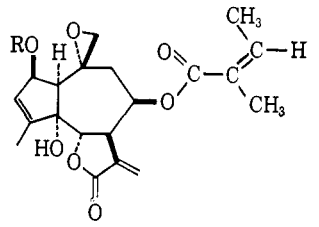


III, R = $COCH_3$
IV, R = H
V, R = $COCH_2Br$

acetate, like the previously reported tumor inhibitors withaferin A,[10,11] elephantin,[12] and elephantopin,[12] possesses epoxide and α,β-unsaturated lactone functions. Investigations are in progress which are aimed at evaluation of the significance of the latter functions, and of other structural features, in relation to the tumor-inhibitory activity of the respective compounds.

(10) S. M. Kupchan, R. W. Doskotch, P. Bollinger, A. T. McPhail, G. A. Sim, and J. A. Saenz Renauld, *J. Am. Chem. Soc.*, **87**, 5805 (1965).

(11) Withaferin A has recently been found to show significant inhibitory activity against Walker carcinosarcoma 256 in rats at 40 mg/kg.[4]

(12) S. M. Kupchan, Y. Aynehchi, J. M. Cassady, A. T. McPhail, G. A. Sim, H. K. Schnoes, and A. L. Burlingame, *J. Am. Chem. Soc.*, **88**, 3674 (1966).

S. Morris Kupchan, Jane C. Hemingway
John M. Cassady, John R. Knox
Department of Pharmaceutical Chemistry
University of Wisconsin, Madison, Wisconsin 53706

A. T. McPhail, G. A. Sim
Department of Chemistry
University of Illinois, Urbana, Illinois
Received November 14, 1966

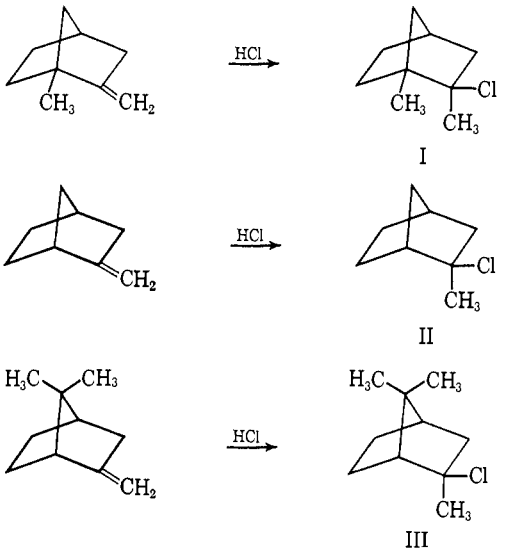
The Hydrochlorination of 2-Methylenenorbornane and Related Derivatives. Evidence for the Absence of a Symmetrical Nonclassical Intermediate in the Hydrochlorination of 1-Methyl-d_3-2-methylenenorbornane

Sir:

We wish to report that the hydrochlorination of 1-methyl-d_3-2-methylenenorbornane can be controlled to yield predominantly unscrambled 1-methyl-d_3-2-methyl-*exo*-norbornyl chloride. Consequently, the formation of a symmetrical intermediate, the 1,2-dimethylnorbornyl nonclassical cation, cannot be significant in this electrophilic addition reaction.

The automatic hydrochlorination technique developed recently[1] provides a simple method for achieving the hydrochlorination of an olefin with a minimum exposure of the product to the further action of hydrogen chloride. This encouraged us to undertake a study of the hydrochlorination of norbornane derivatives in an attempt to see whether the results would throw light on the question of bridged nonclassical intermediates in the carbonium ion reactions of these compounds.

Application of the Wittig reaction to 1-methyl-2-norbornanone produced 1-methyl-2-methylenenorbornane, bp 135–137°, $n^{20}D$ 1.4680, in 70% yield. *Anal.* Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.50; H, 11.55. Treatment of 1-methyl-2-methylenenorbornane with hydrogen chloride at 0° yielded 99% pure 1,2-dimethyl-*exo*-norbornyl chloride (I) in a total reaction time of 2 min. Similarly, 2-methylenenorbornane yielded 99% pure 2-methyl-*exo*-norbornyl chloride (II) in 2 min, and α-fenchene yielded over 90% pure 2,7,7-trimethyl-*exo*-norbornyl chloride (III), together with the Wagner–Meerwein rearranged secondary product,[2] in 8 min.



I

II

III

The structure of 2,7,7-trimethyl-*exo*-norbornyl chloride, mp 19–20°, was confirmed as the *exo* derivative, without significant contamination by the *endo* isomer, by the nmr results described below and by the constancy of its rate of ethanolysis over more than 80% reaction, $k_1^{25} = 8.5 \times 10^{-4}$ sec.$^{-1}$. That no skeletal rearrangement had occurred is confirmed by the results of the earlier borohydride-trapping experiments.[3] The nmr spectrum exhibited methyl proton absorption at δ 1.05, 1.41, and 1.64. The latter peak is assigned to the 2-methyl group, and the large difference in the chemical shift of the first two methyl peaks (attributed to the 7-methyls) is similar to that observed in apoisobornyl chloride (δ 1.03 and 1.33) and isobornyl chloride (δ 0.88 and 1.10), with *exo* chloride substituents, rather than to bornyl chloride (δ 0.88 and 0.92), with its *endo* substituent.

Polar hydrohalogenation of olefinic compounds has long been postulated to proceed *via* intermediates with carbonium ion character.[4] The intermediate leading to the product-determining step might be either a classical carbonium ion pair[5] or a π complex.[6,7] It has also been suggested that the reaction might proceed in some cases *via* a concerted *trans* attack by both the electrophile and the nucleophile on the double bond.[7] The last two possibilities cannot be important in the present cases because the products are almost exclusively tertiary *exo* chlorides. The result with α-fenchene is of particular interest since it has been argued that

(1) H. C. Brown and M.-H. Rei, *J. Org. Chem.*, 31, 1090 (1966). We utilized a commercial unit from Delmar Scientific Laboratories, Maywood, Ill. 60154.

(2) W. Hückel and D. Volkmann, *Ann.*, **664**, 31 (1963).

(3) H. C. Brown and H. M. Bell, *J. Am. Chem. Soc.*, **86**, 5006 (1964).

(4) P. B. D. de la Mare and R. Bolton, "Electrophilic Additions to Unsaturated Systems," Elsevier Publishing Co., New York, N. Y., 1966.

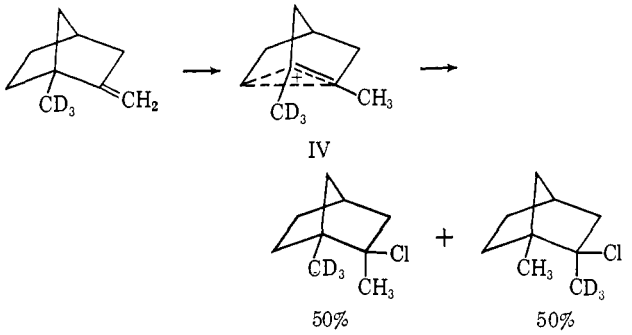
(5) M. J. S. Dewar and R. C. Fahey, *J. Am. Chem. Soc.*, **85**, 2245, 2248, 3645 (1963); *Angew. Chem. Intern. Ed. Engl.*, **3**, 245 (1964).

(6) M. J. S. Dewar and A. P. Marchand, *Ann. Rev. Phys. Chem.*, **16**, 321 (1965).

(7) G. S. Hammond and T. D. Nevitt, *J. Am. Chem. Soc.*, **76**, 4121 (1954); G. S. Hammond and C. H. Collins, *ibid.*, **82**, 4323 (1960).

the presence of the 7,7-dimethyl substituents should, for steric reasons, result in the formation of *endo* product, except in cases where nonclassical bridging directs the entering nucleophile to the *exo* position.[8,9] If this argument is valid, the formation of the 2,7,7-trimethyl-*exo*-norbornyl chloride in the hydrochlorination of α-fenchene would appear to require the formation of a bridged cation.

On this basis, the hydrochlorination of a tagged 1-methyl-2-methylenenorbornane would be expected to proceed through a symmetrical bridged intermediate, requiring complete scrambling of the tag. Indeed, when hydrogen chloride was added to 1-methyl-d_3-2-methylenenorbornane under the usual reaction conditions, *i.e.*, slow addition and long reaction time, the product was completely scrambled as shown by nmr.[10] However, when the addition was carried out in ether or methylene chloride solution at 0° for 1–2 min, the initial product was predominantly 1-methyl-d_3-2-methyl-*exo*-norbornyl chloride, with the distribution of the methyl-d_3 tag corresponding to only 52–56% scrambling, instead of the 100% scrambling required by the symmetrical bridged ion (IV). Addition of hydrogen

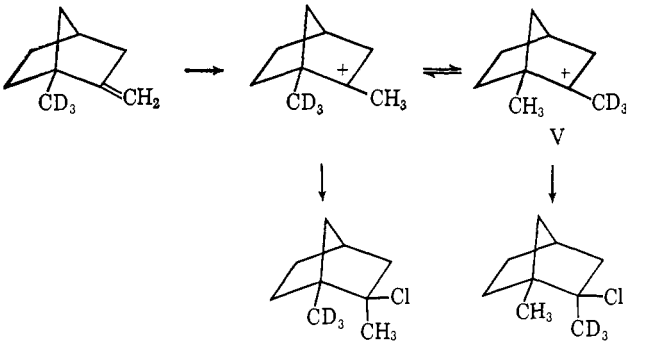


chloride to the neat olefin gave chloride which was even less scrambled, 35%. Exposure of the product to hydrogen chloride results in complete scrambling. These results are summarized in Table I.

Table I. Per Cent Scrambling in the Hydrochlorination of 1-Methyl-d_3-2-methylenenorbornane

Solvent	Temp, °C	Time, min	Scrambling, %
Ether	0	1	53
Ether	0	2	56
Ether	0	20	73
Ether	0	40	82
Ether	0	60	97
Ether	0	120	100
CH_2Cl_2	0	2	52
CH_2Cl_2	−20	2	55
Neat	0	2	42
Neat	0	1	35

Similarly, deuteriochlorination of 1-methyl-2-methylene-d_2-norbornane yielded predominantly 1-methyl-2-methyl-d_3-*exo*-norbornyl chloride. Therefore, the incomplete scrambling is not the results of an isotope effect. The above results make it clear that the bridged nonclassical ion cannot be the major intermediate involved in the hydrochlorination of 1-methyl-d_3-2-methylenenorbornane and related olefins. The results are consistent with the alternative proposal of a rapidly equilibrating pair of classical ions (V),[11] with the addition of chloride ion being somewhat faster than the equilibration.



It might be argued that the hydrochlorination reaction does not involve the formation of carbonium ions. However, we would then be faced with the dilemma of accounting for the almost exclusive formation of tertiary chlorides in these reactions. Moreover, this position would render untenable the argument that reactions of the 7,7-dimethylnorbornyl system must necessarily take an *endo* course in the absence of nonclassical bridging to control the reaction path for the entering nucleophile.

(8) J. A. Berson in "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 130.

(9) A. Colter, E. C. Friedrich, N. J. Holness, and S. Winstein, *J. Am. Chem. Soc.*, **87**, 378 (1965); R. Howe, E. C. Friedrich, and S. Winstein, *ibid.*, **87**, 379 (1965).

(10) All nmr spectra were measured with a Varian A-60 spectrometer using carbon tetrachloride solution containing tetramethylsilane as internal standard. The distinct methyl peaks at δ 1.23 and 1.57 corresponded to the C_1-methyl and the C_2-methyl group, respectively. The ratio of 1-methyl-d_3-2-methyl-*exo*-norbornyl chloride to 1-methyl-2-methyl-d_3-*exo*-norbornyl chloride was calculated from peak height measurement.

(11) For a recent discussion of this problem, see H. C. Brown, *Chem. Brit.*, **2**, 199 (1966).

(12) Research assistant on a grant (G 19878) supported by the National Science Foundation.

Herbert C. Brown, Kwang-Ting Liu[12]
R. B. Wetherill Research Laboratory
Purdue University, Lafayette, Indiana 47907
Received November 5, 1966

Synthesis of 3′-Thioadenosine and Compounds Derived from 3-Thio-D-ribose[1]

Sir:

Chemical changes at C-3 of the D-ribose moiety of nucleosides can result in dramatic changes in biological activity; *e.g.*, the unique biological properties of the antibiotic puromycin have been attributed[2] to the presence of 3-amino-3-deoxy-D-ribose instead of the natural D-ribose moiety; it is noteworthy that change of functionality had to be at C-3, and the sugar of the ribose configuration, for activity. The similar substitution of a 3-thiol group in adenosine to give 3′-thioadenosine might be expected to lead to another biologically interesting nucleoside, but methods for preparing the *cis*-mercaptoalcohol system of 3-thio-D-ribofuranose derivatives have not been available to

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. PH 43-64-500. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center.

(2) B. R. Baker in "The Chemistry and Biology of Purines," Ciba Foundation Symposium, Little, Brown and Co., Boston, Mass., 1957, p 120.