

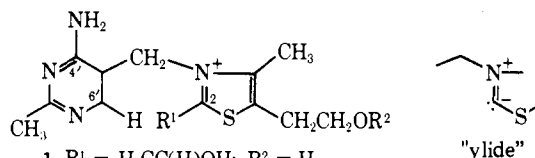
On the Stereochemistry of Intermediates in  
Thiamine Catalysis. I. Crystal Structures of  
2-( $\alpha$ -Hydroxyethyl)-3,4-dimethylthiazolium Bromide  
and DL-2-( $\alpha$ -Hydroxyethyl)thiamine Chloride Hydrochloride<sup>1a</sup>

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**Abstract:** The 2-( $\alpha$ -hydroxyethyl)-3,4-dimethylthiazolium ion is one of several models for 2-( $\alpha$ -hydroxyethyl)-thiamine that were used in elucidating the mechanism of thiamine catalysis. The crystal structures of the title compounds were determined from X-ray diffraction data in order to (1) identify the characteristic steric features of the 2-( $\alpha$ -hydroxyethyl)thiazolium moiety and (2) examine the influence exerted on the thiamine structure when substituents of active intermediates are present at the C(2) position. Both structures were determined from diffractometer data using the  $\theta$ - $2\theta$  scan technique with Cu K $\alpha$  radiation. The structures were refined by the full-matrix least-squares method. The model compound crystallizes in the monoclinic space group,  $P2_1/c$ , with unit cell parameters  $a = 9.771$  (4),  $b = 11.656$  (3),  $c = 8.764$  (2) Å,  $\beta = 90.77$  (4)°, and  $Z = 4$ . The refinement of this structure converged to a conventional  $R$  factor of 0.049 over the 1439 independent observed reflections. The 2-( $\alpha$ -hydroxyethyl)thiamine chloride hydrochloride crystallizes in the triclinic space group,  $P\bar{1}$ , with unit cell parameters  $a = 12.811$  (3),  $b = 10.749$  (3),  $c = 7.108$  (7) Å,  $\alpha = 108.43$  (7),  $\beta = 99.05$  (7),  $\gamma = 96.02$  (7)°, and  $Z = 2$ . The refinement converged to a conventional  $R$  factor of 0.045 based on the 2823 observed reflections. A simple valence bond description of the resonance in the planar thiazolium ring is given which is consistent with the endocyclic bond lengths in both structures. It indicates that there is a partial positive charge of  $\approx 1/2$  on the S atom. The observed intramolecular S...O interaction in both compounds, which is 0.4 Å less than the normal van der Waals separation, provides evidence that the S bonds electrostatically with the unshared electrons on O. The conformation of the 2-( $\alpha$ -hydroxyethyl) side chain appears to be strongly influenced by the S...O interaction. It is remarkably similar in the two compounds. The O(2 $\alpha$ )-C(2 $\alpha$ )-C(2)-S(1) torsion angles agree to within 2.2°. The H(2)-O(2 $\alpha$ )-C(2 $\alpha$ )-C(2) torsion angles both deviate from 90° by less than 12° with the result that they both form a hydrogen bond which is nearly perpendicular to the plane of the thiazolium ring. The analysis of the thiamine derivative shows in addition that its conformation differs considerably from that of thiamine particularly with respect to the relative orientation of the pyrimidine and thiazolium rings. These conformational differences explain the reported shifts in the nmr spectra for these compounds in aqueous solution. On the basis of structural and spectral data, the thiamine and the 2-( $\alpha$ -hydroxyethyl)thiamine molecules may reasonably be expected to assume preferred conformations in aqueous solution closely resembling those in the solid state.

Questions concerning details in the three-dimensional structure of 2-( $\alpha$ -hydroxyethyl)thiamine (**1**) have been raised in several papers dealing with the mechanism of thiamine catalysis.<sup>2-5</sup> In particular, the discussions on possible mechanistic roles for the 4'-amino group have lead directly to speculations about the stereochemistry of **1**. Breslow and McNelis<sup>6</sup> originally suggested that the amino group might assist three steps in the mechanism by internal proton removal. These are, firstly, "ylide" formation from **2** by deprotonating C(2), secondly, generation of a carbanion-like derivative (**3**) from **1** by removing the C(2 $\alpha$ ) hydrogen, and thirdly, releasement of the 2-hydroxyethyl side chain of **1** by abstracting the hydroxyl proton. Kraut and Reed observed that the planes of the thiazo-



- 1, R<sup>1</sup> = H<sub>3</sub>CC(H)OH; R<sup>2</sup> = H  
1a, R<sup>1</sup> = H<sub>3</sub>CC(H)OH; R<sup>2</sup> = P<sub>2</sub>O<sub>7</sub>H<sup>2-</sup>  
1b, Cl·HCl salt of 1  
2, R<sup>1</sup> = H; R<sup>2</sup> = H  
2a, R<sup>1</sup> = H; R<sup>2</sup> = P<sub>2</sub>O<sub>7</sub>H<sup>2-</sup>  
2b, Cl·HCl salt of 2  
3, R<sup>1</sup> = H<sub>3</sub>CC(OH)<sup>-</sup>; R<sup>2</sup> = H

note: N-1' is protonated under mildly acidic conditions and pyrimidine rings in crystalline thiamine chloride hydrochloride (**2b**) are oriented favorably for the amino group to fulfill the first role.<sup>7</sup> The planes are at a dihedral angle of 76°, and the plane defined by atoms C(5'), N(3) and C(methylene bridge) intersects them at 9.4 and 73.5°, respectively. Pletcher and Sax, citing crystallographic data, noted that this is the preferred orientation of the rings in thiamine compounds lacking a substituent on C(2), i.e., to within minor angular variations.<sup>8</sup> The same general

(1) (a) This research was supported in part by NIH Grants NS-09178 and GM-01728. Some parts were presented at the 160th National Meeting of the American Chemical Society, Chicago, Ill., 1970, and at the 162nd National Meeting of the American Chemical Society, Washington, D. C., 1971. (b) In partial fulfillment of requirements for the Ph.D. degree, University of Pittsburgh.

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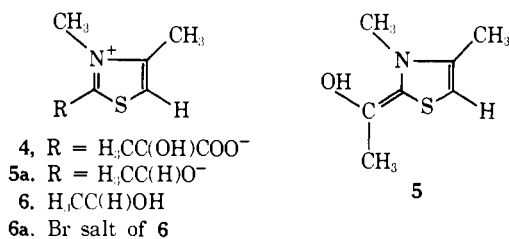
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(7) J. Kraut and H. J. Reed, *Acta Crystallogr.*, **15**, 747 (1962).

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conformation now has been observed without exception in five crystal structures.<sup>8</sup> They speculated that it also may occur in enzymatically bound thiamine pyrophosphate (**2a**) and in intermediates predicted to form in nonenzymatic reactions catalyzed by thiamine. However, they drew attention to the possibility for an internal hydrogen bond to exist between the amino group and the substituent on C(2), which would require for its steric accommodation that at least a slight rotation ( $\approx 10\text{--}15^\circ$ ) of the rings take place about both bonds to the bridging methylene carbon. Such internal hydrogen bonding could be of significance in the second and third roles suggested for the amino group. Schellenberger has proposed that internal hydrogen bonding between the amino and 2-hydroxyl groups will occur when **1a** is bound in the active site of yeast pyruvate decarboxylase.<sup>2</sup> Nevertheless, the orientation of the rings in his model differs substantially from the one seen in crystals of **2b**. He concluded that the C(4) methyl group is almost contiguous with the pyrimidine hydrogen and that the amino group is proximal to the 2-( $\alpha$ -hydroxyethyl) side chain.<sup>2</sup>

The conformations of the 2 side chain in **1**, **1a**, and **3** have been topics of speculation in mechanistic formulations, also. Schellenberger suggested that an internal hydrogen bond between the amino and the 2- $\alpha$ -hydroxyl groups in **3** forces the two residues on C(2 $\alpha$ ) into a plane perpendicular to the thiazonium ring and that this restricts resonance of the lone pair electrons on C(2 $\alpha$ ) with the  $\pi$  electrons of the ring.<sup>2</sup> Moreover, he inferred that the stereospecificity<sup>4,10</sup> and the high basicity of the  $\alpha$  carbon are retained as consequences of the hydrogen bond and of the limitation on resonance. On the other hand, according to Lienhardt, *et al.*, who used model compounds to study the mechanism, the planar neutral enamine (**5**) is most likely the initial product when 2-(1-carboxylato-1-hydroxyethyl)-3,4-dimethylthiazolium zwitterion (**4**) undergoes decarboxyl-



ation to 2-( $\alpha$ -hydroxyethyl)-3,4-dimethylthiazolium ion (**6**).<sup>5</sup> They consider that the hydroxyl group and N(3) are very likely *cis* related in **5** since steric crowding between N(3) and the vinyl methyl group hinders the formation of the *trans* isomer. According to their mechanism, **5** is in tautomeric equilibrium with the dipolar alcoholate ion (**5a**). Protonation converts **5** or **5a** into **6**. The latter has been used frequently as a model for **1** in studying the mechanism of thiamine catalysis.

(9) The conformation occurs in thiamine pyrophosphate hydrochloride (see ref 8), thiamine pyrophosphate tetrahydrate (C. H. Carlisle and D. S. Cook, *Acta Crystallogr., Sect. B*, **25**, 1359 (1969)), thiamine phosphate monophosphate hydrate (I. Karle and K. Britts, *ibid.*, **20**, 118 (1966)), thiamine chloride hydrochloride (ref 7), and thiamine chloride monohydrate (ref 40). In the last compound the pyrimidine ring is not protonated, but in the first four compounds a hydrogen is bonded to N(1').

(10) L. O. Krampitz, G. Greull, C. S. Miller, J. B. Bicking, H. R. Skeggs, and J. M. Sprague, *J. Amer. Chem. Soc.*, **80**, 5893 (1958); L. O. Krampitz, *Annu. Rev. Biochem.*, **38**, 213 (1969).

We have obtained information on several of these points by determining the crystal structures of 2-( $\alpha$ -hydroxyethyl)-3,4-dimethylthiazolium bromide (**6a**) and 2-( $\alpha$ -hydroxyethyl)thiamine chloride hydrochloride (**1b**) from X-ray diffraction data. Thus, the preferred conformation of the 2-( $\alpha$ -hydroxyethyl)thiazolium moiety has been ascertained; a principal force stabilizing it has been identified; the change occurring in the relative orientation of the thiamine rings due to the addition of the 2-hydroxyethyl side chain has been demonstrated; and an adverse conformational aspect of the suggested schemes for internally removing the 2- $\alpha$ -hydroxyl proton or for intramolecularly hydrogen bonding to it has been elucidated.

## Experimental Section

**2-( $\alpha$ -Hydroxyethyl)-3,4-dimethylthiazolium Bromide.** White tabular crystals of the compound<sup>11</sup> were grown from absolute ethanol by slow evaporation at room temperature. The crystals which were elongated in the direction of the *c* axis are bounded by the {100}, {010}, and {001} faces. The space group was determined from oscillation and Weissenberg photographs which indicated systematically absent reflections for *h*0*l* with *l* = 2*n* + 1 and for 0*k*0 with *k* = 2*n* + 1. The unit cell parameters were computed from manual  $2\theta$  scans of all observable axial reflections ( $\sin \theta_{\max} = 0.795$ ) using a Picker four-circle automatic diffractometer and Cu K $\alpha$  radiation ( $\lambda$  1.54178 Å). The crystal data are summarized in Table I. A total of 1690 independent reflections were scanned

Table I. Crystal Data

Compound	2-( $\alpha$ -Hydroxyethyl)-3,4-dimethylthiazolium bromide	2-( $\alpha$ -Hydroxyethyl)-thiamine chloride hydrochloride
Formula	C <sub>7</sub> H <sub>12</sub> ONSBr	C <sub>14</sub> H <sub>21</sub> O <sub>2</sub> N <sub>4</sub> SCl·HCl
Lattice constants $\sim 22^\circ$	<i>a</i> = 9.771 (4) Å <i>b</i> = 11.656 (3) Å <i>c</i> = 8.764 (2) Å $\beta$ = 90.77 (4)°	<i>a</i> = 12.811 (3) Å <i>b</i> = 10.749 (3) Å <i>c</i> = 7.108 (7) Å $\alpha$ = 108.43 (7)° $\beta$ = 99.05 (7)° $\gamma$ = 96.02 (7)°
<i>V</i>	998.1 Å <sup>3</sup>	900.9 Å <sup>3</sup>
Space group	<i>P</i> 2 <sub>1</sub> / <i>c</i>	<i>P</i> 1
<i>Z</i>	4	2
Mol wt	238.153	381.326
$\rho_{\text{calc}}$	1.584 g/cm <sup>3</sup>	1.406 g/cm <sup>3</sup>
$\rho_{\text{obsd}}$	1.580 g/cm <sup>3</sup> (by flotation)	1.384 g/cm <sup>3</sup> (by flotation in <i>n</i> -C <sub>7</sub> H <sub>16</sub> and CCl <sub>4</sub> )
<i>F</i> (000)	480	400
$\mu$ (Cu K $\alpha$ )	76.59 cm <sup>-1</sup>	43.90 cm <sup>-1</sup>

using the  $\theta$ - $2\theta$  mode at a constant rate of 1°/min over a 2.0° range in  $2\theta$ . Stationary 30-sec background counts were taken at both limits of the scan range. Of the independent reflections 251 were classified as unobserved when  $I \leq 3\sigma(I)$  where *I*, the integrated intensity, is given by  $S - 2(B_1 + B_2)$ ; *S* is the total number of counts accumulated during the scan; *B*<sub>1</sub> and *B*<sub>2</sub> are the background counts accumulated at the limits of the scan; and  $\sigma(I) = [S + 4(B_1 + B_2)]^{1/2}$ . During the data collection seven standard reflections were monitored at 12-hr intervals, but in addition staggered groups of two of these reflections were monitored every 2 hr. Over the 1-week period required for the data collection, the intensity of the standards gradually decreased by an overall total of 8%. This decrease was traced to a slow deterioration of the scintillation crystal in the detector rather than the specimen. Consequently, ten normalized scale factors, ranging in value from 1.00 to 1.09, were used to scale the intensity data. Reflections requiring attenuation were remeasured at the end of the data collection with the tube current set at 4 rather than 16 mA. Accordingly these measurements were scaled up by an additional factor of 4.0. The

(11) The compound used in this experiment was kindly given to us by Professor R. Breslow of Columbia University, N. Y.

reflection intensities were also corrected for absorption.<sup>12</sup> The data required for the absorption correction are listed in Table II.<sup>13</sup> The intensities were reduced to their structure amplitudes ( $|F_o|$ ) by applying the Lorentz polarization corrections.<sup>14a</sup>

**2-( $\alpha$ -Hydroxyethyl)thiamine Chloride Hydrochloride.** The compound was synthesized and chromatographically purified for this study by Dr. Anne Bridgewater using the procedure of Miller and Sprague.<sup>16</sup> Crystals were grown at room temperature by adding acetone dropwise to a methanolic solution, but only one could be found that was suitable for collecting X-ray diffraction data. It was a thin white plate. An examination of oscillation and Weissenberg photographs indicated that it had crystallized either in space group  $P1$  or  $P\bar{1}$ . The latter was assumed from the outset as the method of synthesis is known to yield a racemate. The refinement of the crystal structure in space group  $P\bar{1}$  converged satisfactorily. The unit cell parameters were derived from manual  $2\theta$  scans of axial reflections ( $\sin \theta_{\max} = 0.701$ ) that had been measured on a Picker four-circle automatic diffractometer equipped with a scintillation counter detector using Cu K $\alpha$  radiation ( $\lambda$  1.54178 Å). In those cases where the  $\alpha_1$ - $\alpha_2$  doublet was resolved, the values used for  $\lambda$  of  $\alpha_1$  and  $\lambda$  of  $\alpha_2$  are 1.54051 and 1.54433 Å, respectively. The crystal data are summarized in Table I. A total of 3422 independent reflections were scanned using the  $\theta$ - $2\theta$  mode at a constant scan rate of 1°/min over a 2° range in  $2\theta$ . At both limits of this range stationary 30-sec background counts were taken. Of the independent reflections 599 were classified as unobserved when  $I \leq 3\sigma(I)$  with  $I$  and  $\sigma(I)$  defined as above. A total of nine standard reflections, which were chosen from the four octants of the hemisphere, were monitored at approximately 12-hr intervals, although preselected pairs of these were measured every 2 hr. Over the 2.5-week period of data collection, the intensities of the standards gradually decreased by an average of 8%. A slight darkening of the crystal during this period may have been an indication that the loss in intensity was due, in part, to decomposition. Consequently, ten normalized scale factors ranging in value from 1.00 to 1.08 were used to scale the data. The stronger reflections which required attenuation were remeasured immediately after the regular data collection at 4 mA rather than the usual 16 mA. These were scaled by an additional factor of 4.4 that was determined from the standards. The ( $h$  $k$ 0) data were also treated differently in that each independent reflection was measured twice (as equivalent pairs). The conventional agreement index between the equivalent reflections was 0.4%. Each independent reflection in this zone was subsequently replaced by the weighted mean of each equivalent pair where  $\sigma^{-2}(I)$  was taken as the weight. The intensity data were corrected for absorption.<sup>12</sup> The data required for the absorption correction are compiled in Table II.<sup>13</sup> The intensities were reduced to their structure amplitudes ( $|F_o|$ ) by applying the Lorentz polarization corrections.<sup>14a</sup>

### Structure Determination and Refinement

**2-( $\alpha$ -Hydroxyethyl)-3,4-dimethylthiazolium Bromide.** The structure was solved by application of the heavy-atom technique to derive the bromide position and the subsequent use of conventional Fourier methods to locate the remaining nonhydrogen atoms.<sup>14b</sup> The positional and thermal parameters were refined using the full-matrix least-squares program of Busing, Martin, and Levy.<sup>16</sup> The atomic scattering factors used in this analysis are those given by Dawson,<sup>17</sup> Berghuis, *et al.*,<sup>18</sup> McWeeny,<sup>19</sup> and Freeman and Watson.<sup>20</sup> The anom-

alous dispersion corrections for S and Br were taken from Cromer.<sup>21</sup> The variance,  $\sigma^2(F_o)$ , assigned to  $|F_o|$  in the later stages of the refinement, is given by the expression

$$\sigma^2(F_o) = (\sigma_{\text{exp}} + B|F_o|)^2$$

where  $\sigma_{\text{exp}}$  = standard deviation in  $|F_o|$  based upon counting statistics and  $B$  (= 0.05) is an arbitrary constant. This scheme resulted in a reasonably constant value of  $\langle w||F_o| - |F_o||^2 \rangle$  as a function of  $|F_o|$ , where  $w$ , the weight of the reflection, is taken as  $\sigma^{-2}(F_o)$ . Isotropic refinement was continued until an  $R^2$  of 0.106 was reached. Then, the 12 hydrogen atoms in the molecule were located using difference Fourier techniques. The structure was subsequently refined using anisotropic thermal parameters. However, the anisotropic values assigned to the hydrogen atoms were not refined but were arbitrarily made to correspond to those for the heavier atoms to which they are bonded. Positional parameters for the hydrogens, on the other hand, were varied in the final cycles of the least-squares refinement. After correcting the data for absorption, the refinement converged to an  $R$  of 0.056 for all of the reflections or to an  $R$  of 0.049 if the unobserved intensities are excluded. The final structure factors are listed in Table IIIa.<sup>18</sup> The atomic positional and anisotropic thermal parameters, along with their estimated standard deviations, are listed in Table IV. The esd's were obtained from the diagonal elements of the inverse matrix in the final least-squares cycle. The bond distances and angles and their esd's are given in Table V. These were computed using the Oak Ridge Function and Error Program by Busing and Levy.<sup>23</sup> Bond distances involving hydrogen atoms are also listed. The average of the C-H bond lengths in the C(6), C(7), and C(2 $\alpha$ ) methyl groups are 1.03, 0.98, and 0.99 Å, respectively. The individual C-H bonds, which have an estimated standard deviation of 0.06 Å, range from 0.92 to 1.09 Å. In the three methyl groups, the average of the H-C-H and C-C-H tetrahedral bond angles, which do not appear in the table, is  $109 \pm 4^\circ$ . The individual values range from 123 to  $87^\circ$ .

A rigid body analysis of the molecule was undertaken in order to estimate the decrease in bond lengths due to thermal motion.<sup>24</sup> The results indicated an average shortening of 0.006 Å. Since the thermally corrected distances differ only by approximately one esd from the uncorrected values, the latter are used throughout the subsequent discussions.

**2-( $\alpha$ -Hydroxyethyl)thiamine Chloride Hydrochloride.** The structure amplitudes for this compound were converted to  $E$  values (normalized structure factors). The values of the average of  $E$  and  $E^2 - 1$ , 0.783 and 0.987, respectively, are consistent with those predicted by Karle, *et al.*,<sup>25</sup> for a centrosymmetric crystal. Since the asymmetric unit contains three heavy scatterers, two

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Table IV. Fractional Coordinates and Anisotropic Temperature Factors for 2-( $\alpha$ -Hydroxyethyl)-3,4-dimethylthiazolium Bromide<sup>a</sup>

Atom	x	y	z	$\beta_{11}$	$\beta_{22}$	$\beta_{33}$	$\beta_{12}$	$\beta_{13}$	$\beta_{23}$
Br <sup>-</sup> (1)	8221.0 (4)	-4772.7 (4)	-2856.6 (5)	86 (1)	96 (1)	171 (1)	1 (0.3)	-8 (1)	-10 (0.4)
S(1)	4783 (1)	-4908 (1)	-2711 (1)	84 (1)	73 (1)	117 (1)	-10 (1)	1 (1)	3 (1)
O(2 $\alpha$ )	2718 (4)	-3637 (3)	-4303 (4)	150 (4)	78 (2)	148 (5)	-22 (3)	-39 (4)	31 (3)
N(3)	2814 (3)	-5945 (2)	-1525 (3)	79 (3)	57 (2)	94 (4)	-4 (2)	-2 (3)	-7 (2)
C(2)	3081 (4)	-5071 (3)	-2438 (4)	91 (4)	50 (2)	91 (4)	-8 (2)	2 (3)	-13 (3)
C(4)	3976 (4)	-6512 (3)	-970 (4)	101 (4)	59 (3)	96 (4)	6 (3)	-7 (3)	-9 (3)
C(5)	5133 (4)	-6043 (3)	-1530 (4)	89 (4)	73 (3)	116 (5)	5 (3)	-8 (4)	-9 (3)
C(6)	1420 (4)	-6334 (4)	-1138 (5)	87 (4)	82 (3)	150 (6)	-13 (3)	20 (4)	13 (4)
C(7)	3858 (5)	-7488 (4)	108 (5)	148 (6)	75 (3)	136 (6)	10 (4)	-8 (5)	19 (4)
C(2 $\alpha$ )	2067 (4)	-4226 (3)	-3091 (4)	95 (4)	66 (3)	130 (5)	-3 (3)	-20 (4)	5 (3)
C(2 $\beta$ )	1687 (6)	-3366 (4)	-1860 (7)	139 (6)	71 (4)	227 (9)	30 (4)	-13 (6)	-21 (4)
H(1)	127 (6)	-457 (5)	-342 (7)	83	56	135	-3	-21	7
H(2)	253 (7)	-383 (6)	-500 (7)	149	73	147	-14	-30	37
H(3)	96 (6)	-282 (5)	-229 (7)	136	70	190	26	-9	-21
H(4)	131 (7)	-378 (5)	-95 (8)	136	70	190	26	-9	-21
H(5)	243 (7)	-308 (5)	-127 (7)	136	70	190	26	-9	-21
H(6)	608 (6)	-635 (5)	-150 (6)	89	68	112	7	-4	-9
H(7)	461 (7)	-759 (5)	86 (7)	155	66	140	8	-6	23
H(8)	331 (7)	-725 (5)	94 (7)	155	66	140	8	-6	23
H(9)	338 (7)	-814 (5)	-40 (6)	155	66	140	8	-6	23
H(10)	131 (5)	-724 (5)	-140 (6)	76	79	165	-17	15	15
H(11)	71 (6)	-591 (5)	-160 (7)	76	79	165	-17	15	15
H(12)	130 (5)	-607 (5)	-0 (7)	76	79	165	-17	15	15

<sup>a</sup> All values in the table are multiplied by  $10^4$  except the fractional coordinates for the hydrogen atoms which are multiplied by  $10^3$ . The thermal coefficients are in the form  $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$ . The unrefined temperature factors assigned to the hydrogen atoms are included in the table. The estimated standard deviations in parentheses refer to the least significant figure.

Table V. Bond Distances and Angles in 2-( $\alpha$ -Hydroxyethyl)-3,4-dimethylthiazolium Bromide<sup>a</sup>

Distance, Å		Angle, deg	
Thiazolium Ring			
S(1)-C(2)	1.694 (4)	C(5)-S(1)-C(2)	90.9 (2)
C(2)-N(3)	1.324 (4)	S(1)-C(2)-N(3)	111.9 (3)
N(3)-C(4)	1.395 (5)	C(2)-N(3)-C(4)	114.2 (3)
C(4)-C(5)	1.354 (5)	N(3)-C(4)-C(5)	111.2 (3)
C(5)-S(1)	1.712 (4)	C(4)-C(5)-S(1)	111.8 (3)
C(4)-C(7)	1.485 (5)	N(3)-C(4)-C(7)	121.0 (4)
N(3)-C(6)	1.479 (5)	C(5)-C(4)-C(7)	127.8 (4)
		C(2)-N(3)-C(6)	124.3 (3)
		C(4)-N(3)-C(6)	121.4 (3)
2- $\alpha$ -Hydroxyethyl Group			
C(2)-C(2 $\alpha$ )	1.504 (5)	S(1)-C(2)-C(2 $\alpha$ )	121.0 (4)
C(2 $\alpha$ )-C(2 $\beta$ )	1.522 (6)	N(3)-C(2)-C(2 $\alpha$ )	126.8 (3)
C(2 $\alpha$ )-O(2 $\alpha$ )	1.422 (5)	C(2)-C(2 $\alpha$ )-C(2 $\beta$ )	109.1 (3)
		C(2)-C(2 $\alpha$ )-O(2 $\alpha$ )	107.6 (3)
		C(2 $\beta$ )-C(2 $\alpha$ )-O(2 $\alpha$ )	109.1 (4)
		C(2 $\alpha$ )-O(2 $\alpha$ )-H(2)	113 (7)
Hydrogen-Bonding and Short Contact Distances			
O(2 $\alpha$ ) $\cdots$ Br <sup>-</sup> (1)	3.227 (3)	Br <sup>-</sup> (1) $\cdots$ S(1)-C(2)	172.9 (1)
S(1) $\cdots$ Br <sup>-</sup> (1)	3.367 (1)	Br <sup>-</sup> (1) $\cdots$ S(1)-C(5)	82.4 (1)
O(2 $\alpha$ ) $\cdots$ S(1)	2.852 (4)	Br <sup>-</sup> (1) $\cdots$ S(1) $\cdots$ O(2 $\alpha$ )	131.1 (1)
H(2) $\cdots$ Br <sup>-</sup> (1)	2.59 (3)	C(2)-S(1) $\cdots$ O(2 $\alpha$ )	55.8 (1)
		O(2 $\alpha$ ) $\cdots$ S(1)-C(5)	146.2 (2)
		C(2 $\alpha$ )-O(2 $\alpha$ ) $\cdots$ S(1)	72.8 (2)
		Br <sup>-</sup> (1) $\cdots$ H(2)-O(2 $\alpha$ )	159 (7)
		H(2)-O(2 $\alpha$ ) $\cdots$ S(1)	117 (7)
Bond Distances Involving Hydrogen			
C(5)-H(6)	0.99 (5)	C(7)-H(7)	0.99 (7)
C(2 $\alpha$ )-H(1)	0.92 (6)	C(6)-H(8)	0.96 (7)
O(2 $\alpha$ )-H(2)	0.68 (6)	C(7)-H(9)	0.99 (6)
C(2 $\beta$ )-H(3)	1.02 (6)	C(6)-H(10)	1.09 (6)
C(2 $\beta$ )-H(4)	1.01 (7)	C(6)-H(11)	0.94 (6)
C(2 $\beta$ )-H(5)	0.94 (7)	C(6)-H(12)	1.05 (6)

<sup>a</sup> Estimated standard deviations refer to the least significant figures.

chloride ions and a sulfur atom, the conventional Patterson and Fourier methods were selected for deriv-

ing the atomic coordinates. The analysis proceeded straightforwardly until a difference map was computed at an  $R$  index<sup>22</sup> of 0.088 in order to locate the 22 hydrogen atoms in the molecule. An extensive examination of the map revealed that the largest peak ( $\approx 3.2$  electrons), including those already assigned to the 22 hydrogens, could not be accounted for by errors in the data, abnormal thermal motion, or a solvent atom. The peak was located in the immediate vicinity of the 5-( $\beta$ -hydroxyethyl) side chain, about 1.7 Å away from the terminal hydroxyl oxygen, O(10), and 1.3 Å away from C(9), the adjacent methylene carbon (see Figure 3 for the atomic numbering scheme used in the paper for this compound). It was proposed, after several attempts at refining other trial models derived from the map, that this peak represented an alternate disorder position for the terminal hydroxyl oxygen. The disorder site, O(10D), could easily be accommodated by a 97° torsional rotation of O(10) about the C(8)-C(9) single bond. This feature of the crystal structure can be seen in Figures 3, 4, and 5. The occupancy factors which gave the best agreement index are 0.7 for O(10) and 0.3 for O(10D). However, an estimate of the number of electrons in each of the disorder peaks in the difference map gave  $\approx 5$  electrons for O(10) and  $\approx 3$  for O(10D). It was necessary to refine the thermal motion for O(10D) isotropically, while O(10) could be refined anisotropically. Further refinement of the structure resulted in an  $R$  factor of 0.055 for the observed reflections when the model for disorder was included and the hydrogen positional parameters were allowed to vary. At this point, the Hughes<sup>26</sup> weighting scheme was replaced. The variance of  $F_o$  in the weighting scheme finally adopted is given by the expression,  $\sigma^2(F_o) = \sigma_{\text{exp}}^2 + (BF_o)^2$ , where  $\sigma_{\text{exp}}$  is the standard deviation in  $F_o$  based upon counting statistics. A value of the constant,  $B$  ( $= 0.03$ ), was selected such that  $w\Delta^2$  was reasonably constant as a function of  $|F|$ ,

(26) E. W. Hughes, *J. Amer. Chem. Soc.*, **69**, 542 (1947).

**Table VI.** Fractional Coordinates and Anisotropic Temperature Factors of the Nonhydrogen Atoms for 2-( $\alpha$ -Hydroxyethyl)thiamine Chloride Hydrochloride<sup>a</sup>

Atom	x	y	z	$\beta_{11}$	$\beta_{22}$	$\beta_{33}$	$\beta_{12}$	$\beta_{13}$	$\beta_{23}$
Cl <sup>-</sup> (1)	709 (1)	7999 (1)	8085 (1)	97 (1)	163 (1)	204 (2)	65 (1)	-10 (1)	20 (1)
Cl <sup>-</sup> (2)	4224 (1)	855 (1)	2218 (1)	103 (1)	184 (1)	242 (2)	-2 (1)	-19 (1)	93 (1)
S(1)	3825 (1)	5439 (1)	3986 (1)	81 (1)	105 (1)	327 (2)	29 (1)	16 (1)	78 (1)
O(2 $\alpha$ )	5683 (2)	7100 (2)	3681 (4)	65 (1)	162 (3)	417 (7)	33 (2)	16 (3)	59 (4)
O(10)	2083 (4)	5786 (4)	8098 (6)	226 (5)	265 (7)	292 (10)	133 (5)	21 (6)	24 (7)
N(3)	2786 (2)	7013 (2)	2886 (3)	59 (1)	96 (2)	182 (5)	19 (1)	8 (2)	37 (3)
N(11)	2851 (2)	10368 (2)	7891 (3)	81 (2)	113 (2)	156 (4)	15 (2)	-4 (2)	36 (3)
N(13)	1498 (2)	11048 (2)	6046 (3)	77 (2)	105 (2)	205 (5)	28 (2)	21 (2)	36 (3)
N(18)	1004 (2)	10084 (2)	2628 (3)	82 (2)	129 (3)	196 (5)	55 (2)	3 (3)	34 (3)
C(2)	3776 (2)	6739 (2)	3156 (4)	64 (2)	91 (2)	206 (6)	24 (2)	11 (3)	29 (3)
C(4)	2023 (2)	6151 (3)	3264 (4)	65 (2)	117 (3)	175 (6)	10 (2)	12 (3)	13 (3)
C(5)	2465 (2)	5231 (3)	3914 (4)	84 (2)	106 (3)	212 (6)	2 (2)	15 (3)	40 (3)
C(2 $\alpha$ )	4749 (2)	7428 (3)	2704 (4)	61 (2)	116 (3)	301 (8)	20 (2)	28 (3)	50 (4)
C(2 $\beta$ )	4721 (3)	6976 (4)	450 (3)	96 (2)	163 (4)	330 (9)	13 (3)	61 (4)	66 (5)
C(6)	2530 (2)	8223 (3)	2468 (4)	74 (2)	121 (3)	176 (6)	42 (2)	20 (3)	49 (3)
C(7)	863 (2)	7620 (4)	2892 (5)	66 (2)	203 (5)	264 (8)	14 (2)	12 (3)	43 (5)
C(8)	1953 (3)	4185 (3)	4624 (5)	138 (3)	118 (3)	301 (9)	-22 (3)	30 (4)	50 (5)
C(9)	2035 (4)	4556 (3)	6819 (6)	201 (5)	131 (4)	448 (13)	46 (4)	165 (7)	92 (6)
C(12)	2105 (2)	11138 (2)	7766 (4)	81 (2)	100 (3)	180 (6)	15 (2)	22 (3)	33 (3)
C(14)	1619 (2)	10124 (2)	4319 (3)	60 (1)	93 (2)	172 (5)	21 (2)	17 (2)	38 (3)
C(15)	2386 (2)	9248 (2)	4383 (3)	58 (1)	96 (2)	177 (5)	18 (2)	9 (2)	41 (3)
C(16)	2987 (2)	9422 (3)	6212 (4)	70 (2)	108 (3)	199 (6)	28 (2)	3 (3)	51 (3)
C(17)	1964 (3)	12104 (4)	9688 (5)	135 (3)	148 (4)	199 (7)	52 (3)	28 (4)	25 (5)
O(10D) <sup>b</sup>	2953 (7)	4744 (9)	7953 (14)						

<sup>a</sup> All the values in this table have been multiplied by  $10^4$ . The temperature factor expression used in the refinement is  $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$ . <sup>b</sup> This atom was refined isotropically to a  $B$  value of 5.8 (2).

where  $w$  is equal to  $\sigma^{-2}(F_o)$  and is the weight assigned to each reflection in the least-squares refinement, and where  $\Delta^2 = ||F_o| - |F_c||^2$ . The refinement finally converged at an  $R$  index of 0.045 for the observed reflections and 0.058 for all reflections. The quantity minimized was  $\sum w(|F_o| - k|F_c|)^2$ , where  $k$  is a single scale factor. The atomic scattering factors used in this analysis are those of Dawson,<sup>17</sup> Berghuis, *et al.*,<sup>18</sup> and McWeeny.<sup>19</sup> The anomalous dispersion corrections for S and Cl were taken from Cromer.<sup>21</sup> The observed and calculated structure factor data are compiled in Table IIIb.<sup>13</sup> Atomic fractional coordinates for all nonhydrogen atoms and their anisotropic thermal parameters are listed in Table VI. Hydrogen atom positions are given in Table VII. The estimated standard deviations, which accompany each parameter value in these tables, are derived from the diagonal elements of the inverse matrix in the final cycle of least-squares refinement. As expected, atoms comprising the disordered portion of the 5-( $\beta$ -hydroxyethyl) group, *i.e.*, C(9), O(10), O(10D), H(13), H(14), and H(15), have the greatest positional uncertainty and the largest thermal parameters. Although no thermal parameters for hydrogen atoms are tabulated, they were assigned the  $\beta_{ij}$ 's of the heavier atoms to which they are bonded, but these were not varied in the refinement.

The tabulated interatomic distances and angles and their esd's were calculated using Stewart's<sup>27</sup> X-RAY 67 program system. Bond distances and valency angles that do not involve hydrogen atoms are divided into convenient groups that correspond to characteristic structural parts of the molecule, and they are listed in Table VIII. Bond distances and angles involving hydrogen atoms are grouped in Table IX. Hydrogen bonding distances and angles are listed in Table X. Several of the bond distances and angles in these tables

(27) J. M. Stewart, Technical Report 67-58, X-RAY 67 Program System for X-Ray Crystallography, University of Maryland, 1967.

**Table VII.** Fractional Coordinates of the Hydrogen Atoms for 2-( $\alpha$ -Hydroxyethyl)thiamine Chloride Hydrochloride<sup>a</sup>

Atom	x	y	z
H(1)	476 (2)	848 (3)	332 (4)
H(2)	577 (2)	763 (3)	495 (5)
H(3)	474 (2)	596 (3)	0 (5)
H(4)	538 (2)	754 (3)	29 (5)
H(5)	415 (2)	727 (3)	-14 (5)
H(6)	186 (2)	795 (3)	153 (4)
H(7)	307 (2)	855 (2)	200 (4)
H(8)	38 (2)	532 (3)	281 (5)
H(9)	69 (2)	636 (3)	169 (5)
H(10)	76 (2)	702 (3)	380 (5)
H(11)	193 (3)	334 (3)	393 (5)
H(12)	114 (3)	387 (3)	372 (5)
H(13)	121 (3)	487 (3)	628 (6)
H(14)	144 (3)	380 (3)	717 (6)
H(15)	120 (4)	548 (5)	761 (7)
H(16)	352 (2)	897 (3)	645 (4)
H(17)	323 (2)	1049 (2)	895 (4)
H(18)	137 (3)	1228 (3)	961 (4)
H(19)	224 (3)	1195 (3)	1078 (4)
H(20)	224 (3)	1285 (3)	966 (5)
H(21)	97 (2)	951 (3)	153 (4)
H(22)	58 (2)	1053 (3)	273 (4)

<sup>a</sup> All values in table multiplied by  $10^3$ . Estimated standard deviation in parentheses refer to least significant digit.

have been labeled to distinguish them as being influenced exceedingly by the disorder and thermal motion in the 5-( $\beta$ -hydroxyethyl) side chain. For instance, C(8)-C(9), C(9)-O(10), and C(9)-O(10D) represent distances that are clearly shorter in comparison to expected bond length values, by amounts ranging anywhere from 0.07 to 0.13 Å. Likewise, bond angles such as C(8)-C(9)-O(10) and C(8)-C(9)-O(10D) appear to be abnormally widened from the expected tetrahedral values by these effects. Anomalies such as these frequently occur in molecular parameters involving disordered atoms. The other bond distances and valency angles are in excellent agreement with those deter-

Table VIII. Bond Distances (Å) and Angles (deg) for 2-( $\alpha$ -Hydroxyethyl)thiamine Chloride Hydrochloride

Thiazolium ring		Thiazolium ring substituents	
S(1)-C(2)	1.683 (3)	C(2)-C(2 $\alpha$ )	1.512 (4)
C(2)-N(3)	1.331 (3)	C(2 $\alpha$ )-C(2 $\beta$ )	1.513 (5)
N(3)-C(4)	1.392 (3)	C(2 $\alpha$ )-O(2 $\alpha$ )	1.422 (4)
C(4)-C(5)	1.354 (4)	N(3)-C(6)	1.480 (4)
C(5)-S(1)	1.724 (3)	C(4)-C(7)	1.495 (4)
Pyrimidine ring		C(5)-C(8)	1.503 (5)
C(12)-N(13)	1.311 (3)	C(8)-C(9) <sup>a</sup>	1.466 (6)
N(13)-C(14)	1.356 (3)	C(9)-O(10) <sup>a</sup>	1.335 (5)
C(14)-C(15)	1.437 (3)	C(9)-O(10D) <sup>a</sup>	1.27 (1)
C(15)-C(16)	1.349 (3)	Pyrimidine ring substituents	
C(16)-N(11)	1.350 (3)	C(15)-C(6)	1.507 (3)
N(11)-C(12)	1.340 (4)	C(12)-C(17)	1.481 (4)
Thiazolium ring (internal)		C(14)-N(18)	1.315 (3)
S(1)-C(2)-N(3)	111.3 (2)	Thiazolium ring (external)	
C(2)-N(3)-C(4)	114.4 (2)	S(1)-C(2)-C(2 $\alpha$ )	122.3 (2)
N(3)-C(4)-C(5)	112.2 (2)	N(3)-C(2)-C(2 $\alpha$ )	126.3 (3)
C(5)-S(1)-C(2)	92.0 (1)	C(2)-N(3)-C(6)	123.2 (2)
S(1)-C(5)-C(4)	110.3 (2)	C(4)-N(3)-C(6)	122.1 (2)
Pyrimidine ring (internal)		N(3)-C(4)-C(7)	120.7 (3)
C(12)-N(13)-C(14)	118.2 (2)	C(5)-C(4)-C(7)	127.1 (3)
N(13)-C(14)-C(15)	120.4 (2)	C(4)-C(5)-C(8)	129.6 (3)
C(14)-C(15)-C(16)	116.8 (2)	S(1)-C(5)-C(8)	120.1 (2)
C(15)-C(16)-N(11)	120.8 (2)	Thiazolium ring substituents	
C(16)-N(11)-C(12)	120.3 (2)	C(2)-C(2 $\alpha$ )-O(2 $\alpha$ )	108.6 (3)
N(11)-C(12)-N(13)	122.8 (2)	C(2)-C(2 $\alpha$ )-C(2 $\beta$ )	110.9 (2)
Pyrimidine ring (external)		C(2 $\beta$ )-C(2 $\alpha$ )-O(2 $\alpha$ )	108.8 (2)
C(14)-C(15)-C(6)	120.8 (2)	N(3)-C(6)-C(15)	109.8 (2)
C(16)-C(15)-C(6)	122.4 (2)	C(5)-C(8)-C(9)	115.6 (3)
N(11)-C(12)-C(17)	117.1 (3)	C(8)-C(9)-O(10) <sup>a</sup>	125.5 (4)
N(13)-C(12)-C(17)	120.0 (3)	C(8)-C(9)-O(10D) <sup>a</sup>	119.1 (6)
N(13)-C(14)-N(18)	116.6 (2)		
C(15)-C(14)-N(18)	123.0 (2)		

<sup>a</sup> Values influenced by the effects of disorder and thermal motion.

Table IX. Bond Distances (Å) and Angles (deg) Involving Hydrogen Atoms for 2-( $\alpha$ -Hydroxyethyl)thiamine Chloride Hydrochloride

C(2 $\alpha$ )-H(1)	1.08 (3)	S(1)···O(2 $\alpha$ )-H(2)	93 (2)
O(2 $\alpha$ )-H(2)	0.88 (3)	C(2)-C(2 $\alpha$ )-H(1)	108 (2)
C(2 $\beta$ )-H(3)	1.04 (3)	O(2 $\alpha$ )-C(2 $\alpha$ )-H(1)	109 (1)
C(2 $\beta$ )-H(4)	1.03 (3)	C(2 $\beta$ )-C(2 $\alpha$ )-H(1)	111 (2)
C(2 $\beta$ )-H(5)	0.92 (3)	C(2 $\alpha$ )-O(2 $\alpha$ )-H(2)	103 (2)
C(6)-H(6)	0.95 (2)	C(9)-O(10)-H(15) <sup>a</sup>	80 (3)
C(6)-H(7)	0.91 (3)	C(15)-C(16)-H(16)	125 (2)
C(7)-H(8)	1.11 (3)	N(11)-C(16)-H(16)	113 (2)
C(7)-H(9)	0.89 (4)	C(16)-N(11)-H(17)	120 (2)
C(7)-H(10)	0.90 (3)	C(12)-N(11)-H(17)	119 (2)
C(8)-H(11) <sup>a</sup>	0.88 (3)	C(14)-N(18)-H(21)	123 (2)
C(8)-H(12) <sup>a</sup>	1.08 (3)	C(14)-N(18)-H(22)	116 (2)
C(9)-H(13) <sup>a</sup>	1.18 (4)	H(21)-N(18)-H(22)	119 (3)
C(9)-H(14) <sup>a</sup>	1.16 (4)		
O(10)-H(15) <sup>a</sup>	1.10 (5)		
C(16)-H(16)	0.91 (3)		
N(11)-H(17)	0.80 (3)		
C(17)-H(18)	0.80 (4)		
C(17)-H(19)	0.88 (4)		
C(17)-H(20)	0.85 (4)		
N(18)-H(21)	0.82 (2)		
N(18)-H(22)	0.75 (3)		
Average Values for Combined C-C-H and H-C-H Angles			
		Av	Range
C(2 $\beta$ )	Methyl	109 (2)	103-120
C(6)	Methylene	109 (2)	106-114
C(7)	Methyl	109 (2)	106-109
C(17)	Methyl	109 (3)	93-117
C(8) <sup>a</sup>	Methylene	107 (2)	76-119
C(9) <sup>a</sup>	Methylene	91 (2)	75-110

<sup>a</sup> Values influenced by disorder and thermal motion.

mined for thiamine pyrophosphate HCl,<sup>8</sup> thiamine Cl-HCl·H<sub>2</sub>O,<sup>7</sup> and those parts in common with **6a**.

Table X. Hydrogen Bonds and Short Contact Distances for 2-( $\alpha$ -Hydroxyethyl)thiamine Chloride Hydrochloride<sup>a</sup>

a	b	c	$\angle abc$ , deg	$d(a-c)$ , Å	$d(b-c)$ , Å
O(10)-H(15) <sup>b</sup> ···Cl <sup>-</sup> (1)			97 (3)	3.106 (5)	2.77 (6)
N(18)-H(21)···Cl <sup>-</sup> (1 <sup>i</sup> )			172 (3)	3.233 (2)	2.42 (2)
N(18)-H(22)···Cl <sup>-</sup> (1 <sup>iii</sup> )			160 (3)	3.252 (3)	2.53 (3)
N(11)-H(17)···Cl <sup>-</sup> (2 <sup>iii</sup> )			175 (3)	3.148 (2)	2.35 (3)
O(2 $\alpha$ )-H(2)···Cl <sup>-</sup> (2 <sup>iv</sup> )			169 (3)	3.020 (2)	2.14 (3)
O(2 $\alpha$ )···S(1)				2.901 (2)	
O(10D)···O(2 $\alpha$ <sup>iv</sup> )				2.87 (1)	

<sup>a</sup> Symmetry code: none,  $x, y, z$ ; i,  $x, y, z - 1$ ; ii,  $-x, 2 - y, 1 - z$ ; iii,  $x, 1 + y, 1 + z$ ; iv,  $1 - x, 1 - y, 1 - z$ . <sup>b</sup> Values influenced by disorder and thermal motion.

### Description of the Crystal and Molecular Structures

**2-( $\alpha$ -Hydroxyethyl)-3,4-dimethylthiazolium Bromide.** The arrangement of the molecules in the crystal (as drawn by the ORTEP program<sup>28</sup>) is depicted in Figures 1 and 2. The nearest neighbor environment of the bromide ion is a feature of the packing scheme worthy of some comment. The ion lies nearly on a line with the C(2)-S bond (Figure 2) at a distance from sulfur which is 0.43 Å less than the sum of the van der Waals radii<sup>29a</sup> (Table V). On the other hand, it is 4.04 Å from the formally positive quaternary N(3), and this distance is 0.6 Å longer than the expected van der Waals separation. In addition, it is linked to the hydroxyl group by a hydrogen bond for which the stereochemical details are given in Table V. Various views of the hydrogen bonding are shown in the figures.

(28) C. K. Johnson, ORTEP, Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.

(29) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960: (a) p 260; (b) p 143.

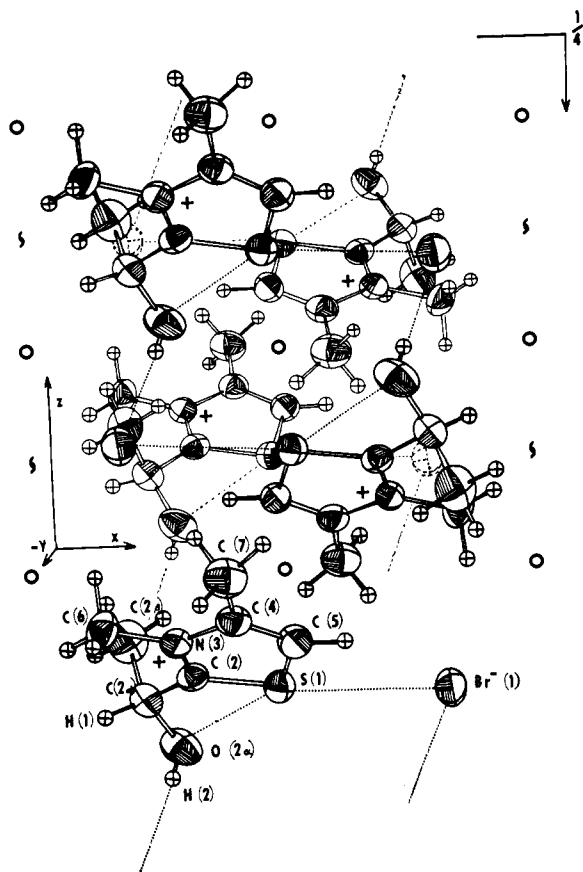


Figure 1. The (010) projection showing several molecules of 2-( $\alpha$ -hydroxyethyl)-3,4-dimethylthiazolium bromide as drawn by ORTEP program. Hydrogen bonding and close contact distances to S(1) are depicted by dotted lines. The atoms are represented by their thermal ellipsoids drawn at 50% probability level except for hydrogens which are drawn as spheres of arbitrary radius.

Another short contact occurs between the sulfur and oxygen atoms within the same molecule. The distance between them is 2.852 Å, whereas the sum of their van der Waals radii is 3.25 Å.<sup>29a</sup> The interactions Br<sup>-</sup>(1)···S(1)···O(2 $\alpha$ )-H(2)···Br<sup>-</sup>(1) are delineated explicitly in Figures 1 and 2 by dotted lines which encircle a center of symmetry.

**2-( $\alpha$ -Hydroxyethyl)thiamine Chloride Hydrochloride.** Stereoscopic views of the compound (as drawn by the ORTEP program<sup>28</sup>) are shown in Figures 3 and 4 where it is apparent that the compound contains a 2-( $\alpha$ -hydroxyethyl)thiamine divalent cation (1c) which is protonated at N(11). Each ring in 1c contains a single positive charge. Also shown in Figure 3 are four strong hydrogen bonds linking 1c to neighboring chloride ions. The data in Table X indicate that these are the strongest in the structure. A substantially weaker hydrogen bond connects O(10) with Cl<sup>-</sup>(1). It is depicted in the molecular packing diagram (orthographic projection<sup>30</sup>) (Figure 5). The O(10)-H(15)···Cl<sup>-</sup>(1) angle is far from ideal for this type of bond even though the O(10)···Cl<sup>-</sup>(1) distance is favorable (Table X). When O(10) occupies its alternate site, O(10D), it comes within hydrogen bonding distance of O(2 $\alpha$ ) in the molecule related by an inversion center at

(30) G. L. Gartland, an IBM 1130 program for orthographic projection of coordinates, Crystallography Department, University of Pittsburgh, 1970.

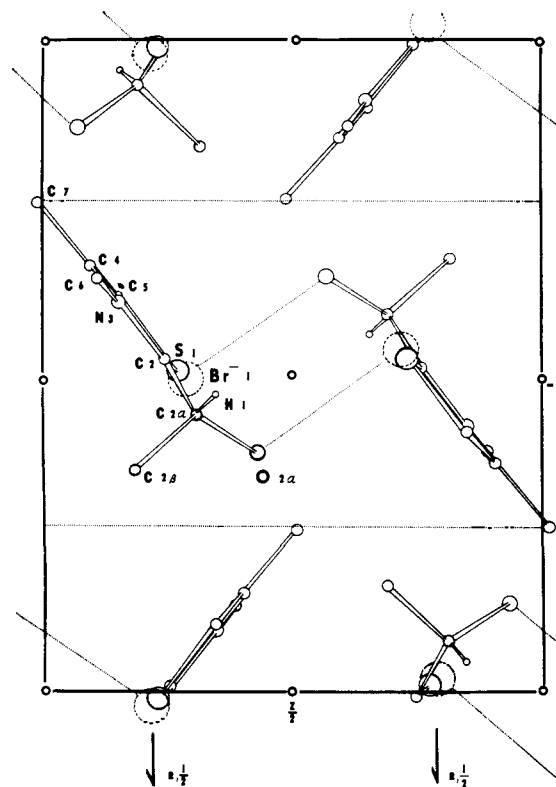


Figure 2. The (100) projection of unit cell contents for 2-( $\alpha$ -hydroxyethyl)-3,4-dimethylthiazolium bromide. Hydrogen bonding between O(2 $\alpha$ ) and Br<sup>-</sup>(1) is depicted by dotted lines.

( $1/2, 1/2, 1/2$ ) (Table X and Figure 5). However, an O(10D)···O(2 $\alpha$ ) hydrogen bond was not demonstrated conclusively in the present experiment, since a position for a disordered hydrogen atom was not apparent in the difference Fourier synthesis. Despite the lack of direct evidence for this particular hydrogen bond, it actually may exist in the crystal in view of the sterically favorable position of O(10D).

Three interactions of the type C-H···Cl<sup>-</sup>, resembling very weak hydrogen bonds, have been detected in the crystal structure. Two of these are easily recognized in Figure 5. They are C(16)-H(16)···Cl<sup>-</sup>(2') and C(6)-H(6)···Cl<sup>-</sup>(1). The third one is C(6)-H(7)···Cl<sup>-</sup>(2). The first is evident also in Figure 3. The respective carbon to chloride distances are 3.64, 3.51, and 3.45 Å, and the corresponding H to Cl<sup>-</sup> distances are 2.85, 2.68, and 2.69 Å. The latter are, respectively, 5, 10, and 10 $\sigma$  under the normal van der Waals separation. Each C-H···Cl angle is within 1° of 147°, a favorable value for a hydrogen bond. This type of interaction has been reported for the same proton on the pyrimidine ring in the crystal structure of thiamine Cl-HCl·H<sub>2</sub>O,<sup>7</sup> where the C···Cl<sup>-</sup> and H···Cl<sup>-</sup> distances are 3.53 and 2.5 Å, respectively, and where the angle at H is 154°. However, the more intriguing result lies with the other two unexpected interactions, which take place at the C(6) methylene bridge. Nevertheless, they are not so unusual, when one considers that the C(6) methylene is bonded to two highly electron-withdrawing, aromatic ring systems.

## Discussion

The structures of both molecules show that the most

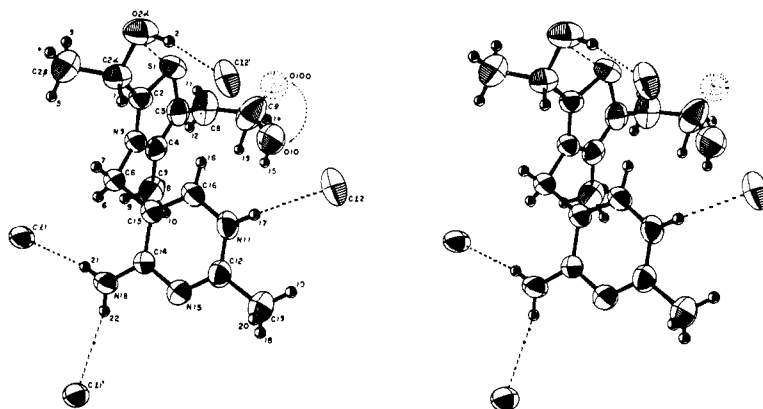


Figure 3. Stereoscopic view of 2-( $\alpha$ -hydroxyethyl)thiamine chloride hydrochloride along the (010) direction as drawn by the ORTEP program. Thermal ellipsoids are drawn at 50% probability level. Hydrogen atoms are represented by spheres of arbitrary radius. Hydrogen bonding is indicated by dashed lines and the disordered oxygen position is indicated by the dotted sphere.

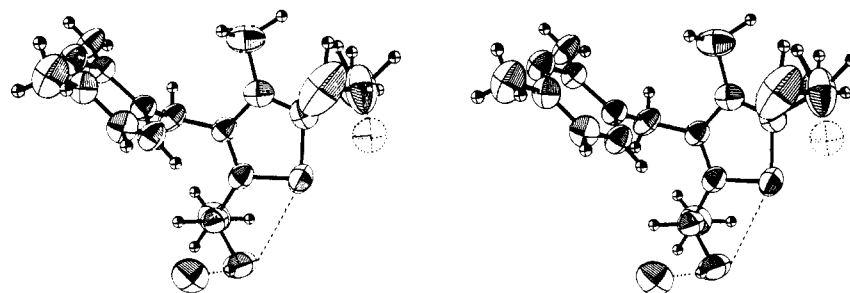


Figure 4. Stereoscopic view of 2-( $\alpha$ -hydroxyethyl)thiamine chloride hydrochloride along the (001) direction as drawn by the ORTEP program. Thermal ellipsoids are drawn at 50% probability level. Long dashed line indicates the intramolecular S $\cdots$ O interaction. Dotted sphere shows disordered oxygen position.

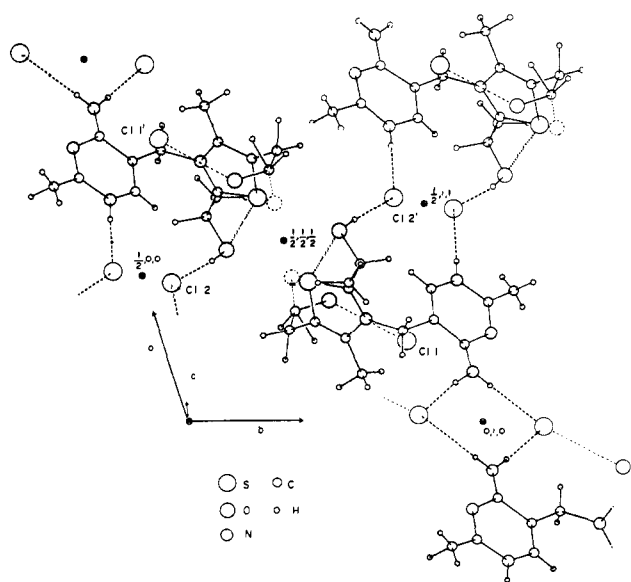
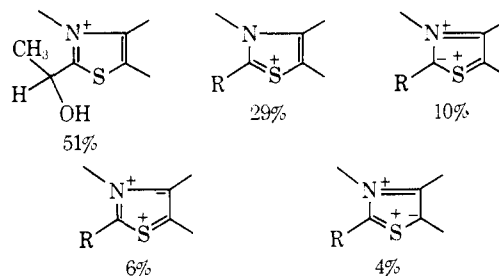


Figure 5. Orthographic projection of the crystal structure of 2-( $\alpha$ -hydroxyethyl)thiamine chloride hydrochloride as viewed along the H(4)-C(2 $\alpha$ ) direction. Hydrogen bonding is represented by dashed lines.

noticeable effect upon the dimensions of the thiazolium ring caused by replacing the hydrogen atom on C(2) with the  $\alpha$ -hydroxyethyl group is to lengthen the C(2)-S bond by about 0.02 Å and to decrease the S-C(2)-N(3) angle by approximately 1°. The bond lengths and valency angles in the thiazolium ring of both compounds are in excellent agreement, and the following resonance description not only explains the observed

bond lengths satisfactorily<sup>31</sup> and predicts a planar ring (Table XI), but it also indicates that the close contact of the sulfur atom with the bromide ion in the model compound and with the O(2 $\alpha$ ) oxygen in both compounds is chemically reasonable. This resonance scheme places partial charges of approximately +0.5 and +0.75 on S and N, respectively. In crystal struc-



tures of compounds containing a thiazolium ring, S often manifests its partial positive charge by making close contacts with negative ions or with O in water molecules or in hydroxyl groups. Moreover, the involvement of sulfur's normally nonbonding 3p electrons in the resonance reduces their exchange repulsions with contiguous atoms located in equatorial positions.<sup>29b</sup> Therefore, in these contacts the effective radius of the S atom is less than its standard van der Waals radius.<sup>32</sup> That S(1) $\cdots$ O(2 $\alpha$ ) and S(1) $\cdots$ Br<sup>-</sup>(1)

(31) The partial contributions of the five canonical structures were calculated by applying an equation (7-3) of Pauling (see ref 29, p 235) relating bond distance and bond number.

(32) Close contacts to thiazolium S occur in the following crystals: *N*-benzyl-4-methylthiazolium bromide (ref 33), thiamine phosphate monophosphate hydrate (see ref 9), and in both compounds in this paper.



Table XI. Least-Squares Planes<sup>a</sup>

Plane	A	B	C	D	$\sigma^d$	Displacements
Thiazolium <sup>b</sup>	36	620	783	5236	9	S(1) 3, C(2) -7, N(3) 8, C(4) -5, C(5) 0.3, C(2 $\alpha$ ) -133, O(2 $\alpha$ ) 251, C(2 $\beta$ ) -1585, C(6) 72, C(7) -35, H(6) 170
Thiazolium <sup>c</sup>	-63	318	785	-3773	10	S(1) 4, C(2) -10, N(3) 13, C(4) -9, C(5) 3, C(2 $\alpha$ ) -106, O(2 $\alpha$ ) 252, C(2 $\beta$ ) -1516, C(6) 215, C(7) -82, C(8) 83, C(15) 1646
Pyrimidine <sup>c</sup>	646	672	-471	-7200	11	N(11) 9, C(12) -10, N(13) -1, C(14) 10, C(15) -10, C(16) 1, C(6) 10, H(16) 43, H(17) 60, C(17) -72, N(18) 39, Cl(1) -191, Cl(1') 245, Cl(2) 48, H(21) -29, H(22) -16
4'-Amino <sup>c</sup>	648	670	-475	-7163	30	C(15) -6, C(14) 10, N(13) -8, N(18) 42, H(21) -21, H(22) -17, Cl(1) -170, Cl(1') 241

<sup>a</sup> Coefficients  $\times 10^3$  in  $Ax + By + Cz - D = 0$  are referred to crystallographic axes in  $\text{\AA}$ . Displacements of the atoms from the plane are in  $\text{\AA} \times 10^3$ . Atoms used to define the plane are designated by boldface type. <sup>b</sup> 2-( $\alpha$ -Hydroxyethyl)-3,4-dimethylthiazolium bromide. <sup>c</sup> 2-( $\alpha$ -Hydroxyethyl)thiamine chloride hydrochloride. <sup>d</sup> Standard deviation in least-squares planes in  $\text{\AA} \times 10^3$ .

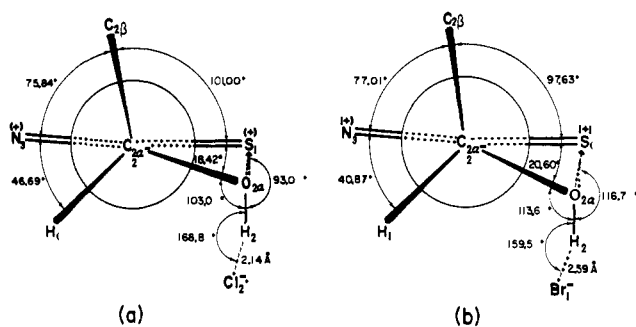


Figure 6. Newman projections of the 2-( $\alpha$ -hydroxyethyl) side chain along the C(2 $\alpha$ )-C(2) bond for: (a) 2-( $\alpha$ -hydroxyethyl)thiamine chloride hydrochloride, and (b) 2-( $\alpha$ -hydroxyethyl)-3,4-dimethylthiazolium bromide.

are equatorial is evident from the small displacements of O(2 $\alpha$ ) and Br<sup>-</sup>(1) from the plane of the ring (Table XI). Significantly, equatorial approaches to S are sterically unhindered. On the other hand, negative ions do not come into close contact with the positively charged N in crystal structures of compounds containing a thiazolium ring because of steric hindrance. Thus, close equatorial contacts are sterically inhibited by the substituent on the N atom, *e.g.*, the C(6) methyl group in **6a** (Figure 1), while the closeness of approach from axial directions is limited by repulsions with the  $\pi$  electrons of the ring. The half-thickness of the latter is about 1.7  $\text{\AA}$ , which exceeds the van der Waals radius of N by 0.2  $\text{\AA}$ .<sup>29a</sup>

The electrostatic attraction of the partial positive charge on S(1) for unshared electrons on O(2 $\alpha$ ) seems to have a great influence on the conformation of the 2-( $\alpha$ -hydroxyethyl) side chain. Torsion angle O(2 $\alpha$ )-C(2 $\alpha$ )-C(2)-S(1)<sup>34</sup> has assumed a value, 20.6°, that allows close contact to occur between S(1) and O(2 $\alpha$ ). H(2)-O(2 $\alpha$ )-C(2 $\alpha$ )-C(2) has a magnitude of 101°. One may infer from the dimensions of these angles that the nonbonding 2p orbital on O(2 $\alpha$ ) is pointed nearly in the direction of S(1). Actually it makes an angle of 27° with the O(2 $\alpha$ ) $\cdots$ S(1) axis. In this conformation the unshared electrons in the orbital are close to the S atom. By influencing the two torsion angles that determine the relative orientation of the O(2 $\alpha$ )-H(2) bond, the S $\cdots$ O interaction exerts some control over the directions that the O(2 $\alpha$ )-H(2) $\cdots$ Br<sup>-</sup> hydrogen

(33) L. Power, J. Pletcher, and M. Sax, *Acta Crystallogr., Sect. B*, **26**, 143 (1970).

(34) The projected angle between bonds C(2 $\alpha$ )-O(2 $\alpha$ ) and C(2)-S(1) when viewed along the C(2 $\alpha$ )-C(2) bond.

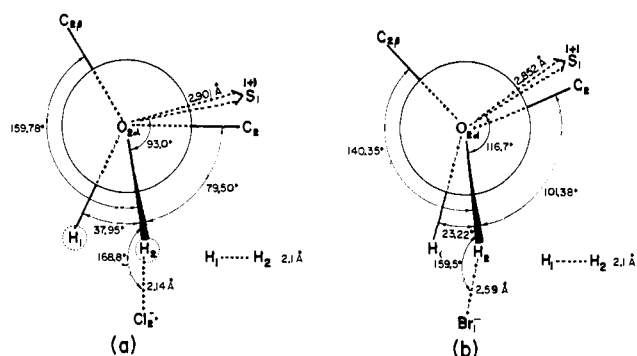


Figure 7. Newman projections of the 2-( $\alpha$ -hydroxyethyl) side chain along the O(2 $\alpha$ )-C(2 $\alpha$ ) bond for: (a) 2-( $\alpha$ -hydroxyethyl)thiamine chloride hydrochloride, and (b) 2-( $\alpha$ -hydroxyethyl)-3,4-dimethylthiazolium bromide.

bond can assume. More specifically, O(2 $\alpha$ )-H(2) is constrained to make a 22° angle with the normal to the plane of the ring, and since O-H $\cdots$ Br<sup>-</sup> is 159°, the angle between H(2) $\cdots$ Br<sup>-</sup> and the normal must be between 1 and 43° (22°  $\pm$  (180-159°)). The observed value is 14°. The relative orientation of H(2) $\cdots$ Br<sup>-</sup> obviously depends upon the O-H $\cdots$ Br<sup>-</sup> angle also. At first glance one might expect the hydrogen bonding scheme, molecular packing requirements, and other lattice forces to have an influence on the 2 side chain conformation (in particular on H(2)-O(2 $\alpha$ )-C(2 $\alpha$ )-C(2)) that equals or surpasses the effect of the S $\cdots$ O interaction. However, the C(2) side chain conformation in the thiamine derivative is almost the same as it is in the model compound (Figures 6 and 7) despite dissimilarities in other parts of the molecules and despite differences in the lattice forces of the two crystals.<sup>35</sup> The S $\cdots$ O(2 $\alpha$ ) distances and the O(2 $\alpha$ )-

(35) Lattice forces and hydrogen bonding do appear to have a more dominant influence over the conformation of the 5-( $\beta$ -hydroxyethyl) side chain even though this oxygen is sterically capable of interacting intramolecularly with the ring sulfur atom. In all of the crystal structures containing thiamine the torsion angle defined by S(1)-C(5)-C(5 $\alpha$ )-C(5 $\beta$ ) is always near 90°. However, the orientation of bond C(5 $\beta$ )-O varies for the different structures in a manner that appears to be dependent on packing and hydrogen bonding. As long as torsion angle S(1)-C(5)-C(5 $\alpha$ )-C(5 $\beta$ ) is nearly perpendicular, the oxygen attached to C(5 $\beta$ ) cannot make contact with the sulfur atom. On the other hand, it is interesting that in the crystal structure of thiochrome (accepted by *Acta Crystallogr.*), which is the planar tricyclic oxidation product of thiamine, there is a significant intramolecular interaction between the  $\beta$ -hydroxy oxygen and the sulfur in the thiazole ring as the S $\cdots$ O distance is 2.94  $\text{\AA}$ . In that structure the bond between the  $\alpha$  and  $\beta$  carbons assumes a syn-periplanar conformation with respect to the ring C-S bond, and the oxygen on the  $\beta$  carbon lies within 0.15  $\text{\AA}$  of the ring plane with its lone pair electrons directed toward the sulfur atom.

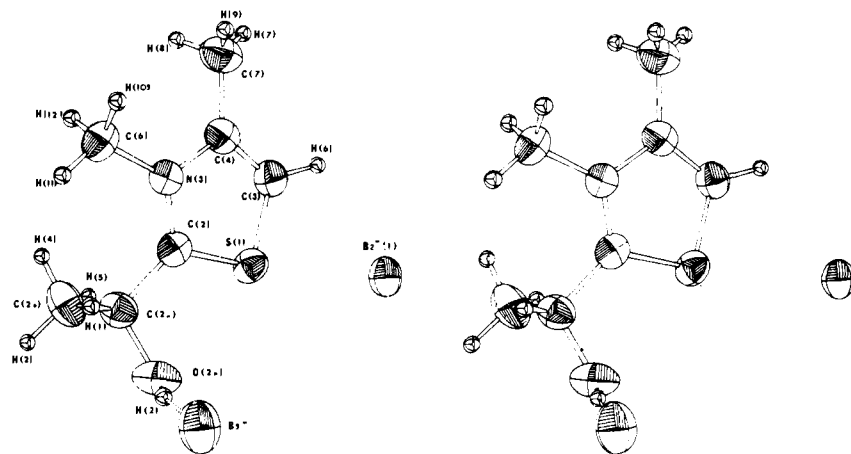


Figure 8. Stereoscopic view of 2-( $\alpha$ -hydroxyethyl)-3,4-dimethylthiazolium bromide with the thermal ellipsoids at the 50% probability level except for those of the hydrogen atoms which are drawn as spheres of arbitrary radius.

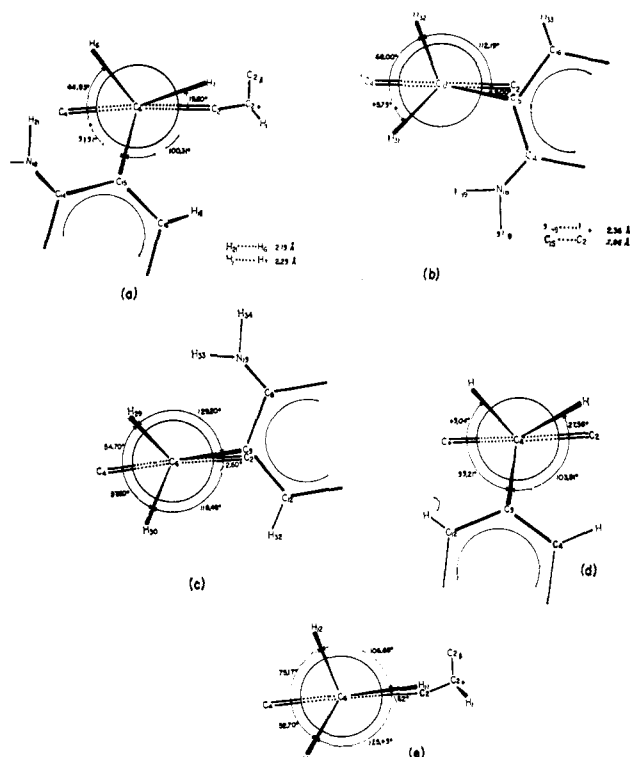


Figure 9. Newman projection along the bond from the methylene carbon to the thiazolium ring nitrogen for: (a) 2-( $\alpha$ -hydroxyethyl)thiamine chloride hydrochloride, (b) thiamine chloride hydrochloride hydrate (ref 7), (c) thiamine pyrophosphate hydrochloride (ref 8), and (d) 3-benzyl-4-methylthiazolium bromide (ref 33). (e) is the analogous projection along the bond from the methyl carbon to the thiazolium ring nitrogen for 2-( $\alpha$ -hydroxyethyl)-3,4-dimethylthiazolium bromide.

$C(2\alpha)-C(2)-S$  torsion angles are remarkably similar in the two molecules, differing only by 0.049 Å and 2.2°, respectively (Figure 6). Although torsion angle  $H(2)-O(2\alpha)-C(2\alpha)-C(2)$  in the thiamine derivative is 22° less than it is in the model compound, its deviation from 90° is less than 12° in each compound (Figure 7). Consequently, the hydrogen bond between  $O(2\alpha)$  and the halide ion is roughly perpendicular to the thiazolium ring in both cases (Figures 3, 4, 6, 7, and 8 (figures drawn using ORTEP program<sup>28</sup>)). Accordingly, it seems reasonable to assume that in solution,

the preferred conformation of the 2 side chain will resemble the one in the crystal structures because of the stabilization by the  $S \cdots O$  interaction. Most likely, there are preferential relative orientations of the hydrogen bond in solution also.

In the first step of the mechanism, advanced by Crosby and Lienhard,<sup>36</sup> for the lyate ion catalyzed elimination of acetaldehyde from **6**, the hydroxyl group is deprotonated by hydroxide in water or by ethoxide in alcohol to give the dipolar alcoholate, **5a**. The present analysis indicates that a syn-periplanar arrangement of the  $C(2)-S$  and  $C(2\alpha)-O$  bonds, resembling that in **1b** and **6a**, should occur in **5a** with perhaps a somewhat shorter  $S \cdots O$  distance because of the larger Coulombic attractive force. Obviously, the larger electrostatic energy should favor the ionization of the hydroxyl proton from **6**. Indeed, its  $pK_a$ , which is quite low for an alcohol, is 11.4 at 25° and 0.5M ionic strength.<sup>5</sup> The low value has been attributed to the positive charge on the thiazolium ring.<sup>37</sup>

Kinetic data on model systems,<sup>5, 36</sup> and evidence from enzymic studies using fluorescent labels<sup>38</sup> support the notion that the thiazolium ring is located in a hydrophobic region of the enzyme. Crosby and Lienhard<sup>36</sup> suggest that the electrostatic interaction between the carboxylate group of the pyruvate ion substrate and the thiazolium ring of the coenzyme should be a significant binding force in a hydrophobic environment. The crystallographic data show that, if this type of substrate-coenzyme binding does occur, it very likely will be mediated by an electrostatic bond between the thiazolium sulfur atom and one of the pyruvate oxygen atoms with a  $S \cdots O$  separation less than the usual van der Waals distance.

Although substitution at  $C(2)$  has no discernible effect on the bond lengths and angles in the pyrimidine ring of the thiamine derivative, the relative orientation of the rings in 2-( $\alpha$ -hydroxyethyl)thiamine is strikingly different from that in thiamine compounds lacking a substituent on  $C(2)$  (Figure 9). In the latter, the bond

(36) J. Crosby and G. E. Lienhard, *J. Amer. Chem. Soc.*, **92**, 5707 (1970).

(37) P. Pulsinelli, Ph.D. Thesis, University of Pittsburgh, 1970, pp 80-93.

(38) J. H. Wittorf and C. J. Gubler, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968. Biol-141; J. Ullrich, *Angew. Chem., Int. Ed. Engl.*, **8**, 82 (1969).

linking the methylene bridge to the pyrimidine ring is always found syn-periplanar with respect to N(3)-C(2)<sup>39</sup> (Figures 9b and c), but in 2-( $\alpha$ -hydroxyethyl)-thiamine, a much larger torsion angle, 100.3°, occurs between these bonds (Figure 9a). Apparently, an increase in the angle is needed to sterically accommodate the 2-( $\alpha$ -hydroxyethyl) side chain. Nevertheless, a pair of somewhat close contacts does occur between certain of the hydrogen atoms. Thus, H(6)···H(21) is 2.13 Å and H(7)···H(1) is 2.24 Å. Although it lacks the 2-( $\alpha$ -hydroxyethyl) side chain, *N*-benzyl-4-methylthiazolium bromide<sup>38</sup> has a conformation similar to that of **1b** (Figure 9d). The relative orientations of the pyrimidine and thiazolium rings are quantitatively indicated by torsion angles  $\varphi_P$ , N(3)-C(6)-C(15)-C(14), and  $\varphi_T$ , C(15)-C(6)-N(3)-C(2), respectively.<sup>41</sup> In thiamines unsubstituted at C(2),  $\varphi_P$  is always fairly close to either  $\pm 90^\circ$  and  $\varphi_T$  is near  $0^\circ$ . These angles are markedly different in 2-( $\alpha$ -hydroxyethyl)thiamine where the respective values of  $\varphi_P$  and  $\varphi_T$  are  $-145.6$  and  $-100.3^\circ$ .

This observed structural difference in the ring orientation between thiamine and its 2-( $\alpha$ -hydroxyethyl) derivative is consistent with the nmr spectra of these compounds in deuterium oxide solution. In the 2-( $\alpha$ -hydroxyethyl) derivative the absorption positions for the protons of H(16) in the pyrimidine ring and the thiazolium 4-methyl hydrogens are shifted to higher  $\tau$  values.<sup>4,42,43</sup> In crystals of **1b** the pyrimidine hydrogen, H(16), is situated 2.16 Å above the plane of the thiazolium ring near the C(2)-N(3) bond where it would be strongly shielded by the ring current effect<sup>44</sup> (Figures 3 and 4). However, in crystals of the unsubstituted thiamines it occupies a position where the shielding would be much weaker.<sup>39</sup> Figures 3 and 4 show in addition that the thiazolium 4-methyl group in **1b** would be shielded by the pyrimidine ring current effect. Again this will not be the case in unsubstituted thiamine since the 4-methyl is far removed from the pyrimidine ring. The increased shielding experienced by these particular protons in the derivative would shift their absorption to higher  $\tau$  values as observed. Accordingly, the nmr data indicate that the

(39) The same relative ring orientation has been observed in all five crystal structures reported to date of thiamine compounds unsubstituted at C(2). These are: thiamine chloride hydrochloride (ref 7), thiamine phosphate monophosphate hydrate (see ref 9), thiamine chloride monohydrate (ref 40), thiamine pyrophosphate hydrochloride (ref 8), and thiamine pyrophosphate tetrahydrate: C. H. Carlisle and D. S. Cook, *Acta Crystallogr., Sect. B*, **25**, 1359 (1969).

(40) J. Pletcher, M. Sax, S. Sengupta, J. Chu, and C. S. Yoo, *Acta Crystallogr., Sect. B*, **28**, 2928 (1972).

(41) As originally defined in ref 8b,  $\varphi_P$  is the angle in projection along the C(6)-C(15) bond between the normals to the plane of the pyrimidine ring and to the plane defined by atoms C(15), C(6), and N(3), and  $\varphi_T$  is the projection along C(6)-N(3) of the angle between the normals to the thiazolium ring and the plane containing the three atoms. As redefined above in the text, these angles are more convenient to compute, and they differ only slightly in value from those calculated according to the original definition.  $\varphi_P$  and  $\varphi_T$  in thiamine chloride hydrochloride are  $-9.4$  and  $-73.5^\circ$ , respectively, by the original definition, but they are  $-9.0$  and  $-76.1^\circ$  as defined in the text.  $\varphi_T$  and  $\varphi_P$  in thiamine pyrophosphate hydrochloride, according to the original definition, are  $3.6$  and  $93.2^\circ$ , respectively, whereas according to the text, they are  $2.7$  and  $93.1^\circ$ .

(42) J. J. Mielal, R. G. Votaw, L. O. Krampitz, and H. Z. Sable, *Biochim. Biophys. Acta*, **141**, 205 (1967).

(43) J. J. Mielal, G. Bantle, R. G. Votaw, I. A. Rosner, and H. Sable, *J. Biol. Chem.*, **246**, 5213 (1971).

(44) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, pp 74-83.

conformations assumed by thiamine and its 2-( $\alpha$ -hydroxyethyl) derivative in the solid state are also the predominant forms which exist in solution. In either conformation there is considerable hydrogen bonding with surrounding molecules. In view of these structural findings, further investigation of the catalytic mechanism is called for in order to show whether hydrogen bonding with the solvent influences the kinetics of the drastic orientational change that occurs in the thiamine rings when C(2) undergoes substitution or elimination.

In an effort to explain the catalytic function of the pyrimidine moiety, several hypotheses have been presented in which the pyrimidine amino group is predicted to form an intramolecular hydrogen bond of the type O(2 $\alpha$ )-H···N(18) or to internally deprotonate O(2 $\alpha$ )-H.<sup>2,6,8a</sup> However, the crystallographic and nmr data do not lend support to either of these ideas. As long as the 2-( $\alpha$ -hydroxyethyl) side chain maintains the preferred conformation which is stabilized by the intramolecular S···O interaction, the pyrimidine amino and the 2-( $\alpha$ -hydroxyl) groups cannot come close enough together to form an intramolecular hydrogen bond. A rotation of the side chain about the C(2)-C(2 $\alpha$ ) bond, sufficient to increase torsion angle S(1)-C(2)-C(2 $\alpha$ )-O(2 $\alpha$ ) to approximately  $60^\circ$ , would move O(2 $\alpha$ )-H(2) into a position where contact between H(2) and the amino nitrogen becomes possible, but this operation would simultaneously lengthen the S···O distance by about 0.25 Å. Consequently, the internal transfer of the proton, if it were to occur, could take place only if the side chain were in a conformation other than its most energetically favorable one. It should also be noted that the deprotonation of O(2 $\alpha$ )-H enhances the S<sup>δ+</sup>···O interaction (S<sup>δ+</sup>···O-H < S<sup>δ+</sup>···O-) and thereby increases the stability of the preferred conformation. Furthermore, from the crystal structures of the two compounds in this paper it does appear as though the 2 side chain could remain in its preferred conformation during the deprotonation of O(2 $\alpha$ )-H if the proton were removed by an external agent. Perhaps an even more significant argument against any substantial internal proton transfer from O(2 $\alpha$ ) to the pyrimidine amino group is the weak basicity of the amino nitrogen. Significantly, this amino group is never protonated in any of the structures of the protonated forms nor does it ever serve as a hydrogen bond acceptor in any of the known structures containing the thiamine moiety, including thiamine chloride monohydrate<sup>40</sup> (*i.e.*, thiamine base). In fact, it is consistently a hydrogen bond donor and the C(14)-N(18) bond always shows considerable multiple bond character.

**Acknowledgment.** The authors thank Dr. B. C. Wang and Dr. C. S. Yoo for helpful comments, suggestions, and discussions about this research.

**Supplementary Material Available.** Tables II and III will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for \$3.00 for photocopy or \$2.00 for microfiche, referring to code number JACS-74-155.