Homoenolization and Related Phenomena. V.[1] Positional Specificity in Camphenilone[2]

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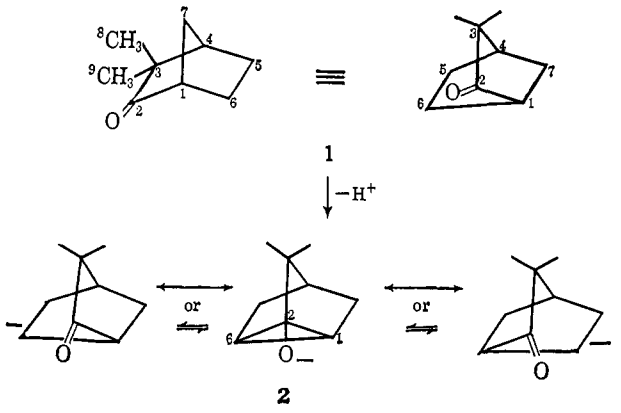
Abstract: Camphenilone undergoes multideuteration on prolonged homoenolization with potassium *t*-butoxide in *t*-butyl alcohol-O-*d* at 185–250°, and species containing up to nine deuteriums per molecule are produced. Infrared and nuclear magnetic resonance spectroscopy on suitable derivatives provided direct evidence that C-6, C-1, and the methyl groups acquire deuterium. Camphenilone-4-*d* and camphenilone-7-*d* were separately synthesized and shown not to lose their label during homoenolization in *t*-butyl alcohol. These results reveal that exchange does not occur at C-4, C-7, or C-5. The positional specificity in the generation of homoenolate ions is understandable in terms of proton abstraction from sites that can undergo orbital interaction with the carbonyl group without excessive strain.

Recent work established that optically active camphenilone (**1**) undergoes racemization and concomitant deuterium incorporation on treatment with potassium-*t*-butoxide in *t*-butyl alcohol-O-*d* at 185°.[1,3] The results were accounted for in terms of hydrogen abstraction from C-6 to generate the "homoenolate" ion **2**, in which the C-6–C-2 and C-1–C-2 bonds become effectively equivalent either by rapid equilibration of nonsymmetrical ions or by adoption of a symmetrical mesomeric structure. On the assumption that both hydrogens at C-6 are exchangeable the homoenolate ion **2** could permit eventual entry of up to three deuterium atoms because the bridgehead position next to the carbonyl group could acquire deuterium indirectly as a consequence of the equivalence of positions 6 and 1 in the ion **2**. After reaction times of up to 48 hr and with potassium *t*-butoxide concentrations from 0.33 to 0.68 *m* volume, the deuterated camphenilone contained mono-, di-, and trideuterated species. Although a comparison between deuterium entry and racemization required that the first hydrogen exchanged be at C-6, it seemed possible that some of the second and third deuteriums could enter by homoenolization at other sites, especially if sufficient stereoselectivity existed at C-6 to make one of its hydrogens more readily abstractable than the other. Homoenolization at sites other than C-6 would be positively confirmed if the ketone could be shown to incorporate more than three deuterium atoms. Our objective in the present work was to attempt more extensive deuteration of camphenilone and to get information on the location of the isotope. Apart from its relevance to homoenolization phenomena such information is potentially useful in other areas (*e.g.*, interpretation of mass spectroscopic fragmentation patterns) because homoenolization affords a direct way to introduce remote deuterium.



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Methods and Results

Camphenilone was dissolved in *t*-butyl alcohol-O-*d* containing potassium *t*-butoxide and the solutions were heated at 185 or 250° in sealed tubes. The ketone was recovered and assayed for deuterium by mass spectroscopy. The deuterated ketone from each run was subjected to a second cycle, *i.e.*, was re-treated with fresh solvent and base at the same temperature and the recovered ketone was reanalyzed for deuterium. In one case (run B) a third cycle was used in an effort to maximize the deuterium incorporation. Table I summarizes the relevant experimental conditions and the final deuterium distributions.

Clearly, some of the molecules pick up far more than three deuterium atoms and this finding establishes that C-6 is not the only homoenolizable site. To preclude the possibility that the alkaline treatment was vigorous enough to exchange nonactivated aliphatic hydrogens, we subjected the corresponding hydrocarbon, camphenilane, to deuterium exchange at 185° for 250 hr and observed no significant incorporation. This control run shows that the carbonyl group in camphenilone does activate the hydrogens. We now turn our attention to the location of the isotopes in the multideuterated ketone.

Our earlier finding that optically active camphenilone is racemized by alkali[1,3] implies that the deuterium will be located on at least one of the two bonding sites at C-6 (*i.e.*, *exo* or *endo*). If the loss and gain of a proton at C-6 were completely and lastingly stereospecific, only one deuterium would be found at C-6 and any label at the adjacent bridgehead position would be a consequence of direct abstraction at C-1 promoted by the inductive effect of the carbonyl group. However,

(1) Part IV: A. Nickon and J. L. Lambert, *J. Am. Chem. Soc.*, **88**, 1905 (1966).

(2) This work was supported by the Petroleum Research Fund, administered by the American Chemical Society, and we are grateful to its donors. The mass spectrometer was obtained with instrument grants from the Atomic Energy Commission and the National Science Foundation.

(3) A. Nickon and J. L. Lambert, *J. Am. Chem. Soc.*, **84**, 4604 (1962).

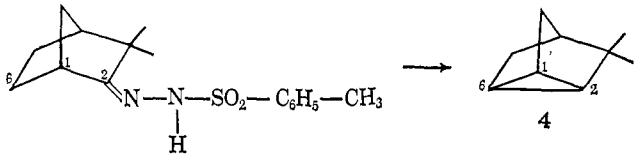
Table I. Polydeuteration of Camphenilone with Potassium *t*-Butoxide in *t*-Butyl Alcohol-O-*d*

		Run[a] A	Run[a] B	Run[a] C
Temp, °C		185	185	250
No. of deuteration cycles		2[b]	3[c]	2[d]
Total heating time, hr		266	1408[e]	431
Relative % of deuterated species in excess of natural abundance[f]	0-D	<1	<1	3
	1-D	7	5	6
	2-D	26	14	14
	3-D	39	25	22
	4-D	21	26	22
	5-D	6	18	16
	6-D	1	8	9
	7-D	...	3	5
	8-D	...	<1	2
	9-D	...	...	1

[a] The ketone used in runs B and C was racemic and was 99% pure; that used in run A was optically active and contained 6% camphor. Although mass spectral corrections for the camphor impurity were always applied, they had very little effect on the final calculations. [b] Molal volume concentration (20°) were: first cycle (100 hr), ketone 0.21, base 0.88; second cycle (166 hr), ketone 0.16, base 0.61. [c] First cycle (488 hr), ketone 1.26, base 2.14; second cycle (490 hr), ketone 1.54, base 2.62; third cycle (430 hr), ketone 0.30, base 1.17. [d] First cycle (216 hr), ketone 0.23, base 1.32; second cycle (215 hr), ketone 0.14, base 0.84. [e] In the first cycle, we used *t*-butyl alcohol-O-*d* that had only about 90% excess deuterium rather than the 99% used in all other cases. After the second and third cycles the camphenilone was purified by elution chromatography on alumina to remove slight coloration that developed. [f] As a check on the mass spectral assays the camphenilone-*d* from the second cycle of run B (total, 2.27-atom excess of deuterium by mass spectroscopy) was converted to its semicarbazone, and was analyzed by an infrared–combustion method (J. L. Lambert, J. H. Hammons, J. Walter, and A. Nickon, *Anal. Chem.*, **36**, 2148 (1964)) which gave a 2.37-atom excess of deuterium.

if both the *exo* and *endo* hydrogens at C-6 can undergo exchange then the bridgehead carbon will also acquire deuterium indirectly on account of the interconvertibility of C-6 and C-1 in the homoenolate ion **2**. Spectroscopic evidence that the label is incorporated at both C-6 and C-1 was obtained in the following ways.

Camphenilone was subjected to exchange for 140 hr at 250° in *t*-butyl alchol-O-*d*. The recovered ketone, which contained a total of 2.6 atoms of excess deuterium, was converted to its *p*-toluenesulfonylhydrazone (**3**). This derivative, which also proved useful for nuclear magnetic resonance (nmr) studies, was transformed to apocyclene (**4**) by treatment with sodium dissolved in ethylene glycol (Bamford–Stevens reaction[4]). The infrared spectrum of natural abundance apocyclene shows sharp, well-resolved absorption at 3040 cm^{-1}, which is assigned to cyclopropyl C–H stretching.[5] In the apocyclene derived from the deuterated camphenilone this band had a considerably lower intensity (relative to aliphatic C–H absorption



3 4

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

(5) R. N. Jones and C. Sandorfy in "Techniques of Organic Chemistry," Vol. 9, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, p 359.

centered around 2930 cm^{-1}). A quantitative analysis was not possible, but this result does reveal the presence of deuterium on the cyclopropyl ring and therefore establishes that the precursor must have had some label at C-6, and possibly also at the adjacent bridgehead.[6]

Direct evidence about the adjacent bridgehead position was obtained with the aid of nmr. In camphenilone, the bridgehead hydrogens appear at lowest field. The proton at C-1 gives an unresolved multiplet centered at δ 2.55; that due to the C-4 hydrogen is centered at 2.23 but overlaps with other signals on the high-field side.[7] In the corresponding tosylhydrazone **3** the C-1 and C-4 proton signals are at δ 3.03 and *ca.* 1.97, respectively. In addition, **3** showed the geminal methyl signals as overlapping singlets at δ 1.01 and 0.96. The camphenilone-*d* from run B (total, 3.72-atom excess of deuterium) was converted to its tosylhydrazone. With the aromatic methyl group (δ 2.41) as an internal integration standard the nmr revealed a substantial reduction (*ca.* 50%) in intensity of the C-1 proton signal and *ca.* 30% intensity reduction in the geminal methyl signals. Although overlap, broadening of signals, and noise level precluded any quantitative analysis, this result confirms the expectation that deuterium can end up at the bridgehead and also identifies the methyl hydrogens as homoenolizable sites. Although the two methyl groups differ stereochemically from each other, nothing can be concluded about their relative ease of exchange because the methyl groups become equivalent in the homoenolate ion **2** and therefore partition themselves between the *exo* and *endo* configurations.

To get information about the remaining sites (C-4, C-5, and C-7) we synthesized camphenilone labeled specifically at these centers to see if the deuterium could be washed out by alkaline treatment in a protonic solvent. Our preparation of camphenilone-4-*d* is outlined in Chart I. Reduction of 4-chloronorcamphor (**5**)[9] with sodium in ethanol-O-*d* gave an epimeric mixture of norborneols (**6**), in which deuterium must necessarily be at C-4 and C-2, and may also be at C-3 if any exchange by enolization occurs prior to reduction. This mixture was oxidized to norcamphor-*d* (**7**), which was then methylated. The oxidation and methylation steps guaranteed the removal of deuterium from C-2 and C-3 and provided camphenilone-4-*d* (**8**), which contained 89.5% monodeuterated and 10.5% of nondeuterated molecules.

The camphenilone-4-*d* was heated at 185° for 200 hr in *t*-butyl alcohol containing potassium-*t*-butoxide (1.6 *m*), was recovered, and was recycled at 185° in fresh solvent for an additional 300 hr (1.8 *m* base). The deuterium assays after the first and second cycles revealed that no deuterium was lost (within experimental error) and we conclude that C-4 is not a homo-

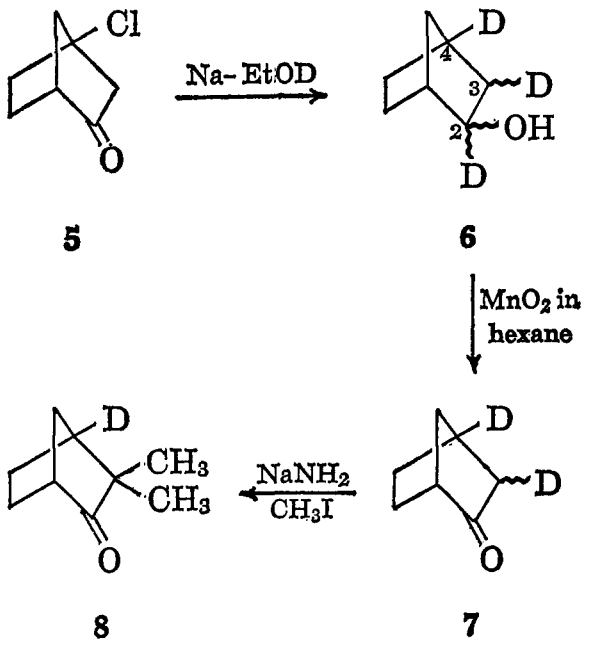
(6) Interestingly, the apocyclene had 2.1 atoms excess of deuterium, and therefore 0.5 atom of deuterium was lost, presumably during the Bamford–Stevens reaction. This aspect has been separately investigated in our laboratory and will be reported on fully in the near future.

(7) That the assignments are correct was confirmed by examination of the bridgehead hydrogen signals in several related compounds: norbornane δ 2.22,[8] fenchone δ 2.13, camphenilone 2,4-dinitrophenylhydrazone (C-1, δ 3.20; C-4, *ca.* δ 2.20); camphenilane (C-4, δ 2.13; C-1 overlaps with upfield protons).

(8) A. Nickon and J. H. Hammons, *J. Am. Chem. Soc.*, 86, 3322 (1964).

(9) K. B. Wiberg, B. R. Lowry, and T. H. Colby, *ibid.*, 83, 3998 (1961).

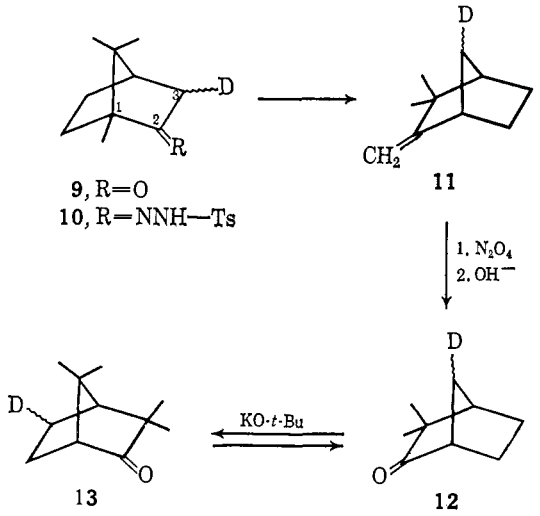
Chart I



enolizable site under the experimental conditions used.[10] This result may be compared with earlier findings that at 185° and at lower base concentration (*ca.* 0.6 *m*) about 25% of the molecules undergo homoenolization at C-6 within 12 hr.

Camphenilone with deuterium located at C-7 was prepared according to the scheme in Chart II. Cam-

Chart II



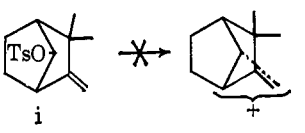
phor-3-d_2 (**9**; analysis 94% 2-D, 6% 1-D) was obtained from (+)-camphor by two exchanges with sodium methoxide in methanol-O-*d* and was converted to the corresponding *p*-toluenesulfonylhydrazone (**10**). A Bamford–Stevens reaction on this derivative gave crude camphene-*d* (**11**), which was transformed to camphenilone-7-*d* (**12**) by the successive action of dinitrogen tetroxide and alkali. During this sequence, which places the label at C-7, some deuterium was lost (probably largely during the Bamford–Stevens step, **10** → **11**) and analysis of the final camphenilone-7-*d* (**12**) showed 25% 2-D, 49.5% 1-D, and 25.5% O-D. This labeled ketone in *t*-butyl alcohol was heated at 185° with potassium *t*-butoxide for 98 hr and then recovered. Mass analysis revealed no deuterium loss, and this was true even when the recovered ketone was recycled at 185° for an additional 200 hr at a higher base concentration. That no deuterium was washed out indicates that C-7 is not a homoenolizable site, and at the same time reveals that C-5 also does not undergo exchange. This latter conclusion follows because the experimental conditions are more than sufficient to generate the homoenolate ion **2**.[1] This process makes C-7 and C-5 equivalent and produces an equal mixture of camphenilone-7-*d* (**12**) and camphenilone-5-*d* (**13**). An adverse feature of this partitioning of the label between C-7 and C-5 is that it lowers the maximum deuterium content possible at either site and therefore considerably reduces the sensitivity of our method. Since no reliable limits of sensitivity can be set at present[10,11] our conclusion that C-7 and C-5 are not homoenolizable sites may be subject to quantitative reappraisal. We note from Table I that even after the prolonged and vigorous treatments of deuterium incorporation in runs B and C, no species with more than 9-D were formed. A maximum of nine exchangeable protons is expected if C-6 and the methyl groups are the only homoenolizable centers. That C-4, C-5, and C-7 do not compete effectively is understandable on geometric grounds and supports the earlier conclusion[1] that inductive effects are not governing factors in homoenolate ion formation. Orbital bonding between C-2 and each of the last three positions would require the molecule to adopt, or at least to distort toward, the relatively strained tricyclic structures **14**, **15**, and **16**, respectively.[12]

The fact that methyl hydrogens are exchangeable implicates a homoenolate ion such as **17**. This ion is unsymmetrically substituted and could have undergone protonation at C-3 to give a rearranged product (**18**), rather than protonation at C-8 to regenerate camphenilone. We obtained no evidence of rearranged products, and in view of the generally good recovery of

(10) Isotope effects could make it more difficult to abstract deuterium than hydrogen, and the magnitude of this effect would decrease with an increase in temperature: (a) A. Streitweiser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Am. Chem. Soc.*, **80**, 2326 (1958); (b) V. J. Shiner, Jr., and M. L. Smith, *ibid.*, **83**, 593 (1961).

(11) Based on a recent report concerning selectivity in deuteration of camphor α to the carbonyl group by simple exchange (A. F. Thomas and B. Willhelm, *Tetrahedron Letters*, **No. 18**, 1309 (1965)) and on the assumption that similar considerations would apply to the loss of some deuterium during the Bamford–Stevens step (**10** → **11**) the monodeuterated component should be richer in the 3-*endo*-*d* epimer in **10**, richer in the 7-*anti*-*d* epimer in **11** and in **12**, and richer in the 5-*endo*-*d* epimer in **13**. If homoenolate ion formation at C-7 and/or C-5 were strongly stereoselective the configurational distribution of the label in the monodeuterated component of **12** and **13** would substantially influence the sensitivity of the method.

(12) Saturated tricyclic skeletons analogous to **16** are known, but nevertheless are strained: (a) W. R. Moore, H. R. Ward, and F. R. Merritt, *J. Am. Chem. Soc.*, **83**, 2019 (1961); (b) H. C. Brown and H. M. Bell, *ibid.*, **85**, 2324 (1963); (c) S. Winstein, A. H. Lewin, and K. C. Pande, *ibid.*, **85**, 2324 (1963). A close structural analogy is available from the work of E. E. van Tamelen and C. I. Judd, *ibid.*, **80**, 6305 (1958), who found no kinetic evidence for homoallylic participation in the solvolysis of the *p*-toluenesulfonate ester (i) of 7-*anti*-hydroxycamphene. In addition, the apparent absence of anchimeric assistance in solvolysis of *endo*-substituted norbornyl esters has been attributed to the increase in strain that would attend formation of a bond between C-7 and C-2 in a bicyclo[2.2.1]heptyl system: J. A. Berson, "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 3.



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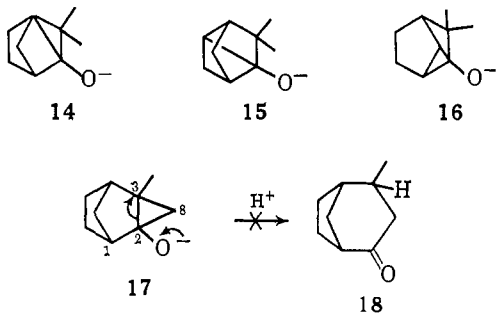

14 15 16

17 18

camphenilone (*e.g.*, 80%[1]) it seems clear that pathway **17** → **18** (or any other pathway that would transform camphenilone to other products) plays a minor role, if any. Possibly in **17** the bond is not as fully developed as, and is therefore weaker than, the C-2–C-3 bond; alternatively, protonation at C-8 might be inherently favored because an incipient primary carbanion (at C-8) is presumably more stable and less hindered than an incipient tertiary carbanion (at C-3).[13]

Experimental Section[14]

Camphenilane. Preparation. Camphenilane was prepared by Wolff–Kishner reduction of camphenilone (4.0 g) according to the Huang-Minlon modification.[15] Crude product was chromatographed over Alcoa alumina (11 g), and camphenilane was eluted with pentane (50 ml of eluent). Camphenilane was dissolved in acetone (25 ml) saturated with potassium permanganate, and the solution was shaken well, then allowed to stand at room temperature (30°) for 1.5 hr. Pentane was added, acetone and permanganate were removed by repeated washings with water, and pentane was separated, dried with sodium sulfate, and evaporated. The clear, colorless oil (*ca.* 0.6 g) obtained was shown to be 90% pure by gas chromatography. Three unidentified components with retention times longer than camphenilane were present (relative concentrations 3, 5, and 2%). Mass spectrometry gave the parent molecular ion at *m/e* 124; weak ion intensities were observed at *m/e* 136 and 138 (sum *ca.* 8% of the *m/e* 124 intensity).

Attempted Deuterium Incorporation. A *t*-butyl alcohol-O-*d* solution of camphenilane (0.78 *m* volume) and potassium *t*-butoxide (1.12 *m* volume) was sealed under nitrogen in a Pyrex tube and heated at 185° for 250 hr. The mass spectrum of recovered camphenilane indicated the presence of 1 ± 0.5% monodeuterated and 1 ± 0.5% dideuterated species. Gas chromatography revealed no volatile components other than the three present in the starting material. This recovered camphenilane was dissolved in pentane, and the solution was washed with concentrated sulfuric acid and 5% sodium bicarbonate, and was dried over sodium sulfate. Camphenilane recovered after removal of pentane was analyzed by gas chromatography and was observed to be 95% pure (the 5% unidentified component was now absent). The mass spectrum of this partially purified camphenilane indicated trace amounts (maximum of 1% each) of mono- and dideuterated camphenilane species. Weak intensities were still observed for *m/e* 136 through 140, and it is possible that fragmentation by these unidentified impurities was contributing to the camphenilane ion intensities. Therefore even this slight deuterium incorporation may not be real.[16]

Camphenilone *p*-Toluenesulfonylhydrazone. Camphenilone (3.66 g) and toluenesulfonylhydrazine (5.0 g) were dissolved in 30 ml of 95% ethanol containing 1% hydrochloric acid. This solution was refluxed for 5 hr, cooled, and poured into 200 ml of water. The white solid was collected, dried, and recrystallized once from ethanol to give 5.74 g (70%) of derivative, mp 151–153°. Camphenilone *p*-toluenesulfonylhydrazone was crystallized from methanol to constant mp 155–156°.

Anal. Calcd for $C_{16}H_{22}N_2O_2S$ (306.42): C, 62.71; H, 7.24. Found: C, 62.68; H, 7.11.

The nmr spectrum shows the following absorptions:[17] (a) aromatic protons, two doublets at δ 7.82 and 7.26 (J = 8.0 hertz); (b) one proton at δ 3.03 (broad) which is probably the C-1 bridgehead proton; (c) aryl methyl, singlet at δ 2.41; (d) geminal dimethyls, two peaks of about equal height at δ 1.01 and 0.96. Area integration gives the following ratio for these bands: a:b:c:d = 4:1:3:6.

The nmr spectrum of deuterated camphenilone *p*-toluenesulfonylhydrazone (*ca.* 0.01 g, recrystallized from methanol, total, 3.72-atom excess of deuterium; derived from run B camphenilone-*d*) was taken in a Varian microcell. Area integration of the four regions described above gave the ratio: a:b:c:d = 4:0.4:3:3.6. The range of accuracy for the ratio values of bands b and d are ±0.02 and ±0.2 respectively.

Apocyclene-*d*. Camphenilone (2.6 g, 0.96 *m* volume) was heated at 250° for 71 hr in *t*-butyl alcohol-O-*d* containing potassium *t*-butoxide (1.6 *m* volume). Recovered camphenilone-*d* (semicarbazone mp 224–225°, 1.95-atom excess of deuterium, by combustion–infrared analysis of the semicarbazone[18]) was dissolved in fresh *t*-butyl alcohol-O-*d* (ketone concentration 0.35 *m* volume) containing potassium *t*-butoxide (0.46 *m* volume) and the solution was heated at 250° for an additional 70 hr. Camphenilone-*d* was recovered which contained a 2.57-atom excess of deuterium, by combustion–infrared analysis of the semicarbazone (mp 219–220°), and was converted to the *p*-toluenesulfonylhydrazone (mp 151–152°, *ca.* 0.020 g, 2.65-atom excess of deuterium by combustion–infrared analysis). This derivative was treated (130°) with sodium ethylene glycoxide in ethylene glycol (Bamford–Stevens reaction[4]). Apocyclene was swept out of the reaction flask by a stream of nitrogen and was collected as a glass-like solid in a Dry Ice–acetone cold trap. Mass spectrometry gave the following distribution of deuterated species (in mole percent): 7% O-D, 24% 1-D, 33% 2-D, 23% 3-D, 10% 4-D, and 3% 5-D; a total excess of 2.14 deuteriums per molecule. This deuterated apocyclene was dissolved in carbon disulfide and its infrared spectrum was recorded. The absorbance ratio of cyclopropyl carbon–hydrogen (3040 cm^{-1}) to aliphatic carbon–hydrogen (2930 cm^{-1}) was observed to be 0.129. For natural abundance apocyclene the corresponding ratio was observed to be 0.227.

Camphenilone-4-*d*. Preparation. 4-Chlorononorcamphor (3.01 g, from norcamphor by the method reported by Wiberg, *et al.*[5]), whose semicarbazone had mp 220–222° dec (lit.[5] mp 222–223° dec), was dissolved in ethanol-O-*d* (16 g, 98% D) and the solution was heated to boiling. Freshly cut sodium (3.6 g) was added in *ca.* 0.4-g portions over a period of 45 min, and the reaction mixture was refluxed for an additional 2 hr. The flask was thoroughly cooled in an ice bath, and deuterium oxide (2.0 g, 99.5% D) was added slowly. The reaction mixture was allowed to warm to room temperature and then was heated briefly to reflux. Water (*ca.* 25 ml) was added and the solution was extracted thoroughly with pentane. Combined pentane extracts were washed with brine and dried over anhydrous sodium sulfate, and pentane was removed with aspirator vacuum. The epimeric deuterated norborneols (1.40 g, 59%) were sublimed from anhydrous sodium sulfate as slightly oily, white solid. The alcohols (0.93 g) were oxidized with activated manganese dioxide[19] (35 g, Beacon, Inc.) in purified petroleum ether (bp 45–60°) to 4-deuterionorcamphor (0.49 g, 54%). The ketone was dissolved in 50 ml of dry ether, and powdered sodium amide (0.80 g, Farchan Research Laboratories) was

(13) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, p 20.

(14) Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer equipped with sodium chloride optics. A Perkin-Elmer Model 226 gas chromatograph with flame detector was used for gas chromatographic analyses. Unless specified otherwise a 150-ft Golay column with polypropylene glycol liquid phase was used. For preparative gas chromatography an Aerograph Autoprep Model A-700 was used, with a 30 ft. × 3/8 in. column containing 30% SE-30 silicone liquid phase on 40–60 Chrom P. Helium was the carrier gas for all chromatography. Mass spectra were taken with a Consolidated Electrodynamics Corp. mass spectrometer, Type 21-103C. A Varian A-60 spectrometer was used for nmr spectra and tetramethylsilane (used internally) was the reference standard. Deuterated solvents were purchased from Merck and Co., Ltd., of Canada. Potassium *t*-butoxide was sublimed *in vacuo* at 250° before use. *t*-Butyl alcohol was distilled first from aluminum–*t*-butoxide and then from potassium. For general procedures regarding homoenolization and mass spectrometric analyses see part IV.[1]

(15) Huang-Minlon, *J. Am. Chem. Soc.*, 68, 2487 (1946).

(16) Similar attempted deuterium incorporation studies with the hydrocarbon camphane (to be described in a forthcoming paper) did not present the complication of trace impurities. Camphane incorporated no deuterium after 336 hr at 185° or even after 215 hr at 250°.

(17) The single proton on nitrogen is at δ 7.62. The remaining seven protons give a complex pattern between δ 2.2 and 1.1.

(18) See Lambert, *et al.*, Table I, footnote *f*.

(19) I. T. Harrison, *Proc. Chem. Soc.*, 110 (1964).

added. The suspension was stirred at room temperature for 1 hr, then at reflux for 7–8 hr. The mixture was cooled to room temperature, 4.0 ml of methyl iodide was added, and stirring was resumed at room temperature for 0.5 hr, then at reflux for 3 hr. The mixture was again cooled to room temperature and another portion of sodium amide (0.80 g) was added, and the sequence was repeated. Four cycles of this sequence were completed. The bulk of ether and of excess methyl iodide was removed by distillation through a 36-in. spinning-band column. Cold 3% sulfuric acid (30 ml) was added dropwise with external cooling to the residue. This mixture was extracted thoroughly with ether, and the combined ether extracts were washed with aqueous sodium thiosulfate and with brine, dried over anhydrous sodium sulfate, and the ether distilled through a spinning-band column until the volume of solution remaining was *ca.* 5 ml. Components of the ether solution (norcamphor-*d*, epimeric monomethylated norcamphors-*d*, and camphenilone-*d*) were separated by preparative gas chromatography. Camphenilone-4-*d* (0.122 g) was shown to be pure by analytical gas chromatography, and mass spectrometry indicated the composition: 89.5% 1-D and 10.5% O-D. Polydeuterated material was not detected.

Homoenolization. A *t*-butyl alcohol solution of camphenilone-4-*d* (0.193 *m* volume) and potassium *t*-butoxide (1.57 *m* volume) was sealed under nitrogen in a Pyrex tube and heated at 185° for 200 hr. The mass spectrum of camphenilone-4-*d* recovered from the reaction was essentially identical with that of the starting material (89.7% 1-D, 10.3% O-D). The recovered camphenilone-4-*d* was dissolved in *t*-butyl alcohol (ketone *ca.* 0.18 *m* volume) containing potassium *t*-butoxide (1.78 *m* volume), and the solution was heated at 185° for 300 hr. The mass spectrum of camphenilone recovered from this repeat reaction gave the species composition: 89.1% 1-D and 10.9% O-D.

The residue, after mass spectral analysis, was dissolved in ether and examined by sensitive analytical gas chromatography. The only volatile components observed (column temperature 145°) were solvent, camphenilone (retention time 10 min, 35 sec), and an unidentified impurity (*ca.* 1% of camphenilone concentration; retention time 8 min, 23 sec).

Camphenilone-7-*d*. Preparation. (+)-Camphor (10.2 g, mp 177.5–178°, α +43°) was deuterated by reflux for 9 hr in a solution of methanol-O-*d* and methanol (30 ml, *ca.* 70% O-D) made 1.4 *M* in sodium methoxide. Camphor-*d* (sublimed) from this first exchange was refluxed for 32 hr in a solution of methanol-O-*d* (15 g, 99% D) and deuterium oxide (7 g, 99.5% D) in which freshly cut sodium (1.1 g) had been dissolved. Recovered camphor-*d* (7.9 g, sublimed) was shown to be 94.2% dideuterated and 5.8% monodeuterated by mass spectrometry. This camphor-*d* and *p*-toluenesulfonylhydrazine (*ca.* 10% excess) were dissolved in dioxane (100 ml, previously treated with 1.0 ml of deuterium oxide and dried with anhydrous sodium sulfate) containing 1.0 ml of concentrated deuterium chloride in deuterium oxide (prepared by passage of deuterium chloride gas through deuterium oxide), and the solution was refluxed for 6 hr. The solution was poured into cold water (400 ml), and the white precipitate was washed with water, dried, and recrystallized from dry carbon tetrachloride, to yield 9.24 g (55%) of camphor-*d* *p*-toluenesulfonylhydrazone, mp 165–166° (lit.[4] mp 163–164°). This derivative was converted to camphenilone-7-*d* by the method reported earlier.[1] Preparative gas chromatography gave 0.054 g; analytical gas chromatography and mass spectrometry indicated the presence of camphor (*ca.* 4%).[20] The mass spectrum showed the isotopic distribution of camphenilone-7-*d* to be 25% 2-D, 49.5% 1-D, and 25.5% O-D.

Homoenolization. A *t*-butyl alcohol solution of this camphenilone-7-*d* (0.26 *m* volume) containing potassium *t*-butoxide (0.84 *m* volume) was heated at 185° for 98 hr. The mass spectrum of recovered ketone indicated 24.5% 2-D, 49.5% 1-D, and 26% O-D. The recovered ketone was redissolved in *t*-butyl alcohol containing potassium *t*-butoxide (2.26 *m* volume, ketone concentration 0.12) and heated at 185° for 200 hr. Camphenilone-*d* recovered from this reaction had a mass spectrum essentially identical with that taken earlier: 24.5% 2-D, 49.5% 1-D, and 26% O-D.

(20) This trace of camphor was observed in earlier preparations (part IV, ref 27).

Nuclear Magnetic Resonance Spectroscopy. Conformational Equilibrations of *cis*-Decalins[1]

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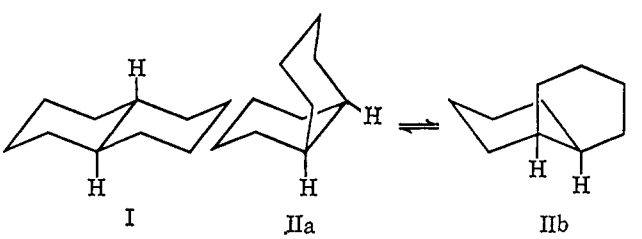
Abstract: The fluorine-19 magnetic resonance spectra of 2,2-difluoro-*cis*-decalin and some of its derivatives have been examined as a function of temperature. For several cases it was possible to determine the rates and activation energy for interconversion of the two possible chair–chair conformations of the compounds. In other instances, the point of equilibrium was found to be such that only one isomer predominated to the extent that kinetic studies were impossible. For 2,2-difluoro-*cis*-decalin, the activation energy was determined to be 14.0 ± 0.8 kcal/mole. The activation energy decreased to 9.7 ± 0.6 kcal/mole upon substitution of alkyl groups at the ring junctions. With methyl groups at the 1, 2, or 6 positions, one isomer was favored to the degree that equilibration could not be detected.

Inspection of models of the *cis* and *trans* forms of decalin which have the rings in the chair forms shows that there is only one *trans*-decalin (I) but that the *cis* isomer has two conformational isomers (IIa,b) which can be interconverted by flipping each ring in a manner similar to the familiar inversion of cyclohexane. The forms IIa and IIb are enantiomers and *cis*-decalin is expected to exist largely, if not completely, as a nonresolvable *d,l* pair of conformational isomers.



(1) Supported in part by the National Science Foundation and the Office of Naval Research; presented at the 19th National Organic Symposium of the American Chemical Society, Tempe, Ariz., June 17, 1965.