Stereospecific α-Hydrogen Exchange in Camphor, Isofenchone, and Carvonecamphor[1]

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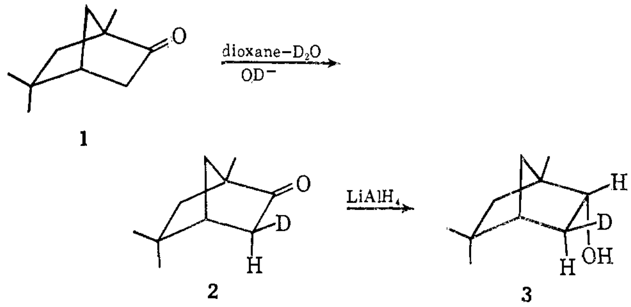
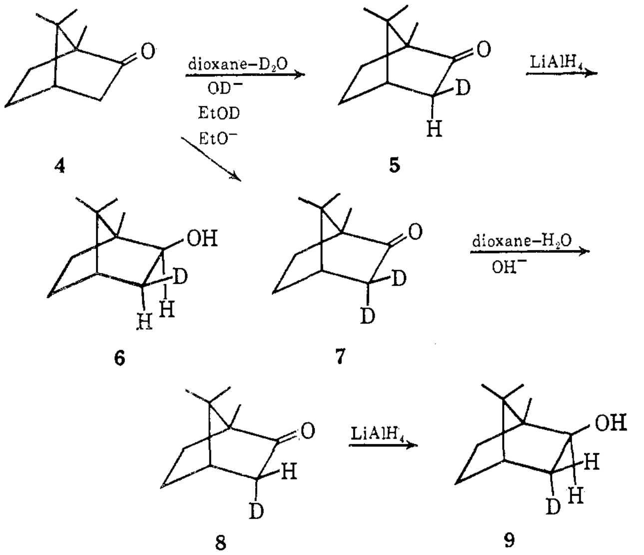
Contribution from the Laboratoires de Recherches, Firmenich & Cie, Geneva, Switzerland, and the Department of Chemistry, Cornell University, Ithaca, New York 14850. *Received August 29, 1966*

Abstract: *endo*-α-Deuteriocamphor (**8**) and *endo*-α-deuterioisofenchone (**11**) are obtained by base-catalyzed removal of one deuterium atom from the corresponding dideuterated ketones. These results confirm the tendency in both of these bicyclo[2.2.1]heptan-2-ones for the *exo*-α-hydrogen atom to be exchanged selectively. In the case of camphor, the operation of some unrecognized steric or stereoelectronic factor is implicated. Analogous techniques allow the preparation of *exo*- and *endo*-α-deuteriocarvonecamphors (**13** and **14**) with a high degree of stereospecificity. As an incidental result, the nmr spectra of several monodeuterated bicyclo[2.2.1]heptan-2-ol derivatives show that the observed vicinal coupling constants ($J_{2,3}$) are consistent with expectations based on an undistorted bicyclo[2.2.1]heptyl nucleus.

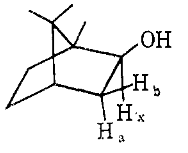
Thomas and Willhalm[3] have established, from the nmr spectrum of the lithium aluminum hydride reduction product (**3**), that isofenchone (**1**) can be specifically monodeuterated in the *exo* position, giving **2**. This observation agrees with expectations, since there is a considerable body of evidence that the *exo* face of a bicyclo[2.2.1]heptane which has no *syn* substituent at C_7 is generally more accessible to attack by external reagents than the *endo* face.[4]



An unexpected result was obtained, however, when camphor (**4**) was monodeuterated. In this case the product again had to be assigned the *exo*-3-deuterated structure (**5**) since lithium aluminum hydride reduction led to a monodeuterated isoborneol (**6**) in which the *endo*-C_2 proton at τ 6.47 appeared as a doublet with J = 8.5 cps. The magnitude of the coupling constant indicates that the C_2 proton is split by a *cis* (and therefore *endo*) C_3 proton. Since a *syn*-7-methyl group had seemed, on the basis of earlier evidence, to make *exo* approach *more difficult* than *endo* approach,[4] The hydrogen exchange reaction of camphor and some related bicyclo[2.2.1]heptanes has been examined further.



Monodeuterated Camphors and Isoborneols. We have now prepared a new α-monodeuteriocamphor (**8**) by selectively removing one deuterium atom from the dideuterated compound (**7**). Reduction of **8** with lithium aluminum hydride gave an isoborneol (**9**) in which the C_2 proton (H_x) at τ 6.45 appeared as a broad, unresolved absorption, the width of which at half-height ($W_{1/2}$) was about 5 cps. This absorption is best rationalized as a doublet ($J_{bx} \cong 2.5$ cps) on which is superimposed the singlet of the d_2 compound (20%) and the triplet (J = 5.2 cps) characteristic of **10** itself (15%).



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The observation of what must be a relatively small vicinal coupling constant for **9** in contrast to the large one (8.5 cps) of **6** is in accord with calculations for gauche and eclipsed protons of bornanes (2.4 and 8.2 cps[5]) as well as with experimental observations on the bornanediols (2.3 and 8.9 cps[6]). It follows that the deuterium must be *exo* in **5** and **6** as previously proposed, and that it must be *endo* in **8** and **9**.

As an incidental result of having prepared these monodeuterated isoborneols, it has become possible to

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[1] The partial support of this research by a grant (GP-4128) from the National Science Foundation is acknowledged with pleasure.

[2] National Science Foundation Cooperative Graduate Fellow, 1962–1965; National Institutes of Health Fellow, 1965–1966.

[3] A. F. Thomas and B. Willhalm, *Tetrahedron Letters*, 1309 (1965).

[4] For a leading reference, see E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 304.

[5] T. J. Flautt and W. F. Erman, *J. Am. Chem. Soc.*, **85**, 3212 (1963).

[6] F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).

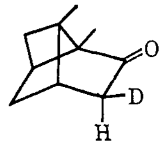
clarify a previously ambiguous point in the analysis of the nmr spectra of some isoborneol derivatives. Flautt and Erman[5] have pointed out that the triplets almost invariably observed for the *endo*-C_2 protons of *exo*-substituted bornanes might arise either because $J_{ax} = J_{bx}$ or because the difference in chemical shift between H_a and H_b is small compared to J_{ab}; the latter situation results in the observation of "deceptively simple spectra,"[7] with H_x appearing as a triplet and $J'_{ax} = J'_{bx} = {}^1/_2(J_{ax} + J_{bx})$. For isoborneol itself, Flautt and Erman found that the triplet which appears in carbon tetrachloride solution is transformed into a quadruplet in pyridine solution, implying that a greater difference between the chemical shifts of H_a and H_b is induced in this solvent, and $J_{ax} \neq J_{bx}$. However, the triplets of isobornyl acetate and of *p*-isobornylphenol remained the same in either solvent. To account for this difference, they suggested that large *exo* substituents may distort the relevant dihedral angles so as to make J_{ax} and J_{bx} more nearly equal. With isoborneol itself the effect might be minor, but with its acetate or with *p*-isobornylphenol (they suggested) it might be important.

Our evidence confirms the supposition that isoborneol itself is not distorted, since the coupling constants observed in **6** and **9** agree with theoretical expectations. In addition, when **6** and **9** are converted into their acetate esters the coupling patterns remain essentially unchanged; *exo*-α-deuterioisobornyl acetate has J_{ax} = 8.4 cps in both carbon tetrachloride and pyridine, and *endo*-α-deuterioisobornyl acetate in carbon tetrachloride shows a broad singlet at τ 5.43 which is shifted to τ 5.23 in pyridine. Therefore, the fact that H_x in isobornyl acetate fails to be split into a quadruplet in pyridine should *not* be taken to suggest that the substituent distorts the dihedral angles of the molecule. Rather, the alternative possiblity envisioned by Flautt and Erman is the better one; the difference in chemical shift between H_a and H_b has remained small, and the spectrum remains "deceptively simple."

Monodeuterated *endo*-Isofenchols. The preparation of *exo*-α-deuterio-*endo*-isofenchol (**3**) has been described.[3] We have now prepared *endo*-α-deuterio-*endo*-isofenchol (**12**) from isofenchone (**1**) *via* **11** in the same way that the corresponding isoborneol (**9**) was prepared from camphor (**4**). This *endo,endo* isomer **12** showed the expected doublet in the nmr spectrum (in carbon tetrachloride) at τ 6.27 (J = 9.5 cps). The corresponding acetate showed J = 10.0 cps. These values are slightly higher than those predicted by Karplus[8] and imply that $J_{exo,exo} > J_{endo,endo}$, a fact which has been established for certain oxabicyclo[2.2.1]heptanes.[9]

11 **12**

Monodeuterated Carvonecamphors. In order to study the stereochemistry of the hydrogen transfer in the photolysis of carvonecamphor (the subject of our following paper[10]), we sought to prepare samples of the α-monodeuterated carvonecamphors by the same procedures used with camphor. Monodeuteration of carvonecamphor proceeded readily to give **13**, and one deuterium atom was removed from α,α-dideuteriocarvonecamphor to give **14**.



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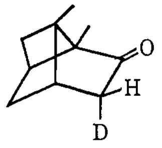

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In each case, the success in achieving exchange of one atom without exchange of both was distinctly greater with carvonecamphor than with camphor, although it has been shown[11] to be much less in the monodeuteration of norcamphor compared to camphor. When the deuterium exchange was carried out with carvonecamphor until 95% of the starting material had been monodeuterated, dideuteration was negligible.

The fact that one α-hydrogen atom in this tricyclic molecule can be exchanged so much more readily than both is evidence that the exchange is stereospecific. This stereospecificity is confirmed by the results of the photochemical experiments described in our following paper.[10]

Reduction of carvonecamphor with lithium aluminum hydride gave a mixture consisting of about equal amounts of the *endo* and *exo* alcohols, as inferred from the nmr spectrum of the product. This finding emphasizes the lack of parallelism between the steric course of complex hydride reductions and hydrogen exchange experiments in these bridged molecules. Unfortunately, we have been unable to separate this mixture adequately,[12] and so we have no direct confirmation of the stereochemical assignments of the monodeuteriocarvonecamphors. However, since it has been established that exchange in the case of both isofenchone (**1**) and camphor (**4**) occurs specifically in the *exo* position, and since with regard to the steric factors which presumably control access to the α position carvonecamphor is intermediate between isofenchone (in which attack from the *endo* side is hindered) and camphor (in which attack from the *exo* side is hindered), it seems reasonable to assume that carvonecamphor also suffers preferential *exo* exchange.

The phenomenon of *exo* hydrogen exchange in the case of camphor (**4** and **7**) must reflect the operation of some as yet unappreciated steric or stereoelectronic effect. It takes on additional, although somewhat vicarious, interest because this apparently general tendency of bicyclo[2.2.1]heptan-2-ones to suffer *exo* protonation in a group of reactions which certainly *cannot* involve carbonium ions mimics the tendency of 2-bicyclo[2.2.1]heptyl *carbonium ions* to yield *exo*-substituted products. Should this similarity prove ultimately to have a common physical basis, it may have

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(7) R. J. Abraham and H. J. Bernstein, *J. Am. Chem. Soc.*, **39**, 216 (1961).

(8) M. Karplus, *J. Chem. Phys.*, 30, 11 (1959).

(9) D. Gagnaire and E. Payo-Subiza, *Bull. Soc. Chim. France*, 2627 (1963).

(10) J. Meinwald, R. A. Schneider, and A. F. Thomas, *J. Am. Chem. Soc.*, **89**, 70 (1967).

(11) See ref 3, and also J. M. Jerkunica, S. Borčić, and D. E. Sunko, *Tetrahedron Letters*, 4465 (1965).

(12) The best glpc column we have found is hexakis(2′-cyanoethoxy)-1,2,3,4,5,6-hexane (Fractonitrile VI), upon which the mixture shows only one peak with a poorly resolved shoulder.

an important bearing on the current controversy concerning the nature of bridged carbonium ions.

Experimental Section

Mass spectra were measured on an Atlas CH-4 apparatus; temperature of source 275°, temperature of introducton 150°, ionizing voltage 70 ev. Gas–liquid partition chromatography was carried out at 200° using a column of 15% Carbowax on Chromosorb W.

endo-α-**Deuteriocamphor** (**8**). A solution of 250 mg of α,α-dideuteriocamphor[13] (97% d_2), five drops of 40% sodium hydroxide solution, and 10 ml of 50% aqueous dioxane was heated for 15 min on a steam bath and then allowed to stand overnight. Pentane was added, and the solution was washed with water and evaporated, giving crude **8**, which after purification by glpc contained 21% d_2, 64% d_1, and 15% d_0.

endo-α-**Deuterioisoborneol** (**9**). To 50 mg of lithium aluminum hydride in 25 ml of dry ether was added 200 mg of *endo*-α-deuteriocamphor (**8**). After 3 hr at room temperature 1 ml of water was added to decompose excess hydride. Filtration and concentration left the crude alcohol (**9**), which was purified by glpc.

endo-α-**Deuterio**-*endo*-**isofenchyl Compounds.** *endo*-α-Deuterioisofenchone, *endo*-α-deuterio-*endo*-isofenchol (**12**), and *endo*-α-deuterio-*endo*-isofenchyl acetate were prepared, starting with isofenchone, by the same procedures used to prepare the corresponding isobornyl compounds. After purification by glpc, **11** contained 7% d_2, 78% d_1, and 15% d_0.

exo-α-**Deuteriocarvonecamphor** (**13**). A pellet of sodium about 1 mm in diameter was dissolved in a solution of 5 ml of deuterium oxide and 5 ml of dry, peroxide-free dioxane; then 250 mg of carvonecamphor was added. The mixture was allowed to stand overnight and then was extracted with pentane. The pentane was washed twice with 2 ml of deuterium oxide, then with water, and then evaporated. The residue was treated with excess potassium permanganate solution in the presence of Dry Ice chips, and then sodium oxalate solution was added and the *exo*-α-deuteriocarvonecamphor was separated by steam distillation. It was found to be pure by glpc analysis, and contained 95% d_1 and 4% d_0.

endo-α-**Deuteriocarbonecamphor** (**14**). This compound was prepared by the same procedure described for *endo*-α-deuteriocamphor, starting with α,α-dideuteriocarvonecamphor prepared as described previously.[14] The product contained 87% d_1 and 13% d_0.

Acknowledgment. We gratefully acknowledge the assistance of Dr. K. H. Schulte-Elte in the preparation of carvonecamphor and Dr. B. Willhalm for assistance with the mass spectra.

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[13] D. S. Weinberg and C. Djerassi, *J. Org. Chem.*, 31, 115 (1966).

[14] J. Meinwald and R. A. Schneider, *J. Am. Chem. Soc.*, 87, 5218 (1965).

Stereospecific Hydrogen Transfer in the Photolysis of Carvonecamphor[1]

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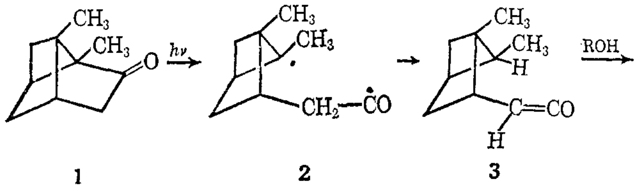
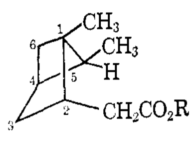
Abstract: *endo*-α-Deuteriocarvonecamphor (**5**) is transformed into the deuterated ester **7**; this change corresponds to transfer of the *exo*-α-proton upon irradiation in methanol solution. The *exo*-α-deuterated isomer **6** gives chiefly ester **9**, *via* deuteron transfer, under similar conditions. The stereospecific transfer of the *exo*-hydrogen atom α to the carbonyl group is thus established. The mass spectra of a variety of deuterated products encountered in this work are presented, and the mechanistic implications of the stereospecific photolytic reaction are explored briefly.

The photolysis of carvonecamphor (**1** → **4**) provides a particularly clean example of the well-known photolytic conversion of cyclic ketones into carboxylic acids or their derivatives.[3] A sizeable body of evidence supports the general mechanism in which an excited ketone molecule suffers homolytic cleavage to give a diradical, which is then transformed into a ketene *via* an intramolecular hydrogen atom transfer.[4] Addition of nucleophilic solvent to the ketene gives rise to the usual products. Consideration of this mechanism, pictured below for the case of carvonecamphor, raises the question of whether the hydrogen atom transfer step (**2** → **3**) would show any appreciable degree of stereospecificity with respect to which of the hydrogen atoms on the donor carbon atom would be transferred.



1 **2** **3**



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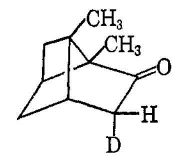

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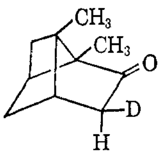

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Since the photochemical formation of **4** is almost free of competing processes, this reaction provides an attrac-

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[2] National Science Foundation Cooperative Graduate Fellow, 1962–1965; National Institutes of Health Fellow, 1965–1966.

[3] J. Meinwald and R. A. Schneider, *J. Am. Chem. Soc.*, 87, 5218 (1965); see also T. Gibson and W. F. Erman, *J. Org. Chem.*, 31, 3028 (1966).

[4] For recent reviews of this group of reactions, see G. Quinkert, *Angew. Chem.*, 77, 229 (1965), and G. Quinkert in "International Symposium on Organic Photochemistry," Butterworth & Co. (Publishers) Ltd., London, 1964 (*Pure Appl. Chem.*, 9, 607 (1964). See also ref 3, and J. Iriarte, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, 47, 1255 (1964).