TABLE VI

pK_{R^+} VALUES FOR VARIOUS CARBONIUM IONS

Carbonium ion	pK_{R^+}	General acid catalysis[a]
Diphenylmethyl[b]	−13.3	−
Di-*p,p'*-methoxyphenylmethyl[b]	−5.71	−
2,3-Diphenylcyclopropenyl[c]	−0.67	−
Tropylium[d]	+4.7	+

[a] Catalysis of the hydrolysis of the respective ketal. [b] N. C. Deno and A. Schriesheim, *J. Amer. Chem. Soc.*, **77**, 3051 (1955); N. C. Deno, J. J. Jaruzelski, and A. Schriesheim, *ibid.*, **77**, 3044 (1955). [c] R. Breslow, H. Hover, and H. W. Chang, *ibid.*, **84**, 3168 (1962). [d] G. Naville, H. Strauss, and E. Heilbronner, *Helv. Chim. Acta*, **43**, 1221, 1243 (1960); W. von E. Doering and L. H. Knox, *J. Amer. Chem. Soc.*, **76**, 3203 (1954).

2,3-diphenylcyclopropenone diethyl ketal, making a reasonable allowance for the difference in temperature at which the rate measurements were made. Tropone ethylene ketal was the only compound in the series for which general acid catalysis was observed. Therefore, the boundary line between the A1 mechanism and one involving general acid catalysis, in terms of carbonium ion stability, lies somewhere between pK_{R^+} values of −0.67 and +4.7, with probability that it lies closest to the more positive figure. Thus, for general acid catalysis of acetal hydrolysis to occur in cases where the leaving group is poor, the intermediate carbonium ion must be exceedingly stable, *i.e.*, the bond-breaking step must be quite easy.

Registry No.—I, 6397-77-9; II, 29182-66-9; III, 29182-67-0; IV, 12512-45-7; V, 17637-62-6.

Acknowledgment.—This work was supported by research grants from the National Institutes of Health and the National Science Foundation.

The Chemistry of Carbanions. XIX. The Alkylation of Enolates from Unsymmetrical Ketones[1a]

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Received January 5, 1971

The alkylation of specific structural isomers of lithium enolates derived from 1-decalone (**1**), 2-methylcyclohexanone (**2**), 2-benzylcyclohexanone (**3**), cyclohexanone, and 2-heptanone (**23**) has been studied. The more highly substituted enolate isomers are best obtained by reaction of the corresponding enol acetates or enol trimethylsilyl ethers with methyllithium. The advantage gained with the silyl enol ethers in avoiding dialkylation is offset by the frequent difficulty in obtaining a single structural isomer of the silyl ether. The less highly substituted lithium enolates of unsymmetrical ketones are best obtained by a kinetically controlled deprotonation of the ketone with the hindered base, lithium diisopropylamide. Although the less hindered lithium enolates from cyclic ketones can be alkylated with good structural specificity, this procedure was not satisfactory for alkylation at the methyl group of 2-heptanone because of a combination of an unfavorable position of enolate equilibria and, especially, an unfavorable ratio of alkylation rates for the structurally isomeric enolates.

Often in the course of a synthesis, the need arises to introduce an alkyl group selectively at one of the two α positions of an unsymmetrical ketone. Among the useful methods for accomplishing this synthetic objective,[2] the reaction of an alkylating agent with a particular structural isomer of an enolate anion is very common. The formation of the desired enolate isomer may be accomplished either by modifying the structure of the starting ketone with a blocking group or an activating group or by generating the enolate from a suitable precursor under conditions where equilibration among the possible enolate structural isomers does not occur.[2] The most useful methods in this latter category have been the reduction with metals of α,β-unsaturated ketones[3] or α-halo ketones[4] and the reaction of enol esters[5] or enol silyl ethers[6,7] with organometallic reagents, especially alkyllithium reagents. Among these possibilities, the use of enol esters or ethers offers the most versatility since the starting material for the alkylation sequence is the saturated ketone. The methods now available for the formation of enol acetates or trimethylsilyl enol ethers sometimes allow a particular structural isomer to be isolated in high yield; furthermore, any of the undesired isomers of these enol derivatives may be easily reconverted to the starting ketone.

By use of equilibrating reaction conditions accompanied, if necessary, by selective hydrolysis, it is usually possible to convert an unsymmetrical ketone to the corresponding more highly substituted enol acetate isomer in 95% purity on a preparatively useful scale.[2,5] The use of equilibrating reaction conditions permits preparation of mixtures of trimethylsilyl enol ethers in which the more highly substituted enol derivative predominates (typically 70–90% of the mixture).[7] However, it is often very difficult to obtain a pure

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(1) (a) This research has been supported by Public Health Service Grant RO1-CA-10933 from the National Cancer Institute. (b) National Institutes of Health Predoctoral Fellow, 1968–1970. (c) National Institutes of Health Predoctoral Fellow, 1966–1968.

(2) For a recent review, see H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, New York, N. Y., Chapter 9, in press.

(3) (a) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, **87**, 275 (1965); (b) H. A. Smith, B. J. L. Huff, W. J. Powers, III, and D. Caine, *J. Org. Chem.*, **32**, 2851 (1967); (c) L. E. Hightower, L. R. Glasgow, K. M. Stone, D. A. Albertson, and H. A. Smith *ibid.*, **35**, 1881 (1970).

(4) (a) M. J. Weiss and coworkers, *Tetrahedron*, **20**, 357 (1964); (b) T. A. Spencer, R. W. Britton, and D. S. Watt, *J. Amer. Chem. Soc.*, **89**, 5727 (1967).

(5) (a) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341, 2502 (1965); (b) H. O. House, *Rec. Chem. Progr.*, **28**, 99 (1967); (c) H. O. House and C. J. Blankley, *J. Org. Chem.*, **32**, 1741 (1967); (d) H. O. House and T. M. Bare, *ibid.*, **33**, 943 (1968).

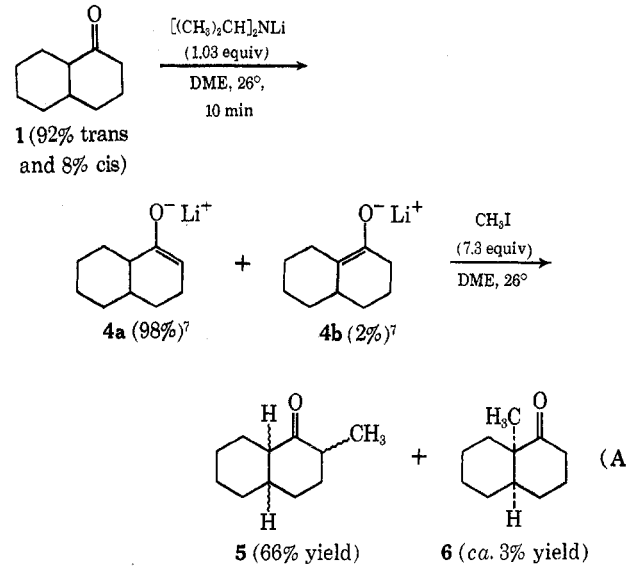
(6) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, **90**, 4462, 4464 (1968).

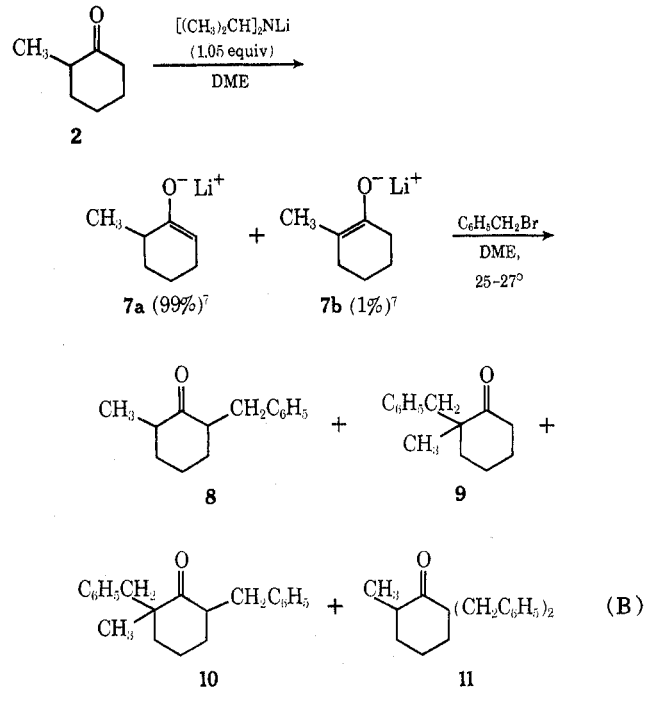
(7) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).

sample of a more highly substituted trimethylsilyl enol ether isomer from an unsymmetrical ketone without recourse to either an efficient fractional distillation or preparative gas chromatography. Acetates and trimethylsilyl ethers of the less highly substituted enol derived from an unsymmetrical ketone are most easily obtained by reaction of the ketone with a very hindered base under nonequilibrating conditions. The mixture of enolates formed by this kinetically controlled proton abstraction is then quenched in excess acetic anhydride or trimethylsilyl chloride. Although bases such as lithium, sodium, or potassium triphenylmethide,[5,6] or the lithium or sodium derivative of bis(trimethylsilyl) amine[8,9] have been used to form mixtures of enolate anions under conditions of kinetic control, we have found the hindered base lithium diisopropylamide to be especially effective in forming mixtures of enolate anions containing mainly the less highly substituted lithium enolate isomer.[7] This strong base offers a number of additional advantages including the fact that it is easily prepared from available materials, it is soluble in common solvents such as ether, tetrahydrofuran (THF), and 1,2-dimethoxyethane (DME), and its presence in these solvents is readily detected by means of the red to purple colored charge-transfer complex it forms with small amounts of 2,2-bipyridyl added to the reaction mixture as an indicator.[10,11] Diisopropylamine, the conjugate acid formed from this base, is a very weak acid and is sufficiently volatile (bp 84°) to be readily separated from the reaction products; this amine is a very poor nucleophile, being so hindered that its reaction with reactive alkylating agents such as methyl iodide, benzyl bromide, and trimethylsilyl chloride is negligible under the conditions required to alkylate enolate anions. Although the mixtures of lithium enolates obtained by the kinetically controlled reaction of this hindered base with unsymmetrical ketones can be quenched with acetic anhydride or, preferrably, trimethylsilyl chloride to form primarily derivatives of the less highly substituted enol,[7] it appeared more profitable to use this mixture of lithium enolates directly for alkylation reactions. This paper reports a study of the alkylation of several lithium enolates generated by these various methods.

Results and Discussion

Equations A–C summarize our results from alkylating the mixtures of lithium enolates obtained from reaction of the cyclic ketones **1**, **2**, and **3** with lithium diisopropylamide under conditions of kinetic control. In these cases the predominant monoalkylated product does not correspond to the enolate isomer expected to predominate at equilibrium; the position of equilibrium for the lithium enolate isomers from ketones **1** and **2** is 34% **4a** ⇌ 66% **4b**[5a] and 10–11% **7a** ⇌ 89–90% **7b**.[12] It will be seen in these cases that the monoalkylated product will contain at least 90% of material resulting from alkylation at the less highly substituted





—Concentration, *M*— 7	$C_6H_5CH_2Br$	Reaction time, min	Product yields, % 8	9	10	11
0.19	0.20	1	9	2		
		5	27	6		
		30	33	19	8	6
0.19	1.00	1	59	3		
		5	68	4	4	4
		10	65	6	5	4
0.38	0.80	1	27	2		
		5	63	6	5	4
		10	58	6	5	5
0.38 (30–50°, preparative scale)	0.80	6	49–55	7–9	Not determined	

(8) C. R. Krüger and E. G. Rochow, *J. Organometal. Chem.*, **1**, 476 (1964).

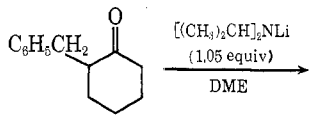
(9) (a) D. H. R. Barton, R. H. Hesse, G. Tarzia, and M. M. Pechet, *Chem. Commun.*, 1497 (1969); (b) M. Tanabe and D. F. Crowe, *ibid.*, 1498 (1969).

(10) For the use of this indicator with organomagnesium and organolithium compounds, see S. C. Watson and J. F. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967).

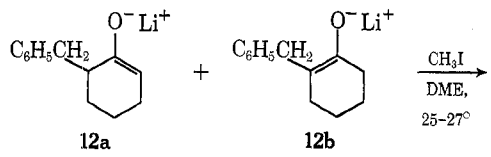
(11) Triphenylmethane may also be used as an indicator for organolithium reagents in DME or THF solution where the red triphenylmethyl anion is formed.

(12) (a) D. Caine and B. J. L. Huff, *Tetrahedron Lett.*, 4695 (1966); 3399 (1967). (b) B. J. L. Huff, F. N. Tuller, and D. Caine, *J. Org. Chem.*, **34**, 3070 (1969).

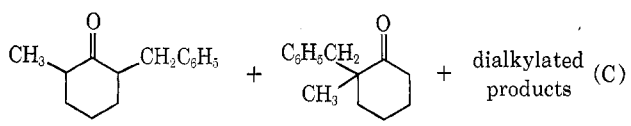
position when suitable precautions are taken to form the mixture of enolates under conditions of kinetic control and to complete the alkylation more rapidly than the alkylated product can equilibrate with the starting enolate. Rapid reaction (total reaction time 10 min or less) of the enolates with the alkylating agent has been achieved in the cases studied here by the use of



3



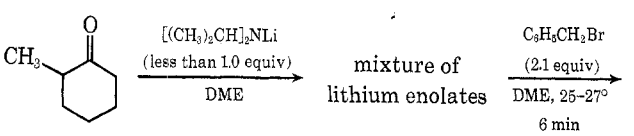
12a 12b



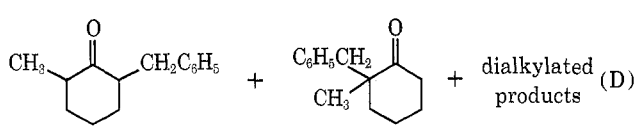
8 9

Concentrations, M		Reaction time,	Product yields, %		
12	CH_3I	min	8	9	Dialkylated
0.19	0.20	1	49	5	3
		5	64	5	6
0.19	1.00	1	76	6	5
		5	73	6	4

relatively high concentrations of reactants, especially the alkyl halide, for this bimolecular reaction. The effect on both the rate of reaction and the composition of the alkylated product is illustrated by the data in eq B. The necessity to prepare the enolates by adding the ketone to a slight excess of the strong base so that no un-ionized ketone is present is best illustrated by comparison of the data summarized in eq B and D. In the latter experiment, the mixture of enolates was formed by adding an excess of the ketone to the solution of strong base so that no excess lithium diisopropylamide was present (*i.e.*, the indicator was colorless) before the alkylating agent was added. However, with suitable precautions the selective alkylation of the ketone **2** to form **8** is a practical preparative procedure; the result is particularly striking when one considers that not only is the "wrong" lithium enolate isomer **7b** favored at equilibrium but also the enolate **7b** is 1.7–2.3 times more reactive toward alkyl halides than is its isomer **7a**.[12]

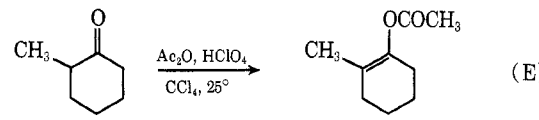


2

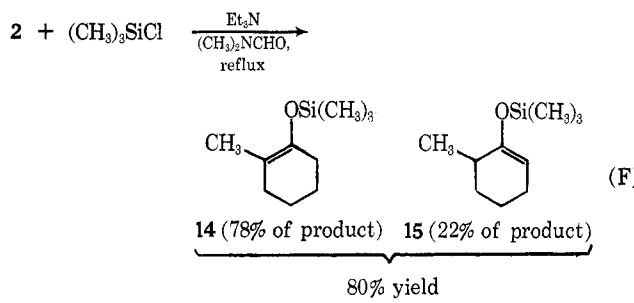


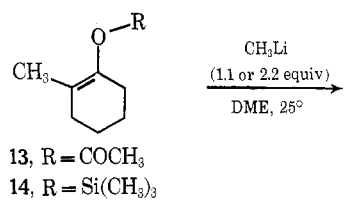
8 (9% yield) (9 31% yield)

As the foregoing comments imply, the selective alkylation of a cyclic ketone at the more highly substituted α position can be accomplished fairly easily since both the position of enolate equilibrium and the rate of reaction with the alkylating agent favor this site. The principal difficulty is encountered in preparing, easily, a pure sample of a suitable precursor for lithium enolate which will not result in competing formation of dialkylated products. As noted earlier, it is relatively easy to obtain pure samples of a more highly substituted enol acetate isomer such as **13** (eq E); however, the corresponding trimethylsilyl enol ethers, *e.g.*, **14** (eq F), are usually obtained as the predominant

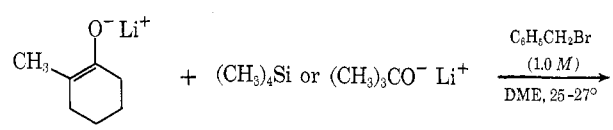


2 13 (87–92% yield)

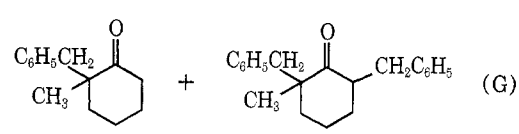




13, R = $COCH_3$
14, R = $Si(CH_3)_3$



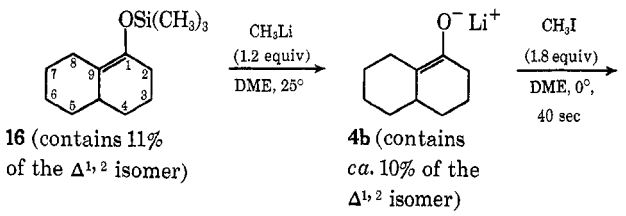
7b (0.19 M)



9 10

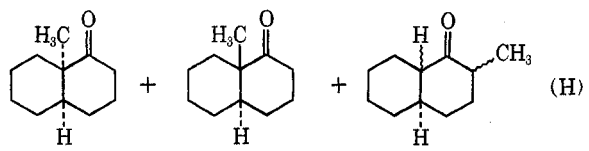
R	Reaction time, min	Product yields, % 9	10
$Si(CH_3)_3$	1	80	3
	5	84	7
$COCH_3$	1	59	22
	5	48	41
$COCH_3$ (preparative scale)	2.5	53–58%	Not determined

components in a difficulty separable mixture. Although each of these pure enol derivatives **13** and **14** is readily converted to a single enolate anion, **7b**, the by-product of these preparations is either the inert

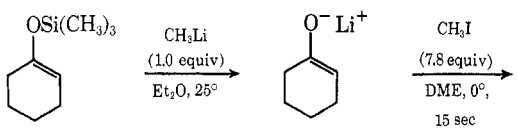


16 (contains 11% of the $\Delta^{1,2}$ isomer)

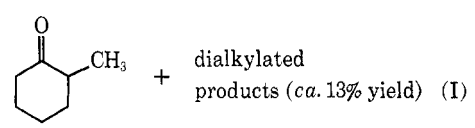
4b (contains *ca.* 10% of the $\Delta^{1,2}$ isomer)



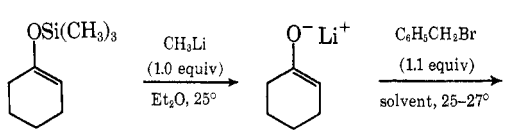
6 (43% yield) **17** (12% yield) **5** (10% yield) + dialkylated products (9% yield) (H)



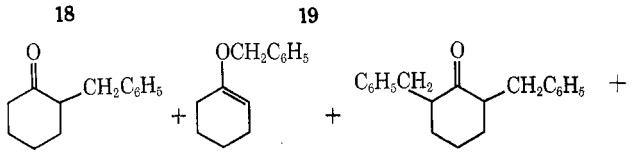
18 **19** (insoluble in Et_2O)



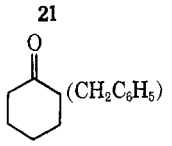
2 (56% yield) + dialkylated products (*ca.* 13% yield) (I)



18 **19**



3 **20** **21** + (J)



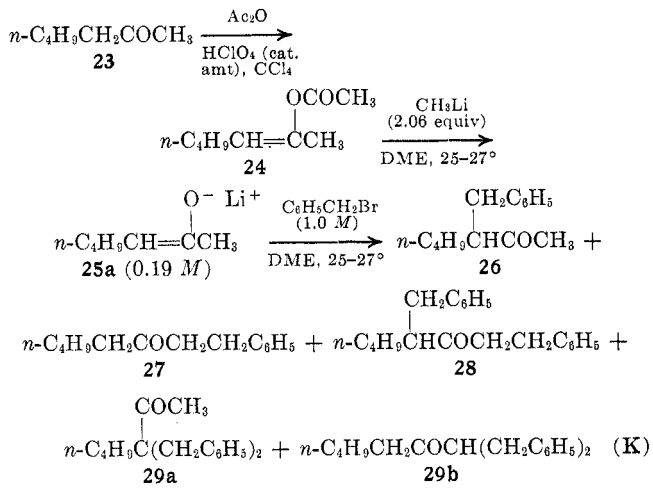
22

Solvent	Reaction time, min	Product yields, % 3	20	21	22
Et_2O (heterogeneous)	60	45		5	5
DME (homogeneous)	60	51		4	9
DME (preparative scale)	15	58		Not determined	
HMP (homogeneous)	15	27	3	5	20

tetramethylsilane or the base, lithium *tert*-butoxide. Since the alkoxide reacts very slowly with alkylating agents under the conditions of enolate alkylation, it remains in the reaction mixture and can react with the initial monoalkylated product **9** to form a new enolate which yields a dialkylated ketone **10**. As eq G illustrates, this problem can be lessened by use of excess alkylating agent with short reaction times. However, if the silyl ether **14** were readily available in pure form, it would clearly be the more satisfactory precursor for the enolate **7b**.

Other examples of alkylations of lithium enolates derived from trimethylsilyl enol ethers are summarized in eq H–J. It will be noted that dialkylation is still a serious side reaction unless precautions (high concentrations of reactants and excess alkylating agent) are taken to make the initial alkylation reaction rapid. Thus, even in the absence of lithium *tert*-butoxide (formed from an enol acetate precursor), the starting enolate anion (*e.g.*, **19**) can serve as a base to convert the initial alkylated product (*e.g.*, **3**) to a new enolate anion. This enolate equilibration becomes particularly troublesome (see eq J) when the reaction is conducted in a polar, aprotic solvent such as hexamethylphosphoramide (HMP). Use of this solvent also leads to the formation of some O-alkylated product (*e.g.*, **20**) as has been noted elsewhere.[2,13] However, the benzylations of the various lithium enolates (*e.g.*, **19**) in 1,2-dimethoxyethane were not complicated by O-alkylation; appropriate control experiments demonstrated that the enolate **19** did not react with the *O*-benzyl ether **20** to form the C-benzylated product **3**.

The foregoing method could also be used successfully to alkylate the more highly substituted α position of the methyl alkyl ketone **23** (eq 11);[14] other examples



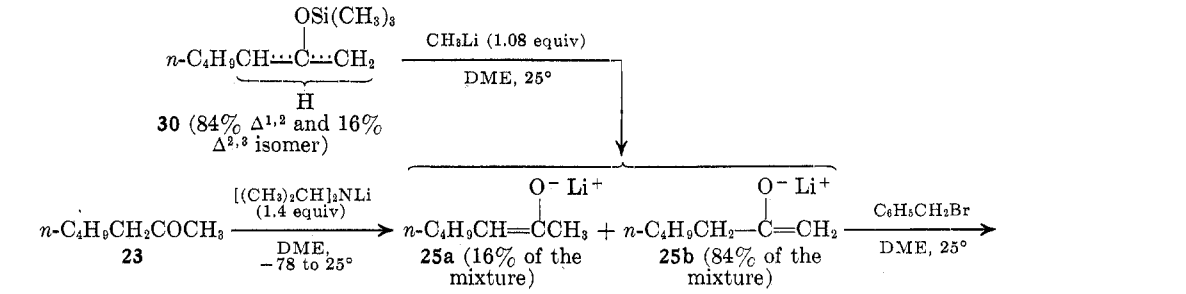
(K)

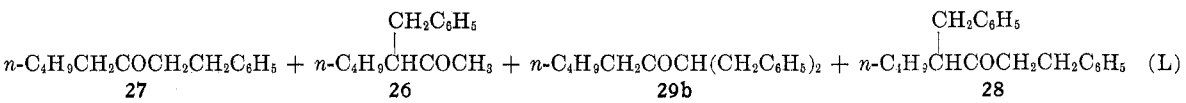
Reaction time, min	Product yields, % 26	27	28	29
1	57	1	4	1
5	70		11	6
45	61		9	27

of this type have been reported elsewhere.[5a,d] As was true for the benzylation of the cyclic ketones, the monoalkylated product **26** was obtained in good purity and the formation of dialkylated products became a serious problem only when relatively long reaction

(13) (a) H. D. Zook, T. J. Russo, E. F. Ferrand, and D. S. Stotz, *J. Org. Chem.*, **33**, 2222 (1968); (b) W. J. leNoble and H. F. Morris, *ibid.*, **34**, 1969 (1969); (c) R. M. Coates and J. E. Shaw, *ibid.*, **35**, 2597, 2601 (1970); (d) A. L. Kurz, I. P. Beletskaya, A. Macias, and O. A. Reutov, *Tetrahedron Lett.*, 3679 (1968); (e) S. J. Rhoads and R. W. Holder, *Tetrahedron*, **25**, 5443 (1969); (f) H. Normant, *Angew. Chem., Int. Ed. Engl.*, **6**, 1046 (1967).

(14) Mixtures of the cis and trans isomers of the enolate **25a** were employed in the present studies. The composition of these mixtures of geometrical isomers are described in ref 5 and 7.





Reactant concentrations, M		Reaction time,	Product yields, %			
25	$PhCH_2Br$	min	27	26	29b	28
0.19	1.00	1	27	19	3	2
		5	16	31	13	9
		45	15	33	14	10
0.17	0.20	10	4	23	*Ca.* 3	*Ca.* 3
		120	1	41	6	6
0.07	0.70	60	13	28	16	12

periods were employed. However, attempts to alkylate this same ketone **23** selectively at the methyl group (the less hindered α position) revealed a clear limitation of these alkylation procedures. Equation L illustrates the fact that addition of this ketone **23** to lithium diisopropylamide offers a reasonably selective procedure for forming the terminal lithium enolate **25b** (84% of the enolate mixture); the same mixture of enolates could also be obtained by reaction of the corresponding mixture of trimethylsilyl enol ethers with methyllithium. In 1,2-dimethoxyethane solution the equilibrium composition of this enolate mixture is *ca.* 13% **25b** $\rightleftharpoons$ *ca.* 87% **25a**.[5a] Irrespective of the method used to obtain this enolate mixture, subsequent reaction with benzyl bromide produced a substantial amount of the product **26** from monoalkylation at the more highly substituted α position and the expected monobenzylated ketone **27** was the major monoalkylated product only when the reaction was run for a short period of time (1 min) with relatively high concentrations of reactants.

Consideration of the data summarized in eq K and L requires that the internal enolate isomer **25a** must react some 5–10 times as rapidly as the terminal enolate **25b** with benzyl bromide. Furthermore, the enolates derived from the monoalkylated product **27** must also react more rapidly than the starting terminal enolate **25b**. The net result of this slow rate of alkylation of the terminal enolate **25b** is to allow time for equilibration between the starting enolates and the alkylated product; this equilibration favors both the consumption of the desired monoalkylated product **27** and the formation of the isomeric monoalkylated ketone **26** from the enolate **25a**, which is both more reactive and is also favored at equilibrium.[15] As a result of these factors, it appears that selective alkylation at the methyl group of ketone RCH_2COCH_3 by any method which involves the generation of the enolate $RCH_2C(O^-)=CH_2$ Li^+ in an ethereal solvent will not be a good synthetic procedure and other synthetic methods (*e.g.*, introduction of an activating substituent)[2] will be preferable.

The fact that less highly substituted alkali metal enolates may sometimes react more slowly with alkyl halides than their analogs having additional α substituents has been noted in several studies.[12,13a,16] These observations initially seem curious since adding α substituents would be expected to increase the steric interference to forming a new bond at the α-carbon atom. However, there is considerable evidence that many of the metal enolates (and the related metal alkoxides) exist in ethereal solvents either as tightly associated ion pairs or as aggregates (dimers, trimers, tetramers) of these ion pairs;[13a,17–19] structures such as **31–34** (M = metal; n = 1, 2, or 3; R = alkyl or the substituted vinyl portion of an enolate) have been suggested for such materials with the smaller aggregates being favored as the steric bulk of the group R increases. Thus, the bromomagnesium enolate of isopropyl mesityl ketone is suggested to have structure **31** (M = MgBr), whereas the enolate of the analogous methyl ketone is believed to have structure **32** (M = MgBr).[18] The sodium enolates of several ketones are suggested to have the trimeric structures **33** in various ethereal solvents.[13a,17] Since the reactivities of metal enolates toward alkyl halides are very dependent on the degree of association and/or aggregation,[2,13,17] we suggest that the decreased reactivity observed for less highly substiuted metal enolates both in this study

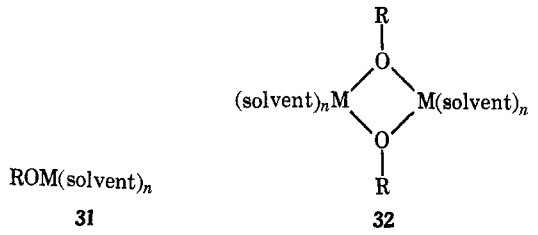
(15) Although data concerning rates of proton transfer from an unionized ketone to each of the enolate anions **25** are not available, it is possible that proton transfer to the terminal enolate isomer **25b** is faster than transfer to the internal isomer **25a**. This circumstance would further complicate attempts to alkylate the terminal enolate **25b** without competing isomerization.

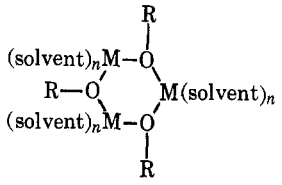
(16) K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **31**, 1035 (1966).

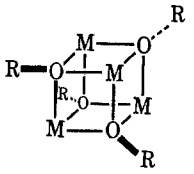
(17) (a) H. D. Zook and T. J. Russo, *J. Amer. Chem. Soc.*, **82**, 1258 (1960); (b) H. D. Zook and W. L. Gumby, *ibid.*, **82**, 1386 (1960); (c) W. L. Rellahan W. L. Gumby, and H. D. Zook, *J. Org. Chem.*, **24**, 709 (1959); (d) H. D. Zook, W. L. Kelly, and I. Y. Posey, *ibid.*, **33**, 3477 (1968).

(18) A. G. Pinkus, J. G. Lindberg, and A. B. Wu, *Chem. Commun.*, 1350 (1969); 859 (1970).

(19) For related studies of the structures of metal alkoxides, see (a) G. E. Coates, J. A. Heslop, M. E. Redwood, and D. Ridley, *J. Chem. Soc. A*, 1118 (1968); (b) E. Weiss, H. Alsdorf, and H. Kühr, *Angew. Chem., Int. Ed. Engl.*, **6**, 801 (1967).







and elsewhere[12,13a,16] may be attributable to a greater degree of aggregation of these enolates.

Experimental Section[20]

Reagents and Starting Materials.—The preparation and characterization of trimethylsilyl enol ethers **14**, **16**, **18**, and **30** and the enol acetates **13** and **24** have been described previously.[5a,7,21] Although the pure silyl ether **14** [bp 100–101° (45 mm), n^{24}D 1.4476, glpc analysis, Apiezon L on Chromosorb P] could be separated from its isomer **15** by fractional distillation, this separation technique was not useful for obtaining single structural isomers from the enol derivatives **16** and **30**. Consequently, the decalone derivative **16** used contained [glpc analysis, 1,2,3-tris-(β-cyanoethoxy)propane on Chromosorb P] 89% of the $\Delta^{1,9}$ isomer and 11% of the stereoisomeric $\Delta^{1,2}$ isomers, and the 2-heptanone derivative **30** used contained (glpc analysis, Carbowax 20M on Chromosorb P) 84% of the $\Delta^{1,2}$ isomer and 16% of the stereoisomeric $\Delta^{2,3}$ isomers. All of these trimethylsilyl enol ether isomers have been separated and characterized in earlier studies.[7] The following paragraphs summarize improved preparative procedures for the previously characterized[21] enol acetates **13** and **24**.

A solution of 230 g (2.25 mol) of Ac_2O, 56 g (0.50 mol) of 2-methylcyclohexanone, and 0.34 ml (2 mmol) of aqueous 70% $HClO_4$ (*added last*) in 600 ml of CCl_4 was stirred at 25° for 3 hr and then poured into a cold (0–5°) mixture of 400 ml of pentane and 400 ml of saturated aqueous $NaHCO_3$. After excess solid $NaHCO_3$ had been added to neutralize all the HOAc formed, the pentane layer was separated and the aqueous phase was extracted with pentane. The combined pentane solutions were dried, concentrated, and distilled to separate 66.6–70.9 g (87–92%) of the enol acetate **13** [bp 81–86° (18 mm), n^{25}D 1.4562–1.4572] which contained (nmr analysis[21]) >95% of the more highly substituted isomer.

A mixture of 114.2 g (1.00 mol) of 2-heptanone, 209 g (2.07 mol) of isopropenyl acetate, and 6.0 g (35 mmol) of *p*-toluenesulfonic acid was refluxed with stirring in an apparatus fitted with a condenser partially filled with refluxing acetone.[22] In this way acetone which formed as the reaction progressed was allowed continuously to distil from the reaction mixture. After 12 hr, when the conversion of 2-heptanone was nearly complete (glpc analysis), the mixture was partitioned between 500 ml of pentane and 600 ml of cold (0–5°) saturated, aqueous $NaHCO_3$. The organic layer was separated, dried, and distilled to separate 146 g (94%) of the crude product [bp 168–176° (760 mm)] which contained (glpc analysis, Carbowax 20M on Chromosorb P) 4% 2-heptanone (retention time 6.5 min), 57% 2-acetoxy-*trans*-2-heptene (11.6 min), 15% 2-acetoxy-1-heptene (12.4 min), and 24% 2-acetoxy-*cis*-2-heptene (14.1 min). Fractional distillation through a 90-cm spinning-band column separated 121 g (76.9%) of product, bp 85–90° (30 mm), n^{23}D 1.4245, which contained >95% of the $\Delta^{2,3}$ enol acetate stereoisomers **24**.

Ethereal solutions of halide-free methyllithium were obtained from Alpha Inorganics; these solutions were standardized by the titration procedure of Watson and Eastham.[10] Diisopropylamine was distilled from CaH_2, benzyl bromide was freshly distilled [bp 78–79° (12 mm)], and 1,2-dimethoxyethane was distilled from $LiAlH_4$ immediately before use. In all reactions involving methyllithium, a few milligrams of either 2,2-bipyridyl or triphenylmethane was added as an indicator to establish when excess methyllithium was present;[10,11] similarly, small amounts of 2,2-bipyridyl were added as an indicator for solutions of lithium diisopropylamide. This amide is a sufficiently strong base that it attacks 1,2-dimethoxyethane at a significant rate; in a 0.5 *M* solution at 0–10°, approximately 25% of this base was consumed after 45 min by reaction with the solvent. For a comparable solution at −20°, less than 10% of the lithium diisopropylamide was consumed after 30 min.

Authentic Samples of the Alkylated Cyclohexanones. A. 2-Benzylcyclohexanone (3).—2-Benzalcyclohexanone, prepared in 62% yield as previously described,[23] was obtained as yellow prisms: mp 54–54.5°; ir (CCl_4) 1690 (conj C=O) and 1610 cm^{-1} (conj C=C); uv maxima (95% EtOH) 223 mμ (ε 7100) and 290 (16,500); nmr (CCl_4) δ 7.0–7.5 (6 H, m, aryl and vinyl CH) and 1.4–3.0 (6 H, m, aliphatic CH). An ethanol solution of this material was hydrogenated[24] over a Pt catalyst (from PtO_2) to yield 56% 2-benzylcyclohexanone (**3**) as a colorless liquid: bp 112–114° (0.6 mm); n^{24}D 1.5347–1.5362 [lit.[24] bp 142° (1.0 mm); n^{18}D 1.5356]; ir (CCl_4) 1710 cm^{-1} (C=O); uv (95% EtOH) series of weak maxima (ε 134–331) in the region 240–284 mμ; nmr (C_6D_6) δ 7.0–7.3 (5 H, m, aryl CH), 3.0–3.5 (2 H, AB part of ABX pattern centered at δ 3.28, benzylic CH_2), and 1.0–2.6 (9 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 188 (13, M^+), 97 (26), 91 (100), 65 (21), 55 (26), 51 (23), 44 (99), 41 (51), 40 (45), and 39 (51).

B. 1-Benzyloxycyclohexene (20).—A mixture of 24.5 g (0.25 mol) of cyclohexanone, 39.0 g (0.375 mol) of 2,2-dimethoxypropane, 216 g of benzyl alcohol, 75 ml of hexane, and 0.1 g of *p*-toluenesulfonic acid was refluxed with stirring over a period of 30 hr, while the low-boiling products (MeOH and acetone) were fractionally distilled from the reaction vessel and portions of hexane were added periodically to the reaction flask.[25] The hexane was then distilled from the reaction mixture and the residual liquid was neutralized (0.1 g of NaOMe in 5 ml of MeOH) and distilled under reduced pressure to separate various lower boiling components [bp 70° (0.35 mm) to 138° (0.05 mm)] followed by 57.01 g (77%) of crude **1,1-dibenzyloxycyclohexane**, bp 138–157° (0.06 mm), n^{25}D 1.5481. On thin layer chromatography (silica gel coating and PhH eluent) the R_f values of the materials formed in this reaction were benzyl alcohol, 0.13; the ketal, 0.50; dibenzyl ether, 0.63; and the enol ether **20**, 0.74. Redistillation in apparatus, previously washed with base, separated the pure ketal as a pale yellow liquid: bp 151–153° (0.03 mm); n^{26}D 1.5479; ir (CCl_4) 1040 and 1090 cm^{-1} (ketal CO); uv (95% EtOH) series of weak (ε 170–392) maxima in the region 240–270 mμ; nmr (CCl_4) δ 6.9–7.6 (10 H, m, aryl CH), 4.45 (4 H, s, benzylic CH_2O), and 1.2–2.1 (10 H, m, aliphatic CH).

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.12; H, 8.28.

A mixture of 9.86 g (33 mmol) of this ketal and 0.5 g of powdered $NH_4H_2PO_4$ was heated to 190–198° for 10 min and then cooled and distilled under reduced pressure. The higher boiling fractions obtained [7.8 g, bp 44–121° (1.0 mm), n^{25}D 1.5388–1.5410] were fractionally distilled to separate 3.30 g (53%) of the pure enol ether **20**, as a colorless liquid: bp 74–76° (0.08 mm); n^{20}D 1.5356; ir (CCl_4) 1660 cm^{-1} (C=C); uv (95%

(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 nmr spectra were determined at 60 Mc with a Varian Model A-60 or Model T-60 nmr spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to a tetramethylsilane internal standard. The mass spectra were obtained with a Hitachi Perkin-Elmer mass spectrometer. All reactions involving strong bases or organometallic intermediates were performed under a nitrogen atmosphere.

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

(22) This procedure was developed in our laboratories by Mr. Allan Y. Teranishi and Dr. Thomas M. Bare.

(23) H. O. House and R. L. Wasson, *J. Amer. Chem. Soc.*, **78**, 4394 (1956), and references therein.

(24) J. D. Billimoria, *J. Chem. Soc.*, 1126 (1955).

(25) This method for preparing ketals was described by N. B. Lorette and W. L. Howard, *J. Org. Chem.*, **25**, 521 (1960).

EtOH) intense end absorption with a series of weak (ε 181–222) maxima in the region 245–270 mμ; nmr (CCl_4) δ 7.2–7.6 (5 H, m, aryl CH), 4.74 (2 H, s, benzylic CH_2O), 4.6 (1 H, m, vinyl CH), and 1.3–2.5 (8 H, m, aliphatic CH); mass spectra M^+ at *m/e* 188 with abundant fragment peaks at *m/e* 92, 91, 65, 55, 51, 41, and 39.

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.79; H, 8.58.

C. 2,6-Dibenzylcyclohexanone (21).—An ethyl acetate solution of 2,6-dibenzalcyclohexanone[26] was hydrogenated at 26° and atmospheric pressure over the catalyst from PtO_2. The crude crystalline product, separated in the usual way, was recrystallized from methanol to separate the pure *cis*-2,6-dibenzylcyclohexanone (**21**, 28% yield) as colorless crystals: mp 121–122° (lit. mp 122°,[27] 124–125°[28]); ir (CCl_4) 1715 cm^{-1} (C=O); uv (95% EtOH) series of weak maxima (ε 438–728) in the region 240–270 mμ with a maximum at 287 mμ (ε 48); nmr (CCl_4) δ 6.9–7.3 (10 H, m, aryl CH), 2.9–3.5 (4 H, m, AB part of ABX pattern centered at 3.21, benzylic CH_2), and 1.2–2.6 (8 H, m, aliphatic CH); in C_6D_6 solution the AB part of the ABX pattern is centered at δ 3.32; mass spectrum *m/e* (rel intensity) 278 (47, M^+), 187 (58), 167 (21), 146 (24), 131 (22), 130 (33), and 91 (100).

D. 2,2-Dibenzylcyclohexanone (22).—Cyclohexanone (24.5 g or 0.25 mol) was alkylated with 0.50 mol of benzyl bromide and 0.53 mol of sodium *tert*-amylate in 567 ml of benzene according to the procedure of Conia.[29] The crude product was fractionally distilled to separate the unchanged benzyl bromide and the monobenzylated ketone as fractions, bp 35–111° (0.10–0.15 mm). The residual viscous liquid was crystallized from a PhH–EtOH mixture to separate 19.9 g (29%) of the 2,2-dibenzyl ketone **22**: mp 64.5–65° (lit.[30] 69–70°); ir ($CHCl_3$) 1705 cm^{-1} (C=O); uv (95% EtOH) series of weak (ε 229–430) maxima in the region 240–270 mμ as well as a maximum at 296 mμ (ε 117); nmr (CCl_4) δ 6.8–7.3 (10 H, m, aryl CH) with an AB pattern at 3.08 (2 H, d, J = 13.6 Hz) and 2.55 (2 H, d, J = 13.6 Hz), attributable to the benzylic CH_2 groups, and 1.4–2.5 (8 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 278 (2, M^+), 187 (100), 91 (60), and 78 (32).

E. 2-Methyl-6-benzylcyclohexanone (8).—A mixture of 84 g (0.79 mol) of benzaldehyde, 60 g (0.54 mol) of 2-methylcyclohexanone, 35.2 g (0.88 mol) of sodium hydroxide, 50 ml of 1,2-dimethoxyethane, 270 ml of H_2O, and 192 ml of EtOH was refluxed for 3 hr and diluted with pentane. The organic layer was separated, dried, and distilled to separate 76.7 g (71.7%) of crude 2-methyl-6-benzalcyclohexanone as a yellow liquid, bp 127–130° (0.05 mm). The pure benzal ketone crystallized from hexane as white needles: mp 58–60° (lit.[31] mp 62°); ir (CCl_4) 1685 cm^{-1} (conj C=O); uv maxima (95% EtOH) 221 mμ (ε 6800) and 287 (15,300); nmr (CCl_4) δ 7.1–7.4 (6 H, m, aryl and vinyl CH), 1.3–3.3 (7 H, m, aliphatic CH), and 1.19 (3 H, d, J = 6.3 Hz, CH_3); mass spectrum *m/e* (rel intensity) 200 (100, M^+), 199 (45), 172 (38), 157 (52), 130 (37), 129 (81), 128 (40), 117 (69), 115 (94), 91 (55), and 81 (89).

A solution of 20.0 g (0.100 mol) of 2-methyl-6-benzalcyclohexanone in 200 ml of EtOH was hydrogenated over 0.5 g of Raney nickel catalyst at 22° and 38 psi. The reaction was stopped after 135 min and the crude product was distilled to separate 18.0 g (89.1%) of the ketone **8** as a colorless liquid: bp 110–112° (0.7 mm); $n^{25}D$ 1.5262–1.5280 [lit.[32] bp 167° (20 mm), $n^{10.5}D$ 1.5309]; ir (CCl_4) 1710 cm^{-1} (C=O); uv (95% EtOH) series of weak (ε 245–335) maxima in the region 240–270 mμ as well as a maximum at 285 mμ (ε 202); mass spectrum *m/e* (rel intensity), 202 (78, M^+), 159 (42), 145 (33), 131 (28), 117 (45), 111 (39), and 91 (100). The nmr spectrum indicates that the product is a mixture of cis (major) and trans (minor) isomers; the spectrum (CCl_4) has absorption at δ 6.9–7.3 (5 H, m, aryl CH), 2.8–3.4 (1 H, m, one benzylic CH), 1.2–2.7 (9 H, m, aliphatic CH and one benzylic CH), and two doublets together corresponding to 3 H at δ 1.04 (J = 6.5 Hz) and 0.97 (J = 6.0 Hz). The more intense (*ca.* 80%) methyl signal (at δ 0.97), attributable to an equatorial methyl group in the cis isomer, was not changed when the solvent was changed from CCl_4 to C_6D_6, whereas the weaker (*ca.* 20%) methyl signal (at δ 1.04 in CCl_4) was shifted upfield (to about δ 0.97) when the solvent was C_6D_6. This is the behavior expected of an axial methyl group[33] and corresponds to *trans*-2-methyl-6-benzylcyclohexanone in which one of the favorable conformers will have an axial methyl group. The presence of these two isomers did not interfere with the subsequently described glpc analyses because the two isomers were equilibrated under the conditions required to elute them from various glpc columns.

F. 2,2-Dibenzyl-6-methylcyclohexanone (11).—An ethereal solution containing 37.8 mmol of methyllithium was concentrated under reduced pressure and the organolithium reagent was redissolved in 145 ml of 1,2-dimethoxyethane containing several milligrams of 2,2-bipyridyl. After the solution had been cooled to 0° and treated with 3.82 g (37.8 mmol) of diisopropylamine, 25 ml of a solution containing 10.0 g (35.9 mmol) of 2,2-dibenzylcyclohexanone (**22**) in 1,2-dimethoxyethane was added dropwise and with stirring over 20 min. The resulting solution of the lithium enolate was warmed to about 35° and then 20.2 g (143 mmol) of methyl iodide was added rapidly and with vigorous stirring. After the mixture had been stirred for 5 min, it was partitioned between pentane and saturated aqueous $NaHCO_3$. The organic layer was separated, washed successively with aqueous 5% HCl and aqueous $NaHCO_3$, dried, and distilled. The crude product, 7.94 g (76%) of a colorless liquid collected at 159–170° (0.1 mm) [lit.[34] bp 230–232° (15 mm)], contained (tlc analysis with a silica gel coating and PhH as an eluent) a mixture of the desired ketone **11** (R_f 0.53) and the starting ketone **22** (R_f 0.39). A 1.914-g sample of this product was chromatographed on silica gel to separate 0.435 g of the starting material **22** (eluted with PhH) and 1.426 g (corresponding to a 57% yield) of the methylated ketone **11** as a colorless liquid which failed to crystallize: ir (CCl_4) 1706 cm^{-1} (C=O); uv (95% EtOH) series of weak (ε 218–418) maxima in the region 240–270 mμ as well as a maximum at 300 mμ (ε 97); nmr (CCl_4) δ 6.9–7.3 (10 H, m, aryl CH), 3.16 (1 H, d, J = 13.5 Hz, one benzylic CH), 2.86 (2 H, s, benzylic CH_2), 2.36 (1 Hd, J = 13.5 Hz, one benzylic CH), 1.6–2.5 (7 H, m, aliphatic CH), and 0.97 (3 H, d, J = 6.0 Hz, CH_3); mass spectrum *m/e* (rel intensity) 292 (1, M^+), 201 (90), 117 (19), 115 (15), and 91 (100).

Anal. Calcd for $C_{21}H_{24}O$: C, 86.25; H, 8.27. Found: C, 86.51; H, 8.35.

2-Benzyl-2-methylcyclohexanone (9). General Procedure for the Formation and Alkylation of an Enolate from an Enol Acetate.—Methyllithium (400 mmol, obtained by concentrating an Et_2O solution under reduced pressure) and 20 mg of 2,2-bipyridyl were dissolved in 400 ml of 1,2-dimethoxyethane and the resulting purple solution was cooled to 0°. While the temperature of the solution was kept at 0–10°, 29.3 g (190 mmol) of the enol acetate **13** was added dropwise and with stirring over 35–45 min. To the resulting cold (10°) red-orange (indicating excess methyllithium) solution was added rapidly (15 sec) 68.4 g (400 mmol) of benzyl bromide. The reaction mixture was stirred for 2–2.5 min (during which time the temperature rose to 30°) and then poured into 500 ml of cold (0–10°) saturated, aqueous $NaHCO_3$ and extracted with pentane. The pentane extract was dried, concentrated, and fractionally distillated to separate 31.4–40.8 g of forerun fractions [bp 71° (20 mm) to 87° (0.03 mm), $n^{25}D$ 1.5045–1.5629] containing (glpc analysis, silicone gum, no. XE-60, on Chromosorb P) varying amounts of 2-methylcyclohexanone (retention time, 5.3 min), benzyl bromide (9.0 min), and bibenzyl (22.6 min).[35] Continued distillation afforded 20.7–22.2 g (53–58%) of 2-benzyl-2-methylcyclohexanone (**9**) as a colorless

(26) H. O. House and A. G. Hortmann, *J. Org. Chem.*, **26**, 2190 (1961), and references therein.

(27) R. Cornubert, M. Andre, M. de Demo, R. Joly, and A. Strebel, *Bull. Soc. Chim. Fr.*, **6**, 103 (1939).

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(29) J. M. Conia, C. Nevot, and P. Gosselin, *Bull. Soc. Chim. Fr.*, 1511 (1959); also see J. M. Conia, *Rec. Chem. Progr.*, **24**, 43 (1963).

(30) R. Cornubert, P. Anziani, M. Andre, M. deDemo, and G. Morelle, *Bull. Soc. Chim. Fr.*, **10**, 561 (1943).

(31) W. S. Johnson, *J. Amer. Chem. Soc.*, **65**, 1317 (1943).

(32) R. Cornubert and C. Borrel, *C. R. Acad. Sci.*, **183**, 294 (1926); *Bull. Soc. Chim. Fr.*, **45**, 1148 (1929).

(33) (a) N. S. Bhacca and D. H. Williams, "Applications of Nmr Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 159–182; (b) J. Ronayne and D. H. Williams, *Ann. Rev. Nmr Spectrosc.*, **2**, 83 (1969).

(34) R. Cornubert and H. LeBihan, *C. R. Acad. Sci.*, **186**, 1126 (1928).

(35) The bibenzyl is formed from reaction of benzyl bromide with any excess methyllithium: see H. Gilman and F. K. Cartledge, *J. Organometal. Chem.*, **2**, 447 (1964); H. Gilman and A. H. Haubein, *J. Amer. Chem. Soc.*, **66**, 1515 (1944).

to pale yellow liquid, bp 87–93° (0.03 mm), $n^{25}D$ 1.5322–1.5335 [lit. 178° (27 mm),[34] 147° (1.8 mm),[36] $n^{15}D$ 1.5385[34]]. Glpc analysis (silicone gum, no. XE-60, on Chromosorb P) indicated that this ketone **9** (retention time 46.2 min.) contained less than 5% of the isomeric ketone **8** (43.0 min): ir (CCl_4) 1710 cm^{-1} (C=O); uv (95% EtOH) series of weak (ϵ 134–253) maxima in the region 240–270 mμ with a maximum at 293 mμ (ϵ 70); nmr (CCl_4) δ 6.9–7.3 (5 H, m, aryl CH), 2.78 (2 H, s, benzylic CH_2), 2.2–2.6 (2 H, m, CH_2CO), 1.4–2.0 (6 H, m, aliphatic CH), and 0.95 (3 H, s, CH_3). The most reliable method we found for analyzing mixtures of ketones **8** and **9** consisted of measuring the nmr spectrum of mixtures in C_6D_6; in this solvent the ketone **9** has a characteristic 2 H singlet at δ 2.78 while the isomer **8** has a 1 H multiplet in the region 2.9–3.5 attributable to one of the two benzylic hydrogen atoms in the molecule. This analytical technique indicated that the product of this reaction, **9**, contained less than 2% of its isomer **8**. The mass spectrum of this product has the following relatively abundant peaks: *m/e* (rel intensity) 202 [32, M^+), 91 (100), 55 (22), 44 (35), and 43 (23).

The brown residue (10 g) from the above distillation was triturated with pentane to separate the crude dibenzylated ketone **10** as white needles. A portion of this product was recrystallized from pentane to separate the pure **2,6-dibenzyl-2-methylcyclohexanone (10)** as white needles: mp 106–107° (lit.[34] mp 105°); ir (CCl_4) 1710 cm^{-1} (C=O); uv (95% EtOH) series of weak maxima (ϵ 265–436) in the region 240–270 mμ as well as a maximum at 296 mμ (ϵ 56); nmr (CCl_4) δ 7.0–7.3 (10 H, m, aryl CH), 3.22 (1 H, d of d, J = 12.0 and 3.5 Hz, one benzylic CH), 2.80 (2 H, s, benzylic CH_2), 2.0–2.7 (2 H, m, CHCO and one benzylic CH), 1.3–2.1 (6 H, m, aliphatic CH), and 1.12 (3 H, s, CH_3); mass spectrum *m/e* (rel intensity) 292 (17, M^+), 201 (14), 117 (20), and 91 (100). In C_6D_6 solution, the nmr spectrum differs in that the benzylic CH_2 singlet is shifted downfield to δ 2.94 and the CH_3 singlet is shifted upfield to δ 0.86. These data indicate that the principle conformer present in the crystalline stereoisomer, mp 106–107°, which we have isolated has the methyl group axis.[33] Accordingly, we assign the crystalline product the configuration in which the benzyl groups at C-2 and C-6 are cis. The subsequently described glpc data indicate that the other stereoisomer, 2-methyl-*trans*-2,6-dibenzylcyclohexanone, was also present in the reaction mixture and that the two isomers were being interconverted under the conditions used for glpc analysis.

The results of other small-scale benzylations of the enolate anion **7b** are summarized in eq G. In these experiments, weighed amounts of an internal standard (hexadecane) were added to the crude alkylated product and it was subjected to glpc analysis employing equipment calibrated with known mixtures of authentic samples. For one of the glpc columns (silicone gum, no. SE-52, on Chromosorb P) employed, the following retention times were observed: **2**, 4.2 min; benzyl bromide, 8.0 min; hexadecane, 23.5 min; monobenzyl products **8** and **9** (not resolved), 25.8 min; *trans*-stilbene, 27.7 min; dibenzyl product **11**, 41.6 min; two stereoisomers of dibenzyl product **10** (partially resolved), 43.0 min. Since the monobenzylated products **8** and **9** were not resolved on this column, the proportions of these two isomers present were determined both by the previously described nmr analysis and by glpc analysis (silicone gum no. XE-60, on Chromosorb P). Retention times were as follows: 2,6 isomers **8**, 34.0 min; 2,2 isomer **9**, 36.0 min; and *trans*-stilbene, 39.9 min. The *trans*-stilbene was produced in small amounts in experiments where benzyl bromide was added to reaction mixtures which contained a substantial excess of lithium diisopropylamide.[37] Collected samples from typical reaction mixtures were identified with the previously described authentic samples by comparison of ir spectra and glpc retention times.

2-Methyl-6-benzylcyclohexanone (8). General Procedure for the Formation and Alkylation of an Enolate from Kinetically Controlled Deprotonation of a Ketone with Lithium Diisopropylamide.—A solution of 200 mmol of methyllithium and 45 mg of 2,2-bipyridyl in 400 ml of 1,2-dimethoxyethane was prepared as previously described and then cooled to −50°. Diisopropylamine (21.0 g or 200 mmol) was added dropwise and with stirring over 2–3 min; during this addition external cooling was used to prevent the temperature of the solution from rising above −20°. The resulting reddish-purple solution was stirred at −20° for 2–3 min and then 50 ml of a solution containing 21.3 g (190 mmol) of 2-methylcyclohexanone (**2**) in 1,2-dimethoxyethane was added, dropwise and with stirring over 25 min, during which time the temperature of the solution was kept between −20 and 0°. The resulting reddish-purple (indicating the presence of excess lithium diisopropylamide) solution was rapidly warmed to 30° with stirring and then 68.4 g (400 mmol) of benzyl bromide was added rapidly (15 sec). The resulting mixture was stirred for 6 min (during which time the temperature rose to 50° and then began to fall) and then poured into 500 ml of cold (0–10°) saturated, aqueous $NaHCO_3$ and extracted with pentane. The pentane extract was washed successively with aqueous 5% HCl and with aqueous $NaHCO_3$ and then dried, concentrated, and fractionally distilled. After separation of the forerun [31–34 g, bp 67° (20 mm) to 91° (0.03 mm)] containing 2-methylcyclohexanone and benzyl bromide, the monoalkylated product was collected as 21.3–23.3 g (54–61%) of colorless liquid, bp 91–97° (0.03 mm), $n^{25}D$ 1.5282–1.5360. The monoalkylated product contained (previously described nmr and glpc analyses) 86–90% of the 2,6 isomers **8** and 10–14% of the 2,2 isomer **9**. In some runs a few per cent of *trans*-stilbene was also present.[37] The pure 2,6 isomer **8** was separated from this mixture by selective formylation of the unwanted 2,2 product **9**.[38,39] A mixture of the monoalkylated product (21–23 g or 104–114 mmol) and 3.74 g (50.5 mmol) of freshly distilled ethyl formate was added to a cold (0°) suspension of 2.59 g (47.8 mmol) sodium methoxide in 90 ml of anhydrous diethyl ether which was cooled in an ice bath. After the resulting suspension had been stirred for 10 min, the ice bath was removed and stirring was continued for an additional 50 min. Then the mixture was diluted with 300 ml of H_2O and extracted with ether. The ethereal extract was washed with aqueous 1 *M* NaOH and then dried, concentrated, and distilled. The pure 2-methyl-6-benzylcyclohexanone (**8**) was collected as 16.2–17.3 g of colorless liquid, bp 95–100° (0.3 mm), $n^{25}D$ 1.5299–1.5328, which was identified with the previously described sample by comparison of glpc retention times and ir and and nmr spectra.

This same alkylation reaction was performed on a small scale utilizing the various conditions summarized in eq B–D. An internal standard (hexadecane) was added to the crude alkylated product and it was subjected to analysis by the glpc and nmr methods previously described. On the glpc column (silicone gum, SE-52, on Chromosorb P) used to determine yields in the alkylation of 2-benzylcyclohexanone (**3**), the following retention times were observed: hexadecane, 24.6 min; ketone **3**, 25.7 min; ketone **8** and **9** (not resolved), 27.0 min; dimethylated products from 2-benzylcyclohexanone, 27.5 min.

2-Benzylcyclohexanone (3). General Procedure for the Formation and Alkylation of an Enolate from a Trimethylsilyl Enol Ether.—A mixture of 15.31 g (90 mmol) of the silyl enol ether **18** and 65 ml of an ether solution containing 91 mmol of methyllithium was stirred at 25° for 30 min and then the ether was removed from the suspension of the lithium enolate. The residue was dissolved in 55 ml of 1,2-dimethoxyethane at 25° and then 16.20 g (94.9 mmol) of benzyl bromide was added. The solution, which was heated to boiling by the exothermic reaction, was stirred for 5 min and then partitioned between pentane and 100 ml of saturated aqueous $NaHCO_3$. Concentration and subsequent distillation of the pentane extract separated 0.36 g of forerun [bp 29–119° (1.1 mm), containing cyclohexanone, benzyl bromide, and the products from self-condensation of cyclohexanone] and 9.76 g (58%) of 2-benzylcyclohexanone (**3**) [bp 110–158° (1.1 mm), containing about 10% of the products from the the self-condensation of cyclohexanone]. The residue (3.97 g of yellow liquid) from the distillation was composed of the 2,2-dibenzyl ketone **22** (*ca.* 65%) and the 2,6-dibenzyl ketone **21** (*ca.* 35%). In a comparable reaction, the lithium enolate **19**, prepared from 17.59 g (103.3 mmol) of the silyl enol ether **18** and 105.5 mmol of methyllithium in 75 ml of ether, was separated by centrifugation, washed with ether, and dried under reduced pressure. The resulting solid enolate (9.52 g or 89% yield) was dissolved in 50 ml of 1,2-dimethoxyethane and then treated with 18.51 g (108.1 mmol) of benzyl bromide to yield

(36) S. Boatman, T. M. Harris, and C. R. Hauser, *J. Amer. Chem. Soc.*, **87**, 82 (1965).

(37) For examples of this transformation, see C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *ibid.*, **78**, 1653 (1956); D. R. Bryant, S. D. Work, and C. R. Hauser, *J. Org. Chem.*, **29**, 235 (1964).

(38) This experiment was performed in our laboratories by Mr. Michael J. Umen.

(39) This procedure was developed by W. J. Bailey and M. Madoff, *J. Amer. Chem. Soc.*, **76**, 2707 (1954); F. E. King, T. J. King, and J. G. Topliss, *J. Chem. Soc.*, 919 (1957).

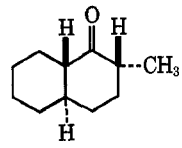
10.58 g (62%) of the monoalkylated ketone **3**, bp 100–160° (1 mm). The distillation residue (2.00 g) contained the dialkylated products **21** and **22**.

The results of a number of small scale alkylations are summarized in eq J. In these reactions known amounts of an internal standard (tetralin) were added to the crude alkylation product before analysis. On the glpc column (Apiezon M on Chromosorb P) used for these analyses, the following retention times were observed: cyclohexanone, 4.0 min; the silyl enol ether **18**, 9.1 min; benzyl bromide, 14.0 min; tetralin, 19.8 min; 2-(1-cyclohexenyl)cyclohexanone and its double bond isomer, 41.0 and 42.4 min; benzyl enol ether **20**, 45.5 min; benzyl ketone **3**, 47.5 min; the 2,2-dibenzyl ketone **22**, 87.0 min; and the 2,6-dibenzyl ketone **21** 93.0 min. The apparatus used for analysis was calibrated with known mixtures of authentic samples and collected samples of the products from representative runs were identified with authentic samples by comparison of the glpc retention times and ir spectra. A collected sample of the selfcondensation product had spectroscopic properties consistent[40] with its formulation as the β,γ-unsaturated ketone, 2-(1-cyclohexenyl)cyclohexanone, accompanied by small amounts of the corresponding α,β-unsaturated isomer: ir (CCl_4) 1710 (strong, unconj C=O), 1685 (weak, conj C=O), and 1620 cm^{-1} (C=C); nmr (CCl_4) δ 5.35 (*ca.* 0.7 H, broad, vinyl CH) and 1.2–3.1 (*ca.* 17 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 178 (72, M^+) 149 (100), 135 (27), 81 (33), 79 (31) 67 (30), and 41 (24).

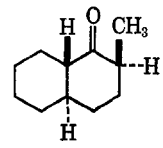
To demonstrate that the *O*-benzyl enol ether **20** does not react with the enolate anion **19** to form the benzyl ketone **3** under the conditions of the alkylation reaction, solutions containing approximately equimolar concentrations of the enolate anion **19** (from the silyl enol ether **18**) and either the benzyl enol ether **20** or the ketone **3** were stirred for 1 hr at 25°. The crude products, isolated as previously described, were mixed with weighed amounts of an internal standard (tetralin) and subjected to the glpc analysis. In one experiment, the recoveries of enol ether **20** and cyclohexanone were 97 and 100%, respectively. In the other experiment, the recovered 2-benzylcyclohexanone (**3**) and cyclohexanone amounted to 98 and 91%; the only other material detected was the previously described 2-(1-cyclohexenyl)cyclohexanone.

2-Methylcyclohexanone (**2**).—The lithium enolate **19**, prepared from 17.0 g (100 mmol) of the silyl enol ether **18**, was separated from ether, dissolved in 120 ml of 1,2-dimethoxyethane, and methylated with methyl iodide to give the results summarized in eq I. The distilled product [8.41 g, bp 153–155° (760 mm)] contained (glpc analysis, Apiezon M suspended on Chromosorb P) *ca.* 8% cyclohexanone (retention time 6.8 min.), *ca.* 75% 2-methylcyclohexanone (**2**, 11.1 min), and *ca.* 17% of dialkylated products (14.8 and 17.2 min). A collected sample of the 2-methyl ketone **2** was identified with an authentic sample by comparison of glpc retention times and ir spectra.

Methylation of 1-Decalone (**1**). **A. Formation of the Enolate Anion by Kinetically Controlled Deprotonation.**—Following previously described procedures, the solution of enolate **4** in 25 ml of cold (−20°) 1,2-dimethoxyethane was prepared from 36 mmol of lithium diisopropylamide and 5.33 g (35.1 mmol) of 1-decalone (**1**). The pink (Ph_3CH indicator) solution was warmed to 26° and then allowed to react with 255 mmol of methyl iodide for 10 min. The crude product, 7.31 g of yellow liquid, contained (glpc analysis) *ca.* 17% of unchanged 1-decalone (**1**), *ca.* 80% of the 2-methyl isomers **5**, and *ca.* 3% of the cis 9-methyl isomer **6**. The 2-methyl-1-decalone mixture was composed of *ca.* 40% of the most stable stereoisomer **5a** and *ca.* 60% of a second stereoisomer believed to have the stereochemistry indicated in structure **5b**. Three different glpc columns were used to analyze the mixtures of decalone derivatives. The retention times observed with the various glpc columns follow. (1) Apiezon M on Chromosorb P: 1-decalone (**1**), 12.3 min; cis 9-methyl isomer **6** accompanied by one or more of the 2-methyl isomers **5**, 16.7 min; *trans*-9-methyl isomer **17** and one or more of the 2-methyl isomers **5**, 19.2 min; dimethylated 1-decalones (isomers not identified), 24.2 min. (2) Carbowax 20M on Chromosorb P: 1-decalone (**1**) and the 2-methyl isomers **5** (not resolved), 31.4 min; cis 9-methyl isomer **6**, 36.3 min; *trans*-9-methyl isomer **17**, 43.8 min. (3) 1,2,3-Tris-(β-cyanoethoxy)propane on Chromosorb P: 2-methyl isomer **5a**, 21.2 min; 2-methyl isomer tentatively assigned stereochemistry **5b** and cis 9-methyl isomer **6** (not resolved), 24.5 min; trans 9-methyl isomer **17**, 31.0 min.



5a



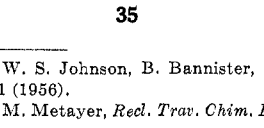
5b

A solution of the crude alkylation product and 0.25 g of $NaOCH_3$ in 50 ml of methanol was refluxed for 1 hr and then concentrated and partitioned between aqueous NaCl and pentane. The mixture of 2-methyl isomers in the recovered product (5.14 g) was composed (glpc analysis) of *ca.* 87% of the most stable isomer **5a** accompanied by *ca.* 9% of the isomer thought to be **5b** and 4% of two minor unidentified components. To remove any remaining 1-decalone, a solution of the crude product, 1.00 g (10.4 mmol) of furfural,[41] 0.60 g (15 mmol) of NaOH, and 4 ml of H_2O in 200 ml of methanol was stirred at 25° for 2 hr, concentrated, acidified (aqueous HCl), and extracted with pentane. The pentane solution was dried, concentrated, and distilled to separate 3.86 g (66%) of 2-methyl-1-decalone, bp 78–80° (1.5 mm), $n^{23}D$ 1.4811. This product contained (glpc analysis) 87% of the most stable isomer **5a** accompanied by 7% of the epimer believed to be **5b**, 3% of the *cis*-9-methyl isomer **6**, and 3% of two minor, unidentified components. This product was identified with the previously described[5a] sample of 2-methyl-1-decalone by comparison of glpc retention times and ir and mass spectra.

B. Formation of the Enolate Anions from the Trimethylsilyl Enol Ethers.—A solution of the enolates **4** in 30 ml of 1,2-dimethoxyethane, prepared from 40 mmol of methyllithium and 7.46 g (33.9 mmol) of the silyl ethers **16** (89% $\Delta^{1,9}$ and 11% $\Delta^{1,2}$ isomer), was cooled to 0° and treated with 8.42 g (59 mmol) of CH_3I. After the mixture had been stirred 40 sec, it was quenched with 50 ml of aqueous 5% HCl and then partitioned between pentane and aqueous NaCl. Distillation of the crude product afforded 4.46 g (79%) of 9-methyl-1-decalone, bp 69–71° (0.6 mm), $n^{23}D$ 1.4874. This product contained (glpc analysis) *ca.* 8% of 1-decalone (**1**), *ca.* 12% of the 2-methyl isomers **5**, *ca.* 54% of the *cis*-9-methyl ketone **6**, *ca.* 15% of the *trans*-9-methyl ketone **17**, and *ca.* 11% of dialkylated products. Collected samples of the 9-methyl ketones **6** and **17** were identified with previously described[5a] samples by comparison of glpc retention times and ir and mass spectra.

Preparation of Authentic Samples of the 2-Heptanone Derivatives. A. 1-Phenyl-3-octanone (**27**).—Condensation of 100 g (0.878 mol) of 2-heptanone with 100 g (0.944 mol) of benzaldehyde in the presence of 6.0 g (0.15 mol) of NaOH and 10 ml of H_2O yielded 58% of crude *trans*-1-phenyl-1-octen-3-one as a yellow liquid, bp 106–110° (0.1 mm). The product crystallized from pentane as white needles: mp 44.5–45.5° (lit.[42] mp 47°); ir (CCl_4), 1690, 1675 (conj C=O), and 1615 cm^{-1} (conj C=C); uv maxima (95% EtOH) 222 mμ (ϵ 11,200) and 288 (21,800); nmr (CCl_4) δ 7.1–7.7 (6 H, m, aryl and vinyl CH), 6.62 (1 H, d, J = 16.6 Hz, vinyl CH), 2.54 (2 H, t, J = 6.7 Hz, CH_2CO), and 0.7–1.9 (9 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 202 (7, M^+), 146 (48), 131 (100), 103 (34), and 77 (20).

The high boiling residue (35 g) also formed in this aldol condensation solidified on standing. Recrystallization from pentane and from hexane separated a white solid, mp 86–92°, believed to be a mixture of the stereoisomers of structure **35**: ir (CCl_4) 1715 (C=O), 1690, 1660 (conj C=O), 1615 (conj C=C), and 980 cm^{-1} (trans CH=CH); uv maximum (95% EtOH), 295 mμ (ϵ 22,200); nmr (CCl_4) δ 6.7–7.4 (11 H, m, aryl and vinyl CH), 6.34 (1 H, d, J = 16.0 Hz, vinyl CH), 3.45 (1 H, q, J =



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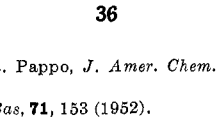

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(40) E. Wenkert, S. K. Bhattacharya, and E. M. Wilson, *J. Chem. Soc.*, 5617 (1964), and references therein.

(41) W. S. Johnson, B. Bannister, and R. Pappo, *J. Amer. Chem. Soc.*, **78**, 6331 (1956).

(42) M. Metayer, *Rec. Trav. Chim. Pays-Bas*, **71**, 153 (1952).

7.0 Hz, CHCO), 2.8–3.2 (1 H, m, CH), 2.71 (2 H, d, J = 7.0 Hz, CH_2CO), 1.9–2.3 (2 H, m, CH_2CO), and 0.3–1.8 (18 H, m, aliphatic CH); mass spectrum m/e (rel intensity) 404 (3, M^+), 202 (13), 131 (100), 103 (30), 99 (18), 77 (16), and 43 (41).

Anal. Calcd for $C_{28}H_{36}O_2$: C, 83.12; H, 8.97. Found C, 83.06; H, 8.93.

The formation of dimers from a Michael reaction also occurred in attempts to generate the enolate from *trans*-1-phenyl-1-octen-3-one. A suspension of NaH (obtained by washing 1.2 g of a 50% dispersion with pentane) in 50 ml of 1,2-dimethoxyethane containing 10.1 g (50 mmol) of *trans*-1-phenyl-1-octen-3-one was stirred at ambient temperature for 6 hr and then partitioned between ether and aqueous $NaHCO_3$. After the ethereal extract had been dried and concentrated, recrystallization of the residual yellow solid from hexane separated 1.2 g of one stereoisomer of the crude diketone **36** as white needles, mp 135–160°. Recrystallization gave a pure stereoisomer of **36**: mp 166–167°; ir (CCl_4), 1720 cm^{-1} (C=O); uv (95% EtOH) a series of weak (ϵ 173–536) maxima in the region 240–275 mμ; nmr ($CDCl_3$) δ 7.0–7.4 (10 H, m, aryl CH), 2.5–3.5 (6 H, m, CH α to CO and phenyl), 0.4–1.6 (20 H, m, aliphatic CH); mass spectrum m/e (rel intensity), 404 (25, M^+), 333 (17), 299 (22), 244 (24), 243 (100), 193 (25), 149 (73), 131 (25), 91 (38), and 43 (50).

Anal. Calcd for $C_{28}H_{36}O_2$: C, 83.12; H, 8.97. Found: C, 83.06; H, 9.12.

A methanol solution of the mother liquors from this separation deposited a second stereoisomer of diketone **36** as white needles: mp 87–88.5°; ir (CCl_4) 1715 cm^{-1} (C=O); uv (95% EtOH) series of weak (ϵ 179–549) maxima in the region 240–270 mμ; nmr (CCl_4) δ 6.8–7.3 (10 H, m, aryl CH), 2.5–3.9 (6 H, m, CH α to CO and phenyl), and 0.4–1.8 (20 H, m, aliphatic CH); mass spectrum m/e (rel intensity), 404 (12, M^+), 348 (16), 299 (22), 277 (25), 243 (48), 193 (45), 160 (100), 131 (41), 117 (53), 115 (32), 104 (36), 99 (31), 91 (48), 71 (26), and 43 (61).

Anal. Calcd for $C_{28}H_{36}O_2$: C, 83.12; H, 8.97. Found: C, 83.02; H, 9.06.

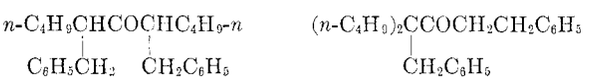
A solution of 20.2 g (0.100 mol) of *trans*-1-phenyl-1-octen-3-one in 150 ml of EtOH was hydrogenated at 25° and 14 psi over the catalyst from 300 mg of PtO_2. After 40 min the H_2 uptake (0.12 mol) ceased and the crude product was isolated and distilled. The 1-phenyl-3-octanone (**27**, 16.9 g or 83%) was collected as a pale yellow liquid: bp 85–88° (0.14 mm); $n^{25}D$ 1.4941 [lit.[42] bp 165–167° (20 mm), $n^{16}D$ 1.5056]; ir (CCl_4) 1720 cm^{-1} (C=O); uv (95% EtOH) series of weak (ϵ 174–220) maxima in the region 240–270 mμ as well as a maximum at 279 mμ (ϵ 49); nmr (CCl_4) δ 6.9–7.2 (5 H, m, aryl CH), 2.0–3.0 (6 H, m, $COCH_2$ and $PhCH_2$), and 0.6–1.8 (9 H, m, aliphatic CH); mass spectrum m/e (rel intensity) 204 (29, M^+), 148 (26), 132 (37), 130 (24), 105 (67), 99 (41), 91 (100), 71 (26), and 43 (47).

B. 3-Benzyl-2-heptanone (26).—A mixture of 53 g (0.47 mol) of 2-heptanone, 58 g (0.55 mol) of benzaldehyde, 125 ml of concentrated aqueous HCl, and 75 ml of 1,2-dimethoxyethane was refluxed for 3.5 hr and then partitioned between pentane and aqueous $NaHCO_3$. The organic layer was dried, concentrated, and distilled to separate 37 g (39%) of 3-benzal-2-heptanone as a yellow liquid: bp 97–98° (0.5 mm); $n^{25}D$ 1.5452 [lit.[42] 154–158° (10 mm); $n^{17}D$ 1.5512]; ir (CCl_4) 1675 (conj C=O) and 1625 cm^{-1} (conj C=C); uv maxima (95% EtOH) 220 mμ (ϵ 8850) and 280 (15,800); nmr (CCl_4) δ 6.9–7.2 (6 H, m, vinyl and aryl CH), 2.26 (3 H, s, CH_3CO), 2.1–2.5 (2 H, m, allylic CH_2), and 0.7–1.6 (7 H, m, aliphatic CH); mass spectrum m/e (rel intensity), 202 (75, M^+), 201 (47), 187 (33), 145 (23), 131 (22), 129 (24), 117 (100), 91 (85), and 43 (54).

A solution of 20.2 g (0.100 mol) of this unsaturated ketone in 150 ml of ethanol was hydrogenated at 25° and 31 psi over 0.5 g of Raney nickel catalyst. The crude product was distilled to separate 16.6 g (81%) of the ketone **26** as a colorless liquid: bp 87–98° (0.25 mm); $n^{25}D$ 1.4968–1.4972 [lit.[42] bp 150° (14 mm.); $n^{16}D$ 1.5040]; ir (CCl_4) 1715 cm^{-1} (C=O); uv (95% EtOH) series of weak (ϵ 180–264) maxima in the region 240–270 mμ; nmr (CCl_4) δ 6.9–7.2 (5 H, m, aryl CH), 2.4–2.9 (3 H, m, CHCO and benzylic CH_2), 1.85 (3 H, s, CH_3CO), and 0.7–1.7 (9 H, m, aliphatic CH); mass spectrum m/e (rel intensity), 204 (7, M^+), 148 (32), 147 (77), 91 (100), 44 (22), and 43 (63).

C. 1-Phenyl-4-benzyl-3-octanone (28).—Dibenzalacetone, mp 110–111° (lit.[43] 111°), was prepared as previously described: ir ($CHCl_3$) 1650 (conj C=O) and 1620 cm^{-1} (conj C=C); uv maxima (95% EtOH) 231 mμ (ϵ 14,300) and 335 (34,100); nmr ($CDCl_3$) δ 7.70 (2 H, d, J = 15.8 Hz, vinyl CH), 7.2–7.6 (10 H, m, aryl CH), and 7.00 (2 H, d, J = 15.8 Hz, vinyl CH); mass spectrum m/e (rel intensity), 234 (100, M^+), 233 (82), 131 (54), 128 (25), 103 (89), 91 (34), 77 (71), and 51 (26). A solution of 20.0 g (85.5 mmol) of this unsaturated ketone in 200 ml of EtOAc was hydrogenated at 23° and 24 psi over 0.5 g of Raney nickel catalyst. After 80 min the H_2 uptake (0.16 mol) ceased and the crude product was separated and distilled. 1,5-diphenyl-3-pentanone was collected as 18.82 g (83%) of colorless liquid: bp 139–145° (0.09 mm); $n^{24}D$ 1.5555–1.5570 [lit.[44] bp 223–227° (15 mm)]; ir (CCl_4) 1720 cm^{-1} (C=O); uv (95% EtOH) series of weak (ϵ 254–426) maxima in the region 240–270 mμ as well as a maximum at 280 mμ (ϵ 81); nmr (CCl_4) δ 6.8–7.3 (10 H, m, aryl CH) and 2.2–3.0 (8 H, m, aliphatic CH_2); mass spectrum m/e (rel intensity), 238 (42, M^+), 134 (26), 133 (61), 106 (26), 105 (23), and 91 (100).

A solution of the lithium enolate in 200 ml of cold (−60°) 1,2-dimethoxyethane was prepared as previously described by reaction of 11.21 g (47.2 mmol) of 1,5-diphenyl-3-pentanone with 60 mmol of lithium diisopropylamide. The purple (2,2-bipyridyl indicator) solution was warmed to 25°, mixed with 8.21 g (50 mmol) of *n*-butyl iodide, stirred for 14 hr, and then partitioned between pentane and aqueous $NaHCO_3$. The organic solution was washed successively with aqueous 10% HCl and aqueous $NaHCO_3$ and then dried and concentrated. Distillation afforded 10.93 g of colorless liquid as fractions, bp 135–146° (0.1 mm), $n^{23.5}D$ 1.5359–1.5431, which contained (glpc analysis, silicone fluid, no. 710, on Chromosorb P) varying proportions of 1,5-diphenyl-3-pentanone (retention time 30.0 min, *ca.* 27% recovery), 1-phenyl-4-benzyl-3-octanone (**28**, 47.6 min, *ca.* 40% yield), and one or both of the dialkylated products **37**, (73.6 min, *ca.* 9% yield). A collected (glpc) sample of the dialkylated material **37** had ir absorption (CCl_4) at 1715 cm^{-1} (C=O); mass



37a **37b**

spectrum m/e (rel intensity) 350 (1, M^+), 161 (15) and 91 (100). A collected (glpc) sample of the ketone **28** was obtained as a colorless liquid: bp 146–147° (0.08 mm); $n^{23.5}D$ 1.5331; ir (CCl_4) 1715 cm^{-1} (C=O); uv (95% EtOH) series of weak (ϵ 268–444) maxima in the region 240–270 mμ as well as a maximum at 290 mμ (ϵ 163); nmr (CCl_4) δ 6.7–7.2 (10 H, m, aryl CH), 2.1–3.0 (7 H, m, benzylic CH and CHCO), and 0.6–1.6 (9 H, m, aliphatic CH); mass spectrum m/e (rel intensity) 294 (13, M^+), 238 (22), 237 (32), 133 (27), 105 (40), and 91 (100).

Anal. Calcd for $C_{21}H_{26}O$: C, 85.66; H, 8.90. Found: C, 85.77; H, 8.91.

D. 1-Phenyl-2-benzyl-3-octanone (29b).—The usual procedure was employed to form the lithium enolate from 10.6 g (51.8 mmol) of 1-phenyl-3-octanone (**27**) and 60 mmol of lithium diisopropylamide in 235 ml of 1,2-dimethoxyethane. After 8.97 g (52.5 mmol) of benzyl bromide had been added, the mixture was stirred at ambient temperature and aliquots were removed periodically, hydrolyzed, and mixed with an internal standard (hexadecane) for glpc analysis. After 25 min the calculated yields were 49% of unchanged ketone **27**, 35% of ketone **29b**, and 15% of ketone **28**. Two glpc columns were employed for this analysis; on a column packed with silicone gum SE-52 on Chromosorb P retention times were for benzyl bromide, 6.0 min; hexadecane, 20.2 min; ketone **27**, 21.6 min; ketone **29b**, 36.0 min; and ketone **28**, 37.2 min. The retention times for a glpc column packed with silicone fluid no. 710 on Chromosorb P follow: ketone **29b**, 13.8 min, and ketone **28**, 15.6 min. The reaction mixture was stirred for 12 hr and then partitioned between pentane and aqueous $NaHCO_3$. Distillation of the organic phase separated 3.24 g (32%) of the starting ketone **27**, bp 90–115° (0.1 mm), $n^{23.5}D$ 1.5056, and 4.46 g (30%) of a mixture of monoalkylated products, bp 142–144° (0.1 mm), $n^{23.5}D$ 1.5301–1.5320, containing 61% of ketone **29b** and 39% of ketone **28**. A pure sample of ketone **29b** was collected (glpc): ir (CCl_4) 1715 cm^{-1} (C=O); uv (95% EtOH) series of weak (ϵ 303–476) maxima in the region 240–270 mμ and a maximum at 287 mμ (ϵ 129); nmr (CCl_4) δ 6.9–7.3 (10 H, m, aryl CH), 2.4–3.1 (5 H, m, benzylic CH and CHCO), and 0.5–2.0 (11 H, m, aliphatic CH); mass

(43) C. R. Conrad and M. A. Dolliver, "Organic Syntheses," Collect. Vol. 2, Wiley, New York, N. Y., 1943, p 167.

(44) J. M. Conia and P. Gosselin, *Bull. Soc. Chim. Fr.*, 836 (1961).

spectrum *m/e* (rel intensity) 203 (29), 91 (100), 71 (20), and 43 (44).

Anal. Calcd for $C_{21}H_{26}O$: C, 85.66; H, 8.90. Found: C, 85.40; H, 8.91.

The Benzylation of 2-Heptanone (23).—Solutions of lithium enolates were prepared from the ketone **23**, the enol acetate **24**, or the silyl enol ether **30** (contains 84% $\Delta^{1,2}$ and 16% $\Delta^{2,3}$ isomers) by the methods previously described. The results of the benzylation reactions are summarized in eq K and L. For small scale reactions the crude alkylated products were mixed with a weighed amount of internal standard (hexadecane) and analyzed by glpc (silicone gum SE-52 on Chromosorb P). The retention times of the various components follow: ketone **23**, 3.4 min; benzyl bromide, 8.4 min; ketone **26**, 19.6 min; hexadecane, 20.6 min; ketone **27**, 22.2 min; ketone **29b**, 34.0 min; and ketone **28**, 37.6 min. The glpc apparatus was calibrated with known mixtures of authentic samples and collected (glpc) samples of products from representative reactions were identified with authentic samples by comparison of glpc retention times and ir spectra. In certain of the alkylation experiments a third dialkylated product, thought to be **29a**, was also detected (retention time, 37.0 min on a glpc column packed with silicone gum SE-52 Chromosorb P). On a glpc column packed with silicone fluid no. 710 on Chromosorb P, retention times were for **29b**, 34.0 min; **29a**, 36.4 min; and **28**, 38.8 min. The nmr spectra (CCl_4) of collected samples containing this component **29a** had an additional singlet at δ 1.75 ($COCH_3$). Although we did not obtain a sufficient amount of this ketone **29a** for complete characterization, the spectra of a collected sample are consistent with the structure assigned: ir (CCl_4) 1705 (C=O) and 1355 cm^{-1} (CH_3CO); mass spectrum *m/e* (rel intensity), 203 (28), 147 (46), 91 (65), and 43 (100).

In a preparative reaction performed in dilute solution where alkylation was relatively slow, the enolate from 11.06 g (87 mmol) of 2-heptanone (**23**) and 116 mmol of lithium diisopropylamide was allowed to react for 2.5 hr at 25° with 17.5 g (102 mmol) of benzyl bromide in 500 ml of 1,2-dimethoxyethane. Distillation of the crude product separated 5.6 g of forerun [bp 32° (60 mm) to 95° (8 mm), mainly 2-heptanone], 8.0 g (41%) of monobenzylated products [bp 70–80° (0.08 mm), $n^{25}D$ 1.4912–1.5071, primarily ketone **26**], and 3.3 g (12%) of a mixture of dibenzylated ketones **28** and **29b** [bp 131–138° (0.08 mm), $n^{25}D$ 1.5203–1.5281].

Registry No.—**1**, 583-60-8; **3**, 946-33-8; **5a**, 29478-32-8; **5b**, 29478-33-9; *cis*-**8**, 29478-34-0; *trans*-**8**, 29478-35-1; **9**, 1206-21-9; **10**, 29478-36-2; **11**, 29494-41-5; **20**, 29494-42-6; **21**, 7382-10-7; **22**, 7382-11-8; **26**, 29494-51-7; **27**, 6047-99-0; **28**, 29494-45-9; **29a**, 29494-46-0; **29b**, 29494-47-1; **35**, 29478-38-4; **36**, 29494-48-2; 1,1-dibenzyloxycyclohexane, 29494-49-3; 2-methyl-6-benzalcyclohexanone, 29494-50-6; *trans*-1-phenyl-1-octen-3-one, 29478-39-5; 3-benzal-2-heptanone, 10225-39-5; 1,5-diphenyl-3-pentanone, 5396-91-8.

Notes

A Comparison of Various Tetraalkylammonium Salts as Supporting Electrolytes in Organic Electrochemical Reactions[1]

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Received February 10, 1971

In both polarographic measurements[2a,b] and preparative electrochemical reactions[2a,c–e] with organic substrates, it has become common to use certain tetraalkylammonium salts as supporting electrolytes, especially with aprotic organic solvents such as acetonitrile, dimethylformamide (DMF), hexamethylphosphoramide (HMP), tetrahydrofuran (THF), or 1,2-dimethoxyethane.[3] In such aprotic solvents, electrochemical reductions at a mercury cathode may be performed at highly negative potentials (−2.5 to −2.9 V *vs.* sce), the reduction potential ultimately being limited by the reduction of the quarternary ammonium cation **1** to form an amalgam **2**.[4] Although a variety of tetraalkyl-

$$R_4N^+ \xrightarrow[\text{Hg cathode}]{e^-} (R_4N)Hg_n$$

1 **2**, n = 12–13

ammonium salts have been prepared and studied,[3,4a,b,5] the salts most commonly used in electrochemical studies have been the readily available tetraethylammonium, tetra-*n*-propylammonium, and tetra-*n*-butylammonium salts, the counterions being iodide, bromide, chloride, perchlorate, and tetrafluoroborate. For polarographic measurements, the selection of a particular supporting electrolyte from among this group of salts is often not critical[6] since these measurements involve very small cell currents and low concentrations of electrolytes. However, the choice becomes more demanding for preparative electrochemical cells. Since relatively high cell currents are involved, it is important to keep the electrical resistance of the cell as low as practical to

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(1) This research has been supported by Public Health Service Grant No. 1-RO1-CA-10933 from the National Cancer Institute.

(2) (a) L. Meites, "Polarographic Techniques," 2nd ed, Interscience, New York, N. Y., 1965; (b) O. H. Müller, "Technique of Organic Chemistry," A. Weissberger, Ed., Vol. 1, Part 4, 3rd ed, Interscience, New York, N. Y., 1960, pp 3155–3279; (c) L. Meites, ref 2b, pp 3281–3333; (d) S. Swann, Jr., "Technique of Organic Chemistry," A. Weissberger, Ed., Vol. 2, 2nd ed, Interscience, New York, N. Y., 1956, pp 385–523; (e) M. J. Allen, "Organic Electrode Processes," Reinhold, New York, N. Y., 1958.

(3) For a review of the properties of these solvents and a brief survey of supporting electrolytes, see C. K. Mann, "Electroanalytical Chemistry," A. J. Bard, Ed., Vol. 3, Marcel Dekker, New York, N. Y., 1969, pp 57–134.

(4) (a) B. C. Southworth, R. Osteryoung, K. D. Fleischer, and F. C. Nachod, *Anal. Chem.*, **33**, 208 (1961); (b) J. D. Littlehailes and B. J. Woodhall, *Discuss. Faraday Soc.*, 187 (1968); (c) J. Myatt and P. F. Todd, *Chem. Commun.*, 1033 (1967); (d) analogous amalgams are formed by the reduction of phosphonium and sulfonium salts [W. R. T. Cottrell and R. A. N. Morris, *ibid.*, 409 (1968)].

(5) For examples, see (a) J. E. Gordon, *J. Amer. Chem. Soc.*, **87**, 4347 (1965); (b) T. G. Coker, J. Ambrose, and G. J. Janz, *ibid.*, **92**, 5293 (1970).

(6) J. P. Petrovich [*Electrochim. Acta*, **12**, 1429 (1967)] has reported changes in the values for polarographic half-wave potentials which appear to depend on the size of the quaternary ammonium cation.