Reaction of Dilithium Derivatives of Oximes with Electrophiles. Regiospecific Substitution of Ketones

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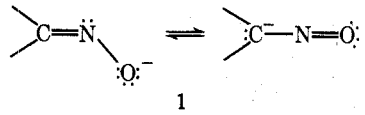
Dilithium derivatives of ketoximes react with alkyl halides and carbonyl compounds to give α-substituted oximes. The position of substitution is governed by the configuration of the oxime. The intermediate monolithio oximes are configurationally stable, allowing successive substitution on the same carbon. Since no oxime exchange is observed with carbonyl compounds, directed aldol condensation is possible.

Many methods have been developed for the introduction of a carbon chain onto the α carbon of a ketone, an important one being alkylation of an enolate or equivalent species. For example, potassium enolates, formed from the ketone with potassium hydride,[1] enamines, from the ketone and a secondary amine,[2] metalloenamines, from ketone and primary amine (via an imine) and an organometallic reagent,[3] all have been developed as a means of introduction of the alkyl group into a ketone. A serious problem which arises in these routes is the lack of control over the position of alkylation if the ketone has two different activated carbons. We now find that the dilithium derivatives of ketoximes, formed from the oxime and 2 equiv of alkyllithium reagent, react with electrophilic reagents (alkyl halides and carbonyl compounds), and that the reaction is regiospecific, the position of substitution being controlled by the stereochemistry of the oxime.

Dilithiation of oximes has previously been demonstrated.[4,5] The oxime of acetophenone was alkylated with benzyl chloride, and oximes of several substituted acetophenones and α-tetralone, cyclopentanone, and cyclohexanone were acylated and cyclized to isoxazoles.[5] Apparently the stereochemical features of the reactions were not examined.

Of all the azomethine ketone derivatives, oximes have been the most thoroughly studied. Generally oximes are configurationally stable, and configuration may be fairly reliably assigned.[6] An anion of an oxime would be expected to have less configurational stability than the oxime itself, since one contributing structure (1) has lost its stereochem-



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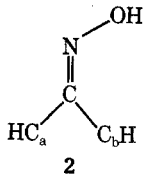
ical identity. However, in none of our studies at −78° or at room temperature (with the possible exception of mesityl oxide oxime) have we observed loss of stereochemical integrity. The configuration would be expected to be maintained in the dianion (2″), since chelation would be expected to play an important role.[4,7] It is this chelation, we believe, that directs the metalation onto that α carbon cis to the oxime hydroxyl group, and which is responsible for the regioselectivity of the reactions reported here. It is interesting to note that although azines, imines, and phenylhydrazones also can show stereoisomerism of the type shown by oximes, and chelation is apparently important in their metal



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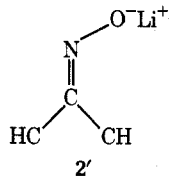

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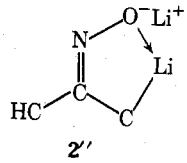
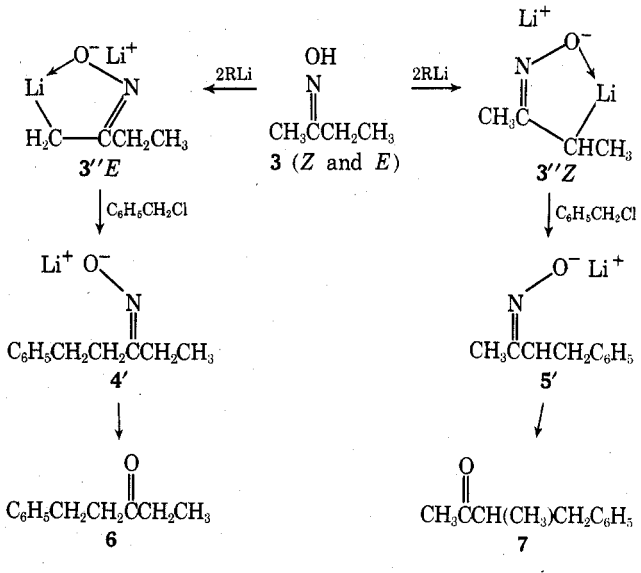


2″

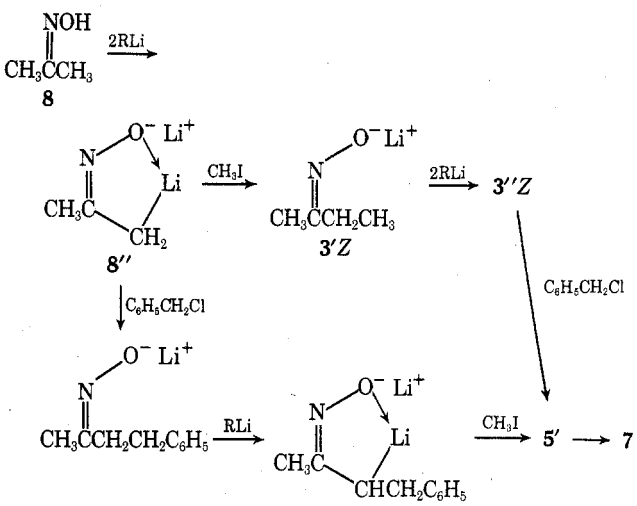
derivatives, no directive effect of geometry has been observed.[3-5]

The oxime prepared from 2-butanone consists of 72% of the *E* and 28% of the *Z* isomer.[8] When a solution of this oxime mixture in tetrahydrofuran was treated with 2 molar equiv of butyllithium, a two-step reaction could be observed. The first half of the butyllithium caused the solution to become white (milky), but the mixture finally became clear and yellow when the second half had been added. The lithium salt (2′) is apparently not completely soluble in the THF–hexane medium, but is converted by the second equivalent of butyllithium to the soluble dilithio derivative (2″). When the yellow solution was treated with 1 mol of benzyl chloride, the yellow color was discharged and the milky appearance noted. After aqueous work-up of the reaction and hydrolysis of the resulting oximes, gas chromatography showed two products in 73:27 ratio, identified (separately) by NMR as, respectively, 1-phenyl-3-pentanone (6) and 3-methyl-4-phenyl-2-butanone (7). This experiment was interpreted as a conversion of the mixture of oximes (3), each stereoselectively, to the corresponding dilithio derivative (3″*E* and 3″*Z*), benzylation without change in configuration to the two lithium salts (4′ and 5′), and hydrolysis to the two isomeric ketones (6 and 7).



That the formation of the dilithio derivative from each oxime is truly stereoselective, and the agreement of product isomer distribution with oxime stereoisomer distribution is not simply a coincidence, was demonstrated by sequential methylation and benzylation of acetone oxime. When acetone oxime (8) was converted to its dilithio derivative (8″) and treated with 1 equiv of methyl iodide, only the lithium salt of the *Z* oxime (3′*Z*) was produced; 3′*Z* was

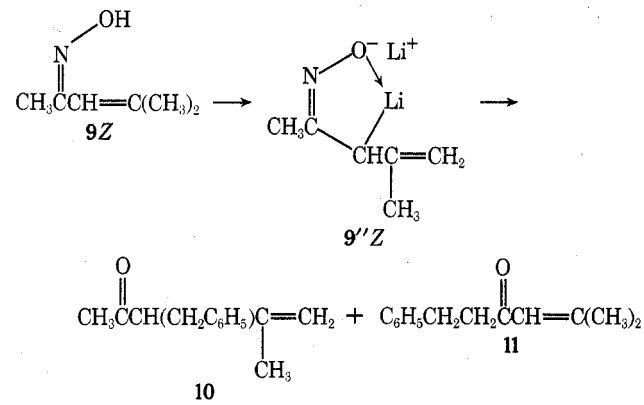
converted to a single dilithio derivative (3″Z) by reaction with a third mole of butyllithium. Reaction of this dilithio derivative with benzyl chloride gave, after hydrolysis, exclusively ketone 7 (67% yield from acetone oxime). Similarly, benzylation of 8″ followed by lithiation and methylation again gave isomer 7 (64% yield from acetone oxime; 1% of isomer 6 was indicated by gas chromatography).



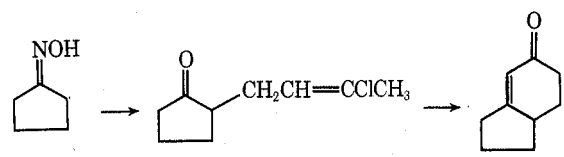
It would be gratifying to report that this method of alkylation is completely successful, but candor compels us to state that attempts to introduce a third alkyl group onto the same carbon atom of acetone failed completely, and in no case have we been successful in alkylating a tertiary carbon atom. Apparently the metalation step fails, since either treatment of the reaction mixture containing 5′ (from either sequence) with a fourth mole of butyllithium, treatment of a Z oxime (such as 5) from a secondary alkyl ketone, or a dialkylation series on a ketoxime such as cyclohexanone oxime did not give the expected yellow solution indicating formation of a dilithio derivative (2″), but generally gave brownish solutions, reaction of which with alkyl halides did not give the desired product. The oxime of 3-methyl-2-butanone was reported to consist of 14% of the Z and 86% of the E isomer.[8] When this mixture of oximes was benzylated via the dilithio derivative the product consisted of 71% of 2-methyl-5-phenyl-3-pentanone, 17% of 1,2-diphenylethane, and 12% of unidentified material which was not 3,3-dimethyl-4-phenyl-2-butanone. Thus it appears that only the E isomer of the oxime undergoes metalation and alkylation.

The oxime obtained directly from an unsymmetrical ketone is usually either mainly or completely that isomer with the hydroxyl trans to the larger group. Thus 2-methylcyclohexanone yields an oily oxime which shows two spots on TLC, but from which the crystalline E isomer, mp 42.5–43.5°, can be obtained. Beckmann rearrangement of the crystalline oxime produces in 69% yield a single lactam, 6-heptanolactam. When cyclohexanone oxime was methylated via its dilithio derivative, none of the E oxime was detected in the product by TLC (a small amount of cyclohexanone oxime was indicated), and Beckmann rearrangement gave 2-methylhexanolactam and 6-heptanolactam in a ratio of 9:1.[9] Similarly, 2-benzylcyclohexanone yields a crystalline (E) oxime, mp 125.5–126°. From the benzylation of cyclohexanone oxime we obtained the crystalline Z oxime, mp 103.6–104.4°, which was converted to the E oxime (mp 125°) when held at 130° for 3 min. Thus this alkylation is an excellent method for stereospecific synthesis of thermodynamically less favored oxime isomers.

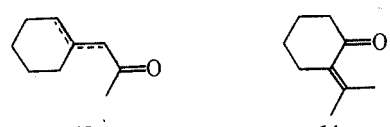
Mesityl oxide forms a mixture of oximes (65% E, 35% Z by NMR), from which the hydrochloride of the Z oxime can be crystallized, and pure crystalline Z oxime (9Z) obtained. When the dilithio Z oxime (9″Z) was benzylated, hydrolysis afforded a mixture consisting of 62% of 3-benzyl-4-methyl-4-penten-2-one (10) and 21% of 1-phenyl-5-methyl-4-hexen-3-one (11). Benzylation of the mixture of oximes (65% E) afforded a mixture containing 71% of 11 and 11% of 10. The oxime of mesityl oxide is more labile than those discussed previously, and formation of 11 from 9Z does not indicate that the reaction is not stereoselective.[10]



Alkylation of cyclopentanone, difficult by other methods owing to the tendency of the ketone to undergo aldol condensation in the presence of basic reagents, was accomplished via the oxime in fair yield. From cyclopentanone oxime 2-butylcyclopentanone was obtained in 59% yield (from butyl iodide), 2-allylcyclopentanone in 64% yield (from allyl bromide), and 2-benzylcyclopentanone in 64% yield. Also, cyclopentanone oxime was converted to 5,6,7,8-tetrahydroindan-5-one (12) by alkylation with 1,3-dichloro-2-butene, hydrolysis to the ketone, and cyclization with sulfuric acid.



Aldol Condensation. The problems associated with directing the aldol condensation between two carbonyl compounds toward one of the four products have been discussed elsewhere.[11] The most successful method has been the reaction of a lithio imine with a ketone.[12] We have found that dilithio oximes react with carbonyl compounds to give aldols, and do not observe exchange or other side reactions which plague the previous methods. Thus from dilithio acetone oxime and cyclohexanone were obtained cyclohexylideneacetone and cyclohexenylacetone (13), while from dilithio cyclohexanone oxime and acetone was obtained isopropylidenecyclohexanone (14).



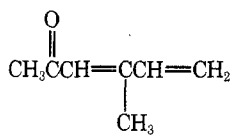
Conjugate Addition Reactions. It is interesting that when conjugate addition reactions were attempted between dilithio oximes and Michael acceptors none of the 1,4 adduct was produced. When dilithio acetone oxime was treated with 3-buten-2-one, none of the expected[13] conjugate addition product was obtained, but the dienone 15 was obtained in 17% yield. Acrolein with 8″ also gave dienone 16

Table I
Alkylation and Aldol Condensation of Dilithio Oximes

Oxime	Alkylating agent	Registry no.	Oxime cleavage[a]	Product	Yield, %
$CH_3\overset{\overset{NOH}{\|}}{C}CH_3$ (8)	$C_6H_5CH_2Cl$	100-44-7	A	$C_6H_5CH_2CH_2\overset{\overset{O}{\|}}{C}CH_3$	72
8	C_4H_9I	542-69-8	B	$C_5H_{11}COCH_3$	63[b]
 (20)	$C_6H_5CH_2Cl$		B	$2\text{-}C_6H_5CH_2C_6H_9O$	77
20	$CH_2{=}CHCH_2Br$	106-95-6	B	$2\text{-}CH_2{=}CHCH_2C_6H_9O$	65
20	C_4H_9I		A	$2\text{-}C_4H_9C_6H_9O$	59
20	C_4H_9Br	109-65-9	A	$2\text{-}C_4H_9C_6H_9O$	35
20	C_4H_9Cl	109-69-3	A	$2\text{-}C_4H_9C_6H_9O$	24
20	C_4H_9I		C	$2\text{-}C_4H_9C_6H_9O$	58
 (21)	$C_6H_5CH_2Cl$		D	$2\text{-}C_6H_5CH_2C_5H_7O$	64
21	C_4H_9I		A	$2\text{-}C_4H_9C_5H_7O$	59
21	$CH_2{=}CHCH_2Br$		B	$2\text{-}CH_2{=}CHCH_2C_5H_7O$	64
8	1. CH_3I 2. $C_6H_5CH_2Cl$	74-88-4	A	$CH_3COCH(CH_3)CH_2C_6H_5$	67
8	1. $C_6H_5CH_2Cl$ 2. CH_3I		D	$CH_3COCH(CH_3)CH_2C_6H_5$	64
8	$(C_6H_5)_2C{=}O$	119-61-9	A[c]	$(C_6H_5)_2C{=}CHCOCH_3$	55
8		108-94-1	A	13	51
20	CH_3COCH_3	67-64-1	B[c]	14	48
20	CH_3CHO	75-07-0	A	$2\text{-}CH_3CH{=}C_6H_8O$	45
8	$CH_3\overset{\overset{O}{\|}}{C}CH{=}CH_2$	78-94-4	B	$CH_3\overset{\overset{O}{\|}}{C}CH{=}C(CH_3)CH{=}CH_2$	17
8	$CH_2{=}CHCHO$	107-02-8	B	$CH_3\overset{\overset{O}{\|}}{C}CH{=}CHCH{=}CH_2$	15
$CH_3CH_2CH{=}NOH$	$C_6H_5CH_2Cl$		B	$C_6H_5CH_2CH(CH_3)CH{=}O$	37
21	$ClCH_2CH{=}CClCH_3$	926-57-8	B	$CH_3CCl{=}CHCH_2C_5H_7O$	54[d]

[a] Yields are based on ketone isolated after hydrolysis of the oxime. Method A employed $Cr(OAc)_2$ with the oxime acetate; see ref 15. Method B employed $TiCl_3$; see ref 16. Method C employed $Na_2S_2O_5$; see ref 17. Method D employed $Ce(NH_4)_2(NO_3)_6$; see ref 18. [b] 2-Heptanone oxime was isolated in 84% yield. We believe that the yields of the oximes in these reactions are substantially higher than the yields of ketones indicated. [c] Hydroxy ketones were obtained from hydrolysis of the oximes; dehydration was effected by steam distillation from a solution containing oxalic acid. [d] After distillation the oxime was obtained in 71% yield. The ketone was cyclized to 5,6,7,8-tetrahydroindan-5-one; see Experimental Section.

in 15% yield, and acrylonitrile or ethyl acrylate with 8″ gave only resinous material.



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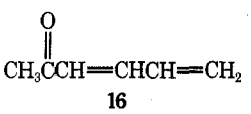

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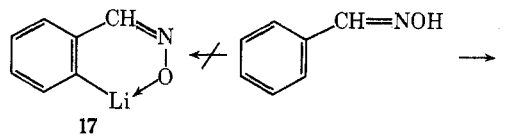
Aldoximes. The alkylation of dilithio aldoximes was not successful. From propionaldehyde oxime the benzylated material was obtained in 33% yield, but attempts to alkylate acetaldehyde oxime gave no identifiable product. Benzaldoxime was of interest because of the possibility of a six-membered chelate to give ortho metalation (17), but reaction of benzaldehyde oxime with 2 mol of butyllithium



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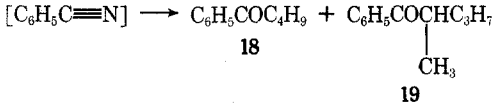

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followed by methyl iodide gave 1-phenylpentanone (18) and 2-methyl-1-phenylpentanone (19), presumably via benzonitrile. Examination of the product mixture from acetaldoxime by infrared spectrometry revealed absorption at 2460 cm^{-1}, suggestive of a nitrile.

Finally, since α-oximino ketones are readily made by nitrosation of ketones, it was of interest to examine such an oxime, which would allow β-alkylation of a ketone. However, 2,3-butanedione monoxime reacted with butyllithium to give the carbonyl adduct, and hydrolysis gave 3-hydroxy-3-methyl-2-heptanone. Butylmagnesium bromide has similarly been reported to add to the carbonyl group of this oxime.[14]

The results of these experiments are summarized in Table I.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus; the thermometer was calibrated with the standards provided. Infrared spectra were determined on a Perkin-Elmer Model 337 spectrometer; NMR spectra on a Varian A-60 spectrometer.

Preparation of Oximes. Generally oximes were prepared in aqueous ethanol from the ketone, hydroxylamine hydrochloride, and sodium hydroxide. Crystalline oximes were recrystallized from hexane or from ethanol. Oximes of 2-butanone, 3-methyl-2-buta-

none, mesityl oxide, benzaldehyde, acetaldehyde, and propionaldehyde were distilled before recrystallization.

Alkylation of Oximes. Since the procedures for the reactions were so similar, a few representative experiments are described in detail. In general the oxime was hydrolyzed without purification. Yields in Table I are yields of distilled ketone. Methods of cleavage of oximes are reported in ref 15–18. Reactions with ketones gave aldol oximes, which were cleaved to aldols in a separate step and dehydrated.

Alkylation of Cyclopentanone Oxime. 5,6,7,8-Tetrahydro-5-indanone. To a stirred solution of 5 g (0.05 mol) of cyclopentanone oxime in 70 ml of tetrahydrofuran at room temperature was added during 5 min 60 ml (0.1 mol) of 1.66 M butyllithium in hexane. After 30 min a solution of 6.3 g (0.05 mol) of 1,3-dichloro-2-butene was added to the yellow-brown lithium derivative during 15 min. The resulting light brown solution was stirred for 1 hr, and 40 ml of water was added. The organic layer was separated, combined with an ether extract of the aqueous layer, dried over magnesium sulfate, and evaporated. Distillation of the residue gave 7.7 g (71%) of 2-(3′-chloro-2′-butenyl)cyclopentanone oxime: bp 131–135° (1.3 mm); ir (film) 3240, 1660, 1656 cm^{-1}; NMR (CCl_4) δ 9.76 (s, 1 H, OH), 5.50 (t, 1 H, vinyl), 2.42 (m, 5 H, α-CH, α-CH_2, allylic CH_2), 2.10 (s, 3 H, CH_3), 1.75 (m, 4 H, CH_2). The oxime was hydrolyzed by the method of Timms[16] to 6.39 g (54% overall) of 2-(3′-chloro-2′-butenyl)cyclopentanone: bp 93–95° (1.2 mm); ir (film) 1736, 1665 cm^{-1}; NMR (CCl_4) δ 5.48 (t, 1 H, vinyl), 2.70–1.30 (overlapping peaks, 12 H).

A portion of the chloro ketone was cyclized. A mixture of 4.3 g (0.025 mol) of ketone and 6 ml of 90% sulfuric acid was stirred at room temperature overnight, poured into 50 g of ice, and extracted with ether. The ethereal solution was dried over magnesium sulfate and concentrated. The residue, 3.4 g, was shown by gas chromatography to consist of 1.6 g of 5,6,7,8-tetrahydroindan-5-one (33% from cyclopentanone oxime) [ir (film) 1660, 1620 cm^{-1}; NMR (CCl_4) δ 5.74 (m, 1 H, vinyl), 2.8–1.1 (overlapping peaks, 11 H); 2,4-dinitrophenylhydrazone mp 196.5–197.5° (lit.[19] 199.5°)] and 1.8 g of 2-hydroxy-2-methylbicyclo[3.2.1]octan-8-one [ir (film) 3400, 1750 cm^{-1}; NMR (CCl_4) δ 2.67 (s, 1 H, OH), 1.84 (overlapping peaks, 10 H), 1.33 (s, 3 H, CH_3)]. The samples for spectra were collected from the gas chromatograph.

Twofold Alkylation of Acetone Oxime. 3-Methyl-4-phenyl-2-butanone. To a solution of 1.46 g (0.05 mol) of acetone oxime in 70 ml of THF was added during 5 min 60 ml (0.1 mol) of 1.66 M butyllithium in hexane. The yellow solution was stirred for 30 min in an ice bath. A solution of 7.46 g (0.053 mol) of methyl iodide in 30 ml of THF was added slowly. The resulting milky white suspension was allowed to warm to room temperature and 34 ml (0.056 mol) of butyllithium was added. The yellow solution was stirred for 30 min and a solution of 6.33 g (0.05 mol) of benzyl chloride in 30 ml of THF was added. The resulting yellow solution was stirred for 1 hr, 50 ml of water was added, and the aqueous solution was separated and extracted with ether. The combined organic solution was dried over magnesium sulfate and evaporated. An aliquot (two-fifths) of the crude oxime was converted to the ketone by the method of Corey.[15] Distillation gave 2.16 g (67%) of 3-methyl-4-phenyl-2-butanone: bp 53–57° (0.05 mm) [lit.[20] 72–73.5° (0.5 mm)]; NMR (CCl_4) δ 7.10 (s, 5 H, Ar), 2.70 (m, 1 H, α-CH), 1.94 (s, 3 H, CH_3), 1.02 (d, 3 H, CH_3); 2,4-dinitrophenylhydrazone mp 75–77° (lit.[21] 76–77°). Gas chromatography indicated the ketone to be homogeneous (the isomers 6 and 7 were separated by GC).

Aldol Condensation. 2-Ethylidenecyclohexanone. Dilithio cyclohexanone oxime was prepared from 5.65 g (0.05 mol) of cyclohexanone oxime in 70 ml of THF and 0.1 mol of butyllithium (60 ml of 1.66 M solution). The yellow solution was stirred in a dry ice–acetone bath for 15 min, and a solution of 2.64 g (0.05 mol) of acetaldehyde in 40 ml of THF was added. The solution was allowed to warm to room temperature and 40 ml of saturated brine was added. The aqueous layer was extracted with 80 ml of a 2:1 mixture of ether and acetone. The organic solutions were combined, dried over magnesium sulfate, and evaporated. The crude oxime was hydrolyzed by the method of Corey[15] to give 2-(1′-hydroxyethyl)cyclohexanone. The crude aldol was combined with 45 g (0.5 mol) of oxalic acid and 300 ml of water and distilled. The distillate was saturated with sodium chloride and extracted with ether. The ethereal solution was dried over magnesium sulfate and distilled to give 2.88 g (46%) of 2-ethylidenecyclohexanone: bp 88–91° (12 mm) [lit.[22] 68–70° (7 mm)]; ir (film) 1695, 1622 cm^{-1}; NMR (CCl_4) δ 6.58 (quartet of triplets, 1 H, vinyl, J_q = 7, J_t = 2 Hz), 2.67–1.17 (overlapping t and m, 4 H, α-CH_2, allylic CH_2), 1.70 (doublet of triplets, 3 H, CH_3, J_d = 7, J_t = 1 Hz), 1.82 (m, 4 H, CH_2); 2,4-dinitrophenylhydrazone mp 216.5–218° (lit.[22] 219–220°).

Isolation of a Less Stable Oxime. 2-Benzylcyclohexanone (*Z*)-Oxime. To a yellow solution of dilithio cyclohexanone oxime, prepared from 5.65 g (0.05 mol) of cyclohexanone oxime in 70 ml of THF and 60 ml of 1.66 M butyllithium (0.1 mol), was added a solution of 6.33 g (0.05 mol) of benzyl chloride in 30 ml of THF. The yellow solution was stirred for 1 hr and 50 ml of water was added. The aqueous layer was extracted with ether and the combined organic solution was dried over magnesium sulfate and evaporated. The residue was recrystallized from methanol to give 8.63 g (85%) of 2-benzylcyclohexanone (*Z*)-oxime: mp 103.6–104.4°; ir (KBr) 3240, 1664 cm^{-1}; NMR ($CDCl_3$) δ 9.76 (s, 1 H, OH), 7.18 (s, 5 H, Ar), 3.74 (m, 1 H, α-CH), 2.78 (d, 2 H, $ArCH_2$), 2.26 (m, 2 H, α-CH_2), 1.50 (m, 6 H, CH_2); 2,4-dinitrophenylhydrazone mp 162.5–164° (lit.[23] 163–165°). A portion (1 g) of the *Z* oxime was heated in an oil bath to 130° for 3 min and cooled, and the solid recrystallized from methanol to give 0.85 g of 2-benzylcyclohexanone (*E*)-oxime: mp 125° (lit.[24] 125.5–126.5°); ir (KBr) 3230, 1675 cm^{-1}; NMR ($CDCl_3$) δ 8.13 (s, 1 H, OH), 7.22 (s, 5 H, Ar), 2.72 (m, 5 H, CH, CH_2), 1.62 (m, 6 H, CH_2).

Registry No.—**7**, 2550-27-8; **8**, 127-06-0; **8″**, 57428-27-0; **12**, 1489-28-7; **20**, 100-64-1; **20** dilithio derivative, 57428-28-1; **21**, 1192-28-5; **21** dilithio derivative, 57428-29-2; 2-(3′-chloro-2′-butenyl)cyclopentanone oxime, 57428-30-5; 2-(3′-chloro-2′-butenyl)cyclopentanone, 57428-31-6; 2-hydroxy-2-methylbicyclo[3.2.1]octan-8-one, 57428-32-7; 2-ethylidenecyclohexanone, 1122-25-4; 2-benzylcyclohexanone (*Z*)-oxime, 57428-33-8; 2-benzylcyclohexanone (*E*)-oxime, 57428-34-9; 2-methylcyclohexanone, 583-60-8; 2-methylcyclohexanone (*E*)-oxime, 32179-89-8.

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