Organic and Biological Chemistry

Homoenolization and Related Phenomena. IV. Evidence for Homoenolate Anions[1,2]

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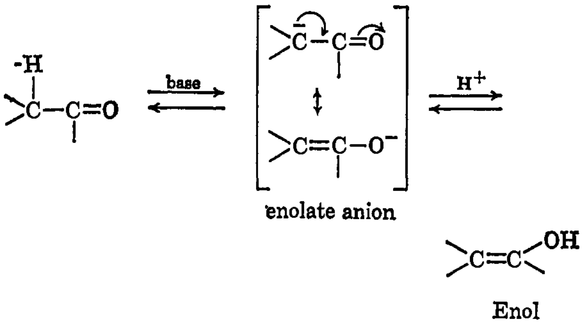
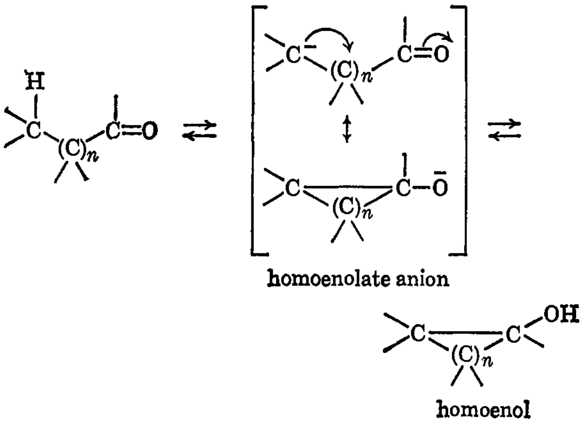
Abstract: Optically active camphenilone undergoes racemization and deuterium incorporation when heated with potassium *t*-butoxide in *t*-butyl alcohol at elevated temperatures. Homoenolate ions, formed by direct abstraction of hydrogens β to the carbonyl group, are advanced to account for the results. Other mechanisms are evaluated and ruled out experimentally. Comparison of racemization *vs.* deuterium entry reveals that the first proton abstracted is at C-6 and that the derived homoenolate ion becomes symmetrical (by mesomerism or by rearrangement) before it can pick up deuterium from the medium. Evidence is presented that homoconjugation is more important than inductive effects in stabilization of homoenolate ions.

The ability of π-electron systems to stabilize positive charges by *conjugation* (orbital overlap between contiguous atoms) and by *homoconjugation* (orbital overlap between noncontiguous atoms) is well documented.[4] Delocalization of *negative* charges by conjugation is also common, and enolate anions represent important examples of this class.[5] In an enolate anion the charge is shared (unequally) by the α carbon and the carbonyl oxygen, and reversible proton capture of either site provides a mechanism for base-catalyzed interconversion of keto and enol tautomers (eq 1). In the present study our objective was to learn if a carbonyl group could activate a more distant hydrogen (*e.g.*, on a β-carbon) sufficiently to allow conversion to an anion stabilized by homoconjugation (eq 2). By analogy such an ion is termed a "homoenolate" anion, and the cyclic alcohol derived by protonation on oxygen is its corresponding *homoenol.*[6]



(1)



(2)

We chose optically active camphenilone (**1**) as the substrate for two principal reasons. Firstly, this ketone has no enolizable α hydrogens[7] but has a variety of β hydrogens (*viz.*, at C-6, C-7, C-8, C-9, and C-4) as well as two γ hydrogens (C-5.) Secondly, if strong base can abstract a β hydrogen from C-6 to give a homoenolate anion whose charge is delocalized to the carbonyl group (represented by resonance structures **2** and **3**), there is an opportunity for the newly created C-6–C-2 bond to become equivalent to the C-1–C-2 bond. The equivalence of these two bonds in **3a** is emphasized in formulation **3b**, in which a plane of

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[1] (a) A preliminary communication of this work has been published (A. Nickon and J. L. Lambert, *J. Am. Chem. Soc.*, **84**, 4604 (1962)) and is considered part I of this series; (b) part II: A. Nickon, J. H. Hammons, J. L. Lambert, and R. O. Williams, *ibid.*, **85**, 3713 (1963); (c) part III: A Nickon, H. Kwasnik, T. Swartz, R. O. Williams, and J. B. DiGiorgio, *ibid.*, **87**, 1615 (1965).

[2] This work was supported in part by the Petroleum Research Fund administered by the American Chemical Society, and was initiated during A. Nickon's tenure as an Alfred P. Sloan Foundation Fellow (1957–1961). The mass spectrometer was obtained with instrument grants from the Atomic Energy Commission and the National Science Foundation.

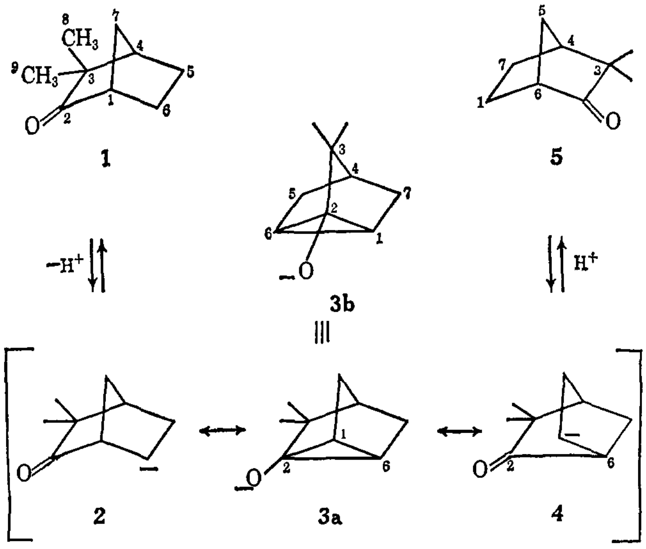
[3] Taken largely from the Ph.D. dissertation of J. L. Lambert, The Johns Hopkins University, 1963.

[4] For discussions and literature references see (a) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961; (b) J. D. Roberts, "Notes on Molecular Orbital Calculations," W. A. Benjamin Inc., New York, N. Y., 1961.

[5] (a) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 10; (b) E. S. Gould "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, Chapter 10.

[6] In the simplest case ($n = 1$) of spatial activation by a carbonyl group the homoenol is a cyclopropyl alcohol. For studies on the syntheses and ring-opening reactions of cyclopropyl alcohols and related systems see C. H. DePuy and L. R. Mahoney, *J. Am. Chem. Soc.*, **86**, 2653 (1964); C. H. DePuy, G. M. Dappen, K. I. Eilers, and R. A. Klein, *J. Org. Chem.*, **29**, 2813 (1964), and references cited therein. Homoenolate formation with $n = 2$ has been observed in camphor[3] and more recently in a "half-cage" ketone: R. Howe and S. Winstein, *J. Am. Chem. Soc.*, **87**, 915 (1965); T. Fukunaga, *ibid.*, **87**, 916 (1965). We are currently investigating cases with $n > 2$.

[7] The α hydrogen at C-1 is not enolizable because the bicyclo[2.2.1]-heptane skeleton prevents the necessary coplanarity in the enolate ion (manifestation of Bredt's rule); see ref 5 and F. S. Fawcett, *Chem. Rev.*, 47, 219 (1950).



symmetry is evident. Capture of a proton at C-6 by the ion regenerates the starting ketone whereas capture at the equivalent site C-1 produces the enantiomer **5**. The possibility that optically active ketone would racemize provided us with an experimental basis for testing the generation of a homoenolate ion.

Methods and Results

Optically active comphenilone (mp 38–38.5°, α +69°; semicarbazone mp 224.5–225.5°, α +255°) was heated with potassium *t*-butoxide in *t*-butyl alcohol in sealed tubes at elevated temperature. The use of a tertiary alcohol precluded a Pondorff–Meerwein–Verley type reduction of the ketone to camphenilol. Crude camphenilone was recovered from the solution in good yields (usually 80% or higher) and was identified by its infrared spectrum and by gas chromatography. The recovered ketone was converted to its semicarbazone, which was recrystallized until pure. All measurements of optical activity were made on the purified derivative. Racemic and optically active semicarbazone have the same melting point, and mixtures of both forms give no melting point depression. Control experiments with an artificial mixture showed that repeated crystallization of a partially racemic semicarbazone does not change its optical rotation and thus established that no optical fractionation occurs during purification of the derivative.

Table I summarizes representative experiments conducted at different conditions of temperature, of reaction time, and of concentrations of ketone and alkali. As is evident from the last column, camphenilone is racemized under appropriate conditions. Whereas no loss of optical activity occurred in the run at 150° (run 1) an increase to 165° together with an increase in time and in concentration of base racemized the ketone substantially (run 2). Clearly, temperature is an important factor (see, *e.g.*, run 8 at 250°) and for most of our studies we adopted 185° as a convenient temperature for the concentrations and experimental techniques being used.[8]

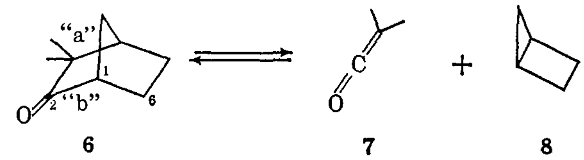
Table I. Racemization of (+)-Camphenilone with Potassium *t*-Butoxide in *t*-Butyl Alcohol

Run	Temp, °C	Time, hr	—Volume molal— concn (20°) Ketone	KO-*t*-Bu	% racemization[a]
1	150	166	0.23	0.46	0
2	165	336	0.29	1.21	92
3	185	12	0.46	0.79	26
4[b]	185	12	0.28	0.60	26
5[b]	185	24	0.16	0.33	52
6[b]	185	36	0.30	0.66	69
7[b]	185	48	0.21	0.68	88
8	250	4	0.46	0.97	100
9	250	113	0.07	Nil	0
10	250	215	0.18	Nil[c]	0

[a] Estimated accuracy ±2%. [b] The solvent was *t*-butyl alcohol-O-*d*. [c] The solution contained potassium perchlorate (0.41 volume molal).

We interpret the racemization as abstraction of a hydrogen from C-6 to generate a homoenolate anion (resonance structures **2**, **3**, and **4**) which either has, or during its lifetime can pass through, a symmetrical (mesoid) structure, and hence can lose optical activity.[9] Other mechanisms for the racemization can be conceived and to establish a convincing case for homoenolate ions we must discuss some of these alternative pathways and the experiments that rule them out.

One possibility is that the thermal treatment alone induces rupture of C–C bonds. For example, cleavage of bonds "*a*" and "*b*" in **6** could produce the two fragments, dimethylketene (**7**) and bicyclo[2.1.0]pentane (**8**). If the process were reversible[10] then racemization is inevitable because neither of the fragments can sustain optical activity. Various intramolecular thermal pathways can also be envisaged. As an illustration, homolytic or heterolytic cleavage of bond "b" in **6** could produce a diradical or a zwitterion. Intramolecular shift of a hydrogen from C-6 to C-1 and then bond formation between C-2 and C-6 would produce



6 **7** **8**

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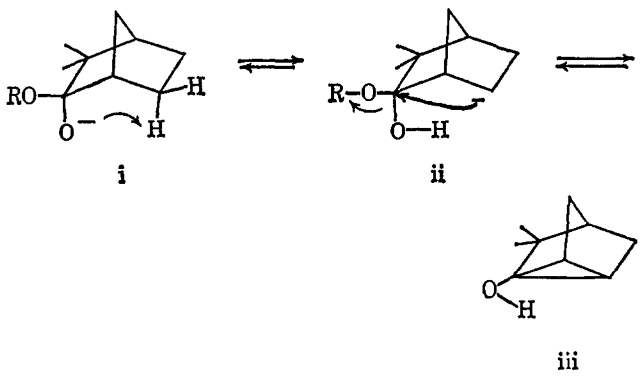
[8] Although kinetic studies were not carried out, comparison of similar runs indicated that at 185° the half-life for racemization is roughly 16–24 hr for alkali concentrations in the range 0.7–0.3 volume molal.

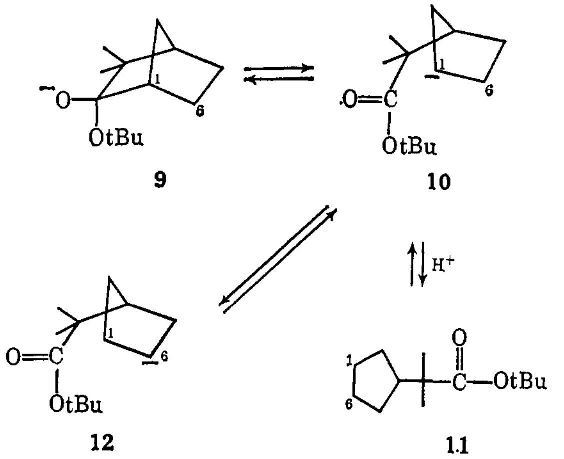
[9] An indirect route to the same homoenolate ion could involve *exo* addition of the alkoxide ion (RO^-) to the carbonyl group, intramolecular abstraction of the *endo* hydrogen at C-6, and ejection of alkoxide ion as indicated in i, ii, and iii. This variant does not alter the present discussion but nevertheless appears to be reasonably ruled out by stereochemical studies[1b] to be described fully in a future publication. Interestingly, the corresponding homoenol, apocyclol (iii), has been prepared by a deamination route: P. Lipp and C. Padberg, *Ber.*, **54**, 1316 (1921).



i ii iii

[10] For recent examples of Diels–Alder reactions with bicyclo[2.1.0]-pentane see P. G. Gassman and K. Mansfield, *Chem. Commun.* (London), 391 (1965).

the enantiomeric ketone. Although various arguments can be mounted against these pathways, we preferred to rule out thermal mechanisms experimentally by conducting two control runs at 250°. In one of these (run 9, 113 hr) the potassium *t*-butoxide was omitted, and in the other (run 10, 215 hr) the potassium *t*-butoxide was replaced by an inert salt (potassium perchlorate) to provide a medium of similar ionic character to those that effect racemization. No loss of optical activity was observed in either case, and these results established that the racemization requires alkali. Purely thermal pathways are further excluded by some deuterium incorporation experiments described later.



A second possibility is that the ketonic ring is reversibly opened by the vigorous alkaline treatment. In this pathway we must assume (a) that an initial intermediate, *e.g.*, **9**, suffers cleavage of the C-1–C-2 bond (**9** → **10**) to give the optically inactive ester **11** (in which C-1 and C-6 become equivalent); (b) that the steps are reversible; and (c) that camphenilone is favored in the equilibria. Rupture of a ketonic ring by alkali is reasonable and has analogy in the well-known Haller–Bauer cleavage of nonenolizable ketones.[11] However, the requirement that the mesoid ester **11** be an intermediate and that it be transformed to camphenilone by a reversal of the sequence renders the pathway unlikely.[12] Nevertheless, we tested this possibility experimentally by synthesizing the ethyl ester counterpart of **11** and subjecting it to conditions that would racemize camphenilone (140 hr at 185° in *t*-butyl alcohol containing 0.22 volume molal potassium *t*-butoxide). On work-up the neutral fraction consisted virtually entirely (>98%) of the original ethyl ester and contained *no camphenilone*, according to gas chromatography sensitive enough to have detected >0.03% of the ketone. Evidently any *t*-butyl ester **11** formed by ester interchange underwent elimination to the corresponding carboxylic acid, which remained in the acidic fraction.[14]

A modification of the ring-opening mechanism can be proposed that does not require neutral ester **11** as an intermediate. In this variant we invoke the equilibrium **9** ⇆ **10** but assume that in the anion **10** a hydrogen can migrate from C-6 to C-1 to produce the enantiomeric anion **12**. This route, which utilizes the alkali but brings about racemization without loss of a proton to the medium, is excluded by deuterium incorporation studies to be discussed below.

The homoenolate ion mechanism for racemization leads to the prediction that camphenilone should incorporate deuterium if the treatment is conducted in *t*-butyl alcohol-O-*d*. If both hydrogens at C-6 are ultimately exchangeable then deuterium would also end up at the bridgehead position because C-6 in the initial enantiomer (**1**) becomes the bridgehead position in the other enantiomer (**5**) and therefore incorporation of up to three deuterium atoms would be possible *via* homoenolate ion **3**. If any other sites in the molecule are homoenolizable then correspondingly more deuterium could be introduced.

Four experiments were conducted at 185° with (+)-camphenilone in *t*-butyl alcohol-O-*d* containing potassium *t*-butoxide. The recovered ketone was assayed for total deuterium and for its polydeuterium distribution by mass spectroscopy. As a check on the technique the total deuterium was independently assayed in two of the runs by a combustion infrared method[15] on the derived semicarbazone, and the agreement between the two methods was excellent. The extent of racemization for each run was also determined to learn if it was related in any way to the extent of deuterium incorporation. Table II summarizes the deuterium results, which demonstrate clearly that

Table II. Deuteration and Racemization in (+)-Camphenilone at 185°

Run[a]	% molecules with—				Total % molecules with D	% Racemization
	0 D	1 D	2 D	3 D[b]		
4	74.8	23.7	1.4	0.1	25.2	26
5	47.7	43.6	8.3	0.4	52.3	52
6	29.3	54.3	15.4	1.0	70.7	69
7	13.4	54.7	28.7	3.2	86.6	88

[a] For the experimental conditions see corresponding runs in Table I. [b] No species with more than 3 D were present.

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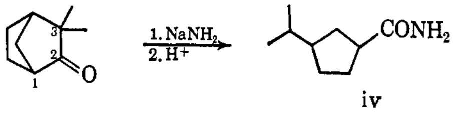
[11] K. E. Hamlin and A. W. Weston, *Org. Reactions*, **9**, 1 (1957).

[12] The cleavage of camphenilone with sodium amide in benzene is reported to produce an amide formulated as 3-isopropylcyclopentanecarboxamide (iv).[13] Because cleavage of the C-2–C-3 bond in preference to the C-1–C-2 bond implies generation of the less stable carbanion, we considered it important to confirm the structure of the



iv

cleavage product. Furthermore, with optically active camphenilone the question arises of whether the sodium amide treatment would effect racemization *via* homoenolate anion formation prior to ring cleavage. If so, product iv could be optically inactive even though it does not possess a mesoid structure. To get information on these points, we treated (+)-camphenilone with sodium amide in isopropyl either and interrupted the reaction after *ca.* 25% completion. The recovered ketone had lost none of its optical activity. In another experiment optically active ketone was cleaved with sodium amide in benzene and the derived acid amide, its related methyl ester, and its related anilide were all shown to be optically active by optical rotatory dispersion. These results confirm the direction of ring cleavage and show that it is not preceded by any significant racemization by homoenolization.

[13] F. W. Semmler, *Chem. Ber.*, **39**, 2577 (1906).

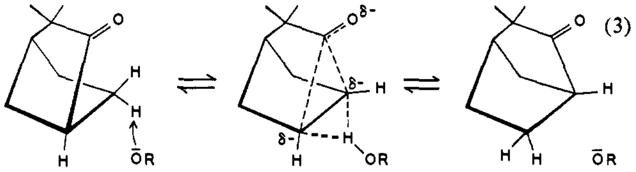
[14] With other ketonic systems, we have observed cases in which *t*-butyl esters from ketonic cleavage do not survive the reaction conditions and undergo elimination to the corresponding carboxylic acids: J. Oliver, unpublished results.

[15] J. L. Lambert, J. H. Hammons, J. A. Walter, and A. Nickon, *Anal. Chem.*, **36**, 2148 (1964).

exchange occurs and thereby confirm the mobility of hydrogens in the ketone.[16]

Importantly, the percentage racemization in each run corresponded closely to the total percentage of molecules that contained deuterium.[17] This agreement is understandable if the process that introduces the *first* deuterium is the same one that creates a mesoid ion (or its equivalent). Subsequent exchanges on the same molecule at the same bonding site would not put in more deuterium whereas exchange at any other sites would. In either case, however, no further optical effect would be observed. Therefore, di- and trideuterated species are not weighted in any way but count the same as though they had only one deuterium. The validity of this analysis is specially evident from the shortest run (4) in which the labeled molecules are comprised almost entirely of monodeuterated species. Therefore, for racemization up to at least 88% the rate of entry of the first deuterium is the same (within the accuracy of our method) as the rate of racemization. This parallelism between the two events allows us to draw the following conclusions.

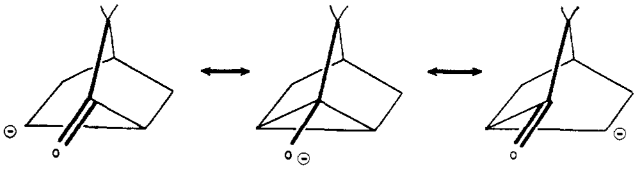
The ketone does not racemize without abstraction of a proton, which departs from the resulting homoenolate ion sufficiently to permit exchange with solvent protons. Therefore we can exclude for the most part an "isoracemization" mechanism (illustrated in eq 3), in which a proton is attacked by the base to give a hydrogen-bonded anion that is mesoid and that can collapse to ketone without exchange with solvents.[18] Isoracemizations induced by alkali have been recognized by Cram and co-workers in systems with allylic-type hydrogens,[19] and its relative nonimportance in the present case will have an important bearing on the stereochemistry of homoenolate ion formation.



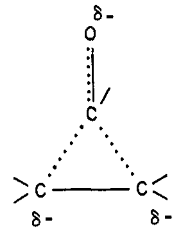
(3)

Another conclusion is that the *first* hydrogen exchanged is located at a site that leads to a symmetrical ion (or its equivalent). Position 6 in the initial ketone (**1**) is the only site that meets this requirement.[20] Hydrogen abstraction elsewhere would give ions that could preserve their optical activity and that would therefore permit deuterium entry without concomitant racemization.

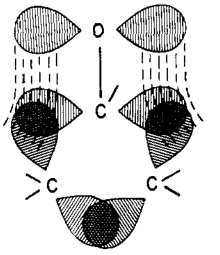
Each time a proton is pulled off from C-6 the derived homoenolate ion becomes symmetrical (*i.e.*, mesoid) before it can pick up deuterium from the solvent. This conclusion is valid because if the ion could maintain an unsymmetrical (*i.e.*, optically active) structure long enough to capture deuterium an opportunity would exist for isotope entry to exceed racemization. Therefore, the homoenolate ion either has a symmetrical structure or, if unsymmetrical, it rearranges to its enantiomer faster than it reverts to ketone. The symmetrical ion may be described approximately by the three canonical forms **13a–c**, or by either of the mesomeric formulations **14a** or **14b** shown as partial structures. The C–O bond is not coplanar with the cyclopropyl ring, and the geometric situation appears qualitatively similar to that in homoallylic cations.[21] Structures such as **13a** and **13b** could represent distinct entities with slight differences in geometry, in which case the resonance arrows (↔) should be replaced by equilibrium arrows (⇌). Here, as in certain areas of carbonium ion chemistry, an experimental distinction between mesomeric and rapidly equilibrating ions is not easy to make. For economical representation of a homoenolate anion a single classical structure with charge localized on oxygen (*e.g.*, **13b**) appears adequate enough for most purposes, although the precise situation could vary from molecule to molecule.



13a 13b 13c



14a



14b

Up to now we have tacitly assumed that the homoenolate ion is stabilized by orbital interaction between the homoenolic carbon and the carbonyl group. However, the ion could derive some stability by inductive effects between the carbanion center and the positive end of the carbonyl dipole. Such inductive stabilization might be transmitted through the σ bonds or coulombically across space and would be much less sensitive to geometry than would stabilization by orbital interaction. If inductive effects were of dominant importance, the bridgehead hydrogen at C-1 (in **1**) should be the most acidic because its departure leaves a negative charge adjacent to the carbonyl carbon.[22] However, since direct abstraction of the C-1 hydrogen would

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[16] In separate experiments (to be published in connection with another study) we showed that under the experimental conditions the corresponding hydrocarbon, camphenilane, does not incorporate any significant amount of deuterium. Therefore, homoenolic hydrogens are activated by the carbonyl group.

[17] An equivalent statement is that the fraction of molecules not racemized corresponds to the fraction that contains no deuterium.

[18] Until some evidence demands it, we dismiss the more involved, but real, possibility that racemization occurs by some intramolecular path whose rate coincidentally equals that of deuterium entry at a site other than at C-6.

[19] (a) D. J. Cram and R. T. Uyeda, *J. Am. Chem. Soc.*, **84**, 4358 (1962); **86**, 5466 (1964); (b) D. J. Cram and L. Gosser, *ibid.*, **86**, 2950 (1964); (c) D. J. Cram, F. Wiley, H. P. Fischer, and D. A. Scott, *ibid.*, **86**, 5370 (1964), and references cited there to related findings by others.

[20] Even though homoenolization involving C-6 could allow *up to* three deuterium atoms to enter (*vide infra*) it does not necessarily follow that the second and third deuterium atoms are at C-6 and C-1. Because of stereochemical differences, exchange of the second hydrogen at C-6 could be appreciably harder than exchange of the first hydrogen at C-6 and therefore other homoenolizable sites (*e.g.*, CH_3) might compete successfully. Forthcoming publications will deal with stereospecificity and with location of deuterium.

[21] (a) M. Simonetta and S. Winstein, *J. Am. Chem. Soc.*, **76**, 18 (1954); (b) W. G. Woods, R. A. Carboni, and J. D. Roberts, *ibid.*, **78**, 5653 (1956).

[22] Hybridization effects might also enhance the acidity of a bridgehead hydrogen relative to those at (*e.g.*) C-6: P. T. Lansbury and J. D. Sidler, *Tetrahedron Letters*, No. **11**, 691 (1965).

allow deuterium entry without racemization, it must not occur as readily as homoenolic abstraction at C-6. Furthermore, camphenilone contains β hydrogens at several locations and if inductive effects were of paramount importance it is hard to understand why a hydrogen at C-6 is abstracted in preference to all others and especially in preference to the methyl hydrogens, abstraction of which not only are favored statistically but would lead to primary carbanions. On the other hand, stabilization by homoconjugation would be a sensitive function of geometry and could well account for such selectivity. We conclude that even though inductive stabilization may contribute to the generation of homoenolate ion **13** in camphenilone it is less important than homoconjugation.

Although potassium *t*-butoxide in *t*-butyl alcohol proved the most satisfactory medium for our homoenolization studies, we explored a few other bases and solvent systems (see the Experimental Section for details) and wish to draw attention to some complications they introduced. Primary alkoxides reduced camphenilone to an epimeric mixture of the corresponding alcohols, camphenilol. Potassium *t*-butoxide in dimethyl sulfoxide at 20° destroyed the ketone, and it is now clear from the work of Gassman and Zalar that this medium effectively cleaves nonenolizable ketonic rings.[23] We found that when *t*-butyl alcohol (*e.g.*, *ca.* 23 mole %) was added to the dimethyl sulfoxide about 30% of the ketone survived (after 20 hr at 128°) and it was partially racemized (16%).

Experimental Section[24]

(+)-Camphenilone. Optically active camphenilone was prepared from (+)-camphor (Eastman, mp 177.5–178°, α +43°). (+)-Camphor-*p*-toluenesulfonylhydrazone (mp 165.5–166°, α +62° (lit.[25] for the racemic derivative mp 163–164°)) was decomposed in ethylene glycol–sodium ethylene glycoxide to give a 75% camphene–25% tricyclene mixture which was treated with dinitrogen tetroxide gas (bubbled through a petroleum ether (bp 40–60°) solution at 0°) to yield ω-nitrocamphene.[26] Treatment with alcoholic base (20 hr of reflux; 2.5 moles of potassium hydroxide, 4.0 moles of ethanol, and 80 moles of water for each mole of camphene) followed by steam distillation gave (+)-camphenilone[27] (15% yield from camphor), bp 192–194°, mp 38–38.5°, α +69° (lit[26] bp 193°, mp 38–39°, α +70.4° (ethanol)). (+)-Camphenilone semicarbazone (from methanol) had mp 224.5–225.5°, α +255°, (lit.[26,28] mp 223–225°, α +263°).

Ethyl 2-Methyl-2-cyclopentylpropanoate. This ester was prepared according to the procedure reported by Talukdar and Bagchi.[29] Reagents were obtained from Aldrich Chemical Co.: cyclopentanone (bp 127–128°) and ethyl α-bromoisobutanoate (bp 160–164°). Final product, 35% yield from cyclopentanone, was 99.6% pure by gas chromatography and had bp 212° (lit.[29] bp 209°).

Anal. Calcd for $C_{11}H_{20}O_2$ (184.3): C, 71.69; H, 10.94. Found: C, 71.66; H, 10.87.

Homoenolization. General Procedure. Reagents were transferred in a drybox, under nitrogen atmosphere, to heavy walled Pyrex tubes, and the tubes were sealed. These tubes were heated in a steel bomb (American Instrument Co., Inc., Silver Spring, Md.) which also contained *t*-butyl alcohol to offset pressure inside the tubes. Temperature was controlled (±3°) by a Brown Electronik Circular Chart Controller equipped with a type J couple calibrated to ±1°. The tubes were opened and the contents were transferred to a separatory funnel with pentane and water. The pentane layer was washed two or three times with water, separated, and dried with anhydrous sodium sulfate, and the pentane was slowly evaporated. Gas chromatography and infrared spectra identified the recovered camphenilone. Mass spectra were taken without further purification. Recovered camphenilone was converted to the semicarbazone (65–70% conversion) and recrystallized from methanol until pure. The specific rotation of the semicarbazone was used to determine the extent of racemization. Recovery of camphenilone was on the order of 80%, based on the quantity of semicarbazone obtained.

To test that the optical purity of partially racemic camphenilone semicarbazone is not altered by recrystallization we combined optically active and racemic camphenilone semicarbazones to give a 30% racemic mixture (mp 221–222°, α +180°) which after two consecutive recrystallizations from methanol had mp 224.5–225.5°, α +179°. Another recrystallization yielded semicarbazone with mp 223–224°, α +182°. We also observed no depression of melting point for racemic mixtures of any composition.

Mass Spectra. Deuterated camphenilone was analyzed by mass spectrometry both for total excess of deuterium and for the relative abundances of mono-, di-, . . ., and polydeuterated molecules. All spectra were taken with an ionizing voltage of 70 v and an ionization current of 10 μamps. Molecular ion (*m/e* 138) intensities were adequate, and all analysis involved measurements of this ion only. The first fragment peak occurred at *m/e* 123. We obtained correction factors for the intensities at *m/e* 139 and 140 due to the natural occurrence of heavy isotopes in the molecular ion by recording the mass spectrum of camphenilone before it was subjected to deuterium-incorporation reactions. The spectra of all natural abundance samples and of most deuterium-enriched samples were recorded for at least two pressures (range 30 to 110 μ) to check if any peaks in the range analyzed were pressure dependent. The intensity of an artifact peak resulting from ion–molecule reactions is directly proportional to the square of the sample pressure.[30] No pressure-dependent peaks were observed in any of the spectra we analyzed. To check against possible isotope effects in fragmentation, camphenilone-*d* samples were analyzed first by mass spectrometry and then, through the semicarbazone derivative, by a combustion infrared method.[14] Four different samples whose atom excess of deuterium by mass spectrometry was 0.63, 1.19, 2.27, and 2.57 gave values of 0.62, 1.12, 2.37, and 2.63, respectively, by the combustion infrared method. The observed close agreement attests to the reliability of the mass spectrometric assays.

Haller–Bauer Cleavage of (+)-Camphenilone. The ketone (0.106 g) was refluxed (67°) for 2.0 hr in 5 ml of isopropyl ether containing an 11.5-fold molar excess of sodium amide. Dilute hydrochloric acid was added to destroy sodium amide, and sodium bicarbonate was added to adjust to pH 7–8. Camphenilone was recovered (*ca.* 75%) from the reaction mixture by steam distillation and was converted to the semicarbazone, mp 223.0–223.5°, α +260°.

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(23) P. G. Gassman and F. V. Zalar, *Tetrahedron Letters*, No. 40, 3031 (1964).

(24) Optical rotations were taken at room temperature (21–25°) in chloroform (10–15 mg of sample in 1 ml of solution) with sodium light, 5893 A, in a 1-dm polarimeter tube. Variations experienced in repeated specific rotation measurements of a single sample indicated that our net experimental error had a maximum range of ±5° for a sample with specific rotation of 255°. A Perkin-Elmer Model 226 gas chromatograph with flame detector was used for gas chromatographic analyses. The carrier gas was helium. Unless specified otherwise a 150-ft Golay column with polypropylene glycol liquid phase was used. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer equipped with sodium chloride optics. Mass spectra were taken with a Consolidated Electrodynamics Corp. mass spectrometer, type 21-103C. *t*-Butyl alcohol was distilled first from aluminum *t*-butoxide and then from potassium. Deuterated *t*-butyl alcohol (minimum isotopic purity 97 atom % deuterium) was purchased from Merck and Co., Ltd. of Canada. Potassium *t*-butoxide was sublimed *in vacuo* at 250° before use.

(25) W. P. Bamford and T. S. Stevens; *J. Chem. Soc.*, 4735 (1952).

(26) W. Hückel, *Ann.*, **549**, 186 (1941).

(27) This (+)-camphenilone contained *ca.* 6% camphor as indicated by gas chromatography and by mass spectrometry, and was used without further purification for racemization and deuterium-incorporation studies. Recrystallization from methanol of the semicarbazones readily gave the pure camphenilone derivative. Camphor and camphor-*d* molecular ions (*m/e* 152) were observed in mass spectra of camphenilone-*d* after deuteration reactions. In separate studies the fragmentation of natural abundance camphor molecular ions indicated that the only significant interfering fragment ions had *m/e* 134 and *m/e* 137. The camphenilone-*d* polyisotopic spectrum intensities were corrected for the camphor fragment-ion contributions. These corrections were always small: on the order of ±0.15% of the relative concentration for camphenilone species.

(28) S. S. Nametkin, E. A. Grekova, and A. M. Khukhrikova, *J. Russ. Chem. Soc.*, **48**, 453 (1961).

(29) P. B. Talukdar and P. Bagchi, *J. Org. Chem.*, 20, 25 (1955).

(30) K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 50.

In another reaction (+)-camphenilone (1.00 g) was completely converted to **3-isopropylcyclopentanamide** (0.99 g, 90%) by reflux with excess sodium amide in benzene. The amide was recrystallized three times from methanol and sublimed, mp 162.5–163° (lit.[12] mp 168°). Optical rotatory dispersion analysis[31] (in methanol) indicated that this amide was optically active; molecular rotations at 600, 350, 310, and 270 mμ were +15°, −7°, −30°, and −75°, respectively.

Anal. Calcd for $C_9H_{17}NO$ (155): C, 69.67; H, 10.96; N, 9.03. Found: C, 69.90; H, 10.72; N, 9.21.

A portion of the amide (0.740 g) was hydrolyzed with potassium hydroxide in aqueous alcohol. The alkaline solution was extracted with ether to remove any ester and unchanged amide. Acidification of the aqueous layer with hydrochloric acid and extraction with three 50-ml portions of ether yielded 0.645 g of the crude acid (86%). A portion of this acid (0.300 g) was treated with ethereal diazomethane. Distillation in a "zigzag" tube yielded 0.270 g (90%) of **methyl 3-isopropylcyclopentanoate.** ORD analysis of the ester (in methanol, without further purification) gave molecular rotations at 600, 290, 280, and 270 mμ of +10°, +6°, −4°, and −28°, respectively. For the analytical sample racemic methyl 3-isopropylcyclopentanoate was prepared, bp 208°.

Anal. Calcd for $C_{10}H_{18}O_2$ (170.1): C, 70.54; H, 10.66. Found: C, 70.58; H, 10.40.

A second portion of the acid (0.320 g) was refluxed in 1.0 ml of thionyl chloride for 1 hr. The excess of thionyl chloride was removed under aspirator vacuum, and a solution of 1.0 ml of aniline in 4.0 ml of dry benzene was added to the acid chloride. The mixture was warmed on a steam bath for 15 min, then transferred to a separatory funnel with ether, which was then washed with water, 5% hydrochloric acid, and 5% sodium bicarbonate. The ether layer was dried with sodium sulfate and evaporated. Crude anilide was chromatographed over alumina and recrystallized twice from pentane to yield 0.160 g of **3-isopropylcyclopentanecarboxylic acid anilide,** mp 84.5–85°. Molecular rotations (in methanol) at 600, 350, 330, 320, and 290 mμ were +60°, +60°, +45°, +70°, and +140°, respectively.

Anal. Calcd for $C_{15}H_{21}NO$ (231): C, 77.92; H, 9.09. Found: C, 78.03; H, 8.92.

Homoenolizations Attempted with Other Reagents and Solvent Systems. Ethylene Glycol and Potassium Ethylene Glycoxide. (+)-Camphenilone (0.060 g) and 3.0 ml of freshly distilled ethylene glycol in which potassium (0.120 g) had been dissolved were sealed in a Pyrex tube, and the tube was heated at 185–190° for 100 hr. Recovered material (0.060 g) had no carbonyl peak and had an infrared spectrum essentially identical with that of the alcoholic product (*ca.* 83% *endo*, 17% *exo* by nmr) obtained by sodium and ethanol reduction of camphenilone. This recovered material was recrystallized once from pentane to give white needles, mp 67.5–68°, α +22° (ethanol) (lit.[32] for *endo*-(+)-camphenilol, mp 98–101°, α +33° (ethanol); for *exo*-(+)-camphenilol, mp 75–76°, α +24° (ethanol)). The fact that the observed specific rotation of camphenilol recovered from this reaction was lower than that expected for material *ca.* 83% *endo* suggests that partial racemization may have occurred.

Table III

Temp, °C	Time, hr	Molality in DMSO: Ketone	KO-*t*-Bu	*t*-BuOH	% ketone recovered	% racemization
20	5.5	0.12	1.18	0.0	0	...
100	6	0.23	1.03	1.83	0	...
128	22.5	0.18	1.03	3.96	*ca.* 30	16
128	20	0.24	0.68	7.04	*ca.* 80	9

Acetic Acid and Perchloric Acid. (+)-Camphenilone (0.050 g) was dissolved in 5.0 ml of glacial acetic acid, and three drops of 70% aqueous perchloric acid was added. The solution was refluxed (115°) for 92 hr. Camphenilone was recovered by the usual method and was converted to the semicarbazone, mp 220–221°, α +252°.

***t*-Butyl Alcohol and Potassium Hydroxide.** This medium racemized (+)-camphenilone but more slowly than did potassium *t*-butoxide in *t*-butyl alcohol. For example, after 490 hr at 185° (+)-camphenilone (0.103 *m*) in *t*-butyl alcohol containing potassium hydroxide (2.7 *m*) and water (2.5 *m*) underwent 29% racemization. In a run at 250° for 216 hr the optically active ketone (0.166 *m*) in *t*-butyl alcohol containing potassium hydroxide (2.3 *m*) and water (3.2 *m*) was 20% racemized.

Dioxane and Potassium Triphenylmethylate. Triphenylmethane (0.800 g, mp 92.5–93.5°) in 5.0 ml of dioxane (Baker, purified over alumina[33]) was added to freshly prepared potassium amide (0.140 g) in a reaction flask protected by a potassium hydroxide drying tube. The gray-brown potassium amide turned a deep red, and ammonia was discharged. (+)-Camphenilone (0.100 g) was then added in an additional 5.0 ml of dioxane. The solution was refluxed (101°) for 24 hr. Camphenilone was recovered in the usual way and converted to the semicarbazone, mp 222–224°, α +256°.

Dimethyl Sulfoxide as Solvent. The usual reaction procedure was followed for preparing reagents in sealed tubes and for work-up. Slight color due to solvent decomposition was removed from the pentane layer with decolorizing carbon (Darco). From reactions with potassium and sodium hydroxide as bases (in excess) camphenilone was recovered in the usual amount and was not racemized.

Reactions with sodium ethoxide (1.48 *m*, 152°, 2 hr) and sodium methoxide (0.99 *m*, 128°, 25 hr; methanol, 1.24 *m*, was added to enhance methoxide solubility) gave complete reduction of camphenilone to an epimeric mixture of camphenilols.

When potassium *t*-butoxide was used as base, camphenilone was recovered only if sufficient *t*-butyl alcohol was added as co-solvent. The recovered ketone was partially racemized. The experimental conditions and results are summarized in Table III.

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(31) We are grateful to Professor W. Klyne of Westfield College, London, for all ORD analyses.

(32) W. Hückel, *Ann.*, **549**, 95, 113, 114, 116 (1941).

(33) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, p 285.