

Stereochemical Studies on 1,6 Additions to 10-Methyl-1(9),7-hexal-2-one by Grignard Reagents

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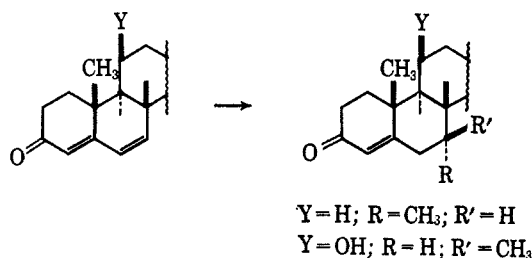
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10-Methyl-1(9),7-hexal-2-one (2) reacts with methyl-, ethyl-, isopropyl-, and *t*-butylmagnesium halides in the initial presence of cupric acetate to give 1,6 adducts in which the predominant isomer has the newly introduced alkyl group in the axial position. No 1,6 adduct was formed when phenylmagnesium bromide was employed in this reaction. The stereoselectivity of the 1,6-addition reaction increases with the steric bulk of the Grignard reagent. The stereochemical findings are explained in terms of mechanistic concepts which stem from earlier studies on 1,4-addition reactions.

Conjugated ketones react with Grignard reagents in the presence of cuprous salts to give varying amounts of conjugate addition products.² We became interested in the stereochemical aspects of this reaction because of its potential utility in the synthesis of natural products. Our earlier reports³ have dealt with 1,4 additions to α,β -unsaturated ketones; we now present some findings on 1,6 additions to $\alpha,\beta,\gamma,\delta$ -dienones.

In contrast to their 1,4 counterparts, the 1,6-addition reactions of Grignard reagents have received little attention.⁴ Campbell and Babcock^{4b} studied the cuprous chloride catalyzed reaction of methylmagnesium iodide with various steroidal 4,6-dien-3-ones. They found axially substituted C-7 methyl derivatives as the predominant 1,6 adducts in the absence of a 12 β -hydroxy group. This grouping appeared to influence the stereochemistry of the reaction since in its presence, products thought to be the equatorially substituted C-7 methyl derivatives were the major 1,6 adducts. In all cases the reaction proceeded in low yield owing to the formation of 1,2-addition products.



In a more recent report, Birch and Smith⁵ noted that cupric acetate effectively promotes conjugate addition reactions of Grignard reagents. They examined only one case of 1,6 addition, the reaction of methylmagnesium iodide with 1(9),7-hexal-2-one. The 1,6 adduct, 7-methyl-1(9)-octal-2-one, was formed in 54% yield. The axial orientation was suggested for the methyl group on mechanistic grounds, but no attempts were made to confirm this point.

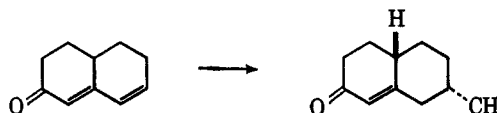
(1) Fellow of the National Institute of General Medical Sciences, Public Health Service, 1965-present.

(2) Cf. H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966), and references cited therein. We are grateful to Professor House for a prepublication copy of his manuscript.

(3) J. A. Marshall and N. H. Andersen, *ibid.*, **31**, 667 (1966); J. A. Marshall, W. I. Fanta, and H. Roebke, *ibid.*, **31**, 1016 (1966).

(4) (a) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-metallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, p 238; (b) J. A. Campbell and J. C. Babcock, *J. Am. Chem. Soc.*, **81**, 4069 (1951).

(5) A. J. Birch and M. Smith, *Proc. Chem. Soc.*, 356 (1962).



In the present study, we were interested in learning whether the steric requirements of the organometallic would influence the stereochemistry of the 1,6-addition reaction. Methyl-, ethyl-, isopropyl-, and *t*-butylmagnesium halides were selected as the Grignard reagents, and 10-methyl-1(9),7-hexal-2-one (2) was chosen as the dienone substrate. This latter choice seemed *a priori* well suited to our objective because the easier steric availability of the 7 *vs.* 9 position in this dienone should ensure a large preponderance of 1,6- over 1,4-addition products.⁵ Furthermore, gas chromatography promised a convenient and accurate means for product analysis, and the stereochemistry of some of the 1,6 adducts appeared to be attainable by chemical degradation and direct comparison with known compounds. Finally, dienone 2 could be easily prepared from 10-methyl-1(9)-octal-2-one (1),⁶ a readily available starting material, *via* dehydrogenation with chloranil.⁷

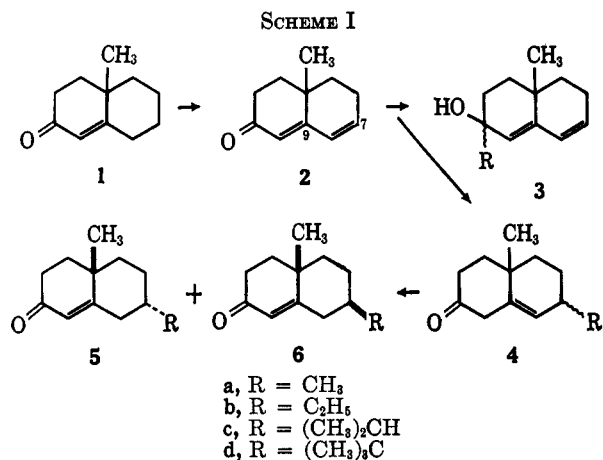
The conjugate additions were carried out by adding excess ethereal Grignard reagent to a solution containing dienone 2 and cupric acetate in tetrahydrofuran at -10 to -20° . The products which were liberated with aqueous ammonium chloride consisted of alcohols 3 (from 1,2 addition) and the β,γ -unsaturated ketones (4), the latter resulting from kinetic protonation⁸ of the enolates formed in the 1,6-addition reaction (Scheme I). We made no attempts to purify the latter materials as chromatography on alumina caused their isomerization to the corresponding α,β -unsaturated isomers 5 and 6. After distillation, the products were analyzed using gas chromatography. Table I summarizes our findings.

Before discussing the stereochemical aspects of the conjugate addition reactions, we will briefly mention some factors which affected the yields of 1,6 adducts. These yields could be duplicated to within 2% provided the same batch of Grignard reagent was employed. However, a new batch of Grignard reagent generally gave the 1,6 adducts in significantly different yield. For example, the 1,6 adducts 5b and 6b were secured in 26% yield using one batch of ethylmagne-

(6) J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29**, 2501 (1964), and references therein.

(7) Cf. E. J. Agnello and J. D. Laubach, *J. Am. Chem. Soc.*, **82**, 4293 (1960).

(8) Cf. S. K. Malhotra and H. J. Ringold, *ibid.*, **85**, 1538 (1963).



sium bromide (Table I, entry 5), whereas a new batch of this reagent gave these adducts in 65% yield (Table I, entry 6). Apart from this random factor, higher yields were obtained with more dilute solutions of a given Grignard reagent (entries 2 *vs.* 3 and 7 *vs.* 8). An increased yield also resulted when ether was used as a cosolvent for the dienone (entry 2 *vs.* 4). A similar trend was observed by House and co-workers,² who report that tetrahydrofuran decreases the ratio of 1,4- to 1,2-addition products obtained from organo-copper reagents and conjugated ketones. At present we cannot account for the variations in yield which we observe with differing batches of a Grignard reagent (entries 1 *vs.* 2, and 5 *vs.* 6 *vs.* 7). Fortunately, the ratio of the stereoisomeric 1,6 adducts 5 and 6 turns out to be independent of this factor, and the observed fluctuations thus do not affect our mechanistic conclusions.

TABLE I
ADDITIONS TO 10-METHYL-1(9),7-HEXAL-2-ONE

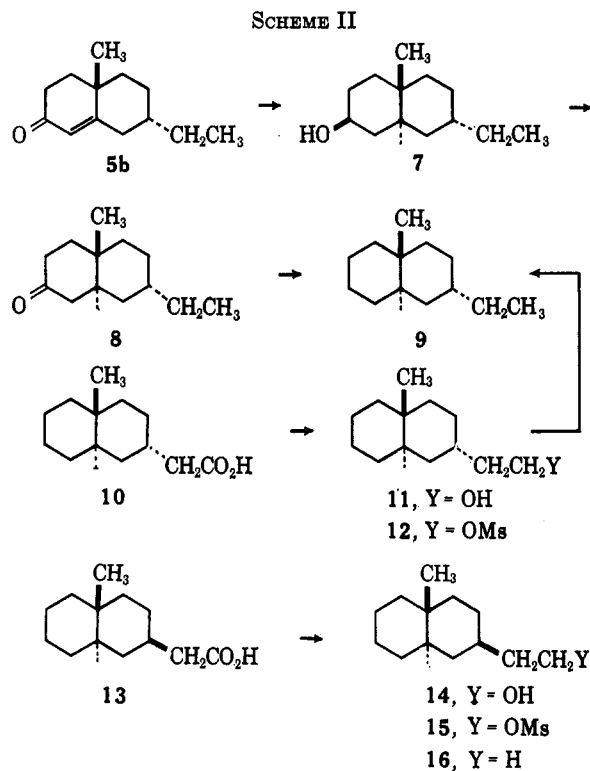
Entry	RMgX	RMgX		1,6 addn.			1,2
		molarity	Batch	% ^a	Ax 5	Eq 6	addn. 3 ^b
1	CH ₃ MgI	0.95	A	30	93	7	70
2	CH ₃ MgI	0.92	B	20 ^c	93	7	80
3	CH ₃ MgI	0.46	B ^d	38	93	7	62
4	CH ₃ MgI	0.92	B	55 ^e	93	7	45
5	CH ₃ CH ₂ MgBr	0.70	A	26 ^c	98	2	74
6	CH ₃ CH ₂ MgBr	0.63	B	65 ^c	98	2	35
7	CH ₃ CH ₂ MgBr	0.89	C	55	98	2	45
8	CH ₃ CH ₂ MgBr	0.45	C ^d	63	98	2	37
9	CH ₃ CH ₂ MgBr	0.89	C	58 ^e	98	2	42
10	(CH ₃) ₂ CHMgBr	0.41	A	58 ^e	100	0	42
11	(CH ₃) ₂ CMgCl	0.46	A	40 ^e	100	0	60

^a The yield of distilled product is given. ^b Calculated by difference. No starting material was found. ^c Duplicate experiments. ^d The Grignard reagent was diluted with ether before use. ^e The dienone was dissolved in a 1:1 mixture of ether and tetrahydrofuran instead of pure tetrahydrofuran.

We used several lines of evidence in deducing the stereochemistry of 1,6 adducts 5 and 6. The stereochemistry of the (+)-enantiomer of the isopropyloctalone 5d has been determined from optical rotatory dispersion measurements.⁹ The corresponding racemic material, obtained as outlined above from dienone 2 and isopropylmagnesium bromide, corresponded ex-

actly in its infrared and nmr spectra and gas chromatographic retention time. Evidently axial substitution offers the most highly preferred reaction pathway in the 1,6-addition reaction leading to octalone 5d.

The major 1,6-addition product from dienone 2 and ethylmagnesium bromide was identified as octalone 5b, the axial substitution product, through degradation to 10β-methyl-2α-ethyldecalin (9) as shown in Scheme II. Thus, reduction with lithium in am-



monia-ethanol afforded decalol 7 which was directly oxidized with chromic acid giving decalone 8. This ketone afforded decalin 9 upon Wolff-Kishner reduction. An authentic sample of decalin 9 was independently synthesized from the decalylacetic acid 10, a compound of known stereochemistry,¹⁰ through a sequence involving reduction to alcohol 11 with lithium aluminum hydride followed by hydrogenolysis of the derived methanesulfonate derivative 12 with lithium in ammonia. The isomeric decalin 16, prepared from the stereochemically defined decalylacetic acid 13¹⁰ *via* the same reduction sequence, clearly differed from 9 according to the infrared spectra and gas chromatographic retention times. Moreover, this material appeared at the identical retention time as that derived from the minor 1,6 adduct 6b which was carried through the degradation sequence outlined in Scheme II. Unfortunately, we could not isolate enough of the minor 1,6 adduct 6b for complete characterization. However, both the infrared and ultraviolet spectra of the available material point to the proposed structure.

We experienced similar difficulties in isolating the minor 1,6 adduct 6a of methylmagnesium iodide and dienone 2. The infrared and ultraviolet spectra were compatible with the indicated structure and the relative gas chromatographic retention time indicated that an epimeric relationship to the major 1,6 adduct 5a was likely. We assign the stereochemistry of this

(9) C. Djerassi, J. Burakevich, J. W. Chamberlin, D. Elad, T. Toda, and G. Stork, *J. Am. Chem. Soc.*, **86**, 465 (1964).

(10) J. A. Marshall and R. D. Carroll, *J. Org. Chem.*, **30**, 2748 (1965).

latter substance on mechanistic grounds and by analogy with the ethyl homolog **5b**.

With *t*-butylmagnesium chloride, as with isopropylmagnesium bromide, dienone **2** gave a single 1,6 adduct. In this case we assign the stereochemistry shown in **5d** using the isopropyl derivative **5c** as an analogy.

Our previous studies of 1,4 additions to α,β -unsaturated ketones by Grignard reagents³ indicated that both steric and stereoelectronic factors play a role in determining the stereochemistry of conjugate addition. These earlier findings suggested a transition state for the reaction where bonding between the incoming Grignard reagent and the electron deficient β carbon atom of the enone had progressed to a point where the latter possessed considerable sp^3 character, but the parallel alignment of adjacent p orbitals in the enolate system with the developing carbon-carbon bond (the stereoelectronic factor) was still very important.¹¹ Where axial attack was sterically opposed, as with bulky Grignard reagents, attack from the opposite side could occur provided the resulting boat conformation (required because of stereoelectronic factors) did not lead to a less stable transition state arrangement. In other words, for some systems reaction through a boat conformation to give an equatorially substituted product could represent the pathway of lowest energy whereas in others, axial attack through a chair conformation would be energetically favored.

Our present findings can be explained using these same arguments. Figure 1 depicts the hypothetical transition states A and B leading to **4**, the precursor of **5** and **6**. In A, the ring undergoing attack maintains a chairlike conformation, a single 1,3 diaxial interaction develops as the group enters, and the adjacent orbitals enjoy maximal overlap. Attack from the opposite face of dienone **2** requires the ring undergoing alkylation to adopt a boat-like conformation, as depicted in B, in order to maintain maximal orbital overlap. In this conformation, the incoming group encounters both an eclipsed 1,2-R/H interaction and, more importantly, a 1,4-CH₃/R interaction which resembles the bowsprit flagpole arrangement of a twist boat form of cyclohexane.¹² Thus, not only is axial attack favored, but this pathway becomes even more favored with increasing steric requirements of the Grignard reagent because of the greater steric interactions which develop in B relative to A.

We originally planned to extend these studies to 1,10-dimethyl-1(9),7-hexal-2-one (**17**) in the hope of synthesizing compounds related to epi- α -cyperone.¹³ Our initial attempts along these lines using isopropylmagnesium bromide proved fruitless. Instead of the

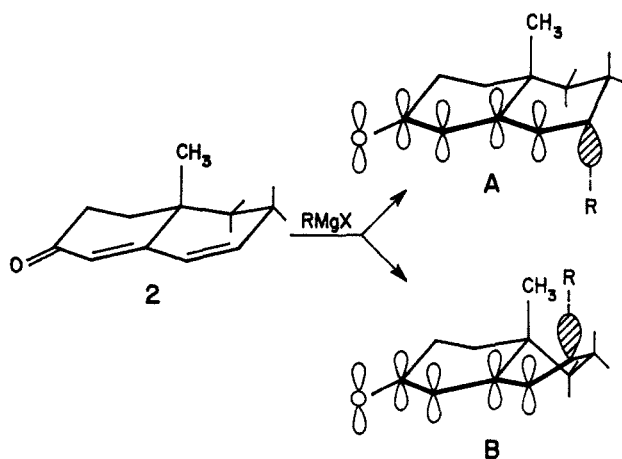


Figure 1.—Hypothetical transition states leading to axially and equatorially substituted 1,6-addition products.

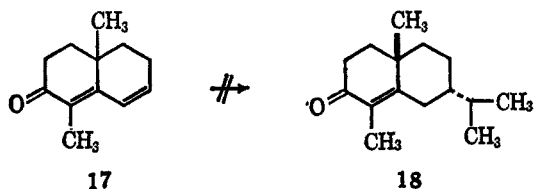
expected dihydroepi- α -cyperone **18**, we obtained a dimeric (?) substance in 30% yield as the only conjugated ketone product. This substance has not yet been structurally elucidated.

Our efforts to prepare a 1,6 adduct of dienone **2** and phenylmagnesium bromide also proved fruitless. Here, about 40% of the starting material was converted to nonvolatile ketonic materials; the remainder appeared to be 1,2-addition products.

In conclusion, the 1,6 addition of Grignard reagents to conjugated cyclohexenones seems controlled by steric and stereoelectronic factors which resemble those found for the analogous 1,4 additions. However, for 1,6-addition reactions, the yields appear to be more subtly affected by factors such as substituents on the dienone and the nature of the Grignard reagent. The failure of phenylmagnesium bromide to give a 1,6-addition product is particularly surprising in view of the ease with which this reagent enters into 1,4 additions.^{3,14}

Experimental Section¹⁵

10-Methyl-1(9),7-hexal-2-one (2).¹⁶—The procedure of Agnello and Laubach⁷ was employed. A mixture of 10.0 g of 10-methyl-1(9)-octal-2-one (**1**)⁶ and 80 g of chloranil in 800 ml of *t*-butyl alcohol was heated to reflux for 3 hr. The cooled mixture was filtered and the solvent was removed from the filtrate under reduced pressure. The residue was dissolved in ether and this solution was thoroughly washed with water, 5% aqueous sodium hydroxide, and water, and dried over anhydrous magnesium sulfate. Distillation afforded 4.8 g (48%) of pale yellow dienone **2**: bp 70–71° (0.05 mm); $\lambda_{\text{max}}^{\text{lim}}$ 6.01 (CO), 6.18, and 6.30 μ (C=C); $\lambda_{\text{max}}^{\text{EIOH}}$ 278 m μ (ϵ 26,800). The semicarbazone derivative, mp 212–213°, was prepared (lit.¹⁶ mp 213–214°). The gas chromatogram of this material exhibited a peak at 18.1 min on a 13 ft



(11) Cf. E. Toromanoff, *Bull. Soc. Chim. France*, 708 (1962).

(12) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 37.

(13) R. Howe and F. J. McQuillin, *J. Chem. Soc.*, 2670 (1956), and references therein.

(14) For example, H. O. House and H. W. Thompson, *J. Org. Chem.*, **28**, 360 (1963).

(15) (a) Melting points were determined on a Fisher-Johns hot stage. (b) The isolation procedure consisted of thorough extraction and back extraction with the specified solvent, washing the combined extracts with saturated brine, and drying the extracts over anhydrous magnesium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a steam bath. (c) The apparatus described by W. S. Johnson and W. P. Schneider [*Org. Syn.*, **30**, 18 (1950)] was used to maintain a nitrogen atmosphere over reaction mixtures. (d) Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. (e) The prefixes " α " and " β " designate the relative stereochemistry of an asymmetric center in a racemic substance. The prefix "*dl*" is omitted from the names of racemic materials. "Octalin" and "hexalin" refer to octahydro- and hexahydronaphthalene, respectively. Double bonds are located with numerical prefixes.

(16) M. Yanagita and A. Tahara, *J. Org. Chem.*, **18**, 792 (1953).

× 0.25 in. column packed with 16% Carbowax 20-M on 60-80 Diatoport S at 210° with a helium flow rate of 96 cc/min.

General Procedure for 1,6 Conjugate Additions.—A solution containing 1.00 g (6.2 mmoles) of 10-methyl-1(9),7-hexal-2-one (2)^{15c} and 0.400 g (2.0 mmoles) of cupric acetate monohydrate in enough dry tetrahydrofuran to bring the final volume of the reaction mixture to 80 ml after addition of the Grignard reagent (about 20-40 ml required) was cooled to -15° in a Dry Ice-acetone bath. The reaction mixture was maintained at -10 to -20° and efficiently stirred while an ethereal solution of the Grignard reagent (21 mmoles) was added over 0.5 hr. The mixture was allowed to reach room temperature over a 2-hr period and heated to reflux for 15 min. Aqueous ammonium chloride was added to the cooled mixture and the product was isolated by thorough extraction with ether. As in our previous studies,³ the aqueous phase remained yellow until it was shaken in the separatory funnel, whereupon it became deep blue owing to air oxidation of the cuprous salts. The combined extracts were washed with sodium thiosulfate solution (only when iodides were used) and saturated brine and dried over anhydrous magnesium sulfate. The solvent was removed from the filtered solution under reduced pressure. At this point the yellow to brown oily residue contained a mixture of the 1,2 adduct, alcohol 3, $\lambda_{\max}^{\text{OH}}$ 3.0 μ (OH), and β,γ -unsaturated ketone 4, $\lambda_{\max}^{\text{OH}}$ 5.85 μ (CO). This mixture was chromatographed on 100 g of basic alumina (Merck) and the desired 1,6 adducts 6 and/or 5 were eluted with benzene to 5% ether in benzene. The combined fractions were distilled at 65-85° (bath temperature) (0.1 mm) and the distillates were analyzed by gas chromatography using a 10 ft × 0.25 in. column packed with 10% Ucon 75H, 90,000 Polar on 60-80 Gas Pack-W with helium as the carrier gas.

Essentially the same results were obtained when the reaction mixtures were slowly added to a rapidly stirred solution of aqueous ammonium chloride. Thus, the addition of residual Grignard reagent to ketone 4 during the above-described work-up procedure³ seems unlikely in these systems.

trans-7,10-Dimethyl-1(9)-octal-2-one (5a).^{15c}—The general procedure was followed using 23 ml of 0.9 M methylmagnesium iodide in ether. With a column temperature of 175° and a helium flow rate of 97 cc/min, the gas chromatogram of the distilled (bp 65° at 0.1 mm) octalone (0.33 g, 30% yield) showed peaks at 12.2 (6a, 7%) and 13.4 min (5a, 93%). This mixture displayed the following spectral characteristics: $\lambda_{\max}^{\text{OH}}$ 5.99 (CO), 6.19 (C=C), 6.88, 7.49, 7.87, 7.99, and 8.27 μ ; $\lambda_{\max}^{\text{OH}}$ 238 m μ (ϵ 14,500); $\delta_{\text{TMS}}^{\text{C}^{14}}$ = 5.56 (C=CH, doublet, J = 1.6 cps), 1.23 (C-10 CH₃), and 0.92 ppm (C-7 CH₃, doublet, J = 7 cps).

The 2,4-dinitrophenylhydrazone derivative exhibited mp 166-167.5° after five recrystallizations from methanol-ethyl acetate. *Anal.* Calcd for C₁₈H₂₂N₄O₄: C, 60.32; H, 6.19; N, 15.63. Found: C, 60.2; H, 6.2; N, 15.5.

The minor component 6a could be isolated from the above mixture by means of preparative gas chromatography using a 12 ft × 0.25 in. column packed with 30% Carbowax 20 M on 60-80 Chromosorb W at 205° (200 cc/min). From 2 g of the mixture we could obtain only about 3 mg of 6a: $\lambda_{\max}^{\text{OH}}$ 240 m μ (ϵ 12,000); $\lambda_{\max}^{\text{OH}}$ 5.98 (CO), 6.19 (C=C), 6.87, 7.52, 8.00, 8.27, and 8.43 μ .

trans-10-Methyl-7-ethyl-1(9)-octal-2-one (5b).^{15c}—The general procedure was followed using 30 ml of 0.7 M ethylmagnesium bromide in ether. With a column temperature of 185° and a helium flow rate of 109 cc/min, the gas chromatogram of the distilled (bp 65° at 0.1 mm) octalone (0.31 g, 26% yield) showed peaks at 11.6 (6b, 2%) and 12.8 min (5b, 98%). This mixture displayed the following spectral characteristics: $\lambda_{\max}^{\text{OH}}$ 5.98 (CO), 6.19 (C=C), 6.87, 7.52, 7.91, 8.02, 8.28, and 8.38 μ ; $\lambda_{\max}^{\text{OH}}$ 239 m μ (ϵ 14,100); $\delta_{\text{TMS}}^{\text{C}^{14}}$ = 5.54 (C=CH, doublet, J = 1.6 cps), 1.88 (CH₂CH₃, triplet, J = 7 cps), and 1.25 ppm (C-10 CH₃).

The 2,4-dinitrophenylhydrazone derivative exhibited mp 129.5-131° after seven recrystallizations from methanol-ethyl acetate.

Anal. Calcd for C₁₉H₂₄N₄O₄: C, 61.27; H, 6.48; N, 15.05. Found: C, 61.2; H, 6.5; N, 15.2.

Using the same batch of ethylmagnesium bromide we were able to duplicate the above experiment. With a new bath of this reagent, the mixture of 1,6 adducts 5b and 6b was formed in 65% yield (duplicate experiments). The ratio of 5b to 6b did not change for the two sets of experiments. Preparative gas chromatography was used to separate the minor 1,6 adduct, 6b. However, only poor separation and recovery could be achieved.

The material obtained in this manner exhibited $\lambda_{\max}^{\text{OH}}$ 247 m μ (ϵ 9,200); $\lambda_{\max}^{\text{OH}}$ 6.00 (CO), 6.22 (C=C), 6.84, 6.87, 7.36, 7.50, 7.93, and 8.33 μ .

trans-10-Methyl-7-isopropyl-1(9)-octal-2-one (5c).^{15c,17}—The general procedure was followed using 52 ml of 0.4 M isopropylmagnesium bromide in ether. With a column temperature of 175° and a helium flow rate of 90 cc/min, the gas chromatogram of the distilled (bp 70° at 0.1 mm) octalone (0.74 g, 58% yield) showed a single peak at 22.5 min. This compound displayed the following spectral characteristics: $\lambda_{\max}^{\text{OH}}$ 6.00 (CO), 6.20 (C=C), 7.92, 8.30, 8.39, 10.19, and 11.67 μ ; $\lambda_{\max}^{\text{OH}}$ 240 m μ (ϵ 13,600); lit.¹⁸ 240 m μ (ϵ 14,000); $\delta_{\text{TMS}}^{\text{C}^{14}}$ = 5.70 (C=CH), 1.28 (C-10 CH₃), and 1.01 ppm [(CH₃)₂CH, doublet, J = 7 cps]. The infrared and nmr spectra and the gas chromatographic retention time (peak enhancement) were identical with those of (+)-10 β -methyl-7 α -isopropyl-1(9)-octal-2-one, prepared from (-)-dihydrocarvone and methyl vinyl ketone as described elsewhere.⁶

Anal. Calcd for C₁₄H₂₂O: C, 81.50; H, 10.75. Found: C, 81.7; H, 11.0.

The 2,4-dinitrophenylhydrazone derivative exhibited mp 199.5-200° after five recrystallizations from methanol-ethyl acetate.

Anal. Calcd for C₂₀H₂₆N₄O₄: C, 62.12; H, 6.78; N, 14.50. Found: C, 62.0; H, 6.9; N, 14.5.

trans-10-Methyl-7-*t*-butyl-1(9)-octal-2-one (5d).^{15c}—The general procedure was followed using 46 ml of 0.5 M *t*-butylmagnesium chloride in ether. With a column temperature of 185° and a helium flow rate of 109 cc/min, the gas chromatogram of the distilled (bp 85° at 0.1 mm) octalone (0.55 g, 40%) showed one peak at 19.6 min. This compound displayed the following spectral characteristics: $\lambda_{\max}^{\text{OH}}$ 5.98 (CO), 6.16 (C=C), 6.80, 7.31, and 8.06 μ ; $\lambda_{\max}^{\text{OH}}$ 242 m μ (ϵ 12,600); $\delta_{\text{TMS}}^{\text{C}^{14}}$ = 5.75 (C=CH), 1.24 (C-10 CH₃), and 0.88 ppm [(CH₃)₃C].

The 2,4-dinitrophenylhydrazone derivative exhibited mp 166-167.5° after four recrystallizations from methanol-ethyl acetate.

Anal. Calcd for C₂₁H₂₈N₄O₄: C, 62.98; H, 7.05; N, 13.99. Found: C, 62.7; H, 7.1; N, 14.1.

trans-10 β -Methyl-7 α -ethyl-2-decalone (8).^{15c}—A solution of 1.00 g of octalone 5b (containing 2% of the epimeric octalone 6b) in 60 ml of ether was added over 0.5 hr to a solution of 0.52 g of lithium in 180 ml of liquid ammonia. The mixture was stirred for 0.5 hr and 29 ml of ethanol in 120 ml of ether was added over 0.5 hr. The ammonia was allowed to evaporate through a mercury bubbler trap, solid ammonium chloride was added, and the residual ethereal solution was thoroughly washed with saturated brine and dried over anhydrous magnesium sulfate. The ether was removed from the filtered solution under reduced pressure to give 1.0 g of oily alcohol, $\lambda_{\max}^{\text{OH}}$ 2.99 μ .

A 0.75-g portion of this alcohol in 80 ml of acetone was cooled to 0° and stirred while 1.95 ml of standard chromic acid reagent¹⁹ was slowly added. After 10 min, isopropyl alcohol was added to discharge the red color followed by solid sodium bicarbonate to neutralize any excess acid. The insoluble salts were removed by filtration and washed well with ether. The filtrate was concentrated under reduced pressure, dissolved in ether, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was distilled giving 0.66 g (89%) of low-melting solid material, bp 65° (bath temperature) (0.1 mm). This material was chromatographed on 60 g of alumina. The fractions eluted with 75% benzene in hexane which gave a single peak in the gas chromatogram were combined and sublimed at 25° (0.1 mm) yielding decalone 8: mp 37.5-39°; $\lambda_{\max}^{\text{OH}}$ 5.83 (CO), 6.87, 7.04, 7.23, 8.06, and 8.73 μ ; $\delta_{\text{TMS}}^{\text{C}^{14}}$ = 1.03 ppm (C-10 CH₃).

Anal. Calcd for C₁₃H₂₂O: C, 80.35; H, 11.41. Found: C, 80.2; H, 11.4.

trans-10 β -Methyl-7 α -ethyldecalin (9).^{15c} **A. From Decalone 8.**—A mixture containing 0.15 g of decalone 8 (95:5 mixture of 7 α and 7 β epimers), 0.20 g of potassium hydroxide, and 0.19 ml of 85% hydrazine hydrate in 20 ml of diethylene glycol was heated to 120° for 14 hr and at reflux for 3 hr.^{15c} The cooled mixture was extracted with hexane and the hexane extracts were

(17) This experiment was first performed in our laboratory by Miss K. R. Arsenon. The experiment described here was carried out several months later using the original batch of Grignard reagent. The same yield of 1,6 adduct was obtained from both experiments.

(18) For the (+) counterpart, Djerassi and co-workers⁹ report $\lambda_{\max}^{\text{OH}}$ 6.00, 6.20, 10.20, and 11.70 μ .

(19) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

washed with saturated brine and dried over anhydrous magnesium sulfate.^{15b} The hexane was removed under reduced pressure and the residue was distilled giving 0.14 g (55%) of pale yellow oil. This material was chromatographed on 5 g of neutral alumina (Woelm, activity I) and the material eluted with pentane was distilled giving 0.07 g of decalin 9 as a colorless liquid: $\lambda_{\text{max}}^{\text{film}}$ 6.89, 7.24, 8.51, 10.10, and 10.42 μ ; $\delta_{\text{TMS}}^{\text{CDCl}_3}$ = 0.98 (CH₂CH₃, triplet, J = 7 cps), and 0.82 ppm (C-10 CH₃).

Anal. Calcd for C₁₀H₁₆: C, 86.58; H, 13.42. Found: C, 86.9; H, 13.2.

The gas chromatogram obtained using a 13 ft by 1/8 in. 10% DC-550 oil on 60-80 Chromosorb W column at 100° with a helium flow rate of 50 cc/min showed one peak at 22.8 min (9) with a shoulder at 24.4 min corresponding to the epimeric decalin 16 (see below).

B. From Decalylacetic Acid 10.—A solution of 20 mg of decalylacetic acid 10¹⁹ in 5 ml of 1,2-dimethoxyethane was added to a solution containing 50 mg of lithium aluminum hydride in 5 ml of 1,2-dimethoxyethane. The mixture was stirred at reflux for 3 hr, cooled, and treated with 0.1 ml of water and 0.08 ml of 10% aqueous sodium hydroxide. After stirring for several hours the mixture was filtered and the filtrate was distilled giving 19 mg of decalylethanol 11: $\lambda_{\text{max}}^{\text{film}}$ 3.02 (OH), 6.91, 9.42, 11.46, and 11.77 μ .

A 15-mg portion of this alcohol in 0.5 ml of pyridine was treated with 45 mg of methanesulfonyl chloride.^{16c} After 3.5 hr, the mixture was diluted with ice-water and thoroughly extracted with ether and benzene. The extracts were washed successively with water, 2% sulfuric acid, water, 10% sodium bicarbonate, and saturated brine and dried. The solvent was removed under reduced pressure affording 22 mg of oily methanesulfonate 12: $\lambda_{\text{max}}^{\text{film}}$ 7.37, 8.49, 10.55, and 12.25 μ .

The above sample of methanesulfonate 12 in 0.5 ml of absolute ethanol and 5 ml of ether was added to 25 ml of liquid ammonia containing 57 mg of lithium wire. After 10 min, an additional 50 mg of lithium wire and 0.5 ml of ethanol was added. The solution was stirred for 1.5 hr, 5 g of ammonium chloride was added, and the ammonia was allowed to evaporate. The residue was treated with saturated brine and extracted with ether. The extracts were dried, the solvent was removed under reduced pressure, and the residue was chromatographed on alumina giving 6 mg (42%) of colorless decalin 9. The infrared spectrum and gas chromatographic retention time were identical with the material described in part A.

trans-10 β -Methyl-7 β -ethyldecalin (16).^{16e}—A 35-mg sample of acid 13¹⁰ was reduced with lithium aluminum hydride according to the procedure described above for acid 10. The resulting

alcohol 14 (30 mg, 92%) was distilled: bp 70° (bath temperature) (0.1 mm); $\lambda_{\text{max}}^{\text{film}}$ 3.02 (OH), 6.89, 9.52, 11.20, and 11.73 μ .

The methanesulfonate derivative 15 ($\lambda_{\text{max}}^{\text{film}}$ 6.89, 7.37, 8.49, 10.55, 12.07, and 12.40 μ) was prepared from 200 mg of alcohol 14 according to the procedure described above for 12.

A 274-mg sample of methanesulfonate was reduced as described above for the preparation of 9. The resulting decalin 16 (100 mg, 55%) exhibited $\lambda_{\text{max}}^{\text{film}}$ 6.89, 7.22, 8.49, 10.03, 10.13, and 12.41 μ .

Anal. Calcd for C₁₀H₁₆: C, 86.58; H, 13.42. Found: C, 86.6; H, 13.6.

The retention time (24.4 min) observed in the gas chromatogram of this material corresponded exactly with that of the minor component obtained *via* degradation of the mixture of octalones 5b and 6b (see above).

Attempted 1,6 Addition of Phenylmagnesium Bromide to Dienone 2.—The general procedure was followed using 35 ml of 0.6 M phenylmagnesium bromide in ether. The resulting viscous dark brown oil was chromatographed on alumina giving 0.32 g of biphenyl and 0.60 g of thick oil [$\lambda_{\text{max}}^{\text{film}}$ 5.83, 5.93 (CO), 13.05, and 14.30 μ], which did not distil at 150° (0.1 mm).

Attempted 1,6-Addition of Isopropylmagnesium Bromide to 1,10-Dimethyl-1(9),7-hexal-2-one (17).^{16e}—To 0.50 g of dienone 17¹⁸ in 50 ml of tetrahydrofuran containing 0.20 g of cupric acetate hydrate was added 25 ml of 0.41 M isopropylmagnesium bromide at -10 to -20° according to the general procedure. The crude product was triturated with ether giving 0.15 g of white solid which exhibited mp 222-223° after two recrystallizations from ether-chloroform; $\lambda_{\text{max}}^{\text{KBr}}$ 6.01 (CO), 6.31 (C=C), 6.83, 7.66, and 8.34 μ ; $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 263 m μ (ϵ 22,000 for molecular wt 439); $\delta_{\text{TMS}}^{\text{CDCl}_3}$ = 0.85 (triplet, or two doublets 12 H), 1.41 (singlet, 6 H), 2.00 (singlet, 6 H), 3.45 ppm (singlet, 2 H) assuming C₃₀H₄₆O₂.

Anal. Calcd for C₃₀H₄₆O₂ (two isopropyl groups): C, 82.13; H, 10.57; mol wt, 438.7. Calcd for C₂₇H₄₀O₂ (one isopropyl group): C, 81.76; H, 10.17; mol wt, 396.6. Calcd for C₂₄H₃₄O₂ (no isopropyl groups): C, 81.31; H, 9.67; mol wt, 354.5. Found: C, 81.14; H, 10.42; mol wt, 399.²⁰

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(20) Analysis was by Miss H. Beck using a Mechrolab Model 303 vapor pressure osmometer.

Aziridines. XVI. 1-Azaspiro[2.5]octane and 1-Azaspiro[2.4]heptane¹

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Under conditions found suitable for the preparation of 1-*p*-nitrobenzoyl-2,2-dimethylaziridine, 1-azaspiro[2.5]octane and 1-azaspiro[2.4]heptane gave instead of the expected *N*-*p*-nitrobenzoyl derivatives the isomeric *N*-cycloalkenylmethyl *p*-nitrobenzamides, which were readily cyclized to the isomeric spirooxazolines. The *N*-*p*-iodobenzenesulfonyl and *N*-*p*-nitrobenzenesulfonyl derivatives of 1-azaspiro[2.5]octane were prepared and found to rearrange smoothly to the unsaturated sulfonamides upon gentle heating. Attempted preparation of the same derivatives of 1-azaspiro[2.4]heptane gave directly the isomeric, unsaturated sulfonamides. A higher temperature and longer time was required for the analogous rearrangement of 1-*p*-nitrobenzenesulfonyl-2,2-dimethylaziridine. The relative ease of rearrangement in the three aziridine systems is better accounted for in terms of a concerted transition state than a zwitterion intermediate.

In previous work from this laboratory,² it was found that the temperature required for the pyrolytic rearrangement of *N*-acyl, fused, bicyclic aziridines (1)

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(2) P. E. Fanta and E. N. Walsh, *J. Org. Chem.*, **30**, 3574 (1965), and previous papers in this series.

to unsaturated amides (3) was greatly dependent on the size of the ring. Thus, when the three contiguous carbon atoms of part structure 1 were part of an eight- or ten-membered ring, the reaction occurred readily even below 80°. A much higher temperature was required when the three carbon atoms were part of a six-membered ring or a five-membered ring.³ These observations are in accord with the view that the isom-

(3) P. E. Fanta and R. J. Smat, manuscript in preparation.