

Reductive Opening of Acyclic Conjugated Cyclopropyl Ketones with Lithium in Liquid Ammonia¹

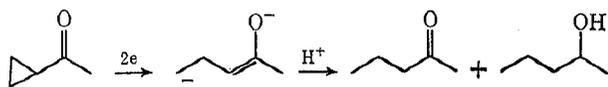
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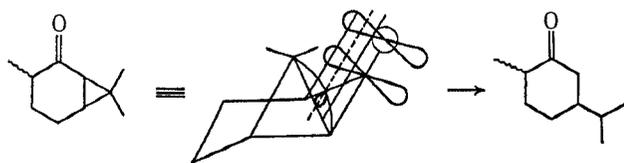
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A series of acyclic 2-methylcyclopropyl alkyl ketones **1** has been reductively cleaved with lithium in liquid ammonia. The selective bond cleavage which occurs depends upon the influence of both steric and electronic factors. The reduction products that predominate in the reaction mixture from the cleavage of 2,2-dimethylcyclopropyl alkyl ketones or *cis*-2-methylcyclopropyl alkyl ketones arise from C-1-C-2 bond breaking. In contrast the *trans*-2-methylcyclopropyl alkyl ketones fragment at the C-1-C-3 bond. The observed ring-opening pattern suggests that steric factors can control the direction of cleavage, presumably through unsymmetrical overlap of the carbonyl π system with one of the cyclopropane bonds. In the absence of these steric elements (as in the *trans*-substituted cyclopropane ring), the bond that cleaves is the one that gives the more thermodynamically stable carbanion intermediate (least substituted carbon).

The reduction of organic compounds with metals in liquid ammonia is a well-established synthetic technique.²⁻⁵ Deuteration^{6,7} and alkylation⁸⁻¹⁰ experiments in the reduction of α,β -unsaturated ketones with lithium in liquid ammonia have shown that the β -carbon atom develops a considerable amount of carbanion character during the reductive process. Cyclopropyl ketones, when reduced with metals in ammonia,¹¹ undergo reductive cleavage of the cyclopropane ring by a mechanism similar to that described for enones, and thus, the developing carbanionic character of the β carbon could be a controlling factor in a ring opening.



In fused bicyclic systems, however, geometrical factors^{12,13} and not electronic factors appear to control the direction of ring opening of the cyclopropane ring, and the bond that cleaves is the one which has the greater overlap with the carbonyl π system. An example of this stereoselective reductive cleavage can be illustrated with the reduction of (+)-carone, which gives only the (-)-carvomenthones upon treatment with lithium in liquid ammonia.^{12,13} None of the product which would



(1) This work was supported in part by Public Health Service Grant CY-04284, National Cancer Institute, U. S. Public Health Service.

(2) For a general discussion of dissolving metal reductions, see H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 50-77.

(3) H. Smith, "Organic Reactions in Liquid Ammonia," Vol. 1, part 2, Interscience Publishers, Inc., New York, N. Y., 1963.

(4) A. J. Birch and H. Smith, *Quart. Rev.* (London), **12**, 17 (1958).

(5) For a survey of metal-ammonia reductions in the steroid field, see "Steroid Reactions," Holden-Day, Inc., C. Djerassi, Ed., San Francisco, Calif., 1963, pp 299-325.

(6) D. H. Williams, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **85**, 2091 (1963).

(7) M. Fetizon and J. Gore, *Tetrahedron Lett.*, 471 (1966).

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

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

(10) H. A. Smith, B. J. L. Huff, W. J. Powers, III, and D. Caine, *ibid.*, **32**, 2851 (1967).

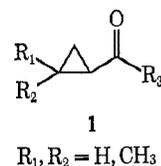
(11) R. V. Volkenburgh, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Amer. Chem. Soc.*, **71**, 3595 (1949).

(12) T. Norin, *Acta Chem. Scand.*, **19**, 1289 (1965).

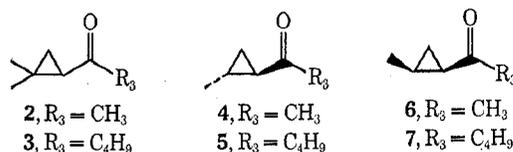
(13) W. G. Dauben and E. J. Devinny, *J. Org. Chem.*, **31**, 3794 (1966).

be derived from the more thermodynamically stable secondary carbanion was found.

The present study extends this reductive reaction of lithium in liquid ammonia to acyclic conjugated cyclopropyl ketones of the general type **1**, where both



bonds of the cyclopropane ring are free to overlap with the carbonyl π system and thus the importance of electronic and steric factors can be evaluated. The six 2-methylcyclopropyl alkyl ketones **2-7** were prepared. The ketones **2**, **3**, and **5** were obtained by treating the



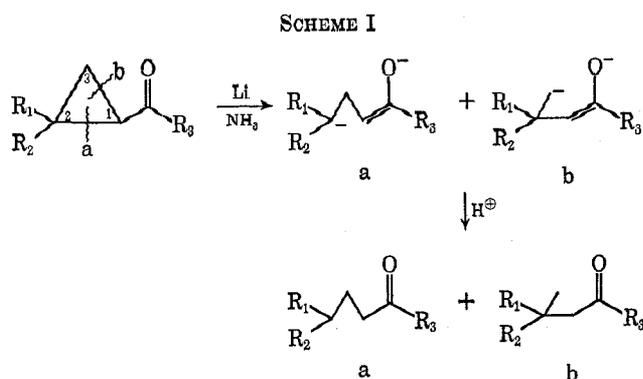
respective enones with dimethylxosulfonium ylide,¹⁴ and ketones **4**, **6**, and **7** were prepared from the corresponding cyclopropylcarbinols which, in turn, were prepared from corresponding *cis*- and *trans*-allylic alcohols using methylene iodide and zinc-copper couple.^{15,16} The allylic alcohols were prepared from the acetylenic alcohols by hydrogenation.

The lithium in liquid ammonia reduction of an unsymmetrically substituted cyclopropyl ketone can lead to two different ring-opened products. The reduction possibilities are shown in Scheme I. If one presumes that the carbonyl group can rotate to the same extent over both bonds of the cyclopropane ring, thermodynamic considerations of the intermediates formed in the reductive cleavage process should allow one to predict which bond of the cyclopropane ring will preferentially break. Path a in Scheme I shows cleavage of the C-1-C-2 bond, leading to the less stable secondary or tertiary carbanion, whereas path b gives the more stable primary carbanion. Under equal

(14) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

(15) H. E. Simmons, E. P. Blanchard, and R. D. Smith, *ibid.*, **86**, 1347 (1964).

(16) W. G. Dauben and G. H. Berezin, *ibid.*, **85**, 468 (1963).



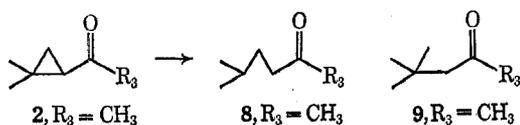
overlap conditions the product resulting from the more stable primary carbanion intermediate would be expected to predominate in the reduction mixture. The results of the lithium-ammonia reductions are shown in Table I.

TABLE I
LITHIUM IN LIQUID AMMONIA REDUCTION OF ACYCLIC
CONJUGATED CYCLOPROPYL KETONES

Ketone	Starting material, %	Products, path a and b, %	Path a, %	Path b, %
2	10	74 ^a	76	24
3	5	87	81	19
4	5	65	6	94
5	5	87	12	88
6	14	53	95	5
7	4	69	91	9

^a The product ratio remained essentially the same even though the yields ranged from 36 to 84%.

The reduction of 2,2-dimethylcyclopropyl methyl ketone (2) with lithium in liquid ammonia afforded two ketonic products, 8 and 9, and the corresponding alcohols. To simplify product analysis the reduction mixtures were routinely oxidized. The major product from such a work-up was isoamyl methyl ketone (8) and the minor component was neopentyl methyl ketone (9).



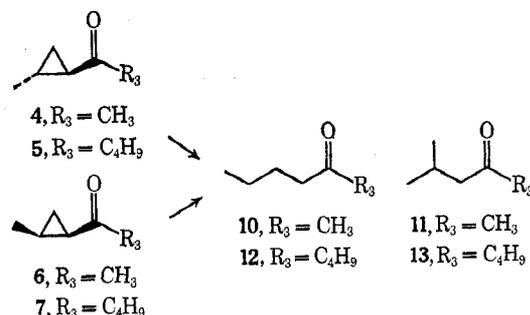
The relative product percentages formed by path a (leading to the less stable tertiary carbanion intermediate) clearly implicated considerations other than simple thermodynamic stabilities of intermediate carbanions in control of the ring-opening process. On the basis of carbanion stabilities, ketone 9 should have been the predominant product. Although the data presented in Table I indicate an 84% recovery of material at the end of the reaction, this result was the best of a series of experiments. The methyl ketones of this series are quite volatile (bp 110–130°), and when attempts were made to isolate the ketonic products the losses were considerable. In order to obviate this difficulty, the *n*-butyl ketone series was studied.

The reductive cleavage of 2,2-dimethylcyclopropyl butyl ketone (3) proceeded to give the same ring-opening pattern as ketone 2. The bond that opened was the one leading to the less thermodynamically stable product, thus suggesting that in this acyclic

system a steric control was again controlling the course of the reaction. From molecular models of ketones 2 and 3, it appeared that the C-1-C-2 bond was in a position to overlap more with the carbonyl π system than the C-1-C-3 bond because of the steric interaction of the *cis*-2-methyl substituent with the carbonyl group.

The reduction of the *trans*-2-methylcyclopropyl ketones 4 and 5 with lithium in liquid ammonia served to substantiate the concept of unsymmetrical overlap in the *cis*-2-methyl-substituted ketones 2 and 3. When the *cis* substituent was absent, the predominant products were formed by way of the primary carbanion intermediate (path b).¹⁷

The *cis*-2-methylcyclopropyl ketones 6 and 7 were reduced with lithium in liquid ammonia and the ratio of products 10/11 and 12/13 were reversed from that observed in the cleavage of the *trans* ketones 4 and 5. The sharp contrast between the ring opening of the *cis* and *trans* ketones clearly indicated that a steric effect was present in the *cis* ketones and that both steric and electronic factors are involved in the reduction process.



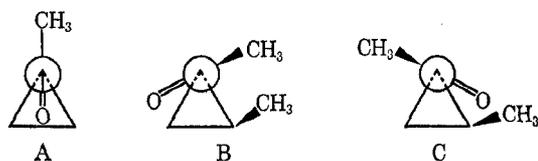
In the case of the *trans*-monomethyl-substituted cyclopropyl ketones 4 and 5, the free rotation of the carbonyl gives equal π -orbital overlap to either cyclopropane bond. The predominant influence of the course of the reduction is the relative thermodynamic stability of the carbanionic intermediates generated. The *cis*-monomethyl cyclopropyl ketones 6 and 7, in a thermodynamic sense, provide the same competition between carbanion centers as the *trans* ketones 4 and 5, but the steric effect is far more important than the relative difference between a primary and secondary carbanion and the ratios are reversed.

The difference in thermodynamic stability of the carbanion is greatest when a tertiary center competes with a primary center, such as in the reduction of the 2,2-dimethylcyclopropyl ketones 2 and 3. The steric situation in the case of 2,2-dimethyl-substituted cyclopropyl ketones should be the same as it is in the *cis*-2-methylcyclopropyl ketones 6 and 7. As one can readily see in Table I, the thermodynamic effect changes the *ca.* 4:1 ratio of path a/path b type products in the ketones 2 and 3 to a ratio of *ca.* 10:1 with 6 and 7. All of these data are consistent with developing carbanion character on a cyclopropyl carbon in the reductive cleavage of cyclopropyl ketones. Recently, similar steric and electronic effects were reported in the reductive cleavage of methyl-substituted phenylcyclo-

(17) After completion of this work, similar results were reported in the literature. See R. Fraisse-Jullien and C. Frejaville, *Bull. Soc. Chim. Fr.*, 4449 (1968). However, their results do not include the *cis*-substituted monomethylcyclopropyl ketones, which are considered necessary to evaluate electronic effects under similar steric conditions.

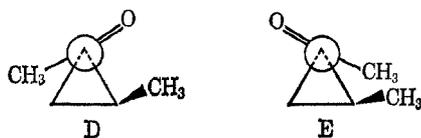
propanes¹⁸ and, thus, indicate a close relationship between these two series of substituted cyclopropanes.

It is of interest to examine the nature of the steric interaction in these reductive cleavages of the *cis*-2-methylcyclopropyl methyl ketones. Electron-diffraction measurements¹⁹ and nmr studies²⁰ indicate that unsubstituted cyclopropyl methyl ketone exists predominantly as the "bisected" *cisoid* conformer A. If



the reductive cleavage proceeds *via* a transition state involving overlap of a bond of the cyclopropane ring and the carbonyl group, then consideration of the two *cisoid gauche* conformations B and C is important. The presence of a substituent on the same side of the cyclopropane ring makes conformation B preferred owing to the unfavorable interaction of the substituent and the carbonyl oxygen in conformation C. In the absence of a substituent on the same side of the cyclopropane, both *gauche* conformations are of equal energy and purely electronic effects control the course of the reaction.

In view of the fact that there is considerable negative character at both the carbonyl oxygen and the β carbon in the transition state, dipolar considerations suggest that a *transoid* configuration for the transition state most likely would be preferred. The steric interactions in the two *gauche* conformations D and E of the *transoid* arrangements place the methyl groups in such a position that the steric interactions would lead to the same conclusion as above with the *cisoid* form.



In view of the sensitivity of the product ratio to the preferred conformations of the starting material, the effect of varying the size of the reducing metal was evaluated. The results, summarized in Table II, show that the metal had no effect on the direction of ring

TABLE II
REDUCTION OF 2,2-DIMETHYLCYCLOPROPYL METHYL
KETONE (2) WITH VARIOUS METALS IN LIQUID AMMONIA

Metal	Starting material, %	Products, ^a %	Path a, ^b %	Path b, ^b %
Li	10	74	76	24
Ca	28	55	74	26
K	10	73	76	24
Na	17	68	78	22
Mg	57	27	87	13

^a Determined by internal-standard method using cyclooctane as an internal standard.

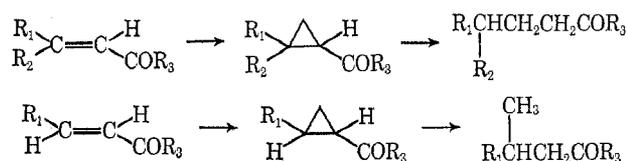
(18) S. W. Staley and J. J. Rocchio, *J. Amer. Chem. Soc.*, **91**, 1565 (1969).

(19) L. S. Bartell, J. P. Guillory, and A. T. Parks, *J. Phys. Chem.*, **69**, 3043 (1965).

(20) J. L. Pierre and P. Arnaud, *Bull. Soc. Chim. Fr.*, 1690 (1966).

opening. The slight shift in the isomer distribution in the magnesium reduction may be anomalous, for the magnesium did not dissolve appreciably in the ammonia and did not give the typical blue color normally associated with metal in ammonia reduction. The insensitivity of the product ratio to various metals suggests that no change in conformer population occurs. This could be due to the fact that the smallest atom, lithium, is already large enough to establish the preferred conformation or that the conformation of the transition state is predominately *transoid* in all cases. A similar insensitivity in product ratio with the metal employed has recently been found in the reduction of ketones,²¹ a result at variance with earlier reports concerning the effect of metals.²²

These findings of a steric effect in the reduction of conformationally mobile cyclopropyl conjugated ketones call attention to the synthetic utility of the process. In the *cis* series, the overall reaction process is



equivalent to a chain-elongation reaction by insertion of the carbon between the original α and β carbons of the starting material. In the *trans* series, the process is equivalent to a 1,4 addition to the unsaturated system to form a tertiary center β to the carbonyl group.

Experimental Section²³

Synthesis of Starting Ketones. *cis*- and *trans*-2-Methylcyclopropyl Methyl Ketones (6 and 4).—These compounds were prepared as described in an earlier publication.²⁴

2,2-Dimethylcyclopropyl Methyl Ketone (2).—Mesityl oxide was allowed to react with dimethylxosulfonium ylide¹⁴ and 2 was obtained in 56% yield. The spectral properties were in agreement with the reported values.^{20,25}

2-Methyl-2-octen-4-one.—Following the general procedure of House and Trost,²⁶ 10 g of 3,3-dimethylacrylic acid and 138 ml of 1.6 M *n*-butyllithium were allowed to react. The reaction mixture, which was composed of the α,β - and β,γ -unsaturated ketone

(21) J. W. Huffman and J. T. Charles, *J. Amer. Chem. Soc.*, **90**, 6486 (1968).

(22) G. Ourisson and A. Rassat, *Tetrahedron Lett.*, **21**, 16 (1960); A. Coulombeau and A. Rassat, *Bull. Soc. Chim. Fr.*, 3338 (1965); J.-C. Esprie, A.-M. Giroud, and A. Rassat, *ibid.*, 809 (1967); A. Coulombeau and A. Rassat, *Chem. Commun.*, 1587 (1968).

(23) Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord or a 237 grating spectrophotometer. Ultraviolet spectra were taken with either a Perkin-Elmer ultraviolet-visible or a Beckman DK-2A spectrometer. Nuclear magnetic resonance spectra were determined on a Varian Associates A-60 or HA-100 spectrometer. Mass spectra were recorded with either a Varian Associates M-66 or a modified Consolidated Electronics Corporations Type 21-103C mass spectrometer. An Aerograph A-90 gas chromatograph, equipped with either a 10 ft \times 0.375 in., 20% XF-1150 Cyanosilicone or a 10% Carbowax-10% KOH column, was utilized for separation of isomeric compounds. Product percentages were determined from vpc trace analyses using either an Aerograph 204 or a Hewlett-Packard F & M Model 5720 gas chromatograph, both of which were equipped with a flame ionization detector. Column chromatographies were done with neutral Woelm alumina (activity II) unless otherwise indicated. All materials used were either reagent grade or purified technical grades. Combustion analyses were performed by the Microanalytical Department of the University of California, Berkeley.

(24) W. G. Dauben, L. Schutte, and R. E. Wolf, *J. Org. Chem.*, **34**, 1849 (1969).

(25) R. M. Roberts, R. G. Landolt, R. N. Greene, and E. W. Heyer, *J. Amer. Chem. Soc.*, **89**, 1404 (1967).

(26) H. O. House and B. Trost, *J. Org. Chem.*, **30**, 2502 (1965).

as well as a hydrocarbon and a tertiary alcohol, was allowed to stand in aqueous ethanolic potassium carbonate solution for 1 hr and then column chromatographed to yield 3.8 g (27%) of 2-methyl-2-octen-4-one: ir (CCl₄) 3060, 1693, 1625, 1130, and 1040 cm⁻¹; nmr (CCl₄) δ 6.02 (m, 1, C=CH), 2.33 (t, 2, *J* = 6.5 Hz, CH₂CO), 2.08 (d, 3, *J* = 1.5 Hz, C=CCH₃, *trans* to CO), 1.83 (d, 3, *J* = 1.5 Hz, C=CCH₃, *cis* to CO), 1.48 (m, 4), and 0.9 (t, 3, *J* = 6.5 Hz, CH₂CH₃).

Anal. Calcd for C₉H₁₆O (mol wt 140.23): C, 77.09; H, 11.50. Found: C, 77.37; H, 11.69.

2,2-Dimethylcyclopropyl Butyl Ketone (3).—Following the procedure described^{24,25} for the preparation of 2,2-dimethylcyclopropyl methyl ketone (2), a solution of 3.0 g (17 mmol, 80% pure) of 2-methyl-2-octen-4-one in 8 ml of dimethyl sulfoxide was added to a flask containing 0.42 g (17.4 mmol) of sodium hydride, 3.8 g (17 mmol) of trimethylsulfonium iodide, and 17 ml of dimethyl sulfoxide.

The crude product (2.6 g) was column chromatographed to yield 1.6 g (61%) of 2,2-dimethylcyclopropyl butyl ketone (3). A vpc-purified sample gave the following spectral and analytical data: uv max (95% C₂H₅OH) 201.5 mμ (ε 5300); ir (CCl₄) 3075, 3010, 1690, 1130, 1090, and 1030 cm⁻¹; nmr (CCl₄) δ 2.42 (t, 2, *J* = 6.5 Hz, CH₂CO), 1.74 (d of d, 2, *J* = 7.5 and 5.5 Hz), 1.6–1.18 (m, 4), 1.18–0.9 [t, 2 s, 9, *J* = 6.5 Hz, CH₂CH₃ and C(CH₃)₂], and 0.7 (d of d, 1, *J* = 3.5 and 7.5 Hz, CCH₃, *H cis* to carbonyl).

Anal. Calcd for C₁₀H₁₈O (mol wt 154.25): C, 77.87; H, 11.86. Found: C, 78.03; H, 11.59.

trans-2-Octen-4-one.—Following the procedure of Cason,²⁷ a 41.6-g (0.4 mol) portion of freshly distilled crotonyl chloride (bp 124–125°) and *n*-butylcadmium reagent were allowed to react in the usual manner. The solvent was removed through an 18-in. Vigreux column and the concentrate was distilled under reduced pressure to yield 28.75 g (57%) of *trans*-2-octen-4-one: bp 34–41° (0.5–0.6 mm); uv max (95% C₂H₅OH) 223 mμ (ε 11,600); ir (CCl₄) 3020, 1695, 1675, and 970 cm⁻¹; nmr (CCl₄) δ 6.79 (d of q, 1, *J* = 6.5 and 15 Hz, C=CH), 6.04 (d of q, 1, *J* = 1.5 and 15 Hz, C=CH), 2.47 (t, 2, *J* = 6.5 Hz, CH₂CO), 1.86 (d of d, 3, *J* = 1.5 and 6.5 Hz, C=CCH₃), 1.44 (m, 4), and 0.91 (t, 3, *J* = 6.5 Hz, CH₂CH₃).

Anal. Calcd for C₈H₁₄O (mol wt 126.20): C, 76.14; H, 11.18. Found: C, 76.33; H, 11.07.

trans-2-Methylcyclopropyl Butyl Ketone (5).—A solution of 12.6 g (0.1 mol) of *trans*-2-octen-4-one in 33 ml of dimethyl sulfoxide was added to a flask containing 2.64 g (0.11 mol) of sodium hydride, 22 g (0.1 mol) of trimethylsulfonium iodide, and 110 ml of dimethyl sulfoxide according to the procedure described for the preparation of 2,2-dimethylcyclopropyl methyl ketone (2).

After the normal work-up, the crude mixture was dried, concentrated, and distilled under reduced pressure to yield 7.55 g (54%) of *trans*-2-methylcyclopropyl butyl ketone (5): bp 67–68° (15 mm); uv max (95% C₂H₅OH) 195 mμ (ε 5,350); ir (CCl₄) 3060, 1695, 1400, and 1080 cm⁻¹; nmr (CCl₄) δ 2.48 (t, 2, *J* = 6.5 Hz, CH₂CO), 1.48 (m, 6), 1.15 (distorted s, 3, CCH₃), 0.91 (t over m, *J* = 6.5 Hz, CH₂CH₃), and 0.65 (m, 1, CCH₃, *H cis* to carbonyl).

Anal. Calcd for C₉H₁₆O (mol wt 140.23): C, 77.09; H, 11.50. Found: C, 77.35; H, 11.29.

2-Octyn-4-ol.^{28,29}—A flame-dried, three-neck flask was fitted with a mechanical stirrer, a pressure-equalized addition funnel, a Dry Ice–acetone condenser, and an adapter to permit the introduction of gaseous samples. The flask was closed to the atmosphere through a mercury bubbler and flushed with dry nitrogen. An 0.11-mol ethyl Grignard solution in 50 ml of diethyl ether was prepared in the reaction vessel.

A 10-g (0.25 mol) portion of methylacetylene (Farchan Laboratories), which had been precondensed into a Dry Ice–acetone-cooled trap, was allowed to distill into the reaction vessel over a 1-hr period through a Drierite-filled drying tube, which was, in turn, connected to the gas-inlet adapter. The reaction mixture was stirred for 3 hr at room temperature.

The two-phase system (the upper layer was nearly water white and the bottom layer was dark gray) was stirred vigorously and cooled in an ice bath. A solution of 8.6 g (0.10 mol) of freshly

distilled valeraldehyde in 75 ml of diethyl ether was added over a 1-hr period to the cold reaction mixture. The Dry Ice–acetone condenser was removed and replaced with a water condenser and the reaction was allowed to stir for 16 hr.

A saturated ammonium chloride solution was added to the mixture until the magnesium salts dissolved. The ethereal layer was separated from the aqueous layer, the aqueous layer was extracted with ether, and the extracts were combined. The ethereal extract was washed with a saturated potassium bicarbonate solution, dried, rotary evaporated, and spinning band distilled to yield 8.9 g (70.5%) of a colorless liquid. The product was identified as 2-octyn-4-ol based on the following data: bp 100–102° (29 mm); ir (CCl₄) 3600, 3440, 2250, 2200, 1100, 1030, 1000, and 885 cm⁻¹; nmr (CCl₄) δ 4.19 (m, 1, CHOH), 2.92 (s, 1, OH, shifts upfield with dilution), 1.81 (d, 3, *J* = 2 Hz, CH₃C≡C), 1.46 (m, 6), and 0.93 (t, 3, *J* = 6 Hz, CH₂CH₃).

Anal. Calcd for C₈H₁₄O (mol wt 126.20): C, 76.14; H, 11.18. Found: C, 76.02; H, 11.03.

cis-2-Octen-4-ol.—The hydrogenation was performed using a Brown² apparatus following the external generation procedure.³⁰ The catalyst was prepared from 1.0 g of Darco G activated charcoal and 1.0 ml of 0.02 *M* palladium(II) chloride solution. To the catalyst suspension was added 2.0 ml of ethylenediamine followed by 6.3 g (50 mmol) of 2-octyn-4-ol. Hydrogen uptake proceeded at a rate of 3.6 mmol/min. The hydrogenation was stopped when 1 molar equiv of hydrogen had been consumed. The hydrogenation mixture, when analyzed on vpc, contained two products in relative amounts of 3.5 and 96.5%.

Spectral and analytical data of the major product were obtained from a vpc-purified sample: bp 63–65° (20 mm); ir (CCl₄) 3600, 3330, 3010, 1660, 965, and 725 cm⁻¹; nmr (CCl₄) δ 5.32 (m, 2, HC=CH), 4.03 (m, 1, CHOH), 3.14 (s, 1, OH), 1.63 (d, 3, *J* = 5.5 Hz, CH₃C=C), 1.32 (m, 6), and 0.91 (t, 3, *J* = 6.5 Hz, CH₂CH₃).

Anal. Calcd for C₈H₁₆O (mol wt 128.22): C, 75.00; H, 12.50. Found: C, 74.74; H, 12.37.

The minor product was not collected. It was assumed to be the saturated carbinol.

trans-2-Octen-4-ol.—A mixture of 630 mg (5 mmol) of *trans*-2-octen-4-one, 100 mg (2.5 mmol) of lithium aluminum hydride, and 15 ml of dry diethyl ether was allowed to stir overnight at room temperature. An additional 47.5 mg (1.25 mmol) of lithium aluminum hydride was added and the mixture was allowed to stir under reflux for 1 hr.

The reaction mixture was treated with a saturated ammonium chloride solution, cautiously, until the dense salts precipitated. The liquid layer was decanted and the salts were washed with ether.

The ethereal extracts were combined, dried, and rotary evaporated, and the concentrate was bulb-to-bulb distilled to yield 104 mg (16%) of a clear liquid.

The spectral data were taken on a sample judged to be 80% pure on the basis of vpc analysis and contaminant peaks in the nmr: ir (CCl₄) 3600, 3350, 1670, and 965 cm⁻¹; nmr (CCl₄) δ 5.45 (m, 1.5), 3.9 (m, 0.8), 3.5 (m, 0.4), 2.83 (s, 1, OH), 1.67 (d, 2.8, *J* = 5 Hz, C=CCH₃), 1.36 (m, 6.2), and 0.9 (t, 3.2, *J* = 6 Hz, CH₂CH₃).

The minor product was assumed to be the saturated carbinol based on the position of contaminant peaks in the nmr of the mixed sample. No attempt was made to further purify the sample.

A vpc coinjection of *trans*-2-octen-4-ol and *cis*-2-octen-4-ol gave one peak on a 20% XF-1150 Cyanosilicone column (150°, 60 psi).

cis-2-Methylcyclopropylbutylcarbinol.—A solution of 3.78 g (30 mmol) of *cis*-2-octen-4-ol in 15 ml of dry diethyl ether was added to a mixture of 5.49 g (84.2 mmol) of zinc–copper couple (Metal Hydrides LPO 100), 17.67 g (66 mmol) of methylene iodide, and 40 ml of diethyl ether, and the resulting mixture was allowed to react according to a literature procedure.¹⁶

Methylene iodide contaminated the product mixture even after sodium methoxide treatment,¹⁶ but it was effectively removed by column chromatography (silica gel) using pentane as the eluting solvent. The more polar product was eluted with blends of pentane–diethyl ether to yield 3.16 g (74%) of a colorless liquid, which was identified as *cis*-2-methylcyclopropylbutylcarbinol by the following spectral characteristics: ir (CCl₄) 3600, 3060,

(27) J. Cason and F. S. Prout, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 601.

(28) I. A. Favorskaia, E. M. Auvinen, and J. P. Artsybashev, *J. Gen. Chem. USSR*, **28**, 1832 (1958); *Zh. Obshch. Khim.*, **28**, 1785 (1958).

(29) I. M. Heilbron, E. R. H. Jones, and R. A. Raphael, *J. Chem. Soc.*, 264 (1943).

(30) C. A. Brown and H. C. Brown, *J. Org. Chem.*, **31**, 3989 (1966). The authors wish to thank Dr. C. A. Brown for his assistance in this hydrogenation.

TABLE III
 REDUCTION OF 2,2-DIMETHYLCYCLOPROPYL METHYL KETONE (2) WITH LITHIUM IN LIQUID AMMONIA

Run	Reagents			Reaction time, hr	Ketones after oxidation, %	Ketone product distribution, %				Ring-opening ratio of 8/9
	Ammonia, ml	Ketone 2, g	Lithium, g			9	2	8	14	
1	200 ^a	2.24	2.8	1	36 ^b	19	15	66	..	3.4
2	200 ^a	2.24	0.31	2	48 ^b	14	40	46	..	3.3
3	200	2.24	1.4	6	51 ^c	20	21	51	8	2.5
4	400	2.24	2.8	2	70 ^c	17	19	59	5	3.4
5	400	2.24	2.8	2	53 ^c	17	22	55	6	3.2
6	60	0.114	0.14	2	... ^{c,d}	21	8	69	..	3.3
7	60	0.112	0.14	2	84 ^c	21	12	67	..	3.2

^a Ammonia was dried over sodium before use. ^b Products were determined by actual isolation. The work-up varied from the standard procedure in that the ammonium chloride was added before the ammonia was evaporated. ^c Products were determined by comparison with an internal standard on vpc. ^d Cyclooctane was included as an internal standard at the start of the reaction. Preferential loss of the standard was noted. The yield was >100%.

3000, and 1015 cm^{-1} ; nmr (CCl_4) δ 3.09 (m, 1, CHOH), 2.67 (s, 1, OH), and 1.7–0.7 (m, 16; at 1.43, m, CH_2 ; at 1.04, d, CCH_3 ; at 0.92, t, CH_2CH_3 ; at 0.8–0.6, m, CCH).

The alcohol was not characterized further and was used without further purification in the next step.

cis-2-Methylcyclopropyl Butyl Ketone (7).—To a rapidly stirred solution of *cis*-2-methylcyclopropylbutylcarbinol in 100 ml of freshly distilled acetone (from potassium permanganate) was added 6.4 ml (17 mmol) of Jones reagent³¹ (prepared from 26.72 g of chromium trioxide and 23 ml of concentrated sulfuric acid diluted with 100 ml of water). After 5 min the excess chromic acid was decomposed with 5 ml of methanol.

The liquid layer was decanted and the salts were washed with three 50-ml portions of acetone. The extracts were combined and rotary evaporated. The concentrate was taken up in ether and the ethereal solution was washed with a saturated sodium chloride solution, dried, and rotary evaporated to yield 1.26 g (69%) of a colorless liquid, which gave one peak on vpc and was identified as *cis*-2-methylcyclopropyl butyl ketone (7) based on the following spectral and analytical data: ir (CCl_4) 3075, 3010, 1695, 1385, 1125, 1068, 1032, and 855 cm^{-1} ; nmr (CCl_4) δ 2.44 (t, 2, $J = 7$ Hz, CH_2CO), a 1.95 (m, 1, CCHCO), and 1.7–0.7 [m, 13; at 1.4, m, $(\text{CH}_2)_2$; at 1.06, a sharp spike, CCH_3 ; at 0.91, t, $J = 6.5$ Hz, CH_2CH_3]. Upon vpc coinjection (20% XF-1150 Cyanosilicone, 150°), the *cis* ketone preceded the *trans* ketone (relative retention time 0.96:1.0).

Anal. Calcd for $\text{C}_9\text{H}_{16}\text{O}$ (mol wt 140.23): C, 77.09; H, 11.50. Found: C, 76.92; H, 11.34.

General Reduction Procedure.—The entire reaction sequence, including drying of the ammonia, was conducted as described previously.¹³ The work-up procedure was changed owing to the volatility of the products, and the modified procedure is as follows.

After the reaction had stirred for the stated time, the ammonia was allowed to evaporate. To the enolate salts were added a 100% excess of a saturated ammonium chloride solution followed by portions of diethyl ether.

The two layers were separated; the aqueous layer was saturated with sodium chloride and extracted with ether. The ethereal extracts were combined, washed with saturated sodium carbonate, and dried. The ethereal solutions were analyzed by vpc and, in all cases, alcohols as well as ketones were observed in the product mixture. The ethereal solution was routinely oxidized with the Brown oxidant solution³² [prepared from 41 g (137 mmol) of sodium dichromate dihydrate, 200 ml of distilled water, and 30.8 ml of 96% sulfuric acid].

Except where indicated, the yield of volatile ketones was determined by mixing a weighed portion of the ethereal solution with a known weight of an internal standard (cyclopentanone, cyclohexanone, or cyclooctane) and relating the relative areas to the amounts of each ketone present.

Reduction of 2,2-Dimethylcyclopropyl Methyl Ketone (2).—Several reductions were carried out using ketone 2 as a substrate. The variations employed and the results obtained are listed in Table III.

Vpc analysis of the oxidized product mixture showed three peaks. On occasion a fourth peak was observed, which was shown to be 2-methyl-1-hexen-5-one (14) by comparison of re-

tention times and ir spectra with those of an authentic sample. This product was assumed to be thermally produced²⁸ (cracking on vpc?) and not the result of the lithium in ammonia reduction. The products were collected by preparative vpc (20% XF-1150 Cyanosilicone, 10 ft \times 0.375 in., 150°, 60 psi).

The minor product (8.5 min) was identified as neopentyl methyl ketone (9) on the basis of the following spectral characteristics: ir (CCl_4) 1718, 1360, 1350, 1220, and 1150 cm^{-1} ; nmr (CCl_4) δ 2.27 (s, 2, CH_2CO), 2.05 (s, 3, CH_3CO), and 1.0 [s, 9, $(\text{CH}_3)_3\text{C}$]. The structure was later confirmed by independent synthesis.

The second product eluted (11 min) was identified as the starting ketone 2 by ir and retention time.

The major product (13.5 min) was identified as isoamyl methyl ketone (8) based on the following spectral characteristics: ir (CCl_4) 1715, 1365, and 1160 cm^{-1} ; nmr (CCl_4) δ 2.35 (t, 2, $J = 7$ Hz, $\text{CH}_2\text{CH}_2\text{CO}$), 2.02 (s, 3, CH_3CO), 1.44 (m, 3), and 0.89 [d, 6, $J = 5.5$ Hz, $(\text{CH}_3)_2\text{CH}$]. The ir and mass spectra were identical with those of an authentic sample.

Reduction of 2,2-Dimethylcyclopropyl Butyl Ketone (3).—From 1.33 g (8.5 mmol) of 2,2-dimethylcyclopropyl butyl ketone (3), 1.18 g (170 mg-atoms) of lithium, and 200 ml of ammonia was obtained 1.3 g (96.4%) of a clear oil. The oil was oxidized with the Brown oxidant solution³³ to yield 1.21 g (91%) of product ketones which, when analyzed on vpc, gave the following product distribution: neopentyl butyl ketone (t_R 19.25 min, 17.3%); starting ketone (t_R 26 min, 4.9%); isoamyl butyl ketone (t_R 32.25 min, 76.6%); and 2-methyl-1-nonen-5-one (t_R 42.25 min, 1.2%).

The first eluted product (t_R 19.25 min) was identified as neopentyl butyl ketone based on spectral data: ir (CCl_4) 1715, 1465, 1365, and 1250 cm^{-1} ; nmr (CCl_4) δ 2.21 [s over t, 4, $(\text{CH}_3)_3\text{CCH}_2\text{CO}$ and $\text{CH}_2\text{CH}_2\text{CO}$], 1.9–1.15 (m, 4), and 0.98 [s over t, 12, $(\text{CH}_3)_3\text{C}$ and CH_3CH_2].

The vpc retention time, ir, and nmr of the second product (26 min) were identical with those of starting ketone 3.

The structure of isoamyl *n*-butyl ketone (t_R 32.25 min) was assigned on the basis of the following spectral data: ir (CCl_4) 1715, 1380, 1365, 1250, 1130 and 1040 cm^{-1} ; nmr (CCl_4) δ 2.31 (t, 4, $J = 6.5$ Hz, CH_2COCH_2), 1.41 (m, 7), and 0.87 [d over t, 9, doublet $J = 7$ Hz, $(\text{CH}_3)_2\text{CHCH}_2$]; mol wt, 156 (mass spectrum).

The final product eluted (t_R 42.25 min) was assigned the structure of 2-methyl-1-nonen-5-one on the basis of the following data: ir (CCl_4) 3060 ($\text{C}=\text{CH}$), 1715 ($\text{C}=\text{O}$), 1645 ($\text{C}=\text{C}$), and 890 cm^{-1} ($\text{CH}_2=\text{C}$); mol wt 154 (mass spectrum of an enriched sample).

Reduction of *trans*-2-Methylcyclopropyl Methyl Ketone (4).—From 0.98 g (10 mmol) of *trans*-2-methylcyclopropyl methyl ketone (4), 1.39 g (200 mg-atoms) of lithium, and 200 ml of ammonia was obtained a calculated yield (by vpc) of 0.48 g (48%) with the following product distribution: methyl isobutyl ketone (11, t_R 10 min, 86.7%); methyl *n*-butyl ketone (10, t_R 13.25 min, 5.9%); and *trans*-2-methylcyclopropyl methyl ketone (4, t_R 15 min, 7.4%).

Methyl isobutyl ketone (11) was identified by comparison of ir, nmr, and vpc retention time with those of an authentic sample.

Methyl *n*-butyl ketone (10) was independently prepared from the oxidation of 2-hexanol, and spectral data were identical with those of the sample from the reduction.

The final product was identified as starting material 4 by spectral and retention-time comparisons with an authentic sample.

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

(32) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).

A second reduction of 98 mg of *trans*-2-methylcyclopropyl methyl ketone (4) gave a calculated yield of 70.5 mg (70.5%) and was composed of 91.6% 11, 2.5% 10, and 5.9% starting material 4.

Reduction of *trans*-2-Methylcyclopropyl Butyl Ketone (5).—From 1.4 g (10 mmol) of *trans*-2-methylcyclopropyl butyl ketone (5), 1.38 g (200 mg-atoms) of lithium, and 200 ml of ammonia was obtained 1.3 g (91.8%) of product ketones. Vpc analysis of the product mixture indicated the following distribution: an unidentified component (t_R 5.5–9.0 min, 10.2%); isobutyl *n*-butyl ketone (13, t_R 19.5 min, 75.3%); di-*n*-butyl ketone (12, t_R 26.0 min, 9.8%); and *trans*-2-methylcyclopropyl butyl ketone (5, t_R 28.0 min, 4.7%).

The first two peaks (t_R 5.5–9.0 min) appeared to be low molecular weight ketones and hydrocarbons on the basis of spectral properties: ir (CCl₄) 1712 (C=O), 1640 (C=C), and 890 cm⁻¹ (CH=C); nmr (CCl₄) complex absorptions at δ 5.32–4.15 (C=CH), 2.41–0.83, and 0.25–0. No attempt was made to further purify the mixture.

The major product (t_R 19.5 min) was identified as isobutyl *n*-butyl ketone (13) based on the following spectral data: ir (CCl₄) 1715, 1380, 1365 [(CH₃)₂CH], 1170, and 1145 cm⁻¹; nmr (CCl₄) δ 2.28 and 2.17 (t over d, 4, J = 6.5 Hz, CH₂CH₂CO); J = 2 Hz, CHCH₂CO), 2.05–1.05 (m, 5), and 0.90 and 0.89 [t over d, 9, J = 6.5 Hz, CH₃CH₂; J = 6 Hz, (CH₃)₂CH].

The third product eluted (t_R 26 min) was enriched by vpc purification (85%) and was assigned the structure of di-*n*-butyl ketone (12) based on the spectral characteristics of the impure sample: nmr (CCl₄) δ 2.30 (t, 4, J = 6.5 Hz, CH₂COCH₂), 1.40 (m, 8), and 0.94 (t, 6, J = 6.5 Hz, CH₃CH₂). The vpc retention time corresponded to that of the major ring-opened product 12 obtained from *cis*-2-methylcyclopropyl *n*-butyl ketone (7).

The final product eluted corresponded with the starting cyclopropyl ketone (5).

Reduction of *cis*-2-Methylcyclopropyl Methyl Ketone (6).—Following the usual procedure, 0.98 g (9.3 mmol) of *cis*-2-methylcyclopropyl methyl ketone (6), 93% pure by vpc, in 5 ml of ether was allowed to react for 2 hr with 1.39 g (200 mg-atoms) of lithium in 200 ml of ammonia. The calculated volatile yield was 52%. The product mixture was composed of 6.1% methyl isobutyl ketone (11), 79.3% methyl *n*-butyl ketone (10), and 14.6% *cis*-2-methylcyclopropyl methyl ketone (6).

In a second run, 98 mg of ketone 6 provided 69 mg (69%, calculated by internal standard) of which the composition was 3.3% 11, 73.1% 10, and 21.2% 6.

Product assignments for methyl isobutyl ketone (11) and methyl *n*-butyl ketone (10) were based on identical vpc retention times, ir spectra, and nmr spectra with those of an authentic sample and an independently prepared sample, respectively.

Reduction of *cis*-2-Methylcyclopropyl Butyl Ketone (7).—A solution of 800 mg (5.7 mmol) of *cis*-2-methylcyclopropyl butyl ketone (7) in 5 ml of ether was allowed to react for 2.5 hr with

790 mg (114 mg-atoms) of lithium in 125 ml of ammonia. The product mixture was concentrated after oxidation to yield 0.58 g (73%) of an oil which, when analyzed on vpc, was composed of 8.5% isobutyl *n*-butyl ketone (13) and 9.15% di-*n*-butyl ketone (12).

The first product eluted was assigned the structure isobutyl butyl ketone (13) on the basis of identical vpc retention times and nmr spectra with those of the major ketone from the reductive cleavage of *trans*-2-methylcyclopropyl butyl ketone (5).

The major product was assigned the structure di-*n*-butyl ketone (12) from the following spectral data: ir (CCl₄) 1718 and 1260 cm⁻¹; nmr (CCl₄) δ 2.30 (t, 4, J = 6.5 Hz, CH₂COCH₂), 1.40 (m, 8), and 0.94 (t, 6, J = 6 Hz, CH₃CH₂). The vpc retention time was identical with that of the minor ketone 12 obtained from the reductive cleavage of *trans*-2-methylcyclopropyl butyl ketone (5).

Metal Reduction of 2,2-Dimethylcyclopropyl Methyl Ketone (2). **A. With Calcium.**—The same procedure as described for run 7 (Table III) was employed to reduce 114 mg of ketone 2 with 0.08 g (21 mg-atoms) of pentane-washed calcium metal. The calculated yield was 97 mg (83%) and the product mixture was composed of 17% neopentyl methyl ketone (9), 34% starting ketone (2), and 49% isoamyl methyl ketone (8). The normalized percentage of 8/9 was 74:26.

B. With Potassium.—From 112 mg of ketone 2 and 0.08 g of potassium metal was obtained 95 mg (83%) of a product mixture composed of 21% ketone 9, 12% ketone 2, and 67% ketone 8. The normalized percentage of 8/9 was 76:24.

C. With Sodium.—From 114 mg of ketone 2 and 0.46 g of hexane-washed sodium metal was obtained 99 mg (85%) of a product mixture containing 18% ketone 9, 20% ketone 2, and 62% ketone 8. The normalized percentage of 8/9 was 78:22.

D. With Magnesium.—To an ammonia solution of 0.49 g of magnesium turnings was added 112 mg of ketone 2 as before. The typical blue color did not develop with the addition of magnesium to liquid ammonia, and throughout the reaction the metal did not appear to be dissolving. The sequence of reduction-oxidation was carried out as with the other metals. The calculated yield was 96 mg (84%), and the composition was 4% ketone 9, 68% ketone 2, and 28% ketone 8. The normalized percentage of 8/9 was 87:13.

Registry No.—3, 22286-91-5; 5, 22286-92-6; 7, 22286-93-7; 8, 110-12-3; 9, 590-50-1; 12, 502-56-7; 13, 7492-38-8; 2-methyl-2-octen-4-one, 19860-71-0; *trans*-2-octen-4-one, 22286-99-3; 2-octyn-4-ol, 22286-98-2; *cis*-2-octen-4-ol, 22287-00-9; *trans*-2-octen-4-ol, 20125-81-9; *cis*-2-methylcyclopropylbutylcarbinol, 22287-01-0; neopentyl butyl ketone, 22319-52-4; isoamyl *n*-butyl ketone, 22287-02-1; 2-methyl-1-nonen-5-one, 22319-53-5.