transfers in the solvent system BuOH–benzene–0.05% AcOH (3:2:5). A symmetrical peak with a *K* value of 1.04 was obtained as determined by measurement of the Folin–Lowry color values, and the avian depressor activity was associated with the material of this peak. The contents of 20 tubes, representing the middle portion of this peak, were pooled, concentrated, and lyophilized to yield 0.029 g of the deamino-6-seleno-oxytocin, $[\alpha]^{21}\text{D}$ −54.0° (*c* 1, 1 *N* AcOH).

Anal. Calcd for $C_{43}H_{65}N_{11}O_{12}SSe$: C, 49.7; H, 6.31; N, 14.8. Found: C, 49.6; H, 6.50; N, 14.6.

The deamino-6-seleno-oxytocin was indistinguishable from deamino-oxytocin and from deamino-1-seleno-oxytocin upon thin layer chromatography, paper chromatography (R_f 0.78 (S_1),[15] R_f 0.75 (S_2)), and gel filtration. The ninhydrin-active substances of the acid hydrolysate of a sample of deamino-6-seleno-oxytocin showed the following molar ratios, with glycine taken as 1.0: $Asp_{1.0}Glu_{1.0}Pro_{1.0}Gly_{1.0}Ile_{1.0}Leu_{1.0}Tyr_{1.0}NH_{3\ 3.1}$. In addition, selenocystine and 1-amino-3-seleno-4-thiohexane-1,6-dicarboxylic acid were found.[33]

Bioassay Methods. Avian vasodepressor assays were performed on conscious chickens according to the procedure employed by Munsick, Sawyer, and van Dyke.[34] Oxytocic assays were performed on isolated uteri from rats in natural estrus according to the method of Holton[35] modified by Munsick[36] with the use of magnesium-free van Dyke–Hastings solution as the bathing fluid. Rat pressor assays were carried out on atropinized, urethane-anesthetized male rats as described in the United States Pharmacopeia.[37] Assays for antidiuretic activity were performed on anesthetized, hydrated male rats according to the method of Jeffers, Livezey, and Austin[38] as modified by Sawyer.[39] The milk-ejecting activity in anesthetized, lactating rabbits was determined by the method described by van Dyke, Adamsons, and Engel[40] as modified by Chan.[41] In all of these bioassays the four-point design was used; the biological activities were measured against the USP Posterior Pituitary Reference Standard.

Acknowledgments. R. W. gratefully acknowledges the guidance and interest to Drs. Vincent du Vigneaud (in whose laboratory this work was initiated) and I. L. Schwartz (in whose laboratory this work was continued). We are indebted to Dr. D. Yamashiro for the supply of the C-terminal protected octapeptide of oxytocin; to Dr. Theodore Mahowald, Mrs. Caroline Holzhauser, and Mr. David H. Schlesinger for amino acid analyses; and to Miss Margitta Wahrenburg, Mrs. Maxine Goldberg, and Miss Gloria Bisesi for the bioassays. We also wish to thank Miss Patricia Herling and Mr. Louis Trauth for technical assistance.

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(33) The position of the latter amino acid was found at 147.5 ml of buffer under the same conditions as described in ref 27 and 28.

(34) R. A. Munsick, W. H. Sawyer, and H. B. van Dyke, *Endocrinology*, **66**, 860 (1960).

(35) P. Holton, *Brit. J. Pharmacol.*, **3**, 328 (1948).

(36) R. A. Munsick, *Endocrinology*, **66**, 451 (1960).

(37) "The Pharmacopeia of the United States of America," 17th revised ed, Mack Printing Co., Easton, Pa., 1965, p 749.

(38) W. A. Jeffers, M. M. Livezey, and J. H. Austin, *Proc. Soc. Exptl. Biol. Med.*, **50**, 184 (1942).

(39) W. H. Sawyer, *Endocrinology*, **63**, 694 (1958).

(40) H. B. van Dyke, K. Adamsons, Jr., and S. L. Engel, *Recent Progr. Hormone Res.*, 11, 1 (1955).

(41) W. Y. Chan, *J. Pharmacol. Exptl. Therap.*, 147, 48 (1965).

Communications to the Editor

Hydrochlorination of Bornylene and 1-Methylnorbornene. Absence of a Significant Directive Influence of the 1-Methyl Substituent in a Carbonium Ion Reaction

Sir:

Addition of hydrogen chloride to bornylene, under typical electrophilic conditions, results in the formation of *exo* chlorides, in spite of the steric influence of the 7,7-dimethyl substituents. Hydrochlorination of 1-methylnorbornene also proceeds to the *exo* products. In both cases, protonation of the double bond occurs approximately equally at the C-2 and C-3 positions, thus failing to show the large directive influence of the 1-methyl substituent anticipated for a σ-bridged intermediate.

In the past heavy reliance has been placed on data from solvolytic reactions to support the proposal for the σ-bridged norbornyl cation.[1] However, there is growing evidence that solvolytic reactions, even with the 2-octyl arenesulfonates in highly aqueous dioxane,[2] proceed to ion pairs, rather than to the free carbonium ions usually written as the reaction intermediate.[3] Consequently, the possibility exists that the complete loss of optical activity or the complete scrambling of the tag observed in the solvolysis of norbornyl derivatives may be the result of a relatively long life for the *exo* ion pair, which gives it adequate time to equilibrate completely, rather than the result of the formation of a σ-bridged intermediate, such as has been so long accepted as an explanation for the observed racemization.[4]

It would appear desirable to examine other representative carbonium ion reactions[5] in order to establish whether those characteristics which are now used to support a σ-bridged structure for the norbornyl cation are general, or whether they are essentially restricted to solvolytic reactions.

Polar hydrochlorination of olefins is a typical electrophilic reaction, one which has long been considered to involve carbonium ions as intermediates.[6,7] The successful adaptation of the automatic hydrogenator[8] to hydrochlorinations[9,10] encouraged us to undertake a systematic study of the influence of structure on the products obtained in the hydrochlorination of representative bicyclic olefins. The present study was devoted to examining the question of whether a 1-methyl sub-

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(1) For a recent review see G. D. Sargent, *Quart. Rev.* (London), **20**, 301 (1966).

(2) H. Weiner and R. A. Sneen, *J. Am. Chem. Soc.*, **87**, 292 (1965).

(3) For a review see C. A. Bunton, "Nucleophilic Substitution at a Saturated Carbon Atom," Elsevier Publishing Co., New York, N. Y., 1963, pp 135–148.

(4) S. Winstein and D. Trifan, *J. Am. Chem. Soc.*, 74, 1154 (1952).

(5) E. J. Corey, *et al.*, *ibid.*, **85**, 165, 169 (1963).

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

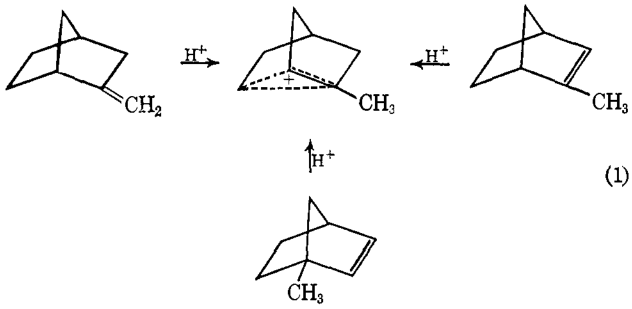
(7) M. J. S. Dewar and R. C. Fahey, *J. Am. Chem. Soc.*, **85**, 2245, 2248, 3645 (1963); *Angew. Chem. Intern. Ed. Engl.*, 3, 245 (1964).

(8) C. A. Brown and H. C. Brown, *J. Org. Chem.*, 31, 3898 (1966).

(9) H. C. Brown and M.-H. Rei, *ibid.*, 31, 1090 (1966).

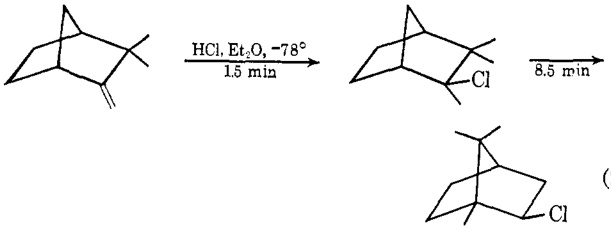
(10) H. C. Brown and K.-T. Liu, *J. Am. Chem. Soc.*, **89**, 466 (1967).

stituent in norbornene would exert the same sort of directive effect as a 2-methyl substituent or the isomeric 2-methylenenorbornane.[10] All three olefins should yield the same nonclassical cation (1).



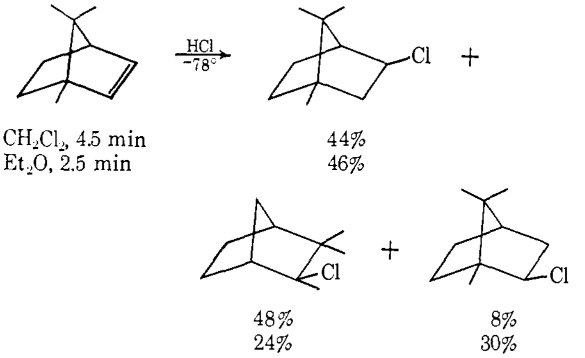
(1)

Both at 0 and at −78° camphene adds hydrogen chloride to give camphene hydrochloride of apparently 100% purity, as indicated by the pmr spectrum.[11] The reaction is very fast, being complete in 1.5 min at −78°. Following addition, a rapid isomerization ensues, so that in 10 min the product is almost entirely isobornyl chloride (2). Both the addition and the isomerization proceed less rapidly in methylene chloride than in ether, and still less rapidly in *n*-pentane solution.



(2)

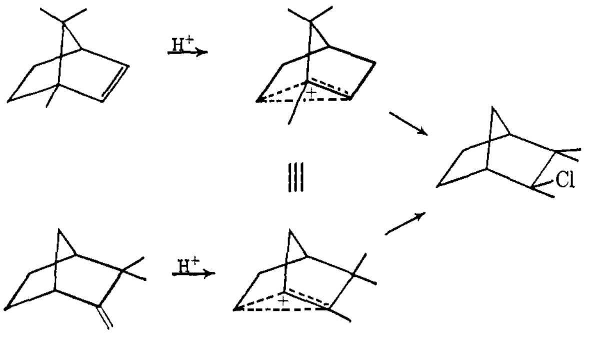
Hydrochlorination of bornylene at −78° yields 45% of epiisobornyl chloride and 55% of a mixture of camphene hydrochloride and isobornyl chloride (3).



(3)

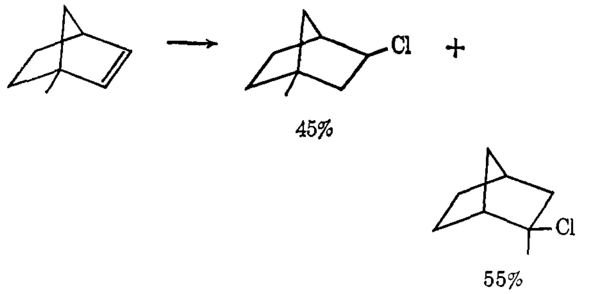
Longer reaction times result in an increase in the isobornyl chloride at the expense of the camphene hydrochloride, but there is no change in the yield of epiisobornyl chloride.[12]

The pmr spectra reveal the absence of *endo* product in any measurable amount (>2%). Such stereospecificity for *exo* product formation in the presence of 7,7-dimethyl substituents has been considered to require a σ-bridged intermediate.[13,14] However, on this basis one would expect a marked preference for protonation to occur at C-3 to give the stabilized σ-bridged cation which should lead to the almost exclusive formation of camphene hydrochloride, just as it is the sole product from camphene (4).



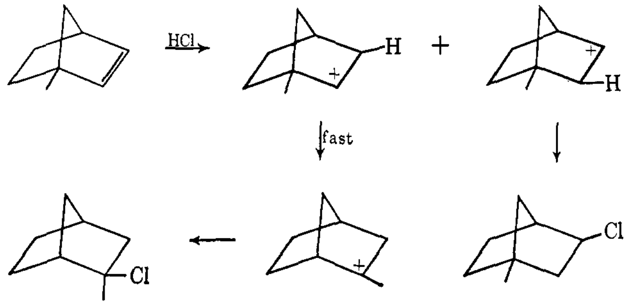
(4)

Under the same conditions hydrochlorination of 1-methylnorbornene also gives a 55:45 distribution between attack at the two positions of the double bond (5).[15]



(5)

These results are readily explicable, as one mechanistic possibility, in terms of protonation to produce the two isomeric classical secondary cations, of approximately equal stability, in the protonation stage (6).



(6)

The slight preference for protonation at the 3 position (55:45) is of a magnitude that can be rationalized in terms of a small inductive influence of the 1-methyl substituent.

However, there appears to be no simple means for rationalizing the results in terms of the formation of σ-bridged intermediates. Methyl groups exert an exceedingly powerful directive effect in protonic additions to the double bond, as indicated by the exclusive formation of one isomer in the hydrochlorination of un-

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(11) All pmr spectra were taken with a Varian A-60A spectrometer using carbon tetrachloride solutions containing tetramethylsilane as standard.

(12) The chlorides were examined by pmr immediately following the hydrochlorination. However, we have observed that the solutions are reasonably stable following removal of dissolved hydrogen chloride. The hydrochlorinations and analyses were easily reproducible to ±2–3%.

(13) J. A. Berson, "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp 130–133.

(14) 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).

(15) Compare P. von R. Schleyer, *ibid.*, **89**, 3901 (1967).

symmetrically substituted olefins, such as 2-methyl-2-butene (Markovnikov rule). In these electrophilic reactions the methyl group is believed to exert its effect by stabilizing the intermediate cation.[6] Consequently, if the σ-bridged cation were an intermediate in the hydrochlorination of norbornene and related olefins, the presence of the 1-methyl substituent would be expected to exert a similar (albeit smaller) stabilizing effect on one of the two isomeric cations produced by addition of the proton to the double bond. This stabilizing influence would be expected to make itself felt in the transition states leading to those isomeric cations, resulting in a major directive effect in the hydrochlorination of bornylene and 1-methylnorbornene. The absence of any significant directive influence observed in this study is therefore incompatible with the formation of a σ-bridged carbonium ion in the hydrochlorination reaction.[16]

[16] See also H. C. Brown and K.-T. Liu, *J. Am. Chem. Soc.*, **89**, 3900 (1967).

[17] Research assistant on Grants G 19878 and GP 6492 X supported by the National Science Foundation.

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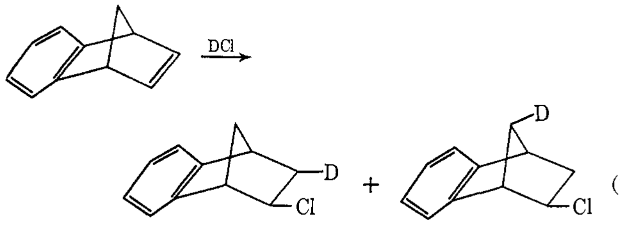
Received April 5, 1967

Deuteriochlorination of Norbornene and Apobornylene. Evidence for the Trapping of the Norbornyl Cation in an Unsymmetrical State

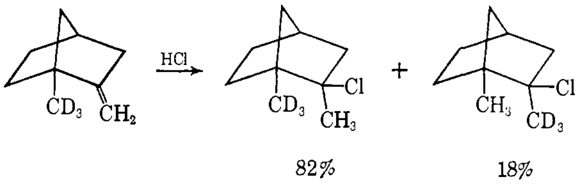
Sir:

The deuteriochlorination of benzonorbornadiene in methylene chloride at −78° has been reported to give a 50:50 mixture of the two deuteriochlorides anticipated either for a bridged cation or a fully equilibrated pair of classical cations[1] (1). We have now observed that under identical conditions norbornene adds deuterium chloride to give *exo*-norbornyl chloride-d_1 with an unequal distribution of deuterium at the *exo*-C-3 and *syn*-C-7 positions. Clearly the reaction cannot involve the symmetrical σ-bridged norbornyl cation as the sole reaction intermediate.



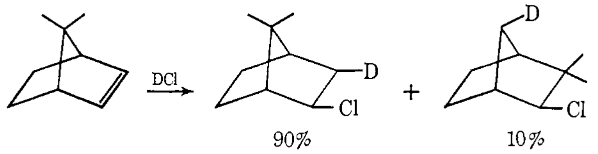
(1)

We previously demonstrated that the addition of hydrogen chloride to 1-methyl-d_3-2-methylenenorbornane proceeded without the scrambling required by a nonclassical intermediate[2] (2). However, there appears to be growing acceptance for the position that tertiary norbornyl cations are classical.[3] Accordingly, we turned our attention to the addition of deuterium chloride to norbornene to see if we could trap the secondary norbornyl cation in its classical unsymmetrical form.[4]



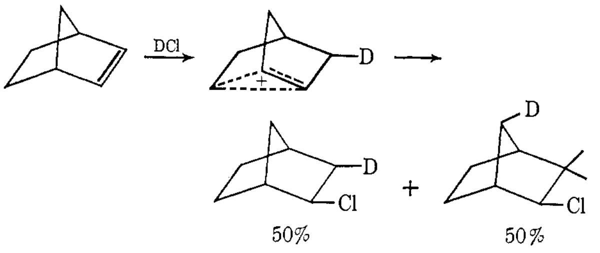
(2)

The addition of deuterium chloride to apobornylene in ethyl ether or in methylene chloride at −78° proceeds to give 90% of apoisobornyl chloride-d_1, with the deuterium in the *exo*-3 position, together with 10% of the Wagner–Meerwein rearranged product, with the position of the deuterium presumably in the *syn*-7 position, but not established experimentally (3).



(3)

The structure of *exo*-3-*d*-apoisobornyl chloride is confirmed by the pattern of the pmr signal[5] of the methine proton α to chlorine. The distinct doublet at δ 3.85 with $J \sim 8$ cps indicates that it arises from *endo*-2-H and *endo*-3-H coupling.[6,7] In apoisobornyl chloride this absorption appears as a quartet, similar to that observed in isobornyl chloride, rather than the multiplet observed in bornyl chloride.[8] The significant point about this experiment is that the pmr spectrum fails to show any measurable formation of *endo* chloride. It has been argued that such additions to norbornene systems should be forced to proceed *endo* by the 7,7-dimethyl substituents in the absence of σ bridging to control the reaction path.[9,10] On this basis, it might have been anticipated that the addition of deuterium chloride to norbornene would proceed to give equal amounts of the two isomers (4) in the same way that benzonorbornadiene yields a 50:50 mixture.[1,11]



(4)

This expectation is not realized. Deuterium chloride adds rapidly (3 min) to norbornene in methylene chloride at −78° to yield 60% of *exo*-3-*d*-*exo*-norbornyl chloride, 34% of *syn*-7-*d*-*exo*-norbornyl chloride, and about 6% of the hydride-shifted product (5). The

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[1] S. J. Cristol and R. Caple, *J. Org. Chem.*, 31, 2741 (1966).

[2] H. C. Brown and K.-T. Liu, *J. Am. Chem. Soc.*, **89**, 466 (1967).

[3] P. von R. Schleyer, *ibid.*, **89**, 701 (1967).

[4] Compare (a) H. Kwart and J. L. Nyce, *ibid.*, **86**, 2601 (1964); (b) J. K. Stille, F. M. Sonnenberg, and T. H. Kinstle, *ibid.*, **88**, 4922 (1966).

[5] Taken with a Varian A-60A spectrometer using carbon tetrachloride solution and tetramethylsilane as standard.

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

[7] P. M. Subraminian, M. T. Emerson, and N. A. LeBel, *J. Org. Chem.*, **30**, 2624 (1965).

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

[9] J. A. Berson, "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp 130–133.

[10] A. Colter, E. C. Friedrich, N. J. Holness, and S. Winstein, *J. Am. Chem. Soc.*, **87**, 371 (1965); R. Howe, E. C. Friedrich, and S. Winstein, *ibid.*, **87**, 379 (1965).

[11] In this discussion we are ignoring any small secondary isotope effect of the deuterium substituent in directing the chloride ion to the two alternative neighboring positions.