NAcOH) (lit.[27] $[\alpha]^{25}D$ −69.2 (*c* 1, *N* AcOH)). Amino acid analysis of an acid-hydrolyzed sample gave the following ratios: Glu, 1.04; His, 1.00; Pro, 0.96; ammonia, 1.01. The biological activity of the synthetic TRH compared favorably to the standard preparation used by Bowers, *et al.*, when tested in the T_3-TRH assay in mice.[28] Doses of 3, 9, and 18 ng of the synthetic TRH raised the ^{125}I level in the blood by 3981, 4144, and 6668 cpm, respectively; identical doses of standard gave values of 3432, 4322, and 5871 cpm. An acid–saline control experiment gave a value of Δ cpm of 145.

The dinitrophenylene group played a dual function in the synthesis of TRH; it served both as a protection for the imidazole nucleus of histidine and as a bridge between the histidine and the solid support. The known reactions of cysteinyl and tyrosyl derivatives with fluoro-2,4-dinitrobenzene to yield thiol-sensitive S-DNP and O-DNP derivatives[5] suggests that the dinitrophenylene-attachment method may be extended to the solid-phase synthesis of cysteinyl- and tyrosyl-containing peptides.

The dinitrophenylene bridging of cysteine, tyrosine, and histidine residues to solid supports promises a useful set of resin-bound amino acids from which peptide chains can be extended bidirectionally. The versatility of such a system, along with the mild conditions required for cleavage of the peptide from the resin, significantly expands the scope of the "side-chain attachment method."[29,30]

Acknowledgment. We are grateful to Dr. C. Y. Bowers and Mrs. G. Reynolds of the Tulane University School of Medicine, New Orleans, La., for bioassay, and to Dr. G. Flouret of Northwestern Medical School for supplying us with a sample of highly purified TRH for chromatographic comparison with synthetic TRH. Thanks are also due to Mrs. I. Mintz for amino acid analyses.

(27) D. Gillessen, F. Piva, H. Steiner, and R. O. Studer, *Helv. Chim. Acta*, **54**, 1335 (1971).
(28) C. Y. Bowers, A. V. Schally, F. Enzmann, J. Bøler, and K. Folkers, *Endocrinology*, **86**, 1143 (1970).
(29) L. Yu. Sklyarov and I. V. Shaskova, *Zh. Obshch. Khim.*, **39**, 2779 (1969).
(30) J. Meienhofer and A. Trzeciak, *Proc. Nat. Acad. Sci. U. S.*, **68**, 1006 (1971).

* Address correspondence to this author at the Department of Physiology, Mount Sinai School of Medicine, New York, N. Y. 10029.

J. D. Glass, I. L. Schwartz, Roderich Walter*
Mount Sinai School of Medicine
City University of New York
New York, New York 10029

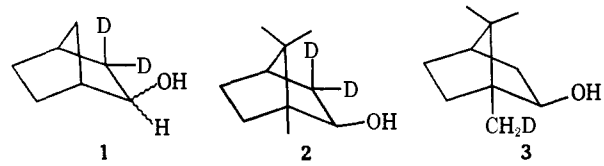
Brookhaven National Laboratory
Upton, New York 11973

Received May 19, 1972

An Unusual Stereospecific Elimination of Water in the Mass Spectra of Bicyclo[2.2.1]heptan-2-ols

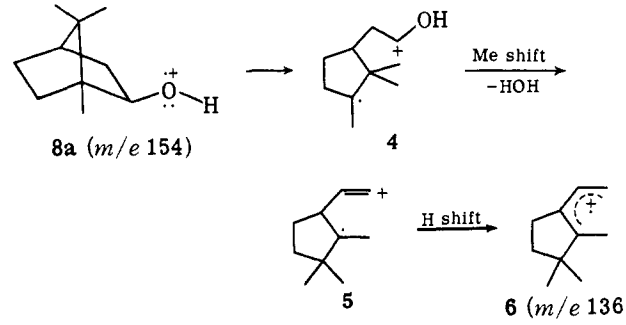
Sir:

The exact means by which water is lost from alcohols when subjected to electron impact has been the subject of several investigations.[1-3] Prior to this work, deuterium labeling studies have established that loss of water does not occur by a 1,2 elimination. For example, Green and coworkers[2] have demonstrated that both a very stereospecific cis-1,4 elimination and a nonstereospecific 1,3 elimination of water occur in cyclohexanol. Another example is that of the isomeric 3,3-dideuterionorbornanols (**1**), exo and endo, which do not lose HOD on electron impact.[3]



1 **2** **3**

In contrast to these findings, 3,3-dideuterioisoborneol (**2**) loses HOD approximately 50% of the time on electron impact.[4] The mass spectrum of deuterated isoborneol **3** showed that the remaining 50% water loss involves the C-10 methyl group.[4] This latter way of losing water is equivalent to the solution chemistry dehydration of isoborneol to camphene. At the time, we explained the 1,2 water elimination (involving carbons 2 and 3 of the bicyclic skeleton) by evoking a postulate of Bieman's[5] that dehydration could occur after fragmentation

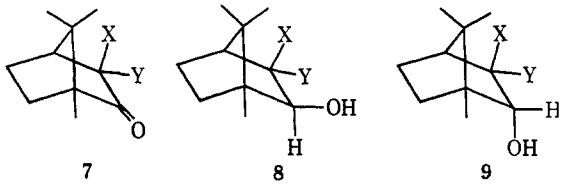


8a (*m/e* 154) **4** **5** **6** (*m/e* 136)

The results reported herein, however, demonstrate that the mechanism **8a** → **6** is not correct and that a uniquely different type of dehydration is occurring.

Camphor was stereospecifically deuterated to give ketones **7b** and **7c**.[6] Under the conditions employed,[7] the ketones were contaminated by some d_0 and d_2 ketones. The structural assignments of **7b** and **7c**, which rely on the nmr spectra of the hydride reduction products, were in agreement with that reported in the literature.[6] Lithium aluminum hydride reduction of the ketones gave a 9:1 mixture of deuterated isoborneol–borneol, which were separated by preparative gas chromatography.

(1) H. Budzkiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, San Francisco, Calif., 1964, Chapter 2.
(2) M. M. Green, R. J. Cook, J. M. Schwab, and R. B. Roy, *J. Amer. Chem. Soc.*, **92**, 3076 (1970), and references therein.
(3) K. Humski and L. Klasinc, *J. Org. Chem.*, **36**, 3057 (1971); (b) H. Kwart and T. A. Blazer, *ibid.*, **35**, 2726 (1970); (c) K. Biemann, "Mass Spectrometry Organic Chemical Applications," McGraw-Hill, New York, N. Y., 1962, pp 108–110.
(4) D. R. Dimmel and J. Wolinsky, *J. Org. Chem.*, **32**, 410 (1967).
(5) Reference 3c, p 95.
(6) (a) A. F. Thomas, R. A. Schneider, and J. Meinwald, *J. Amer. Chem. Soc.*, **89**, 68 (1967); (b) A. F. Thomas and B. Willhalm, *Tetrahedron Lett.*, 1309 (1965).
(7) The conditions that we found were best for the production of the desired monodeuterated camphor were 1 part **7a** (or **7d**): 80 parts D_2O (or H_2O): catalytic amount of base in sufficient dioxane to make the solution homogeneous and stirring at room temperature for 48 hr. Analysis of the deuterium content was accomplished by comparing the molecular ion region of the mass spectra of the ketones.



7 8 9

a, X = Y = H
b, X = D; Y = H
c, X = H; Y = D
d, X = Y = D

Mass spectra were recorded[8] for commercial samples of **8a** and **9a** and vpc collected samples of pure **8d** and **9d** and mixtures of 2% **a**, 74.5% **b**, and 23.5% **d** for **8** and **9** and 15% **a**, 62.5% **c**, and 22.5% **d** for **8** and **9**. Then by analyzing the *m/e* 136–141 region of the mass spectrum of each and using subtraction techniques[9] for the mixtures, it was possible to obtain the mass spectra of **8a–d** and **9a–d** over the *m/e* 136–141 region. The results are presented in Table I. The numbers shown are estimated to be about ±5% accurate. The inlet temperature was varied from 80 to 140° and the source temperature from 90 to 250° with no change in the *m/e* 136–141 region; thus, the loss of water is not due to a thermal dehydration but rather an electron impact.

Table I. Mass Spectral Dehydration Patterns of 3-Deuterated Isoborneols and Borneols[a]

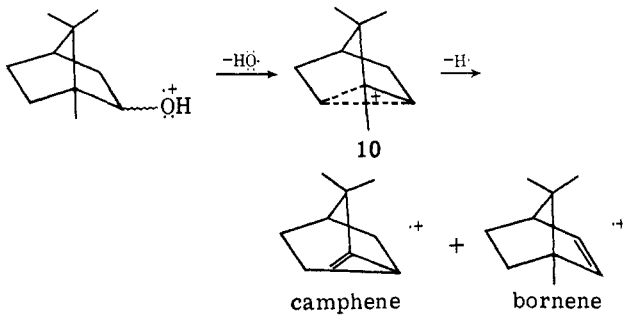
Compd	Loss of HOH, %	Loss of HOD, %
8d	45	55
8b	45	55
8c	85	15
9d	56	44
9b	56	44
9c	92	8

[a] Estimated error by the methods employed is about ±5%.

The data of Table I lead to the following conclusion: in the 1,2 loss of water from *either isoborneol or borneol* the 3-exo hydrogen (or deuterium) is eliminated much more often than the 3-endo hydrogen (or deuterium). These results indicate that the intact bicyclic molecule, and not a fragment, is losing water, since fragmentation such as that proposed in mechanism **8a** → **6**, would be expected to render the exo and endo positions equivalent due to bond rotations.

If indeed the alcohols are not fragmenting prior to water loss, how can we explain the fact that isoborneol and borneol show the same stereospecific loss of an exo-3 hydrogen? The answer cannot be a distance effect as Green argued in the case of cyclohexanol,[2] since one would not expect the 2-endo hydroxyl of borneol to eliminate with the 3-exo hydrogen when there is a closer 3-endo hydrogen. In fact, according to models, the distance between the cis related 2-exo hydroxyl and 3-exo hydrogen (and 2-endo hydroxyl and 3-endo hydrogen) is greater than the 1.7-Å distance which is believed to be the outer limit for concerted mass spectral dehydrations.[2] Consequently, a mechanism by which borneol converts to isoborneol prior to a cis 1,2 water elimination would also seem to be ruled out. (Actually, one would not expect the more thermodynamically stable borneol to convert to the less thermodynamically stable isoborneol.[10]) If concerted 1,2 eliminations across the C-2–C-3 bond of isoborneol and borneol were allowed, should they not also occur with norborneol? The geometries are not that different. Thus, a concerted dehydration cannot account for the similarities of **8** and **9**[11] and the dissimilarities of **8** (or **9**) and **1**.

A mechanism which could possibly explain the data is presented below. The intermediate ion **10**, whether it be nonclassical or equilibrating classical structures, could lose a hydrogen atom from the C-10 methyl to give camphene or an exo-3 hydrogen to give bornene. Based on the argument of microscopic reversibility, one would expect to lose the exo-3 hydrogen in preference to the endo-3 hydrogen.[12] Borneol and isoborneol could both presumably give **10**. The intermediate **10** would be expected to be more stable than the ion derived from **1**, which would lack the stabilization by methyl at C-1. It is possible that the methyl at C-1 may be enough to upset the delicate balance between competing pathways of hydroxy radical elimination *vs.* concerted dehydration (which may lead to tricyclenes) *vs.* initial fragmentation, etc.



The loss of water by a two-step process of first loss of hydroxy radical and then hydrogen atom has some good points and some bad points. As Bieman points out,[3c] the high electron affinity of radicals like SH, CN, NH_2, and OH should hinder their formation in preference to elimination of neutral molecules such as HCN, H_2S, NH_3, and H_2O. Chlorine is also probably in the same class as these others; yet, loss of Cl· occurs in preference to loss of HCl in simple secondary and tertiary alkyl chlorides.[13] (The reverse is true for primary alkyl chlorides.) Consequently, for relatively stable carbonium ions, chlorine atoms can be eliminated upon electron impact. An examination of the data of Friedel, *et al.*,[14] on the mass spectral analysis of a large variety of alcohols shows some striking similarities to

(8) Using a CEC 103C mass spectrometer with an inlet temperature of 105°, source temperature of 245°, ionizing potential of 70 eV, ionizing current of 10 mA and sample pressures of about 1×10^{-6} mm.

(9) R. W. Kiser, "Introduction to Mass Spectrometry and Its Applications," Prentice-Hall, Engelwood Cliffs, N. J., 1965, pp 218–226.

(10) J. A. Berson, "Molecular Rearrangements," Part I, P. DeMayo, Ed., Interscience, New York, N. Y., 1963, p 127.

(11) The greater loss of H_2O *vs.* HOD for borneol is probably an indication that some concerted elimination of the endo C_5 hydrogen is occurring to give a tricyclene ion. Isoborneol is not geometrically set up for this type of elimination. 1-Methyl-2-*endo*-norborneol shows a 25% loss of HOH from the endo-5,6 hydrogens.[3a]

(12) Stepwise additions to the corners of 7,7-dimethylnorbornene and related compounds are known to go in an exo-cis fashion; see H. C. Brown, J. H. Kawakawi, and K. T. Liu, *J. Amer. Chem. Soc.*, **92**, 3816 (1970), and references therein.

(13) F. W. McLafferty, *Anal. Chem.*, **34**, 2 (1962).

(14) R. A. Friedel, J. L. Schultz, and A. G. Sharkey, Jr., *ibid.*, **28**, 926 (1956).

alkyl chlorides. Their data on $C_4H_{10}O$ alcohols are shown in Table II.[15] For the borneols, the peak for

Table II. A Comparison of the Loss of HOH *vs.* OH for Isomeric Butyl Alcohols[a]

Compound	M − HOH intensity	M − OH rel intensity
n-Butyl alcohol	1	0.074
Isobutyl alcohol	1	1.3
sec-Butyl alcohol	1	2.8
tert-Butyl alcohol	1	6.3

[a] Taken from the data of ref 13.

loss of OH is about $^1/_{20}$th as intense as the M − HOH peak.

From the data of Table II, it seems reasonable to conclude that, when a stable carbonium ion results, loss of hydroxy radical can occur. We would expect that ion **10** would fall in the class of a fairly stable carbonium ion and could conceivably be formed in the manner shown. If our conclusions are correct, it leaves open the question as to how many other electron impact dehydrations are also two-step eliminations of water. This hypothesis may also explain why so many bicyclic alcohols which are endo and exo isomers show nearly identical mass spectra.[16] Work is continuing in this area to attempt to verify these ideas.

Acknowledgments. We are grateful to the Research Corporation for their support of this work and Dr. T. C. Ehlert for his assistance.

(15) Comparing two mass spectral peaks for relative abundance may or may not be valid depending on whether these ions are further reacting to approximately the same extent.

(16) D. R. Dimmel and J. Wolinsky, *J. Org. Chem.*, 32, 2735 (1967).

Donald R. Dimmel,* Jean M. Seipenbusch
Department of Chemistry, Marquette University
Milwaukee, Wisconsin 53233
Received March 16, 1972

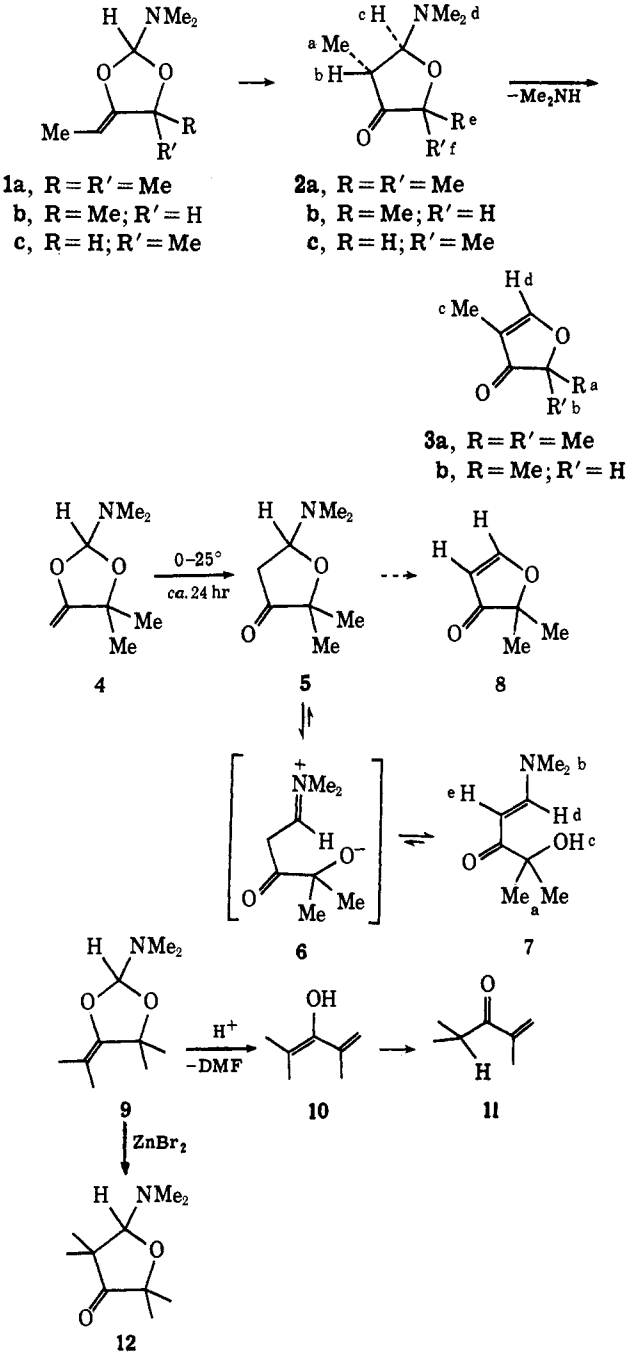
Synthesis of 3(2*H*)-Furanones

Sir:

3(2*H*)-Furanones have been used as building blocks for the synthesis of muscarins[1] and are valued by perfumers owing to their pleasant and varied odors.[2] We here describe a new and efficient route to these heterocycles,[3] which uses 2-dimethylamino-4-methylene-1,3-dioxolanes[4] as the key intermediates.

Experimentally, the reactions are simple and can be monitored conveniently by nmr. For instance, on being heated in a 1 *M* dimethylformamide solution to 60°, **1a** disappears with a half-life of less than 1 hr to form the α-amino ether **2a** (Scheme I) (nmr δ (TMS) a 1.00

Scheme I



(3 H, d, J = 7 Hz), b 2.5 (complex, largely obscured by other signals), c 4.42 (1 H, d, J = 9 Hz), d 2.39 (s, 6 H), e, f 1.11 (s, 3 H), 1.20 ppm (s, 3 H)). As a β-ketoamine which is rendered even more labile by an α-ether grouping, **2a** would be expected to be very reactive and indeed was found to suffer loss of dimethylamine almost before its formation from **1a** was complete, yielding 2,2,4-trimethyl-3(2*H*)-furanone (**3a**): nmr δ (TMS, DMF) a, b 1.28 (s, 6 H), c 1.64 (3 H, d, $J \sim 1$ Hz), d 8.2 (br, 1 H); ir 1710, 1760 cm^{-1}; mass spectrum 126, 71, 69, 58, 57, 55. Alternatively, the transformation of **1a** into **3a** can be brought about simply by leaving a solution of **1a** in CCl_4 for 1 week at room temperature.

Analogously, the epimeric mixture of aminoacetals **1b** + **1c** was heated to 60° and found to rearrange into **2b** (or **2c**) [nmr a 0.99 (3 H, d, J = 7 Hz), b 2.3 (com-

(1) Reviews: S. Wilkinson, *Quart. Rev., Chem. Soc.*, **15**, 153 (1961); C. H. Eugster, *Advan. Org. Chem.*, **2**, 427 (1960).

(2) R. Teranishi in "Gustation and Olfaction," G. Ohloff and A. F. Thomas, Ed., Academic Press, New York, N. Y., 1971, p 165; see also R. E. Rosenkranz, K. Allner, R. Good, W. v. Philipsborn, and C. H. Eugster, *Helv. Chim. Acta*, **46**, 1259 (1963); A. Hofmann, W. v. Philipsborn, and C. H. Eugster, *ibid.*, **48**, 1322 (1965); L. Re and G. Ohloff, U. S. Patent 3,576,014 (1971).

(3) Work described in part at the SCB Symposium in Louvain, Belgium, Sept 1971; see also H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **11**, 324 (1972).

(4) H. M. R. Hoffmann, K. E. Clemens, E. A. Schmidt, and R. H. Smithers, *J. Amer. Chem. Soc.*, **94**, 3201 (1972).