydrolyzed with refluxing aqueous hydrochloric acid to give 462 mg. (40%) of the **keto diacid 16** as colorless needles, m.p. 120-122° (lit.[13b] m.p. 121.5-122°) from an ethyl acetate-pentane mixture.

A solution of 3.80 g. (20 mmoles) of the keto dinitrile **15** and 13 ml. of boron trifluoride etherate in 66 g. (60 ml. or 1.06 moles) of ethylene glycol was stirred at 25° for 72 hr. and then poured into cold, dilute aqueous potassium hydroxide and extracted with ethyl acetate. After the organic extract had been dried and concentrated, the residue, a yellow oil which solidified on standing in the refrigerator, was recrystallized from an ethyl acetate-pentane mixture to separate 2.50 g. (60%) of the **ketal 17** as colorless needles, m.p. 95-96°. The product has infrared absorption[21] at 2250 cm.$^{-1}$ ($C\equiv N$)

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(31) G. C. Harrison and H. Diehl [Org. Syntheses, **Coll. Vol. 3**, 372 (1955)] report b.p. 169-174° (760 mm.); H. R. Henze and T. R. Thompson [*J. Am. Chem. Soc.*, **65**, 1422 (1943)] report b.p. 78° (25 mm.), n^{20}_{D} 1.4061.

with n.m.r. peaks[22] at 4.03 and 3.96 δ (4H, CH_2-O) as well as a multiplet in the region 1.2-2.5 δ (14 H).

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.29; H, 7.73; N, 11.82.

Preparation of the Triketone 13.-- To a solution of 2.44 g. (9.92 mmoles) of the ketal 12 in 150 ml. of ether was added, dropwise and with stirring under a nitrogen atmosphere, 53.5 ml. of an ethereal solution containing 58.9 mmoles of methyllithium. The reaction mixture, in which a white precipitate formed almost immediately, was stirred for 6 hr. and then 100 ml. of 10% aqueous hydrochloric acid was added, dropwise and with stirring, to the reaction mixture. After the resulting mixture had been stirred for 1 hr., the ether layer was separated, combined with an ethereal extract of the aqueous layer, dried and concentrated. Recrystallization of the residual white solid from an ethyl acetate-pentane mixture afforded 1.91 g. (81%) of the crude triketone as colorless needles, m.p. 65-68°. Further recrystallization gave the pure triketone 13, m.p. 69-70°, with infrared absorption[21] at 1710 cm.$^{-1}$ (C=O) and an n.m.r. singlet[22] at 2.14 δ (CH_3-CO) superimposed on a complex multiplet in the region 1.1-2.7 δ.

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.38; H, 9.37.

A solution of 0.50 g. (2.1 mmoles) of the triketone 13 and 0.35 g. (4.9 mmoles) of pyrrolidine in 15 ml. of benzene was refluxed for 18 hr. with continuous separation of water. The solution was cooled, mixed with 10 ml. of acetate buffer solution[25] and the resulting mixture was refluxed for 3 hr. The organic layer was separated, combined with the benzene extract of the aqueous phase, dried and concentrated. Recrystallization of the residue from an ethyl acetate-pentane mixture separated 0.45 g. (97%) of the diketone **5**, m.p. 160-162°, which was identified with the previously described sample by a mixed melting point determination and comparison of infrared spectra.

*Preparation of the Triketone **18***.-- A mixture prepared from 712.6 mg. (3.05 mmoles) of the ketal **17** and 18.0 mmoles of methyllithium in 45 ml. of ether was stirred for 15 hr. at 25° and then treated with 25 ml. of 10% aqueous hydrochloric acid and stirred for an additional 1 hr. After the ethereal solution of the crude organic product had been separated, dried and concentrated, the residual white solid was recrystallized from an ethyl acetate-pentane mixture to separate 520 mg. (76%) of the **triketone 18** as colorless needles, m.p. 82-83°. This product was identified with the subsequently described sample of the triketone by a mixed melting point determination and by comparison of the infrared and n.m.r. spectra of the two samples.

A solution of 1.0 g. (4.5 mmoles) of the triketone **18** and 0.35 g. (4.9 mmoles) of pyrrolidine in 10 ml. of benzene was refluxed overnight with continuous separation of water. Then 5 ml. of an acetate buffer solution[25] was added and refluxing was continued for

4 hr. A benzene solution of the crude organic product was washed successively with dilute, aqueous hydrochloric acid and aqueous sodium chloride and then dried and concentrated. The residual oil was distilled under reduced pressure in a short-path still to give 520 mg. of product as a colorless liquid which exhibited a single peak on gas chromatography[32] and rapidly turned yellow on exposure to air. Redistillation (139° at 0.08 mm.) afforded a sample of colorless liquid, believed to be the diketone 19 with infrared absorption[27] at 1720 cm. (C=O) but no absorption in the 3 or 6µ region attributable to a hydroxyl group or a carbon-carbon double bond. The material has a complex n.m.r. multiplet[27] in the region 1.2-2.8 δ with no lower field absorption; the highest peak in the mass spectrum of the material is at m/e 206 (corresponding to $C_{13}H_{18}O_2^+$) with abundant fragment peaks at m/e 149, 148, 79, 77, 55, 41 and 39. We were unsuccessful in efforts either to crystallize this product or to obtain the liquid in analytically pure form.

4-(2-Ketocyclopentyl)-2-butanone (20).--A mixture of 29.70 g. (0.353 mole) of cyclopentanone and 32.45 g. (0.227 mole) of 1-diethylamino-3-butanone[33] was refluxed under a nitrogen atmosphere for 16

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(32) A column packed with silicone gum suspended on diatomaceous earth was employed.

(33) A. L. Wilds, R. M. Novaks and K. E. McCaleb, Org. Syntheses, 37, 18 (1957).

hr. and then cooled and poured onto a mixture of ice and hydrochloric acid. After the resulting mixture had been saturated with ammonium sulfate and extracted with ether, the ethereal solution was dried and concentrated. Fractional distillation of the residual liquid separated 8.78 g. (25% yield based on the amount of 1-diethylamino-3-butanone) of the diketone 20, b.p. 119-120° (9 mm.), n^{26}_{D} 1.4625 [lit.[18a] b.p. 144-146° (18 mm.)], with infrared absorption[27] at 1720 (C=O) and 1737 $cm.^{-1}$ (C=O in 5-membered ring) and n.m.r. absorption[27] at 2.50 δ (3H singlet, CH_3-CO-) superimposed on complex absorption in the region 1.3-2.8 δ (9H, aliphatic C-H). These spectra were identical to those of an authentic sample.[17]

The pot residue was crystallized from a cyclohexane-ethyl acetate mixture to separate 2.42 g. (5% yield) of the triketone 18 as white needles, m.p. 82-84°. This product has infrared absorption[21] at 1710 (C=O) with a shoulder at 1730 $cm.^{-1}$ (C=O in a 5-membered ring) and an ultraviolet maximum[28] at 281 mμ (ε 65). The sample has an n.m.r. singlet[22] at 2.17 δ (CH_3-CO) superimposed on complex absorption in the region 1.2-2.9 δ (aliphatic C-H). These spectra were identical to those of the previously described triketone.[17]

Appendix

The Michael Reaction of 2-Methylcyclopentanone

Appendix

Of all the reactions involving enolate anions as intermediates, the Michael reaction is anomalous because there appears to be no logical explanation for the orientation observed with an unsymmetrical ketone. It is generally acknowledged[1] that condensation occurs at the more highly substituted position, i.e. the order of reactivity of the Michael donors is CH > CH_2 > CH_3. Although this generalization is based primarily upon early work, more recent investigations[2] have verified it in at least one case. Condensation occurred at the methinyl position of 2-methylcyclohexanone with no detectable amount of the isomeric product.

This orientation is not explicable in terms of either the kinetically or thermodyanmically formed enolate mixtures.[3] In order to investigate the possible reasons, an investigation of the Michael reaction of 2-methylcyclopentanone (1) was begun. Reaction of 1 with either methyl or ethyl acrylate in t-butanol using a catalytic

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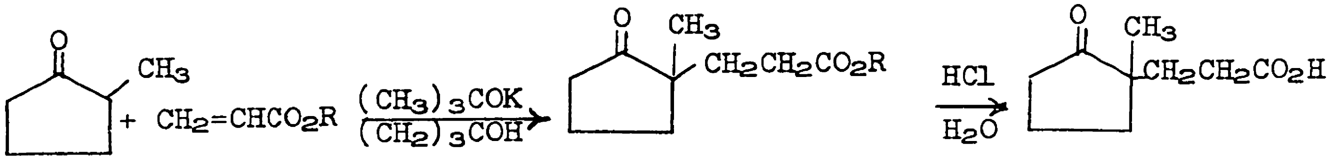
(1) E. D. Bergman, D. Ginsberg, and R. Pappo, Org. Reactions, 10, 183 (1959).

(2) H. O. House and M. Schellenbaum, J. Org. Chem., 28, 34 (1963).

(3) (a) Part I of this thesis; (b) H. O. House and V. Kramar, J. Org. Chem., 28, 3362 (1963).

amount of potassium t-butoxide yielded a single isomeric product 2 or 3. These compounds were hydrolyzed to the same single carboxylic acid 4.



1

2 R = CH_3

3 R = C_2H_5

4

To insure the absence of the isomeric product 7, this compound was synthesized. The initial attempt, modelled after a similar synthesis in the 2-methylcyclohexanone case,[2] involved a Mannich reaction to form 2-methyl-5-dimethylaminocyclopentanone. However, contrary to previous claim,[4] only the 2,2 isomer was formed in this reaction.[5] A mixture of the cis and trans isomers of the desired ketoester 6 was prepared by the method outlined below. Only cleavage products were obtained when potassium ethoxide in an ethanol-ether mixture[6] or potassium t-butoxide in t-butanol was employed in the

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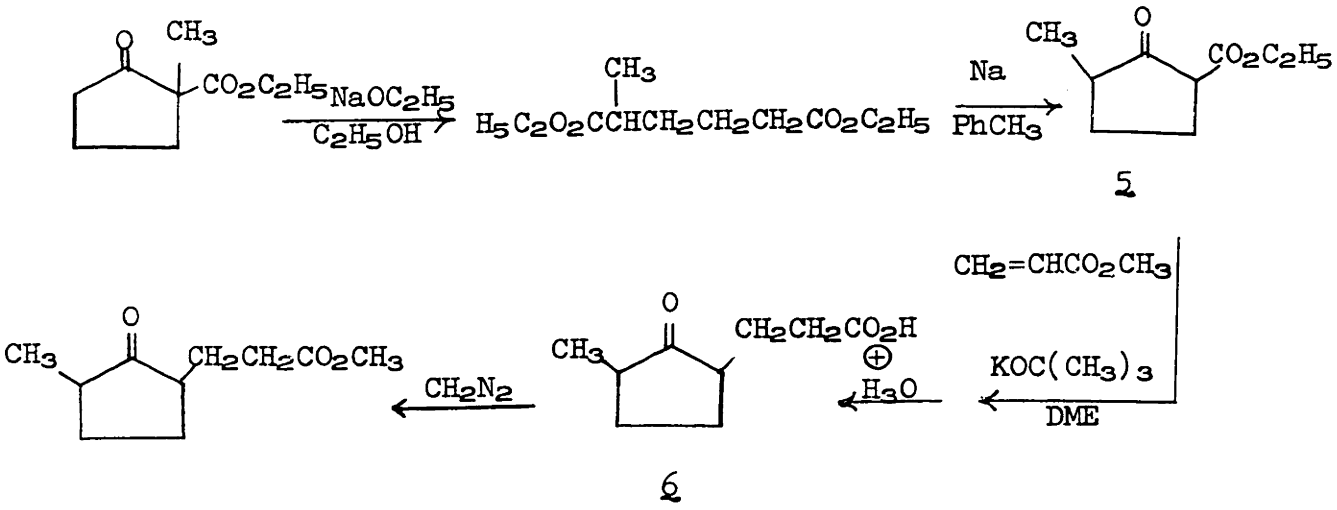
(4) E. C. duFeu, F. J. McQuillin, and R. Robinson, J. Chem. Soc., 53 (1937).

(5) Part III of this thesis.

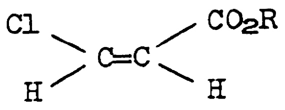


Michael reaction. Although vapor phase chromatography failed to differentiate this product from the direct Michael product 2, the n.m.r. and mass spectra (see Experimental) verify their lack of intercontamination.

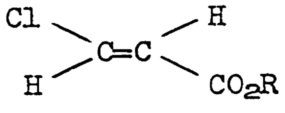
The preparation and characterization of the cis and trans isomers of 3-chloroacrylic acid and their methyl esters as well as propiolic acid were carried out. Only a cursory study of their reactions with ketone 1 was performed with equivocal results.

$HC\equiv CCO_2H$

8



9a, R = H
b, R = CH_3



10a, R = H
b, R = CH_3

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(6) P. Sen-Gupta, K. K. Chakraborti, and B. K. Bhattacharyya, J. Indian Chem. Soc., 24, 249 (1947).

Experimental[7]

Reaction of 2-Methylcyclopentanone (1) with Acrylic Acid Esters.

A. With Methyl Acrylate.-- To a solution of 4.9 g. (50 mmoles) of 2-methylcyclopentanone (**1**) and 5.2 mmoles of potassium *t*-butoxide in 50 ml. of *t*-butyl alcohol was added, dropwise and with stirring at room temperature, 4.5 g. (50 mmoles) of methyl acrylate. After the addition, which was accompanied by evolution of heat, was complete, the reaction mixture was stirred overnight at room temperature and then poured into dilute, aqueous sulfuric acid and extracted with ether. The organic extract was washed with aqueous sodium chloride, dried, concentrated and distilled to separate 4.9 g. (53%) of the *keto ester* **2**, b.p. 83-84° (0.05 mm.), $n^{26.5}_{D}$ 1.4571. The product has infrared absorption[8] at 1735 cm.$^{-1}$ (C=O of ester and cyclopentanone) with n.m.r. singlets[8] at 3.64 δ (3H, CO_2CH_3) and 0.98 δ (3H, $-\overset{|}{\underset{|}{C}}-CH_3$)

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[7] All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated, magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin Elmer, Model 237, infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The n.m.r. spectra were determined at 60 Mc. with a Varian, Model A-60, n.m.r. spectrometer. The mass spectra were obtained with a CEC, Model 21-130, mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

[8] Determined as a solution in carbon tetrachloride.

as well as a complex multiplet in the region 1.5-2.5 δ (10 H, aliphatic C-H). The mass spectrum of the product has a weak molecular ion peak at m/e 184 with abundant fragment peaks at m/e 128, 98, 97, 96, 74, 69, 68, 55, 41, and 39. This product was identified with a subsequently described sample by comparison of infrared spectra.

B. With Ethyl Acrylate.-- Reaction of 6.95 g. (71 mmoles) of 2-methylcyclopentanone (**1**), 6.4 g. (64 mmoles) of ethyl acrylate, and 4.1 mmoles of potassium *t*-butoxide in 60 ml. of *t*-butyl alcohol as described above afforded 1.60 g. of unchanged cyclopentanone (b. p. 139-140°) and 5.52 g. (54% based on unrecovered cyclopentanone) of the **keto ester 3**, b.p. 125-126° (6 mm.,), $n^{26.5}_{D}$ 1.4555 [lit.[9a] b.p. 130° (9 mm.)]. This product has infrared absorption[8] at 1735 $cm.^{-1}$ (C=O of ester and cyclopentanone) with n.m.r. peaks[8] at 4.09 δ (2H quadruplet with J = 7 c.p.s., $O-CH_2-$), at 1.22 δ (3 H triplet with J = 7 c.p.s., methyl group of $-O-CH_2-CH_3$) and at 0.98 δ (3H singlet, $-\overset{|}{\underset{|}{C}}-CH_3$) as well as a complex multiplet in the region 1.5-2.5 δ (10H, aliphatic C-H). The mass spectrum of the material has a weak molecular ion peak at m/e 198 with abundant fragment peaks at m/e 98, 97, 96, 69, 55 and 41.

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(9) Each of the following reactions with 2-methylcyclopentanone has been reported to give the 2,2-disubstituted product: (a) with methyl β-bromopropionate, P. C. Mukharji, *J. Indian Chem. Soc.*, **24**, 91 (1947); (b) with acrylonitrile, N. K. Chaudhuri and P. C. Mukharji, *ibid.*, **33**, 155 (1956); (c) with a Mannich base precursor of methyl vinyl ketone, E. C. du Feu, F. J. McQuillin and R. Robinson, *J. Chem. Soc.*, 53 (1937).

Preparation of the Keto Acid 4.-- A solution of 4.0 g. (22 mmoles) of the keto ester **2** in 80 ml. of 20% aqueous hydrochloric acid was refluxed overnight and then concentrated, saturated with ammonium sulfate and extracted with ether. The ethereal solution was extracted with aqueous sodium carbonate and the aqueous layer was separated, acidified and extracted with ether. This final ether extract was dried, concentrated and distilled to separate 3.2 g. (87%) of the **keto acid 4** as a colorless liquid, b.p. 130-131° (0.05 mm.), n^{28} D 1.4700. The product has broad infrared absorption[8] in the 3μ region (carboxyl assoc. O-H) with peaks at 1735 (cyclopentanone C=O) and 1710 cm.$^{-1}$ (carboxyl C=O). It has n.m.r. singlets[8] at 11.70 δ (1H, COOH) and 1.00 δ (3H, $-\overset{|}{\underset{|}{C}}-CH_3$) as well as a complex multiplet in the region 1.5-2.5 δ (10 H, aliphatic C-H). The mass spectrum of the product has a weak molecular ion peak at m/e 170 with abundant fragment peaks at m/e 114, 98, 69, 55, 41 and 39.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.21; H, 8.28.

Similarly, hydrolysis of 4.5 g. (23 mmoles) of the keto ester **3** with 80 ml. of refluxing 20% aqueous hydrochloric acid for 12 hr. afforded 2.52 g. (65%) of the **keto acid 4**, b.p. 130-131° (0.05 mm.), n^{25} D 1.4700. This product was identified with the previous sample by comparison of infrared spectra. In addition a 1.0-g. sample of the keto acid **4** (from the ethyl ester **3**) was esterified with excess ethereal diazomethane to yield 0.97 g. (90%) of the **keto ester 2**, b.p. 80-84° (0.05 mm.), $n^{26.5}$ D 1.4570. This sample was identified with the methyl ester from the Michael reaction as already described.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.10; H, 8.76.

Michael Reaction with 2-Carboethoxy-5-methylcyclopentanone (5).--2-Carboethoxy-2-methylcyclopentanone was cleaved with refluxing ethanolic sodium ethoxide to diethyl α-methylglutarate [yield 87%, b.p. 140-142° (24 mm.), n^{25}_{D} 1.4262, lit.[10] b.p. 133-134° (18 mm.)] and the diester was reclosed by reaction with sodium in toluene at 120° to form **2-carboethoxy-5-methylcyclopentanone (5)** [yield 63%, b.p. 116-117° (19 mm.), $n^{24.5}_{D}$ 1.4530, lit.[11] b.p. 123-124° (31 mm.)].[12]

To a cold (-5°) mixture of 1.70 g. (10 mmoles) of the ester **5** and 185 mg. of a potassium *t*-butoxide-*t*-butyl alcohol 1:1 complex in 20 ml. of 1,2-dimethoxyethane was added, dropwise with stirring, 0.86 g. (10 mmoles) of methyl acrylate. The resulting mixture was stirred for 3 hr. at -5° and then poured into cold, dilute aqueous hydrochloric acid and extracted with ether. The extract was concentrated

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(10) R. Cornubert and C. Borrell, *Bull. soc. chim. France*, 301 (1930).

(11) A. Haller and R. Cornubert, *Bull. soc. chim. France*, 1621 (1926).

(12) This preparative sequence has recently been discussed by (a) W. L. Meyer, A. P. Lobo and E. T. Marquis, *J. Org. Chem*., **30**, 181 (1965); (b) K. Sisido, K. Utimoto and T. Isida, *ibid*., **29**, 2781 (1964).

and heated overnight with 25 ml. of refluxing 20% aqueous hydrochloric acid. After the solution had been concentrated under reduced pressure, it was saturated with ammonium sulfate and extracted with ether. This ethereal extract was dried and concentrated to leave 1.15 g. of the crude **acid 6** as a yellow oil with infrared absorption[8] at 3000 (broad, carboxyl assoc. O-H), at 1740 (cyclopentanone C=O) and at 1710 cm.$^{-1}$ (carboxyl C=O). This product was esterified with excess ethereal diazomethane to yield 0.95 g. (52% based on the ester **5**) of the **keto ester 7**, a mixture of stereoisomers, as a colorless liquid, b.p. 77-78° (1.5 mm.), $n^{24.5}_{D}$ 1.4533. The material has infrared absorption[8] at 1735 cm.$^{-1}$ (ester and cyclopentanone C=O) with an n.m.r. peak[8] at 3.57 δ (3H, CO_2CH_3) and two overlapping doublets (J = 6 c.p.s. for each) at 1.02 and 1.05 δ (3H, methyl protons of the CH_3-CH$<$ grouping in the cis and trans isomers) as well as a complex multiplet in the region 1.2-2.5 δ (10H, aliphatic C-H). The mass spectrum has a weak molecular ion peak at m/e 184 with abundant fragment peaks at m/e 152, 124, 111, 110, 98, 97, 82, 74, 59, 55, 42, 41 and 39.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.13; H, 8.79.

The two stereoisomers of keto ester **7** were not resolved on our gas chromatography column;[13] also the keto esters **7** were eluted[13]

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(13) A column packed with Silicone fluid, No. 710, suspended on ground firebrick was employed.