

Bromides were found to be more reactive than chlorides at low temperatures.

Grignard Reactions in Diethyl Ether. A. Chlorides. Magnesium turnings were amalgamated by treatment in several portions with a solution of mercuric bromide in ether,²¹ washed well with ether, and placed in an oven-dried, 50-ml., two-necked flask fitted with a water-cooled reflux condenser to which was attached an acetone-Dry Ice cooled trap. The system was flushed with helium that had been passed through Fieser's solution²² and concentrated sulfuric acid. The reaction flask was then charged with the appropriate proportion of C₄H₇Cl, a drop or two of methyl iodide, any addend desired, and 5-7 ml. of dry ether. Liquid reagents were added from a 1-ml. hypodermic syringe graduated to 0.01 ml.; about 5 mmoles of C₄H₇Cl was customarily used.

When the Grignard reaction had been initiated, the mixture was warmed to the reflux temperature. If an addend was present, the reflux period extended until all hydrocarbon products were driven into the Dry Ice trap (48-72 hr.). If an addend was not used, the mixture was transferred after the desired reflux time through a glass wool plug to a nitrogen-filled dropping funnel. This was attached to an identical apparatus containing an ether solution of hydrolyzing agent, the Grignard solution was added, and the mixture was heated to

(21) J. E. Nordlander, Ph.D. Thesis, California Institute of Technology, 1961.

(22) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1955.

reflux with a water-cooled condenser until all hydrocarbons had been collected in the cold trap. The products and the unreacted chloride were analyzed by v.p.c.

B. Bromides and Iodides. Magnesium (0.01 g.-atom) in 30 ml. of ether was placed in a 100-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer, dropping funnel, and reflux condenser. The magnesium was activated by scratching the surface in the presence of a few drops of methyl iodide. The flask was swept with a steady flow of purified nitrogen, then heated at such a rate as to maintain gentle reflux. The halide (0.01 mole) in 10 ml. of ether was added to the flask, and the reaction was allowed to proceed for the required time. The hydrolyzing agent (0.01 mole) in 10 ml. of ether was added through a serum stopper and the gaseous products were collected in a Dry Ice cooled trap and analyzed by v.p.c. In the Grignard reactions involving *in situ* hydrolysis, the hydrolyzing agent was added to the refluxing ethyl ether before addition of halide.

Kinetic Experiments. The kinetic runs were carried out in refluxing dimethyl ether in a system flushed with purified nitrogen. The Grignard reagent from cyclopropylcarbinyl bromide was prepared in dimethyl ether as described above and filtered through a sintered-glass disk into another flask. Portions of this Grignard reagent were then withdrawn at intervals and hydrolyzed with benzoic acid in refluxing dimethyl ether. Analysis of the hydrocarbons was carried out by v.p.c.

Olefinic Cyclizations. VIII.¹ The Butenylmethylcyclohexenol System

William S. Johnson, Pedro J. Neustaedter, and Klaus K. Schmiegel

Contribution from the Department of Chemistry, Stanford University, Stanford, California. Received July 11, 1965

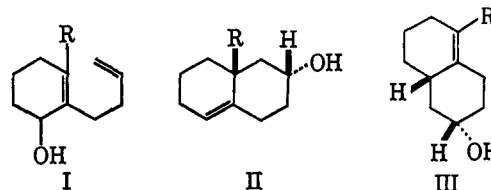
The diene I (R = CH₃), prepared by the sequence IV → V → VI → I (R = CH₃), was cyclized readily by formic acid at room temperature. The product was shown to consist of approximately 30% of the methyl-octalol VII, 35% of the diol VIIIa, and 22% of the C-1 epimeric diol VIIIb. None of the product with an angular methyl group was found. The isomeric diene XI (R = CH₃) was prepared by the sequence *m*-cresyl methyl ether → XIII → XIV → XV → XVI → XI (R = CH₃). Cyclization with formic acid gave, in almost quantitative yield, the product XII (R = CH₃) with an angular methyl group.

In a previous study² it was shown that 2-(Δ³-butenyl)-2-cyclohexenol (I, R = H), on mild treatment with formic acid, underwent rapid, stereoselective cycliza-

(1) Part VII: W. S. Johnson and J. K. Crandall, *J. Org. Chem.*, **30**, 1785 (1965).

(2) W. S. Johnson, W. H. Lunn, and K. Fitz, *J. Am. Chem. Soc.*, **86**, 1972 (1964).

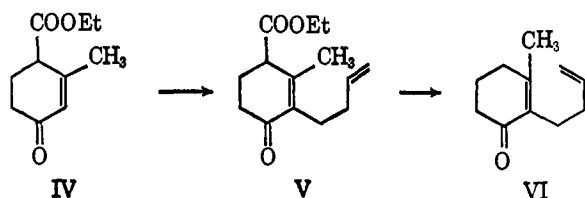
tion to give, after hydrolysis of the formates, *syn*-Δ^{1,9}-6-octalol (II, R = H) in 80% yield along with some of the C-6 epimeric octalol and small amounts of olefins. In anticipation of the possible use of this reaction for the synthesis of fused-ring systems containing the angular methyl group,³ it was considered of interest to examine the cyclization of the homolog I (R = CH₃), in order to ascertain if this system was suitable for producing the desired substance II (R = CH₃), or to what extent cyclization would proceed in the opposite possible sense so as to produce the isomeric



(3) Cf. W. S. Johnson, *Pure Appl. Chem.*, **7**, 317 (1963).

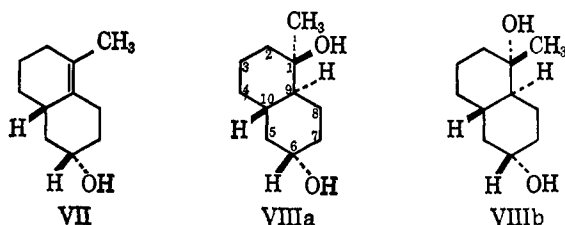
octalol III ($R = \text{CH}_3$). The present paper constitutes a report of the synthesis and cyclization of the dienol I ($R = \text{CH}_3$) as well as of the isomeric substance XI ($R = \text{CH}_3$).

The dienol I ($R = \text{CH}_3$) was obtained as follows. Hagemann's ester (IV) was alkylated with 4-bromo-1-butene; and the resulting keto ester V was converted, on treatment with ethanolic potassium hydroxide, into the dienone VI which was thus obtained in 27% over-all yield from IV.⁴ The dienone VI, on treatment with lithium aluminum hydride, was transformed, in 89% yield, into the dienol I ($R = \text{CH}_3$). Unlike the lower homolog I ($R = \text{H}$), this new dienol was unstable to vapor phase chromatographic conditions. Analysis by nuclear magnetic resonance spectroscopy (see the Experimental Section), however, indicated that the substance was at least 97% pure.



The dienol I ($R = \text{CH}_3$) was treated, as in the case of I ($R = \text{H}$),² with anhydrous formic acid at 23° for 5.5 min. After saponification, the product, which was unstable to the vapor phase chromatographic conditions examined, was purified by column chromatography. Three major fractions were isolated which proved (see below) to be $\Delta^{1,9}$ -1-methyl-*syn*-6-octalol (VII, a liquid), *trans*-1-methyl-*syn*-1-*syn*-6-decalindiol (VIIIa), m.p. 116–119°, and the C-1 epimeric diol VIIIb, m.p. 179–183°. The approximate yields of these substances were 30, 35, and 22%, respectively.

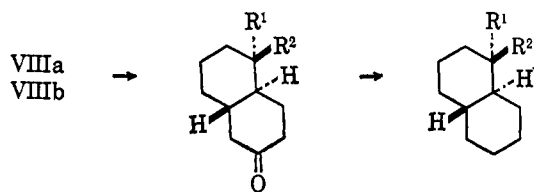
Evidence for the constitution of the solvolysis products was obtained as follows. Compositional analysis indicated the formula $\text{C}_{11}\text{H}_{18}\text{O}$ for the liquid product



and $\text{C}_{11}\text{H}_{20}\text{O}_2$ for both crystalline substances. The n.m.r. spectrum of the liquid product in deuteriochloroform showed singlet absorption at $\delta = 1.63$ p.p.m. ($\text{C}=\text{CCH}_3$) relative to tetramethylsilane, a multiplet over the region from 3.4 to 4.1 (axial H on carbon bearing oxygen), and no signal in the region for a vinyl hydrogen. Since the methyl group was located on a trigonal carbon atom, the liquid product must have been formed by cyclization to the position originally occupied by the allylic hydroxyl group, and is therefore assigned, by direct analogy to the established constitution of the major product of cyclization (II, $R = \text{H}$) in the lower homologous series,² the structure and configuration shown in formula VII. Further support of the assignment followed from a study of the constitution of the crystalline solvolysis products described below.

(4) Cf. R. A. Barnes and M. Sedlak, *J. Org. Chem.*, **27**, 4562 (1962).

The 119° substance was shown to be a secondary-tertiary diol, because oxidation with excess chromium trioxide in acetic acid afforded a hydroxy ketone (IXa): m.p. 71.5–73.5°, $\lambda_{\text{max}}^{\text{film}}$ 2.89 (OH) and 5.89 μ ($\text{C}=\text{O}$). The n.m.r. spectrum of the 119° diol showed absorption for one proton as a broad unresolved multiplet at $\delta = 3.2$ –4.0 p.p.m. which is characteristic of an axial proton on a carbon bearing a hydroxyl group; therefore the secondary hydroxyl group was considered to be equatorial. The spectrum also showed strong singlet absorption at $\delta = 1.18$ p.p.m. corresponding to the methyl group which therefore was located on the carbon holding the tertiary hydroxyl group. The 119° diol consequently must have resulted from addition of formic acid to the olefinic bond of the formate of the methyl octalol VII so as to give rise, after saponification, to the substance VIIIa, or a stereoisomer thereof.



IXa, $R^1 = \text{CH}_3$; $R^2 = \text{OH}$ Xa, $R^1 = \text{CH}_3$; $R^2 = \text{OH}$
 IXb, $R^1 = \text{OH}$; $R^2 = \text{CH}_3$ Xb, $R^1 = \text{OH}$; $R^2 = \text{CH}_3$

Since the methyl octalol VII was the likely progenitor of the 119° diol, the latter may be presumed also to have the *syn* relationship between the hydrogen atoms at C-6 and C-10. Evidence for the rest of the configuration of the 119° diol was afforded by reduction of the hydroxy ketone IXa, *via* the *p*-toluenesulfonylhydrazide,⁵ to a methyldecalol which was shown, by infrared spectroscopy and vapor phase chromatography peak enhancement experiments, to be identical with *trans*-1-methyl-*syn*-1-decalol (Xa). Authentic Xa was prepared by the reaction of methylmagnesium iodide with *trans*-1-decalone.⁶ The preponderant product of the resulting mixture of epimers, which could be obtained in a pure form by preparative vapor phase chromatography, was regarded as substance Xa arising from equatorial attack by the Grignard reagent.⁷ This preponderant epimer was the least polar of all of the four racemic 1-methyl-1-decalols which is also consistent with the configuration Xa, since this is the only stereoisomer with a pure axial hydroxyl group.

The n.m.r. spectrum of the 183° isomer showed absorption for one proton as a broad multiplet at $\delta = 3.51$ –4.15 p.p.m., suggestive of an axial proton on a carbon bearing a hydroxyl group. The spectrum also showed strong singlet absorption at $\delta = 1.24$ p.p.m., indicative of a methyl group on a carbon holding a tertiary hydroxyl group. That the 183° compound was a stereoisomeric form of the 119° diol followed from its conversion, *via* the oxidation-reduction sequence described above, into a 1-methyl-1-decalol, m.p. 67–68°. Vapor phase chromatography experiments showed this substance to have a retention time identical with that of the less preponderant epi-

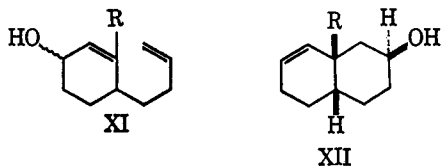
(5) The method of L. Caglioti and M. Magi, *Tetrahedron*, **19**, 1127 (1963).

(6) Cf. J. English, Jr., and G. Cavaglieri, *J. Am. Chem. Soc.*, **65**, 1085 (1943).

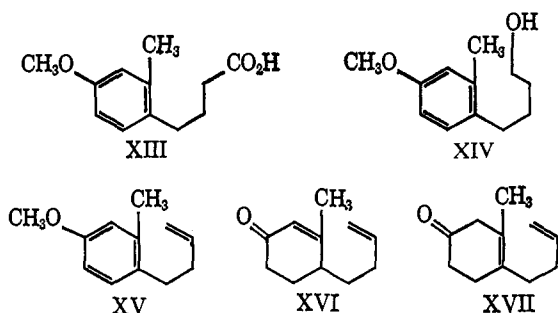
(7) Cf. H. O. House and W. L. Respass, *J. Org. Chem.*, **30**, 301 (1965).

mer arising from the action of methylmagnesium iodide on *trans*-1-decalone (see above), and different from that of the epimeric mixture obtained by the reaction of methylmagnesium iodide on *cis*-1-decalone. The 1-methyl-1-decalol, m.p. 67–68°, therefore is assigned the *trans-anti* configuration (Xb); and the 183° diol, accordingly, is regarded as *trans*-1-methyl-*anti*-1-*syn*-6-decalindiol (VIIIb).

When the 183° diol was treated with formic acid as in the cyclization experiments, it was converted into a mixture of products showing behavior on thin layer chromatography which was identical with that of the product obtained on cyclization of the dienol I (R = CH₃). This result suggests, but does not prove, that a rapid equilibrium is established among these products, and that the predominance of the *trans-syn-syn* diol (VIIIa) is a reflection of its thermodynamic stability relative to the other products. We could not find any of the product derived from addition of formic acid to VII in the alternative manner to give the angular formyloxy group. The most stable of such products, with the rings *trans* fused and the methyl group equatorial, would be a higher energy form than the major product found, because the axial angular formyloxy group has four 1,3-interactions with axial hydrogens, while there are only three such interactions involving the tertiary axial formyloxy group in the diformate of VIIIa. It is not obvious, however, why such an angular formyloxy isomer should be significantly less stable than the diformate of VIIIb.



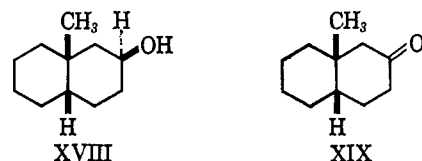
Since the cyclization of the allylic alcohol I (R = CH₃) failed to give the product with an angular methyl group, we decided to explore the cyclization of the isomeric allylic alcohol XI (R = CH₃) with the hope of producing a substance like XII (R = CH₃) in analogy to the conversion XI (R = H) → XII (R = H).²



The allylic alcohol XI (R = CH₃) was prepared as follows. The acid XIII, which is readily available *via* reduction of the succinoylation product of *m*-cresyl methyl ether,⁸ was converted, by treatment with lithium aluminum hydride, to the alcohol XIV. The latter substance was transformed, by pyrolysis of its ester (the benzoate, methyl carbonate, and ethyl carbonate were all examined) into the butenyl compound XV which, on Birch reduction with lithium and ethanol in

(8) See W. S. Johnson, S. Shulman, K. L. Williamson, and R. Pappo, *J. Org. Chem.*, 27, 2015 (1962).

ammonia at –78°⁹ followed by acid hydrolysis, was converted to a mixture of the α,β - and β,γ -unsaturated ketones XVI and XVII. These last two isomers could be separated by chromatography on silica gel. The α,β -unsaturated ketone XVI was then converted, by lithium aluminum hydride reduction, into the desired allylic alcohol XI (R = CH₃) which, by analogy to the case of XI (R = H),² was assumed to be a mixture of stereoisomers epimeric about the carbon bearing the hydroxyl group; however, in the present case the product was heat sensitive and could not be analyzed satisfactorily by vapor phase chromatography. Quantitative analysis by n.m.r. spectroscopy indicated that this product was contaminated with a maximum of 9% of the isomeric alcohol derived from the β,γ -unsaturated ketone XVII; hence it was regarded as satisfactory for cyclization studies. The allylic alcohol XI (R = CH₃), on treatment with formic acid for 5.5 min. at room temperature, was essentially quantitatively converted to bicyclic material which proved (see below) to be a mixture of XII (R = CH₃) and its C-2 epimer.



The constitution of the cyclized product was demonstrated by catalytic hydrogenation over palladium on carbon which gave a mixture of *cis*-9-methyl-*anti*-2-decalol (XVIII) and its C-2 epimer. Oxidation of this last mixture afforded, as the exclusive product, *cis*-9-methyl-2-decalone (XIX), the infrared and n.m.r. spectra of which were identical with those of authentic material.

By analogy with the established stereochemical course of the cyclization of XI (R = H),² the major product of the ring closure of XI (R = CH₃) is most probably the *cis-anti* isomer XII (R = CH₃). This predominant isomer was isolated and purified by conversion to, and recrystallization of, the 3,5-dinitrobenzoate, m.p. 128–129°. Saponification of the pure ester afforded what is presumably *cis*-9-methyl- Δ^7 -*anti*-2-octalol (XII, R = CH₃), m.p. 75–76°. Catalytic hydrogenation of the octalol gave the corresponding decalol, m.p. 72–74°, which may be identical with the *cis*-9-methyl-2-decalol, m.p. 72°,¹⁰ isolated from the mixture produced on acid-catalyzed cyclization of 2-methyl-1- Δ^3 -butenylcyclohexanol.¹¹ It is presumed (see above) that the angular methyl group and the hydrogen atom at C-2 are *anti* to each other, and that the methyldecalol is therefore *cis*-9-methyl-*anti*-2-decalol (XVIII).

Experimental Section¹²

2-(Δ^3 -Butenyl)-3-methylcyclohexenone (VI). The following is an adaptation of the procedure of Barnes and Sedlak.⁴ To a solution of 4.66 g. of sodium in

(9) See footnote 7 of ref. 2.

(10) R. P. Linstead, A. F. Millidge, and A. L. Walpole, *J. Chem. Soc.*, 1140 (1937).

(11) Unpublished studies by F. E. Brot indicate that, unlike the case of the lower homolog,¹ this cyclization is not stereospecific.

(12) All asymmetric substances described in this section are racemic compounds; the prefix *dl* is omitted. Melting points were determined on a Kofler hot stage microscope unless otherwise noted. N.m.r. spectra were determined under the supervision of Dr. L. J. Durham on a

120 ml. of absolute ethanol was added 36.4 g. of Hagemann's ester,¹³ b.p. 69° (0.065 mm.), followed by 27.0 g. of 4-bromo-1-butene.¹⁴ The mixture was heated at reflux in an atmosphere of nitrogen with stirring for 18 hr.; then most of the ethanol was removed by distillation, and the residue was diluted with water. The mixture was extracted with ether, and the combined organic layers were dried over anhydrous sodium sulfate. The product obtained on removal of the solvent was distilled through a base-washed, 60-cm., Podbielniak-type column to give 25.1 g. of colorless alkylation product V: b.p. 100–118° (0.55–0.60 mm.), $\lambda_{\max}^{\text{film}}$ 5.80 (CO₂Et), 6.00 (C=O), and 10.95 (C=CH₂) μ . This material appeared to be homogeneous by thin layer chromatography. The forerun, b.p. 94–103° (0.55–0.60 mm.), amounted to 6.35 g. and was shown by thin layer chromatography to consist of a mixture of Hagemann's ester and the alkylation product.

The aforementioned 25.1-g. sample of the alkylated keto ester V was slowly added over a period of 30 min. to a refluxing solution of 6 g. of 85% potassium hydroxide pellets in 60 ml. of absolute ethanol. The system was maintained under an atmosphere of nitrogen during this addition and for an additional 18 hr. of refluxing. The infrared spectrum of the product, which was isolated in the usual manner by ether extraction, indicated ester absorption at 5.79 μ ; therefore it was resaponified as described above except that 3 ml. of water was added to the original reaction mixture in order to increase the concentration of hydroxide ion. After a 3-hr. heating period, the mixture was diluted with water, extracted with ether, and the combined organic layers were washed with saturated brine, and finally dried over anhydrous sodium sulfate. The residue obtained upon removal of the solvent was distilled through a base-washed, 60-cm., Podbielniak-type column to give 8.9 g. of colorless liquid, b.p. 111–118° (9–14 mm.). This material appeared to be essentially homogeneous by thin layer chromatography. After redistillation the product had the following properties: $n_{\text{max}}^{25\text{D}}$ 1.4997; $\lambda_{\max}^{95\% \text{ EtOH}}$ 243 m μ (ϵ 12,000); $\lambda_{\max}^{\text{film}}$ 6.02 (C=O), 6.15 (C=C), and 11.00 (C=CH₂) μ .

Anal. Calcd. for C₁₁H₁₆O: C, 80.44; H, 9.81. Found: C, 80.3; H, 10.1.

The *semicarbazone* was obtained from dilute methanol as colorless prisms: m.p. 150.5–151.5°, $\lambda_{\max}^{95\% \text{ EtOH}}$ 267 m μ (ϵ 25,100).

Varian Associates A-60 n.m.r. spectrometer. The chemical shifts are reported as δ values in p.p.m. relative to tetramethylsilane = 0. Vapor phase chromatographic analyses were performed on an Aerograph Hy-Fi gas chromatograph (Model A-600) equipped with a hydrogen flame ionizer detector. The columns used were (a) 5 ft. \times 0.125 in., packed with: 15% Carbowax or 5% neopentylglycol sebacate on 80–100 mesh Chromosorb W, 5% SE-30 or 20% phenyldiethanolamine succinate on 60–80 mesh Chromosorb W, and 15% Carbowax on base-washed 60–80 mesh Chromosorb P; and (b) 7.5 ft. \times 0.125 in., packed with 15% Craig succinate on 60–80 mesh Chromosorb W. Some analyses were performed on a Perkin-Elmer gas chromatograph equipped with 150 ft. \times 0.01 in. Goley columns. Preparative vapor phase chromatography was performed on an Aerograph Autoprep gas chromatograph (Model A-700). The helium flow rate was approximately 200 ml./min., and the column used was 20 ft. \times 0.375 in., packed with 20% Carbowax on 45–60 mesh Chromosorb W. The elution order used in column chromatography was pentane or petroleum ether (b.p. 60–68°), benzene, ether, chloroform (approximately 1% ethanol content), and methanol.

(13) L. I. Smith and G. F. Rouault, *J. Am. Chem. Soc.*, **65**, 631 (1943).

(14) Prepared from Δ^3 -butenyl alcohol (R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 1995 (1934)) according to the procedure described for the higher homolog (F. B. LaForge, N. Green, and W. A. Gersdorff, *J. Am. Chem. Soc.*, **70**, 3707 (1948)).

Anal. Calcd. for C₁₂H₁₉N₃O: C, 65.13; H, 8.65; N, 18.99. Found: C, 64.8; H, 8.85; N, 18.7.

2-(Δ^3 -Butenyl)-3-methyl-2-cyclohexenol (I, R = CH₃). A solution of 9.99 g. of the aforementioned butenylmethylcyclohexenone VI in 150 ml. of anhydrous ether was added slowly over a 3-hr. period with stirring to a cooled (ice bath) suspension of 11.4 g. of lithium aluminum hydride in 500 ml. of anhydrous ether. The mixture was then vigorously stirred and cooled while 45.6 ml. of water was added slowly over a 1.5-hr. period. The mixture was filtered, the precipitate was washed thoroughly with ether, and the combined ether solutions were dried over anhydrous sodium sulfate. The oily residue obtained upon removal of the solvent was distilled through a base-washed Claisen head to give 9.03 g. of a colorless liquid: b.p. 99–100° (3.35–3.50 mm.), $n_{\text{max}}^{25\text{D}}$ 1.4962, $\lambda_{\max}^{\text{film}}$ 3.00 (OH) and 11.00 (C=CH₂) μ . This product appeared to be essentially homogeneous by thin layer chromatography. It could not be analyzed by vapor phase chromatography since it decomposed on a Craig succinate column at 187–190° as well as on a base-washed Carbowax column at 181°. The n.m.r. spectrum (carbon tetrachloride solvent) showed absorption for approximately (A) one proton as a multiplet at δ = 5.46–6.17 p.p.m. (HC=C), (B) two protons as a multiplet at 4.76–5.17 (C=CH₂), (C) one proton as a broad band at 3.78–4.06 (HCO), and (D) 6.2 protons as a singlet at 1.63 (CH₃C=C superimposed on unidentified protons). From six integrations of the region from 3–6.5 p.p.m., it was estimated that the ratio of band C to band A was 0.951 (theoretical 1.000), and the ratio of band C to band B was 0.498 (theoretical 0.500). These results indicate an average purity of 97.4% for the alcohol provided the butenyl side chain is present only as the Δ^3 isomer. The latter condition requires that the ratio of band A to band B equal 0.500; the spectrum showed an average value of 0.525.

Anal. Calcd. for C₁₁H₁₈O: C, 79.46; H, 10.92. Found: C, 79.25; H, 10.8.

Cyclization of 2-(Δ^3 -Butenyl)-3-methyl-2-cyclohexenol (I, R = CH₃). A. In Dilute Solution. A 148-mg. sample of the dienol was dissolved in 45 ml. of anhydrous formic acid¹⁵ and allowed to stand for 5.5 min. at 23°. The solution, which had turned to a brown color after approximately 30 sec., then was poured slowly with stirring into a mixture of 180 ml. of cold 30% sodium hydroxide solution and 250 g. of ice. This neutralization step required approximately 1 min., and the temperature, measured at the point of mixing, did not rise above 30°. The alkaline mixture was stirred for 2 hr. at room temperature, then was saturated with sodium chloride, and extracted with three 150-ml. portions of ether. The residue obtained upon evaporation of the solvent from the combined organic layers was heated at reflux for 30 min. with a solution of 1.83 g. of sodium hydroxide in 25 ml. of water. The mixture was cooled, saturated with sodium chloride, and extracted with three 150-ml. portions of ether. The combined organic layers were washed with saturated brine and dried over anhydrous sodium sulfate. The residue obtained upon evaporation of the solvent was chromatographed on 10 g. of neutral

(15) Prepared by distillation from boric anhydride: see H. I. Schlesinger and A. W. Martin, *ibid.*, **36**, 1589 (1914).

alumina (Woelm grade III). The fraction eluted with 40–70% benzene in petroleum ether (b.p. 60–68°) corresponded to the methyloctalol VII (see below) and amounted to 45 mg. Thin layer chromatography indicated that the product was essentially homogeneous, containing only traces of extraneous materials. The fraction eluted with 30–60% ether in benzene corresponded to the diol VIIIa (see below) and amounted to 58 mg. The fraction eluted with 70% ether in benzene to 100% ether corresponded to isomeric diol VIIIb (see below) and amounted to 36 mg. Thin layer chromatography of the diols showed that each was contaminated with only traces of the other.

B. On a Preparative Scale. A 1.67-g. specimen of the dienol was dissolved in 35 ml. of anhydrous formic acid.¹⁵ After 5.5 min. at 22.5° the solution was neutralized and saponified just as described above (part A) except that 7.5 g. of sodium hydroxide in 100 ml. of water was employed for the saponification treatment. The crude product was chromatographed on 101 g. of Florisil. The methyloctalol fraction (1.03 g.) was eluted with benzene through 10% ether in benzene, and the mixture of diols (0.56 g.) was eluted with 60% ether in benzene through 5% chloroform in ether.

Repeated chromatography of the methyloctalol fraction on Florisil finally gave 0.6 g. of $\Delta^{1,9}$ -1-methylsyn-6-octalol (VII). This material was a colorless, viscous oil: b.p. 100° (1.5 mm.), n_D^{25} 1.5166, $\lambda_{\max}^{\text{film}}$ 3.00 (OH) μ . Thin layer chromatography indicated that the product was homogeneous. Vapor phase chromatographic analysis on Craig succinate at 187° showed the presence of one major component with traces of three contaminants which appeared as very weak shoulders on the sides of the main peak. The n.m.r. spectrum (deuteriochloroform solution) showed absorption for approximately one proton as a multiplet at $\delta = 3.40$ – 4.10 p.p.m. (axial proton on a carbon bearing an OH) and three protons as a singlet at 1.63 (CH₃C=C).

Anal. Calcd. for C₁₁H₁₈O: C, 79.46; H, 10.92. Found: C, 79.2; H, 10.7.

A total of 0.38 g. of *trans*-1-methyl-syn-1-syn-6-decalindiol (VIIIa), which was essentially homogeneous to thin layer chromatography, was isolated from the aforementioned diol fraction by a combination of fractional crystallization from ether–chloroform and repeated chromatography on Florisil. Repeated recrystallization from ether gave clusters of fine, colorless needles: m.p. 116–119°, $\lambda_{\max}^{\text{KBr}}$ 2.98 (OH) μ . Thin layer chromatography indicated that the product was homogeneous. The n.m.r. spectrum (deuteriochloroform solution) showed absorption for approximately one proton as a broad band at $\delta = 3.2$ – 4.0 p.p.m. (axial proton on a carbon bearing an OH) and 4.8 protons as a singlet at 1.18 (CH₃CO superimposed on unidentified protons).

Anal. Calcd. for C₁₁H₂₀O₂: C, 71.69; H, 10.94. Found: C, 71.8; H, 10.9.

The fractional crystallization and chromatography mentioned above also gave a total of 0.09 g. of the more polar *trans*-1-methyl-anti-1-syn-6-decalindiol (VIIIb), which was essentially homogeneous by thin layer chromatography. Repeated recrystallization from chloroform gave small, colorless needles: m.p. 179–183° (sealed capillary), $\lambda_{\max}^{\text{KBr}}$ 2.97 μ (OH). Thin layer chro-

matography indicated that the material was homogeneous. The n.m.r. spectrum (pyridine solution) showed absorption as a broad band at $\delta = 3.51$ – 4.15 p.p.m. (axial proton on a carbon bearing an OH) and as a singlet at 1.24 (CH₃CO).

Anal. Calcd. for C₁₁H₂₀O₂: C, 71.69; H, 10.94. Found: C, 71.4; H, 10.8.

C. At Low Temperature. A 46-mg. specimen of the dienol was treated with 5 ml. of anhydrous formic acid¹⁵ at 8–10° for 1 min., then immediately treated with alkali as described above (part A). Thin layer chromatography of the crude product indicated the complete disappearance of starting material and a pattern of products which was the same as that obtained in the experiment described above (part A). It is concluded therefore that the cyclization was complete even under these mild conditions.

Treatment of the 183° Diol with Formic Acid. A 9.2-mg. specimen of the aforementioned diol, m.p. 179–183°, was dissolved in 7 ml. of anhydrous formic acid.¹⁵ After 5.5 min. at 24°, the colorless solution was made alkaline and saponified, and the product was isolated as described in the preceding experiment (part A). The thin layer chromatogram of the crude material showed the same pattern of major spots as that obtained with the crude product of the cyclization of the dienol (see above).

Conversion of *trans*-1-Methyl-syn-1-syn-6-decalindiol (VIIIa) into *trans*-1-Methyl-syn-1-decalol (Xa). To 40 mg. of chromium trioxide dissolved in the minimum amount of water was added a solution of 92.1 mg. of the diol, m.p. 116–119°, in 5 ml. of glacial acetic acid. The mixture was stirred for 4 hr. at 26°, then poured into 125 ml. of saturated sodium bicarbonate solution. The mixture was extracted thoroughly with ether, and the combined organic layers were washed with saturated sodium bicarbonate solution and saturated brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent left a residue of the hydroxy ketone IXa (see below for purification) which was mixed with a solution of 140 mg. of *p*-toluenesulfonylhydrazine in 3 ml. of absolute methanol. The mixture was heated at reflux for 4 hr., cooled, and diluted with ether. The ethereal solution was washed in turn with 10% aqueous acetic acid, saturated sodium bicarbonate solution, saturated brine, and finally dried over anhydrous sodium sulfate. Evaporation of the solvent afforded an oily residue: $\lambda_{\max}^{\text{film}}$ 2.81 (OH), 3.09 (NH), 6.09 (C=N), and 8.62 (SO₂) μ . This crude product was dissolved in 15 ml. of absolute methanol, 757 mg. of sodium borohydride was added, and the mixture was heated at reflux for 17 hr. The mixture was cooled, poured into a solution of 40 g. of sodium chloride in 150 ml. of water, and extracted with ether. The combined organic layers were washed with saturated brine, saturated sodium bicarbonate solution, again with saturated brine, and dried over anhydrous sodium sulfate. The residue obtained on evaporation of the solvent was chromatographed on 5.3 g. of Florisil. The fraction eluted with 50% benzene in petroleum ether (b.p. 60–68°) through 2% ether in benzene amounted to 11.9 mg. of an oil, the infrared spectrum of which was identical with that of authentic *trans*-1-methyl-syn-1-decalol (Xa, see below). Vapor phase chromatography on Craig succinate at 136–137° indicated that

this substance was homogeneous and, by peak enhancement, exhibited the same retention time as the authentic material.

trans-1-Methyl-*syn*-1-hydroxy-6-decalone (IXa) was prepared by oxidation of the diol VIIIa just as described in the first step of the preceding experiment. Thus 79.7 mg. of diol VIIIa, m.p. 116–119°, afforded 82 mg. of crude hydroxy ketone IXa, which appeared to be homogeneous by thin layer chromatography. Evaporative distillation of this material at 100° (1.5 mm.) gave a colorless oil which solidified, giving shiny, colorless prisms: m.p. 71.5–73.5°, $\lambda_{\max}^{\text{KBr}}$ 2.89 (OH) and 5.89 (C=O) μ .

Anal. Calcd. for $\text{C}_{11}\text{H}_{18}\text{O}_2$: C, 72.49; H, 9.96. Found: C, 72.2; H, 9.8.

Conversion of trans-1-Methyl-*anti*-1-*syn*-6-decalindiol (VIIIb) into *trans*-1-Methyl-*anti*-1-decalol (Xb). A 79.7-mg. sample of the aforementioned diol, m.p. 179–183°, was submitted to the degradative sequence described above for the conversion of VIIIa to Xa. Thus 19 mg. of crystalline IXb was obtained after the chromatography on Florisil. This product was homogeneous to thin layer chromatography. The n.m.r. spectrum (carbon tetrachloride solution) showed absorption for approximately 5.4 protons as a singlet at $\delta = 1.03$ p.p.m. (CH_3CO superimposed on unidentified protons). The sample which was recovered from the carbon tetrachloride solution was crystallized from pentane and sublimed at approximately 65° (2.5 mm.) to give colorless needles: m.p. 67–68°, $\lambda_{\max}^{\text{KBr}}$ 2.96 (OH) μ .

Anal. Calcd. for $\text{C}_{11}\text{H}_{20}\text{O}$: C, 78.51; H, 11.98. Found: C, 78.4; H, 11.8.

By vapor phase chromatography on a Castorwax Gelay column at 152° and a flow rate of 1.57 ml./min., this material was shown to enhance the 17.4-min. peak response due to authentic *trans*-1-methyl-*anti*-1-decalol (see below).

4-(4-Methoxy-2-methylphenyl)-1-butanol (XIV). A solution of 25.0 g. of 4-(4-methoxy-2-methylphenyl)butyric acid,⁸ m.p. 87–89°, in 100 ml. each of anhydrous ether and tetrahydrofuran was added slowly, over a 45-min. period, to 300 ml. of a 2.0 *N* solution of lithium aluminum hydride in ether. The mixture was heated at reflux for 3.5 hr., then, while cooling, was treated with water followed by 3 *N* hydrochloric acid. The acidified mixture was saturated with sodium chloride and extracted with ether. The combined organic layers were washed with water, followed by saturated brine and dried over anhydrous sodium sulfate. The residue obtained on evaporation of the solvent at reduced pressure was distilled through a 7-cm. Claisen head to give 22.1 g. of a colorless liquid: b.p. 125–127° (0.4 mm.); $n_D^{24.5}$ 1.5287; $\lambda_{\max}^{\text{film}}$ 3.0 (OH) and 9.54 (CO) μ ; $\lambda_{\max}^{95\% \text{ EtOH}}$ 226 μm (ϵ 9300), 277 (2010), and 284 (1870).

Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{O}_2$: C, 74.19; H, 9.34. Found: C, 74.05; H, 9.4.

The *benzoate*, m.p. 54–56°, was obtained in 98% yield by the benzoyl chloride–pyridine method. Two recrystallizations of this product from 95% ethanol gave colorless prisms: m.p. 58–58.5°; $\lambda_{\max}^{\text{KBr}}$ 5.85 μ ; $\lambda_{\max}^{95\% \text{ EtOH}}$ 228 μm (ϵ 22,600) and 277 μm (ϵ 2730).

Anal. Calcd. for $\text{C}_{19}\text{H}_{22}\text{O}_3$: C, 76.48; H, 7.43. Found: C, 76.2; H, 7.4.

The *ethyl carbonate* was prepared from ethyl chloro-

formate essentially according to the procedure of O'Connor and Nace.¹⁶ The crude product from 15.55 g. of alcohol was distilled through a 5-cm. Vigreux column to give 1.25 g. of a forerun, b.p. 135–148° (1 mm.), and a main fraction amounting to 18.40 g., b.p. 148–150° (1 mm.). The residue from the distillation was chromatographed on 10 g. of basic alumina (Merck and Co.), and an additional 0.94 g. of the ester was obtained in the fraction eluted with petroleum ether (b.p. 60–68°). Redistillation of a portion of the main fraction afforded a colorless liquid: b.p. 138–141° (0.4 mm.); $n_D^{24.5}$ 1.4984; $\lambda_{\max}^{\text{film}}$ 5.77 μ ; $\lambda_{\max}^{95\% \text{ EtOH}}$ 226 μm (ϵ 8600), 277 (1940), and 284 (1770).

Anal. Calcd. for $\text{C}_{15}\text{H}_{22}\text{O}_4$: C, 67.64; H, 8.33. Found: C, 67.5; H, 8.3.

The *methyl carbonate* was obtained as described in the preceding experiment except that methyl chloroformate was used instead of the ethyl ester. Thus from 21.43 g. of the alcohol XIV there was obtained 25.37 g. of a colorless liquid: b.p. 130–134° (0.30–0.35 mm.); n_D^{21} 1.5047; $\lambda_{\max}^{\text{film}}$ 5.74 μ ; $\lambda_{\max}^{95\% \text{ EtOH}}$ 226 μm (ϵ 8250), 277 (1680), and 284 (1530).

Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_4$: C, 66.64; H, 7.99. Found: C, 67.1; H, 8.0.

1-(Δ^3 -Butenyl)-4-methoxy-2-methylbenzene (XV).

A. From the Benzoate of XIV. A dropping funnel equipped with a nitrogen gas inlet tube was charged with 5.8 g. of the aforementioned benzoate of XIV, b.p. 52–56°. The solid was melted by gentle warming of the funnel with a free flame, and the liquid was then passed through a 13-cm. glass tube packed with Pyrex glass beads heated to 400–440°. During the pyrolysis the system was maintained in an atmosphere of nitrogen by slow passage of a stream of gas through the pyrolysis tube. A condenser cooled with Dry Ice was employed in order to trap the pyrolysate which was chromatographed on 30 g. of silica acid (Mallinckrodt, 100 mesh). The fraction eluted with 10–20% benzene in petroleum ether (b.p. 60–68°) afforded 0.615 g. of oily product. Further elution with benzene gave 4.95 g. of recovered benzoate which was resubjected to the pyrolysis to give an additional 0.374 g. of product. One more recycling of the recovered benzoate afforded 0.370 g. of product. The combined fractions were evaporatively distilled at 130–140° (40 mm.) to give 0.992 g. of a colorless liquid. Distillation of a sample through a shortpath distillation head gave a colorless oil; b.p. 138–140° (26 mm.); $n_D^{24.5}$ 1.5199; $\lambda_{\max}^{\text{film}}$ 6.10, 10.02, and 10.96 ($\text{CH}=\text{CH}_2$) μ ; $\lambda_{\max}^{95\% \text{ EtOH}}$ 226 μm (ϵ 9000), 277 (1650), and 284 (1530).

Anal. Calcd. for $\text{C}_{12}\text{H}_{16}\text{O}$: C, 81.77; H, 9.15. Found: C, 81.85; H, 9.2.

B. From the Ethyl Carbonate. This ester was pyrolyzed under the same conditions as above for the benzoate except that the cracking temperature was 360–380°. Thus from 18.5 g. of the ethyl carbonate there was obtained (one pass), after chromatography on 100 g. of Florisil, 4.54 g. of product eluted with petroleum ether (b.p. 60–68°). Distillation gave 3.66 g. of colorless material, b.p. 138–140° (26 mm.). Further elution with 20–60% benzene in petroleum ether (b.p. 60–68°) gave 1.67 g. of recovered ethyl carbonate,

(16) G. L. O'Connor and H. R. Nace, *J. Am. Chem. Soc.*, 74, 5454 (1952).

and elution with benzene to 20% ether in benzene afforded 5.35 g. of the alcohol XIV.

C. From the Methyl Carbonate. This ester was pyrolyzed at 400–420° as described above. Thus from 25.27 g. of the ester there were obtained 8.00 g. of distilled product, b.p. 79–83° (0.65–0.75 mm.), and 3.00 g. of crude recovered ester, b.p. 83–142° (0.6 mm.).

4-(Δ^3 -Butenyl)-3-methyl-2-cyclohexenone (XVI). A solution of 8.00 g. of the butenylmethoxymethylbenzene XV, b.p. 79–83° (65–75 mm.), in 64 ml. of dimethoxyethane and 360 ml. of ammonia was cooled with an isopropyl alcohol–Dry Ice bath while 2.56 g. of lithium wire was added in small pieces with vigorous stirring. After the addition was complete, the solution was stirred for 12 min.; then 6.40 ml. of absolute ethanol was added slowly over a 2-min. period. Stirring was continued for an additional 7 min.; then solid ammonium chloride was added. The residue obtained on evaporation of the ammonia was extracted with ether. The oily residue obtained on evaporation of the ether was dissolved in a mixture of 110 ml. of 95% ethanol and 50 ml. of 3 *N* hydrochloric acid, and the mixture was stirred at room temperature for 19 hr. in an atmosphere of nitrogen. The mixture was then saturated with sodium chloride and extracted with ether. The combined organic layers were washed with water, followed by saturated brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 7.4 g. of a yellow oil which was chromatographed on 200 g. of 100–200 mesh silica gel. The fraction eluted with 50% benzene in petroleum ether (b.p. 60–68°) amounted to 3.70 g. of recovered starting material XV. Further elution with 10% ether in benzene afforded 3.63 g. of a mixture of the unsaturated ketones. Evaporative distillation of the latter fraction at 160° (30 mm.) gave 3.34 g. of an oil, $\lambda_{\max}^{\text{film}}$ 5.83 (weak, C=O) and 5.99 (strong, C=CC=O) μ . Thin layer chromatography on silica gel (1:1 ether–benzene) showed two spots, R_f 0.49 (α,β -unsaturated ketone) and 0.62 (β,γ -unsaturated ketone). This material was rechromatographed on 200 g. of 200–300 mesh silica gel. The fraction eluted with benzene amounted to 0.29 g. of an oil consisting mainly of the β,γ -unsaturated ketone XVII; $\lambda_{\max}^{\text{film}}$ 5.83 (C=O), 6.09, 10.02, and 10.95 (CH=CH₂) μ . A shoulder at 5.96 μ in the infrared spectrum indicated contamination by the α,β -unsaturated ketone. Further elution of the column with 200 ml. of 1% ether in benzene gave 0.90 g. of a liquid which on analysis by vapor phase chromatography (Carbowax column at 173°) proved to consist of about 80% of the α,β -unsaturated ketone XVI (retention time 20.5 min.) and 15% of the β,γ -unsaturated ketone XVII (retention time 16.2 min.). Continued elution with 600 ml. of 1% ether in benzene afforded 1.91 g. of material which on analysis by vapor phase chromatography (see above) was shown to consist of 93% of XVI and 5% of XVII. The aforementioned two fractions eluted with 1% ether in benzene were combined and rechromatographed on 230 g. of 200–300 mesh silica gel. Elution with benzene removed 0.14 g. of XVII, and further elution with benzene through 1% ether in benzene gave 2.16 g. of an oil which was evaporatively distilled at 160° (30 mm.). The colorless oil amounted to 1.95 g.; $n_{\text{D}}^{23.5}$ 1.5027; $\lambda_{\max}^{\text{film}}$ 6.01 (C=CC=O), 6.10, 6.17 (C=C), 10.05, and 10.99 (CH=CH₂) μ .

Vapor phase chromatographic analysis (see above) indicated that this material was 96% pure.

Anal. Calcd. for C₁₁H₁₆O: C, 80.44; H, 9.83. Found: C, 80.1; H, 9.85.

The *2,4-dinitrophenylhydrazone* was obtained from 95% ethanol as red microneedles, m.p. 90.5–91°. After some time this material underwent a polymorphic change into a form melting at 115–116.5°: $\lambda_{\max}^{95\% \text{ EtOH}}$ 254 m μ (ϵ 17,700), shoulder 287 (11,200), and 384 (25,300).

Anal. Calcd. for C₁₇H₂₀N₄O₄: C, 59.29; H, 5.85; N, 16.27. Found: C, 59.1; H, 6.1; N, 16.5.

4-(Δ^3 -Butenyl)-3-methyl-2-cyclohexenol (XI, R = CH₃). A solution of 1.73 g. of the aforementioned distilled α,β -unsaturated ketone XVI in 60 ml. of anhydrous ether was added over a 15-min. period with stirring and cooling (ice bath) to a suspension of 1 g. of lithium aluminum hydride in 100 ml. of anhydrous ether. Stirring was continued for 45 min.; then 4.74 ml. of water was added dropwise, and the resulting slurry was filtered and washed thoroughly with ether. The combined filtrate and washings were dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the solvent was evaporatively distilled at 160° (0.5 mm.) to give 1.72 g. of a colorless liquid: n_{D}^{23} 1.4939; $\lambda_{\max}^{\text{film}}$ 3.0 (OH), 6.03, 6.11, 10.10, and 11.05 μ . The n.m.r. spectrum (deuteriochloroform solution) showed absorption for two protons as a multiplet at 5.3–6.2 p.p.m. (nonterminal vinylic protons), two protons as a multiplet at 4.8–5.2 (terminal vinylic protons), one proton as a broad singlet at 4.1 (allylic proton on carbon bonded to OH), one proton as a sharp singlet at 2.77 (OH), and three protons as a singlet at 1.68 (CH₃C=C).

Anal. Calcd. for C₁₁H₁₈O: C, 79.46; H, 10.92. Found: C, 79.2; H, 10.9.

Since this allylic alcohol could not be analyzed satisfactorily by vapor phase chromatography, apparently because of its tendency to dehydrate, n.m.r. spectroscopy was employed for determination of the isomeric purity. It was assumed that the major impurity was the Δ^3 isomer derived from XVII. The integral ratio of terminal to nonterminal vinylic protons was equal to 1.028 which corresponds to a purity of 95%. The ratio of total vinylic protons to the total number of protons was 0.217 which corresponds to a purity of 91%. The substance XI (R = CH₃), as prepared above, therefore was contaminated with a maximum of 9% of the Δ^3 isomer and was therefore considered satisfactory for the cyclization experiments.

Cyclization of 4-(Δ^3 -Butenyl)-3-methyl-2-cyclohexenol (XI, R = CH₃). A 0.262-g. sample of the allylic alcohol was treated with 72 ml. of anhydrous formic acid¹⁵ at 22.5° for 5.5 min., and the product was isolated as described above for the isomeric substance I (R = CH₃). The crude pale yellow oily product obtained on evaporation of the extraction solvent was dissolved in carbon disulfide so as to bring the volume to 25.00 ml. Analysis by vapor phase chromatography on Craig succinate at 193° indicated the relative yield of *cis*-9-methyl- Δ^7 -2-octalol to be 98%. For determination of the absolute yield, 1-(Δ^3 -butenyl)-4-methoxy-2-methylbenzene (XV) was used as a reference compound, its retention time being 6.3 min. as compared with 9.3 min. for the authentic (see below) *cis*-octalols. When

0.0134 g. of authentic *cis*-octalols was added to a 2.0-ml. aliquot of the cyclization mixture containing 0.0129 g. of the reference compound, the average ratio (three injections) of reference compound to octalols was 0.496. When the same amounts of authentic *cis*-octalols and reference compound were analyzed in the absence of the cyclization mixture, the average ratio (four injections) was 1.19. From these ratios it is calculated that the cyclization product contained 0.235 g. of *cis*-octalols, corresponding to an absolute yield of 90%. When this value is corrected for the purity of the starting material (91–95%), the yield is 94–98%.

A 0.638-g. sample of crude cyclization product prepared as described above was evaporatively distilled at 110–150° (40 mm.) to give 0.500 g. of semicrystalline octalol mixture, m.p. 25–70°. The 3,5-dinitrobenzoate was prepared with 3,5-dinitrobenzoyl chloride in pyridine, and 0.422 g. of one pure epimer (m.p. 128–129°) was obtained as pale yellow needles by repeated recrystallizations from 95% ethanol.

Anal. Calcd. for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.9; H, 5.6; N, 8.0.

A 0.300-g. sample of the 3,5-dinitrobenzoate, m.p. 127–128.5°, was saponified with 12 ml. of 10% sodium hydroxide in 12 ml. of 95% ethanol. The mixture was heated at reflux for 1 hr. in an atmosphere of nitrogen. After removal of the alcohol by distillation, the octalol was steam distilled and isolated from the distillate by adding sodium chloride and extracting with ether. The combined organic layers were dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 0.134 g. of *cis*-9-methyl- Δ^7 -*anti*-2-octalol¹⁷ (XII, R = CH₃), m.p. 73–75°. Recrystallization from pentane gave fine, colorless needles: m.p. 75–76°, $\lambda_{max}^{CHCl_3}$ 2.79 and 2.92 (OH) μ . The n.m.r. spectrum (deuteriochloroform solution) showed a multiplet at 5.20–5.75 p.p.m. (two vinylic protons), a multiplet at 3.45–4.1 (proton on carbon bearing an OH), a concentration-dependent singlet at 2.85 (OH), and a singlet at 1.03 (CH₃).

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.5; H, 10.8.

cis-9-Methyl-*anti*-2-decalol¹⁷ (XVIII). A sample of *cis*- Δ^7 -9-methyl-2-octalol was hydrogenated quantitatively by E. Meier using a microhydrogenation apparatus. Thus, 21.55 mg. (0.130 mmole) of octalol, m.p. 74.5–76°, in 3 ml. of absolute ethanol was hydrogenated in the presence of 21.6 mg. of platinum oxide at 24° and 760 mm. The hydrogenation was completed in 10 min. with a hydrogen uptake of 3.24 ml. (2.98 ml. corrected to standard temperature and pressure). The theoretical hydrogen uptake for molecular weight 166 is 2.91 ml. The catalyst was filtered and washed with absolute ethanol. Evaporation of the solvent left 26.7 mg. of residue. Pentane was added and the solution was filtered. Evaporation of the pentane left 21.5 mg. of colorless solid, m.p. 72–73.5°. Recrystallization from pentane gave micro-needles, m.p. 72–74°. The n.m.r. spectrum (carbon tetrachloride solution) showed a multiplet at 3.4–4.1 p.p.m. (one proton on a carbon bearing an OH), a broad singlet at 2.44 (OH), and a sharp singlet at 0.96 (CH₃).

(17) The *anti* configuration is presumed (see Discussion).

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.8; H, 12.0.

The 3,5-dinitrobenzoate was obtained from 95% ethanol as pale needles, m.p. 130.5–132°.

Anal. Calcd. for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.6; H, 6.2; N, 7.9.

Conversion of the Total Cyclization Product to cis-9-Methyl-2-decalone (XIX). A solution of 0.021 g. of the aforementioned crude oily cyclization product in 13 ml. of petroleum ether (b.p. 60–68°) was hydrogenated for 20 hr. at atmospheric pressure over 0.02 g. of 5% palladium on carbon (Engelhard Industries, Inc.). The mixture was filtered, and the residue obtained upon concentration of the filtrate was chromatographed on 1 g. of silica gel. Elution with 10% acetone in benzene gave 0.013 g. of an oil which crystallized on standing: m.p. 25–60°, λ_{max}^{film} 2.98 (OH) and 9.58 (CO) μ . This product was dissolved in 1 ml. of acetone and titrated at 0° with Jones' reagent¹⁸ until a slight excess of the oxidant remained. A drop of isopropyl alcohol was added to decompose the excess reagent; then water was added, and the mixture was extracted with ether. The combined organic layers were washed with water, followed by saturated brine, and dried over anhydrous sodium sulfate. The residue obtained on removal of the solvent at reduced pressure was chromatographed on 1 g. of basic alumina (Merck and Co.). The fraction eluted with carbon tetrachloride amounted to 0.007 g. of a colorless oil which showed behavior identical with that of *cis*-9-methyl-2-decalone on vapor phase chromatography on a Golay SE-30 column at 120° and a flow rate of 1.3 ml./min. (retention time 24.0 min.). No trace of the *trans* isomer (retention time 23.4 min.) could be detected. The infrared spectrum of the oxidation product was identical with that of authentic *cis*-9-methyl-2-decalone and distinctly different from that of the *trans* isomer. The n.m.r. spectrum (carbon tetrachloride solution) was also identical with that of *cis*-9-methyl-2-decalone, showing sharp singlet absorption for the angular methyl group at 0.97 p.p.m. There was no absorption at 0.78 p.p.m. corresponding to the signal for the methyl group in the *trans* isomer.

Preparation of Comparison Substances. cis-1-Decalone. cis-syn-1-Decalol, m.p. 90–90.5° (prepared by hydrogenation of α -naphthol over ruthenium oxide (Engelhard Industries, Inc.) was oxidized according to the procedure that Djerassi and Staunton¹⁹ developed for the levorotatory isomer. In order to minimize the possibility of isomerization, our *dl* product was not distilled but was used directly in the Grignard reaction described below. The infrared spectrum (film) of the crude ketone showed a band at 10.56 μ that is characteristic of *cis*-1-decalone.

trans-1-Decalone was produced from the aforementioned *cis* isomer by acid-catalyzed isomerization.¹⁹ The undistilled product was used for the Grignard reaction (see below). The infrared spectrum (film) of the crude ketone showed the band at 11.02 μ that is characteristic of *trans*-1-decalone. Although there was no discernible absorption at 10.56 μ , the vapor phase chromatography experiments on the Grignard

(18) Cf. C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, 21 1547 (1956).

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

adduct (see below) indicated that this product was contaminated with a small amount of the *cis* isomer.

The cis-1-Methyl-1-decalols. A mixture of the *syn* and *anti* epimers was produced by the action of excess methylmagnesium iodide on the aforementioned *cis*-1-decalol. The procedure was similar to that of English and Cavaglieri⁶ except that ammonium chloride was used for decomposing the adduct. Since the infrared spectrum of the crude product still showed weak absorption for the carbonyl group at 5.88 μ , it was treated with excess methyllithium and reisolated in the usual way. The undistilled product, which was dried by azeotropic distillation, was obtained as a pale yellow oil, $\lambda_{\text{max}}^{\text{film}}$ 2.95 μ . Thin layer chromatography showed two, barely separable, spots. The vapor phase chromatographic analysis is described below.

The trans-1-Methyl-1-decalols. A 2.83-g. sample of the aforementioned *trans*-1-decalone was treated with excess methylmagnesium iodide as described in the preceding experiment for the *cis* compound, and the crude product was chromatographed on 300 g. of Florisil. The fraction eluted with 20–60% benzene in pentane amounted to 2.28 g. of crude *trans*-1-methyl-*syn*-1-decalol (*Xa*), $\lambda_{\text{max}}^{\text{film}}$ 2.91 μ . Vapor phase chromatography (see below) and thin layer chromatography indicated this material to be identical with pure material which was isolated directly from another run (without column chromatography) by preparative vapor phase chromatography over Carbowax at 150–155°, followed by evaporative distillation at 100° (2.5 mm.) to give a colorless liquid, n^{25}_D 1.4912.

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.3; H, 11.8.

Further elution of the aforementioned Florisil column with 70% benzene in pentane to 2% ether in benzene afforded 0.79 g. of the crude *anti* isomer. Since the infrared spectrum of this material showed weak absorption at 5.89 μ for the carbonyl group, it was treated with methyllithium as described above. The product thus obtained was a pale yellow oil, $\lambda_{\text{max}}^{\text{film}}$ 2.97 μ , which was used for the vapor phase chromatographic studies described below.

Vapor Phase Chromatographic Analyses of the Four 1-Methyldecalols. On a Craig succinate column at 132–134°, the major product from the reaction of methylmagnesium iodide with *trans*-1-decalone exhibited a retention time of about 25 min. while the other three 1-methyldecalols showed retention times in the range of 34–38 min. This short retention time (also observed on thin layer chromatography) is consistent with the assignment of the *trans-syn* configuration to this major product. On a Castorwax Golay column at 152°, the *trans*-1-methyl-*anti*-1-decalol fraction (see above) showed four peaks with the following retention times relative to ether: 14.6, 17.4 (intense), 18.7, and 19.5 min. When the mixture of *cis*-1-methyl-1-decalols (see above) was also introduced, the 18.7- and 19.5-min. peaks were enhanced. When pure *trans*-1-methyl-*syn*-1-decalol was introduced, the 14.6-min. peak was enhanced. Therefore the 17.4-min. peak must correspond to *trans*-1-methyl-*anti*-1-decalol.

cis-9-Methyl-2-decalone. A 4:1 mixture of $\Delta^{1,9}$ - and $\Delta^{9,10}$ -2-octalones²⁰ was treated with methylmag-

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

nesium iodide in the presence of cuprous chloride,²¹ and the crude ketonic product was isolated as the semicarbazone. After three recrystallizations from 95% ethanol, this derivative melted at 201–203.5° dec. (lit.²¹ m.p. 212–213°). Hydrolysis with aqueous oxalic acid gave *cis*-9-methyl-2-decalone, b.p. 151° (45 mm.), n^{25}_D 1.4907 (lit.¹⁰ n^{16}_D 1.4937). The n.m.r. spectrum (carbon tetrachloride solution) showed absorption for three protons as a singlet at $\delta = 0.97$ p.p.m. (angular methyl group). Vapor phase chromatography showed a single peak on a Carbowax (at 182.5°) as well as on a 5% SE-30 column (151°). Single peaks were also shown on a Golay Castorwax column at 178° and a flow rate of 1.3 ml./min. (retention time 18.7 min.) and on a Golay SE-30 column at 120° and the same flow rate (retention time 24.0 min.). Thin layer chromatography on silica gel showed a single spot on development either with benzene–0.5% *n*-butyl alcohol or with benzene–5% acetic acid–5% ethyl acetate.

cis-9-Methyl-2-decalols. F. E. Brot submitted the aforementioned *cis*-9-methyl-2-decalone to reduction with lithium aluminum hydride. Vapor phase chromatography of the semicrystalline product on a 5-ft. Carbowax column at 180° showed a single peak (retention time 14.5 min.). The mixture of epimers was resolved on a Golay Castorwax column at 200° and a flow rate of 1.3 ml./min. (retention times 12.0 and 14.5 min.).

The acetates of the epimeric mixture of *cis*-9-methyl-2-decalols were prepared by Brot using the pyridine-acetic anhydride method. Vapor phase chromatography of the product on a Golay Castorwax column at 170° and a flow rate of 3.4 ml./min. showed two peaks of approximately equal area (retention times 9.38 and 10.25 min. relative to ether).

(+)-*trans*-9-Methyl-2-decalone.²² We are indebted to Professor Carl Djerassi and Dr. J. E. Gurst for providing us with a pure specimen of this material which was used for the vapor phase chromatography comparison studies with the Jones' oxidation product of the hydrogenated cyclization products described above. Vapor phase chromatography of the pure enantiomer gave a single peak on a 150-ft. Golay Castorwax column at 178° and a flow rate of 1.3 ml./min. (retention time 18.4 min.) and on a Golay SE-30 column at 120° and a flow rate of 1.3 ml./min. (retention time 23.4 min.).

trans-9-Methyl-2-decalone was prepared by Dr. E. W. Della from the aforementioned mixture of 2-octalones according to the procedure of Nagata, *et al.*²³ The infrared spectrum of the product, b.p. 135–137° (17 mm.), n^{25}_D 1.4875 (lit.²³ b.p. 130° (15 mm.), n^{23}_D 1.4889), was identical with that of a specimen obtained from Nagata by Djerassi. The n.m.r. spectrum (carbon tetrachloride solution) showed absorption for three protons as a singlet at $\delta = 0.78$ p.p.m. (angular methyl group).

The semicarbazone was obtained from methanol as colorless leaflets, m.p. 204–205° (lit.²³ m.p. 209–211°).

(21) Cf. A. J. Birch and R. Robinson, *J. Chem. Soc.*, 501 (1943).

(22) C. Djerassi and J. E. Gurst, *J. Am. Chem. Soc.*, **86**, 1755 (1964).

(23) W. Nagata, I. Kikkawa, and M. Fujimoto, *Chem. Pharm. Bull. (Tokyo)*, **11**, 226 (1963); W. Nagata and I. Kikkawa, *ibid.*, **11**, 289 (1963).

The melting point of a mixture with the semicarbazone of *cis*-9-methyl-2-decalone showed considerable depression.

Acknowledgment. Acknowledgment is made to the

U. S. Public Health Service, the National Science Foundation, and to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Conformational Barriers in Medium-Sized Rings.

I. *trans*-Cyclodecene-1,2,4,4,9,9-*d*₆¹

Gerhard Binsch and John D. Roberts

Contribution No. 3242 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California. Received April 26, 1965

The peculiar conformational situation in *trans*-cycloalkenes of medium ring size is discussed. It is concluded that one pair of optical isomers should exist in the odd-membered rings and two such pairs in the even-membered rings. For a given ring size, the various isomers are expected to be separated from one another by a substantial energy barrier. Cope and co-workers have shown previously that, for *trans*-cyclooctene, at least one of the barriers is high enough to allow isolation of two very stable optical isomers. Optically active *trans*-cyclononene was found to be much less stable and *trans*-cyclodecene gave no detectable optical activity. In the present investigation, the n.m.r. spectrum of *trans*-cyclodecene-1,2,4,4,9,9-*d*₆ has been studied as a function of temperature. Two processes which are slow on the n.m.r. time scale at low temperatures have been discovered. One of them, which involves rotation of the *trans*-alkene group through the loop formed by the methylene groups, was found to have an activation energy $\Delta E^* = 10.7 \pm 0.3$ kcal./mole and a frequency factor $A = 10^{11.7 \pm 0.3}$ sec.⁻¹. The other process, for which no accurate rates could be determined, appears to involve restricted rotation of the C-6-C-7 molecular segment in the cyclodecene ring.

Optical activity in solution can be associated with asymmetric substituted atoms or with "inherently dissymmetric" compounds. Although only relatively few classes which produce stable enantiomers are known for the latter type of isomerism,² the phenomenon is almost omnipresent among organic molecules when one considers all species characterized by potential-energy minima as individual entities. N.m.r. spectroscopy is particularly valuable as a tool for obtaining quantitative information about racemization processes which cannot be studied by classical means.³ The characteristic realm of the n.m.r. line-shape method extends just from the borderline where the antipodes become too unstable to be isolated, down to interconversion barriers of a few kilocalories.

(1) Supported in part by the National Science Foundation and the Office of Naval Research.

(2) For a review see E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(3) For a case where the n.m.r. method has been applied to a dissymmetric molecule see W. L. Meyer and R. B. Meyer, *J. Am. Chem. Soc.*, **85**, 2170 (1963).

It has been proposed⁴ that *trans* cyclic olefins of medium ring size should be resolvable into stable optically active conformations. Experimental evidence bearing on this prediction has been provided by Cope and his co-workers⁵ who succeeded in isolating two isomers of *trans*-cyclooctene having opposite rotations. The levorotatory enantiomer was subsequently assigned the (*R*)-configuration.^{5b} Molecular models indicate, however, that, in addition to the unsymmetrical environment of the double bond, *trans*-cyclooctene contains a second element of dissymmetry, the C-5-C-6 bond. Furthermore, it appears that rotation of the C-5-C-6 segment through the ring is about as difficult as the analogous movement of the double bond, a conclusion which is substantiated by the results to be discussed below. The reasoning leads to the four isomers 1a-d shown in Figure 1. Interconversion of the antipodes requires two processes, which may or may not occur simultaneously, whereas either process alone would only produce the corresponding diastereomer. The sequence used by Cope and Mehta^{5b} to establish the absolute configuration of a (-)-*trans*-cyclooctene isomer could not by its very nature give any information as to which pair of enantiomers of 1 these authors actually had in hand. A similar situation is found also in *trans*-cyclodecene, whereas in the odd-membered *trans*-cycloolefins the only source of dissymmetry stems from the environment of the ethylenic linkage.

Recently the kinetics of racemization of optically active *trans*-cyclooctene have been studied⁶ by the conventional polarimetric method. An activation energy of 35.6 kcal./mole was calculated from an Arrhenius plot of the rate data. It is not clear, however, whether this number refers to the true racemization process which requires two steps as pointed out above, or whether it is only a measure of the restricted rotation of the *trans* olefinic bond. It has been claimed⁷ that the optical rotation of *trans*-cyclooctene mainly arises from the out-of-plane twisting of the olefinic bond system. If this is the case, differences in the relative orientation

(4) A. T. Blomquist, L. H. Liu, and J. C. Bohrer, *ibid.*, **74**, 3643 (1952); V. Prelog in "Perspectives in Organic Chemistry," A. Todd, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, p. 129.

(5) (a) A. C. Cope, C. R. Ganellin, and H. W. Johnson, Jr., *J. Am. Chem. Soc.*, **84**, 3191 (1962); A. C. Cope, C. R. Ganellin, H. W. Johnson, Jr., T. V. VanAuken, and H. J. S. Winkler, *ibid.*, **85**, 3276 (1963).

(b) A. C. Cope and A. S. Mehta, *ibid.*, **86**, 5626 (1964).

(6) A. C. Cope and B. A. Pawson, to be published.

(7) A. Moscovitz and K. Mislow, *J. Am. Chem. Soc.*, **84**, 4605 (1962).