zation constant for the hydroxyl group of the adduct and/or a lower rate of expulsion of the thiazolium zwitterion from the ionized adduct. Since the inductive effect of the HO group and the RS group are the same[42] and since the thiazolium group, which is common to all the adducts, probably has a major effect in determining their acidities, the pK values of hemithioketal and the hydrate may be estimated as about the same. Consequently, the expulsion of the thiazolium zwitterion from the ionized hemithioketal is probably slower than that from the ionized hydrate. In fact, on the basis of these considerations and of the observation of Diago and Reed[13] that the reaction of 2-acetyl-3,4-dimethylthiazolium iodide with 0.1 M butanethiol and 1.1 M H_2O in dimethoxyethane under basic conditions yields 35% thiol ester, the ratio of the rate of cleavage of the ionized hemithioketal to that of the ionized hydrate can be estimated as 0.045. This result is expected because the less basic RS group (pK of RSH, 8–10) should be less able to aid in the cleavage by electron donation than the HO group (pK of H_2O, 15.7).

Ohishi and Fukui[43] have reported that ultraviolet irradiation of a dilute solution of 2-(1-hydroxyethyl)-thiamine and oxidized lipoic acid in 50% aqueous ethanol yields, upon paper chromatography and electrophoresis at pH 5, a compound which appeared to be the hemithioketal of reduced lipoic acid and 2-acetylthiamine. Because of the small equilibrium constants for hemithioketal formation with 2-acetyl-3,4-dimethylthiazolium ion reported here and the rapidity of hemithioacetal formation and breakdown,[44] it seems unlikely that the hemithioketal of reduced lipoic acid and 2-acetylthiamine could be isolated under these conditions.

Enzymatic Reactions. Previous studies of 2-acetylthiazolium salts have emphasized their rapid solvolysis[3,12,13] and thus have created the impression that the direct isolation of 2-acylthiamine pyrophosphate from enzymatic reactions would not be possible. This study has shown that 2-acylthiazolium salts are stable in acid. Thus, the isolation of 2-acylthiamine pyrophosphate from those enzymatic reactions in which it or a carbonyl adduct of it has been implicated as an enzyme-bound intermediate (see introductory section) may be possible by acidifidation of substrate amounts of the enzymes. In addition, the marked ultraviolet absorption of the 2-acetyl-3,4-dimethylthiazolium ion in the 300–310-mμ region (ϵ 6600–3900) suggests that in favorable cases spectrophotometric identification of an enzyme-bound 2-acylthiamine intermediate may be possible. For instance, in the phosphoketolase reaction neither the substrates nor products absorb in this region, and estimates of the absorbance of the protein in the 300–310 mμ range[45] indicate that if an appreciable fraction of the enzyme-bound thiamine pyrophosphate were in the 2-acyl form, its detection would not be obscured by protein absorption.

Acknowledgment. The author thanks W. P. Jencks for a valuable discussion.

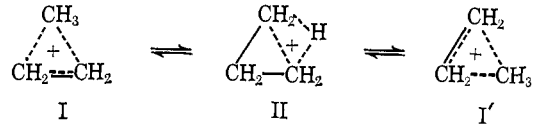
(42) R. W. Taft, Jr., and I. C. Lewis, *J. Am. Chem. Soc.*, 80, 2436 (1958).
(43) N. Ohishi and S. Fukui, *Biochem. Biophys. Res. Commun.*, 20, 21 (1965).
(44) See Lienhard and Jencks, ref 39.
(45) D. B. Wetlaufer, *Advan. Protein Chem.*, 17, 310 (1962).

Communications to the Editor

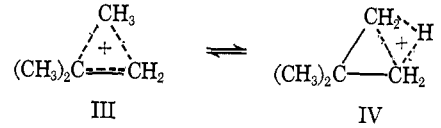
Carbonium Ions. VIII. The Question of Protonated Cyclopropanes in the Nitrous Acid Deamination of Isobutylamine

Sir:

We have shown[1] that in the aqueous nitrous acid deamination of n-propylamine methyl-bridged ions (I) and edge-protonated cyclopropanes (II) are intermediates leading to isotope-position-rearranged n-propyl alcohol. In contrast, the intermediacy of III and IV could not be detected in the corresponding deamination of neopentylamine.[2] Although IV was rigorously excluded, III might have been an intermediate leading solely to the t-amyl cation.



I II I′

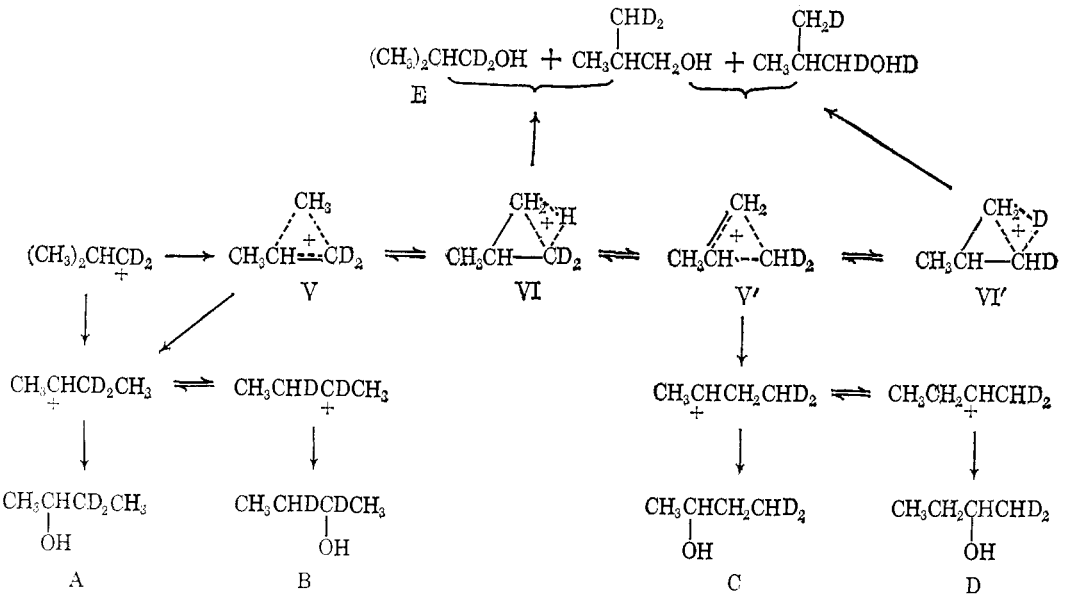


III IV

To assess the factors associated with the relative stability of simple bridged ions and edge-protonated cyclopropanes with respect to their classical ions, we have studied the deamination of suitably labeled isobutylamines. The isobutyl system is structurally intermediate between the n-propyl and the neopentyl. Under deamination conditions n-propylamine gives cyclopropane, isobutylamine gives methylcyclopropane to a lesser extent, and neopentylamine gives no dimethylcyclopropane.[3]

(1) G. J. Karabatsos, C. E. Orzech, Jr., and S. Meyerson, *J. Am. Chem. Soc.*, 87, 4394 (1965). See also C. C. Lee, J. E. Kruger, and E. W. C. Wong, *ibid.*, 87, 3985 (1965); C. C. Lee and J. E. Kruger, *ibid.*, 87, 3986 (1965).
(2) G. J. Karabatsos, C. E. Orzech, Jr., and S. Meyerson, *ibid.*, 86, 1994 (1964).
(3) P. S. Skell and I. Starer, *ibid.*, 82, 2971 (1960); M. S. Silver, *ibid.*, 82, 2971 (1960); J. H. Bayless, F. D. Mendicino, and L. Friedman, *ibid.*, 87, 5790 (1965).

Scheme I



Assessment of the isotope-position distribution in isobutyl and *sec*-butyl alcohols obtained from the deamination of isobutylamine-1,1-d_2 could in principle establish the intermediacy of V (V′) and VI (VI′) and the extent to which they interconvert prior to irreversible formation of methylcyclopropane and alcohols (see Scheme I).

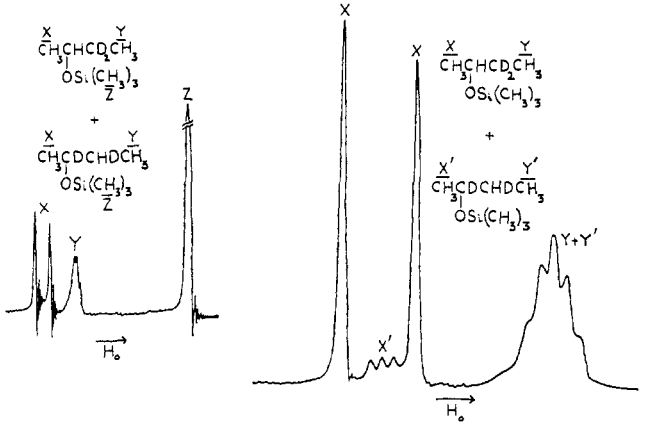


Figure 1.

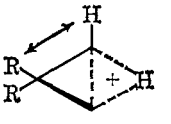
To a solution of 17.5 g (0.1 mole) of isobutylammonium-1,1-d_2 perchlorate (97.8% d_2 and 2.2% d_1) in 40 ml of water and 12.9 g (0.09 mole) of 70% perchloric acid was added dropwise in the course of 80 min a solution of 15.2 g (0.22 mole) of sodium nitrite in 25 ml of water. The temperature was about 30–35°. A 70% yield of alcohol mixture, composed of 71.5% *t*-butyl alcohol, 18.0% *sec*-butyl alcohol, and 10.5% isobutyl alcohol, was obtained.[4] The alcohols were separated by gas chromatography and converted to their trimethylsilyl derivatives.[1]

Mass spectral analysis of the trimethylsilyl ether of the isobutyl alcohol gave 97.8% d_2 and 2.2% d_1 (P − CH_3); 96.8% d_2, 2.9% d_1, and 0.3% d_0 (P − C_3H_7). The corresponding ether of isobutyl-1,1-d_2 alcohol that was prepared by lithium aluminum deuteride reduction of methyl isobutyrate gave 97.9% d_2 and 2.1% d_1 (P − CH_3); 97.0% d_2, 2.8% d_1, and 0.2% d_0 (P − C_3H_7). The isobutyl alcohol is, therefore, isotopically unrearranged (E).

Mass spectral analysis of the trimethylsilyl ether of the *sec*-butyl alcohol gave 97.8% d_2 and 2.2% d_1 (P − CH_3); 7.7% d_1 and 92.3% d_0 (P − C_2H_5). As 21% of the (P − CH_3) ions arise from loss of the 1-methyl of the 2-butyl group,[5] the results rule out D or any species with deuterium on carbon 1. The distribution of (P − C_2H_5) ion is consistent with 7.7% B and 92.3% A + C. Of these, species C is ruled out by nmr.

Figure 1 (left) shows part of the nmr spectrum of the trimethylsilyl ether of the *sec*-butyl alcohol. Under our instrumental conditions the integrated area ratios of X:Y:Z (1.07:1.00:2.94) are identical with those of the corresponding ether of unlabeled *sec*-butyl alcohol (1.09:1.00:2.93). In Figure 1 (right) the methyl region of the 2-butyl group is shown in more detail. In addition to the methyl doublet arising from A, a methyl triplet arising from B is also seen. The ratio of the integrated areas under the two signals is 93:7. This value compares favorably with the more accurate mass spectral ratio of 92.3:7.7.

We are now in a position to state the following: I can be detected by formation of cyclopropane and isotope-position-rearranged *n*-propyl alcohol. III, if present, cannot be detected. V, if present, can be detected only by formation of methylcyclopropane. Apparently III rearranges to the very stable tertiary *t*-amyl cation much faster than it equilibrates with IV or forms 1,1-dimethylcyclopropane. V rearranges to the stable secondary 2-butyl cation much faster than it equilibrates with VI, but not fast enough to prevent formation of methylcyclopropane. I is stable with respect to the *n*-propyl cation, and thus it equilibrates with II. Another factor that might further hinder



VII

(4) The same alcohol composition was obtained by L. G. Cannell and R. W. Taft, Jr., *J. Am. Chem. Soc.*, 78, 5812 (1956).

(5) G. J. Karabatsos, R. A. Mount, D. O. Rickter, and S. Meyerson, *ibid.*, 88, 5651 (1966).

the equilibration of V with VI and III with IV is the 1,2-eclipsing interactions (VII) in VI and IV that are absent in II.

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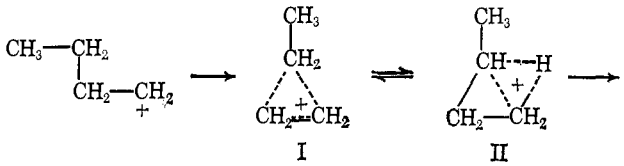
Carbonium Ions. IX. The Deamination of Isotopically Labeled 1-Butylamines

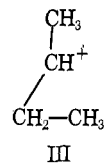
Sir:

We have commented[1] on the effect that alkyl substitution at C-2 of the 1-propyl system has on the relative stability and detectability of alkyl-bridged ions and edge-protonated cyclopropanes. We wish now to discuss the effect of alkyl substitution at C-3.

Formation of methylcyclopropane in the deamination of 1-butylamine[2] has implicated I and/or II and raised the question[2a] of the intermediacy of path II → III.



I II



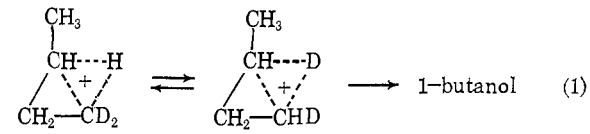
III

Mass spectral analysis of the trimethylsilyl ether of 1-butanol obtained from the deamination[3] of 1-butylamine-1,1-d_2 gave 99.5% d_2 and 0.5% d_1 (P − CH_3); 97.7% d_2 and 2.3% d_1 (P − C_3H_7). That of 1-butanol obtained from lithium aluminum deuteride reduction of the corresponding acid gave 98.5% d_2 and 1.5% d_1 (P − CH_3); 96.7% d_2 and 3.3% d_1 (P − C_3H_7).

From the deamination of 1-butylamine-2,2-d_2 the corresponding values were 96.3% d_2 and 3.7% d_1 (P − CH_3); 0.8% d_2, 7.0% d_1, and 92.2% d_0 (P − C_3H_7). From authentic 1-butanol-2,2-d_2 the values were 97.3% d_2 and 2.7% d_1 (P − CH_3); 0.8% d_2, 7.2% d_1, and 92.0% d_0 (P − C_3H_7).

From the deamination of 1-butylamine-3,3-d_2 the values were 96.3% d_2 and 3.7% d_1 (P − CH_3); 0.2% d_2, 0.4% d_1, and 99.4% d_0 (P − C_3H_7). From authentic 1-butanol-3,3-d_2 the values were 96.5% d_2 and 3.5% d_1 (P − CH_3); 0.3% d_2, 0.5% d_1, and 99.2% d_0 (P − C_3H_7). In all reported cases duplicate experiments gave identical results.

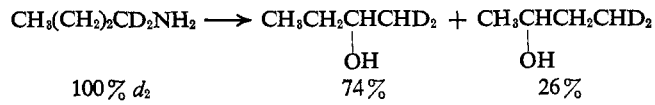
Since the 1-butanol obtained is less than 0.1% isotopically rearranged, both I and sequence 1 are excluded from the paths leading to 1-butanol. Furthermore, 1,4-hydride and 1,2- and 1,3-alkyl shifts are also excluded.



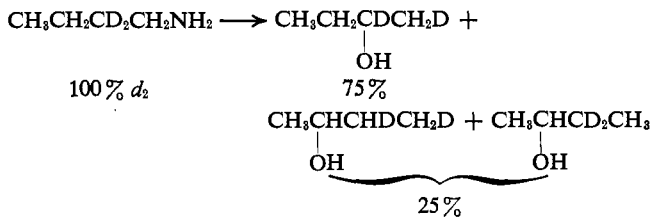
(1)

We now examine sequence II → III, *i.e.*, the question of a nominally 1,3-hydride shift.

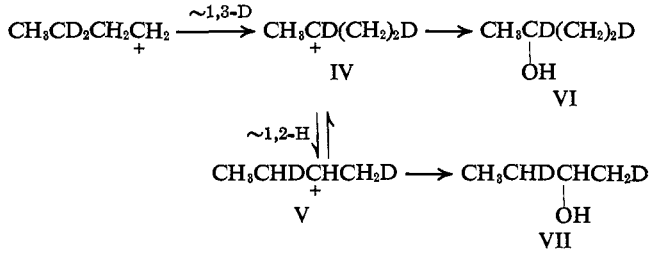
Mass spectral analysis of the trimethylsilyl ether of 2-butanol obtained from the deamination of 1-butylamine-1,1-d_2 (97.0% d_2 and 3.0% d_1) gave 82.3% d_2, 2.8% d_1, and 15.0% d_0 (P − CH_3); 71.8% d_2, 2.7% d_1, and 25.5% d_0 (P − C_2H_5). From the (P − C_2H_5) ion, after removing the contribution of the singly deuterated amine, the following may be written.[4]



From the deamination of 1-butylamine-2,2-d_2 (96.3% d_2 and 3.7% d_2) the values were 81.0% d_2 and 19.0% d_1 (P − CH_3); 72.0% d_2, 3.9% d_1, and 24.1% d_0 (P − C_2H_5). The data are consistent with



From the deamination of 1-butylamine-3,3-d_2 (96.3% d_2 and 3.7% d_1) the values were 96.5% d_2 and 3.5% d_1 (P − CH_3); 19.0% d_1 and 81.0% d_0 (P − C_2H_5). From these results an upper limit may now be calculated for the contribution of 1,3-hydride shifts. From the fact that the d_1 contribution (3.5%) to the (P − CH_3) ion is not larger than the d_1 already present in the starting material (3.7% d_1 amine), VII cannot comprise more than 0.5% of the alcohol. Taken in conjunction with conclusions based on nmr data, this places an upper limit of 2–3% on VI.



In Figure 1 the pertinent region of the nmr spectrum of the trimethylsilyl ether of 2-butanol obtained from the deamination of 1-butylamine-3,3-d_2 is shown.

(1) G. J. Karabatsos, N. Hsi, and S. Meyerson, *J. Am. Chem. Soc.*, 88, 5649 (1966).

(2) (a) P. S. Skell and I. Starer, *ibid.*, 82, 2971 (1960); (b) J. H. Bayless, F. D. Mendicino, and L. Friedman, *ibid.*, 87, 5790 (1965).

(3) For reaction conditions see ref 1. All deuterated amines reported in this paper were prepared from the reduction of the corresponding nitriles with lithium aluminum hydride or deuteride.

(4) The (P − CH_3) ions arise 21% by loss from the 2-butyl group [15.0/(97.0 − 25.5) × 100 = 21.0%] and 79% by loss from the trimethylsilyl group. Details will appear in a full paper.