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The Chemistry of Thiamine: Studies on the Dimerization of Thiazolium Salts[1]

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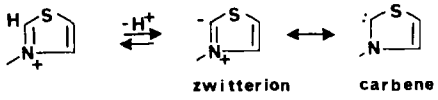
In this communication we report on our studies into the previously undetected dimerization chemistry of thiazolium salts. Thiazolium salts with electron-withdrawing substituents, such as 3,4-dimethyl-5-ethoxycarbonylthiazolium iodide, yield acid- and oxygen-sensitive ethylenic dimers under conditions originally used to detect the dimerization of 3-methylbenzothiazolium iodide. The 5-ethoxycarbonyl-4-methyl-3-phenylmethylthiazolium and 5-(2-*O*-triphenylmethyl-hydroxyethyl)-4-methyl-3-phenylmethylthiazolium bromides yield stable rearranged dimers, rather than the labile ethylenic dimers, under identical conditions. 4-Methyl-5-(2-hydroxyethyl)-3-phenylmethylthiazolium bromide and thiamine hydrochloride yield rearranged dimers which were isolated as their *N,O*-ketal derivatives when these salts were heated in aprotic solution in the presence of DBN and K_2CO_3, respectively. Rearrangement of the ethylenic dimer of 3-phenylmethylbenzothiazolium bromide to 2-(benzothiazol-2-yl)-2,3-diphenylmethylbenzothiazoline (J. Baldwin, S. E. Branz, and J. A. Walker (1977) *J. Org. Chem.* **42,** 4142) demonstrates that rearranged dimers of these thiazolium salts are produced via a mechanism involving 1,3-sigmatropic rearrangement of intermediate ethylenic dimers. Based on literature precedent we argue that this dimerization chemistry demonstrates the nucleophilic carbene nature of C-2 deprotonated thiazolium salts in aprotic basic solution.

INTRODUCTION

Since the discovery by Breslow that the C-2 proton of thiamine is acidic and exchanges with solvent deuterium in neutral deuterium oxide (*1*), several groups have attempted to elucidate the features important in the stability and chemical reactivity of Breslow's proposed zwitterion (Eq. [1]).



[1]

For the most part these studies have been limited to comparing the relative rates of C-2 H-D exchange of thiazolium salts and their analogs in acidic D_2O. The success of this approach has been the demonstration that necessary features of

[1] Taken in part from the dissertation of M. B. Doughty, Louisiana State University, 1982.

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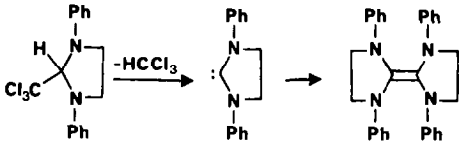
thiazolium salts required for the exchange are the formal positive charge at nitrogen (*2*), the partial positive charge at C-2 (*3*), and the angle strain in the planar —S – C=N$^+$< ring system (*4a*).

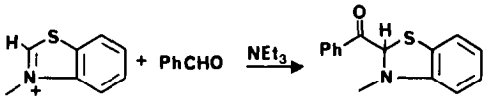
By contrast, there is still little agreement on those factors which stabilize the exchange intermediate itself. As one example, Haake *et al.* argue that an important property of the thiamine exchange intermediate is its proposed aromaticity (*5*). However, Breslow argues that aromaticity is a stabilizing property of the thiazolium ring, and cannot possibly stabilize the deprotonated intermediate, at least relative to the starting salt (*1*). There is sufficient data to confirm Breslow's well-taken point. For example 1,3-dimethylimidazolium exchanges its C-2 proton some 10^4 times slower than its nonaromatic counterpart;[3] although aromaticity stabilizes the starting salt (i.e., to hydrolysis), there is not a concomitant stabilization of the transition state to deprotonation.[4]

A more direct approach for studying the thiamine deprotonated intermediate has been to study the chemistry of thiazolium salts and their analogs. In a series of studies on the chemistry of thiazolium analogs, Wanzlick discovered that 1,3-diphenyl-2-trichloromethylimidazoline (Eq. [2]) decomposes to chloroform and an intermediate which dimerizes with the production of bis[1,3-diphenyl-2-imidazolidinylidene] (*7*).



[2]

This ethylenic dimer was also obtained by suspending 1,3-diphenylimidazolinium salt in aprotic basic solution (*7*); subsequently, the structurally related 3-methylbenzothiazolium (*8*), 1,3-dithiolium (*9*), and 1,3-benzodithiolium (*10*) salts were shown to yield ethylenic dimers in aprotic basic solution. The C-2 deprotonated intermediates of these salts also react with benzaldehyde to yield nonaromatic benzoyl ketones, as illustrated for 3-methylbenzothiazolium salt in Eq. [3] (*8*).



[3]

Based on the reactivity of these intermediates to nonaromatic products, Wanzlick argued along the lines of Breslow that these reactive intermediates are best con-

[3] The first-order rate constant for exchange of 1,3-diphenylimidazolinium, the nonaromatic counterpart of 1,3-dimethylimidazolium, was calculated from the data of Hafferyl *et al.* (*4*). The rate constant for exchange of 1,3-dimethylimidazolium (*5*) was determined in basic DMSO, and so this comparison is a low estimate.

[4] As another example Duclos and Haake (*6*) demonstrated a correlation between increasing aromaticity of azolium ring systems (as measured by k_{OH^-} for hydrolysis) and decreasing rates of their C-2 exchange.

sidered as being quasi-aromatic, i.e., as intermediates which appear to be but are actually not aromatic (*7*).

Although Wanzlick extrapolated his conclusions to include thiazolium salts, their related nucleophilic carbene chemistry has not been observed—for example, Hafferyl *et al.* were unable to detect dimerization products of 3,4-dimethylthiazolium iodide (*4a*). We now report conditions under which several thiazolium salts, including thiamine, react to yield ethylenic or rearranged dimer products. Based on this chemistry we suggest that under the conditions of dimerization the C-2 deprotonated intermediates of these thiazolium salts react as nonaromatic nucleophilic carbenes.

EXPERIMENTAL

General. Thiamine chloride hydrochloride (MCB) was purified by several washings with hot ethanol and dried at 100°C overnight in a ventilated drying oven prior to use. Potassium carbonate (MCB) was pulverized and also dried at 100°C overnight prior to use. Dimethylformamide was dried by repetitive distillations over calcium hydride and used immediately. Triethylamine (Aldrich) was purified from distillation over calcium hydride, and acetone (reagent grade) was purified by distillation from potassium carbonate. 1,5-Diaza-[4.3.0]-bicyclonon-5-ene (Aldrich), 5-(2-hydroxyethyl)-4-methylthiazole (Merck), and benzothiazole (Aldrich) were purified by distillation. All other reagents and solvents were reagent grade. Matheson purity nitrogen was used in all experiments, and atmos-bags (I^2R) were routinely used to provide an inert atmosphere. For deoxygenating solutions, reaction vessels were connected to a Firestone valve equipped with nitrogen and vacuum lines; solutions were degassed by alternating cycles of evacuating and flushing with zero-grade nitrogen.

5-Ethoxycarbonyl-4-methyl-3-phenylmethylthiazolium bromide **4**, 3-phenylmethylbenzothiazolium bromide **13**, and 5-(2-hydroxyethyl)-4-methyl-3-phenylmethylthiazolium bromide **8** were prepared by refluxing the appropriate thiazole with two equivalents of benzyl bromide for 24 h in toluene; product **4** was purified by precipitation from ethanol/ethyl ether [mp = 184°C; mp (lit) = 186°C (*11*)], product **13** was purified by precipitation from methanol/ethyl ether [mp = 190°C; mp (lit) = 186°C (*12*)], and product **8** was purified by recrystallization from acetone [mp = 195°C; mp (lit) = 193°C (*13*)].

Proton NMR spectra were recorded on a Varian A60A spectrometer and chemical shifts are reported relative to tetramethylsilane. Ultraviolet spectra were recorded on a Beckman Model 25 spectrophotometer. The pH of aqueous solutions was measured on a Radiometer/Copenhagen PH82 standard pH meter. Melting points were determined with a Melt-Temp apparatus and were not corrected. Mass spectral analyses were performed on a Hewlett–Packard HP5985 mass spectrometer. All elemental analyses were performed by Mr. Ralph Seab, scientific research specialist of the Louisiana State University Chemistry Department.

Synthesis of 5,5'-biethoxycarbonyl-3,3';4,4'-bi-dimethyl-$\Delta^{2,2'}$-bi-thiazoline **2.** All glassware was dried in an oven overnight. A 150-ml, three-neck round-bottom

flask was equipped with a reflux condenser, a Firestone valve, and a magnetic stirring bar. While flushing with zero-grade nitrogen, the flask was charged with dry **1** (1.0 g, 3.2 mmol), freshly distilled anhydrous acetone (15 ml), and triethylamine (0.89 ml, 6.4 mmol). The solution was deoxygenated and refluxed for 3 h under a positive nitrogen pressure. The reaction vessel was transferred to an inert atmosphere in a cold room (4°C) and this reaction mixture was added, dropwise, into cold ethyl ether (50 ml). The solution was filtered and the solvents were removed *in vacuo*. The resultant red oil was dissolved in ethyl ether (50 ml) and the mixture was again filtered to remove undissolved salts. The ether was removed *in vacuo* yielding 650 mg (63%) of **2** as a light red oil. mass spec: *m/e* (abundance) 370 (3,M^+), 355 (*9*), 186 (100), 158 (57), 142 (26); ^{1}H NMR ($CDCl_3$): δ 1.20 (t,3H,J = 7 Hz), 2.23 (s,3H), 3.15 (s,3H), 4.17 (q,2H,J = 7Hz).

Oxidation of **2** *to 3,4-dimethyl-5-ethoxycarbonyl-2-thiazolone* **3**. A solution of **2** (659 mg, 1.8 mmol) in benzene (10 ml) was refluxed in the presence of molecular oxygen for 4 h. After roto-evaporation, thiazolone **3** was purified from the resultant oil by sublimation yielding 420 mg of **3** as light yellow crystals. mp = 61–63°C; mp (lit) = 63°C (*14*). ^{1}H NMR (CCl_4): δ 1.18 (t,3H,J = 7 Hz), 2.42 (s,3H), 3.13 (s,3H), 4.08 (q,2H,J = 7 Hz). IR (KBr): 1630, 1570.

Conversion of dimer **2** *to thiazolium salt* **1** *in dilute acid*. Dimer **2** (530 mg, 1.4 mmol) was dissolved in 10 ml of a 10% ethanolic hydrogen iodide solution, and the reaction solution was flushed with nitrogen and stirred at room temperature for 4 h. The volume was reduced by flash evaporation and 5-ethoxycarbonyl-3,4-dimethylthiazolium iodide **1** was precipitated by dropwise addition of this solution into cold ethyl ether (50 ml). The precipitate was recrystallized from hot acetone/ethyl ether yielding 560 mg (64%) of **1** as a light yellow solid. mp= 151°C, ^{1}H NMR identical with a pure sample of **1**.

Synthesis of 2,3-diphenylmethyl-2-(5-ethoxycarbonyl-4-methylthiazol-2-yl)-5-ethoxycarbonyl-4-methylthiazoline **6**. A three-neck round-bottom flask was equipped with a reflux condenser, a Firestone valve, and a magnetic stirring bar. The apparatus was flamed while purging with nitrogen, and the flask was charged with 5-ethoxycarbonyl-4-methyl-3-phenylmethylthiazolium bromide **4** (1.0 g, 2.9 mmol), freshly distilled triethylamine (0.8 ml, 5.8 mmol), and anhydrous acetone (50 ml). The solution was deoxygenated and refluxed under a positive nitrogen pressure for 4 h. The following purification (except roto-evaporation) was performed under a nitrogen atmosphere at 4°C. Solvent and excess base were removed *in vacuo*, and triethylammonium bromide was precipitated by the addition of ethyl ether. After filtration, the solution was reduced to a small volume by roto-evaporation and the product was precipitated by the addition of cold methanol. Recrystallization from methanol afforded 520 mg (68%) of **6**. mp = 164°C.

Anal. Calcd for $C_{28}H_{30}N_2O_4S_2$: C,64.34; H,5.79; N,5.36. Found: C,64.22, H,5.99, N,4.93. mass spec: *m/e* (abundance) 431 (27), 91 (100). MW (based on depression of mp of benzophenone) = 550 ± 40, MW (calcd) = 522. ^{1}H NMR ($CDCl_3$): δ 1.38 and 1.42 (two t,6H,J = 7 Hz), 2.25 (s,3H), 2.77 (s,3H), 3.83 (m,2H), 4.28 and 4.38 (two q,4H,J = 7 Hz), 5.00 (m,2H), 7.28 (m,10H).

Synthesis of 4-methyl-3-phenylmethyl-5-(2-O-triphenylmethyl-hydroxyethyl) thiazolium bromide **7**. A solution of freshly distilled 5-(2-hydroxyethyl)-4-methyl-

thiazole (5.0 g, 35 mmol), freshly distilled triethylamine (5.4 ml, 39 mmol), tritylchloride (5.4 ml, 39 mmol), *N,N*-dimethylaminopyridine catalyst (0.5 g), and methylene chloride (50 ml) was stirred for 5 h at room temperature. The reaction mixture was extracted with two 50-ml portions of cold 0.5 N HCl; the methylene chloride extract was dried over sodium sulfate, filtered, reduced to a small volume by roto-evaporation, and the product was precipitated by addition of this solution to cold methanol. The white product was recrystallized from methanol yielding 7.0 g (50%) of 4-methyl-5-(2-*O*-triphenylmethyl-hydroxyethyl)thiazole as a white solid. mp = 139°C.

Anal. Calcd for $C_{13}H_{13}NO_2S$: C,77.89; H,6.01; N,3.63. Found: C,77.64; H,6.25; N,3.59. ^{1}H NMR ($CDCl_3$): δ 2.25 (s,3H), 2.85 (m,2H), 3.25 (m,2h), 7.25 (m,15H), 8.50 (s,1H).

This trityl ether of the thiamine thiazole (5.0 g, 13 mmol) and benzylbromide (2.0 ml, 26 mmol) were refluxed in 2-butanone (30 ml) under nitrogen for 24 h. The salt was precipitated by addition of the reaction solution into ethyl ether, and the collected precipitate was recrystallized from methanol/ethyl ether yielding 6.6 g (71%) of **7** as a white solid. mp = 220°C (dec).

Anal. Calcd for $C_{20}H_{20}NO_2SBr$: C,69.06; H,5.61; N,2.52. Found: C,68.96, H,5.25; N,2.34. ^{1}H NMR (d_6 acetone): δ 2.35 (s,3H), 3.25 (m,4H), 5.75 (br s,2H), 7.25 (m,5H), 7.40 (br s,15H).

Synthesis of 2,3-diphenylmethyl-2-[4-methyl-5-(2-O-triphenylmethyl-hydroxyethyl)thiazol-2-yl]-4-methyl-5-(2-O-triphenylmethyl-hydroxyethyl)thiazoline **9**. A three-neck round-bottom flask was equipped with a magnetic stirring bar, a reflux condenser, and a Firestone valve. The flask was flamed while purging with zero-grade nitrogen and charged with thiazolium salt **7** (500 mg, 1.2 mmol), anhydrous acetone (15 ml) and freshly distilled 1,5-diaza-[4.3.0]-bicyclonon-5-ene (DBN)[5] (0.18 ml, 1.07 mmol). The solution was deoxygenated and refluxed for 1 h under a positive nitrogen pressure. The following purification was performed in an inert atmosphere at 4°C. The solvent was removed *in vacuo* and the product was precipitated by the addition of cold methanol (10 ml). The product was recrystallized from chloroform–petroleum ether yielding 160 mg (37%) of **9**. mp = 89–90°C (dec).

Anal. Calcd for $C_{40}H_{38}N_2O_4S_2 \cdot H_2O$: C,77.85; H,6.31; N,2.84. Found: C,77.73; H,6.37; N,2.89. ^{1}H NMR ($CDCl_3$: δ 1.35 (s,3H), 2.15 (s,3H), 2.25 (m,2H), 2.80 (m,2H), 3.00 (m,4H), 3.60 (m,2H), 4.45 (m,2H), 7.25 (m,40H).

Synthesis of 2,3-diphenylmethyl-2-[5-(2-hydroxyethyl)-4-methylthiazol-2-yl]-3a-methyl-perhydrofuro-(2,3d)-thiazole **10**. A three-neck round-bottom flask was equipped with a magnetic stirring bar, a reflux condenser, and a Firestone valve. The flask was flamed while purging with zero-grade nitrogen and charged with thiazolium salt **8** (1.0 g), anhydrous acetone (30 ml), and freshly distilled DBN. The solution was deoxygenated and refluxed for 1 h under a positive nitrogen pressure. The following purification was performed at 4°C. The reaction mixture was acidified with two equivalents of acetic acid and stirred an additional 30 min. The solution was poured into 30 ml of deionized water and extracted with three

[5] Abbreviation used: DBN, 1,5-diaza-[4.3.0]-bicyclonon-5-ene.

volumes of ethyl ether; the organic layers were dried over $MgSO_4$ and roto-evaporated to a small volume. Two silica gel flash columns were run; the solvent system of the first contained chloroform and ethyl ether (6 : 4) and the second chloroform and methanol (8 : 2). This yielded the rearranged dimer **10** as a mixture of two diastereomers.

Anal. Calcd for $C_{26}H_{30}O_2S_2N_2$. C,69.34; H,5.48; N,4.04. Found: C,69.29; H,5.52; N,3.92. 250 MHz ^{1}H NMR ($CDCl_3$): δ 1.15 (s,1.6H,3-C**H**$_3$ *cis* to benzyl), 1.30 (s,1.4H,3-C**H**$_3$ *trans* to benzyl), 2.0 (m,2H,C-C**H**$_2$-C), 2.20, 2.25 (two s,3H, thiazolyl-C**H**$_3$), 2.81 (m,2H,thiazolyl-C**H**$_2$), 3.2 (m,2H,C-C**H**$_2$-phenyl), 3.6 (m,1H,C**H**), 3.6 (m,2H,C**H**$_2$OH), 4.0 (m,2H,-C**H**$_2$O-), 4.5 (m,2H,N-C**H**$_2$), 7.2 (m,10H). mass spec: *m/e* (abundance) 376 (100), 286 (10), 91 (100).

Synthesis of 2,3-di-[(4-amino-2-methylpyrimidin-5-yl)methyl]-2-[5-(2-hydroxyethyl)-4-methylthiazol-2-yl]-3a-methyl-perhydrofuro-(2,3-d)-thiazole **12**. A dry, 300-ml, three-neck round-bottom flask was equipped with a stirring bar and a Firestone valve and charged with dry thiamine chloride hydrochloride (10 g), dry potassium carbonate (8.2 g), and freshly distilled dimethylformamide (100 ml). The mixture was deoxygenated and heated, with vigorous stirring, at 45°C under a positive nitrogen pressure for 4 h. The following purification (except for roto-evaporation) was performed at 4°C under a nitrogen atmosphere. Methylene chloride (100 ml) was added to the cooled reaction mixture and the white precipitate was collected by suction filtration and discarded. The mother liquor was roto-evaporated *in vacuo* to remove solvent without heating the flask above 45°C. The resultant oil was dissolved in chloroform (50 ml), suction filtered when necessary to remove salts, and finally precipitated by the slow addition of the chloroform solution into cold ethyl ether (100 ml). The solid was collected by suction filtration, dissolved in anhydrous methanol (50 ml) containing glacial acetic acid (1.2 ml), and this solution was flushed with zero-grade nitrogen and stirred for 1 h at 0°C. Methanol was removed by roto-evaporation; the yellow oil was dissolved in chloroform (50 ml), and the chloroform solution was extracted with two 50-ml portions of cold water. The water layer was neutralized with 5% sodium hydroxide and extracted with two 50-ml portions of chloroform. The combined chloroform extracts were dried over sodium sulfate, filtered, roto-evaporated to a small volume, and the dimer was precipitated by the slow addition of the chloroform solution into cold ethyl ether (50 ml). The white solid was collected by suction filtration, and the dimer was reprecipitated by dissolving in chloroform (25 ml), filtering, precipitating in cold ethyl ether, and collecting the solid by gravity filtration yielding 2.3 g (32%) of **12** as a mixture of diastereomers (50% *cis*, 50% *trans* based on NMR). For an analytical sample, the reprecipitation step was repeated twice, and excess solvent was removed *in vacuo* at 4°C. The dimer was stored at −70°C to avoid decomposition. mp = 81°C (dec).

Anal. Calcd for $C_{24}H_{32}N_8O_2S_2 \cdot 2H_2O$: C,51.04; H,6.43; N,19.84. Found: C,51.11; H,6.09; N,19.73. mass spec: *m/e* (abundance) 406 (51), 285 (81), 243 (40), 122 (100). MW (based on depression of the mp of benzophenone) = 580 ± 60, MW (calcd) = 528. ^{1}H NMR ($CDCl_3$): δ 1.28 (s,1.5H,3-CH_3 *cis* to pyr), 1.65 (s,1.5H,3-CH_3 *trans* to pyr), 2.15 and 2.20 (two s,3H), 2.37 (s,3H), 2.50 (s,3H), 2.6–3.0 (4H), 3.33 (br s,1H,exchangeable O-H), 3.5–4.3 (5H), 5.57, 5.78, 5.73, and

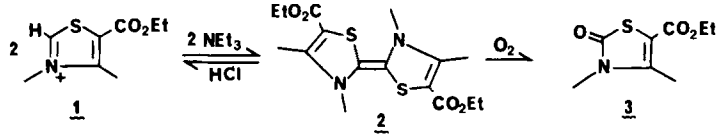
6.0 (four br s,4H,exchangeable N-H), 7.70, 7.95, 8.07, and 8.20 (four s,4H,pyr-H).

Synthesis of 2-(benzothiazol-2-yl)-2,3-diphenylmethylbenzothiazoline **15**. A three-neck round-bottom flask was equipped with a reflux condenser, a magnetic stirring bar, and a Firestone valve. The apparatus was flamed while purging with nitrogen and charged with 3-phenylmethylbenzothiazolium bromide **13** (850 mg, 2.78 mmol), freshly purified triethylamine (0.84 ml, 6.0 mmol), and freshly distilled anhydrous acetone (15 ml). The reaction solution was deoxygenated and refluxed under a positive nitrogen pressure for 2 h. The reaction mixture was cooled to 4°C, and the solvent was removed *in vacuo*. The following purification was performed under a nitrogen atmosphere at 4°C. The solid was dissolved in chloroform and dropped, with stirring, into ethyl ether. The precipitated triethylammonium bromide was removed by filtration; the filtrate was reduced to a small volume by roto-evaporation, and the resulting dimer was precipitated by the addition of cold methanol. The solid was recrystallized from chloroform/petroleum ether yielding 450 mg (72%) of **15** as white crystals. mp = 160–161°C (dec).

Anal. Calcd for $C_{28}H_{22}N_2S_2$: C,74.63; H,4.92, N,6.22. Found: C,74.53, H,5.28; N,6.17. MW (based on the depression of the mp of benzophenone) = 480 ± 40. MW (calcd) = 450. mass spec: *m/e* (abundance) 359 (34), 268(2.3), 91(100). ^{1}H NMR ($CDCl_3$): δ 3.73 (d,1H,*J*a,b = 13 Hz), 4.34 (d,1H,*J*a,b = 13 Hz), 4.38 (d,1H,*J*a,b = 16 Hz), 4.99 (d,1H,*J*a,b = 16 Hz), 6.03–8.15 (18H).

RESULTS

Our initial investigations into the dimerization of thiazolium salts was based on the assertion by Breslow (*1*) that the carbene resonance structure might be stabilized by resonance effects. We prepared the electron-deficient 5-ethoxycarbonyl thiazolium salt **1** since we expected the electron-withdrawing 5-ethoxycarbonyl group to resonantly stabilize the deprotonated intermediate and thus facilitate the initial detection of dimerization products. In fact, our initial results demonstrated that the rate constant for exchange (k_{OH^-}) of **1** is twofold larger than k_{OH^-} for exchange of 3-methylbenzothiazolium iodide, and 80-fold larger than k_{OH^-} for exchange of the *N*-methyl salt of the thiamine thiazole. It was not surprising, then, that salt **1** yields the ethylenic dimer **2** in refluxing acetone in the presence of excess NEt_3 (Scheme 1), i.e., under conditions used for dimerization of 3-methylbenzothiazolium iodide (*8*). This ethylenic dimer was identified by its characteristic ^{1}H NMR and mass spectra and by its chemical reactivity (see Experimental). Dimer **2** oxidizes to 3,4-dimethyl-5-ethoxycarbonyl-2-thiazolone **3** in refluxing benzene and decomposes with regeneration of thiazolium salt **1** in ethanolic hy-



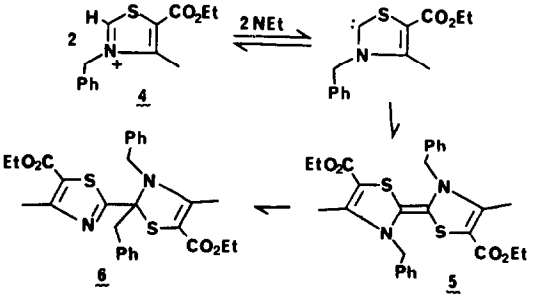
SCHEME 1

drogen iodide. Such chemistry is also characteristic of the labile ethylenic dimers derived from 1,3-diphenylimidazolinium (*15*) and 3-methylbenzothiazolium iodide (*16*).

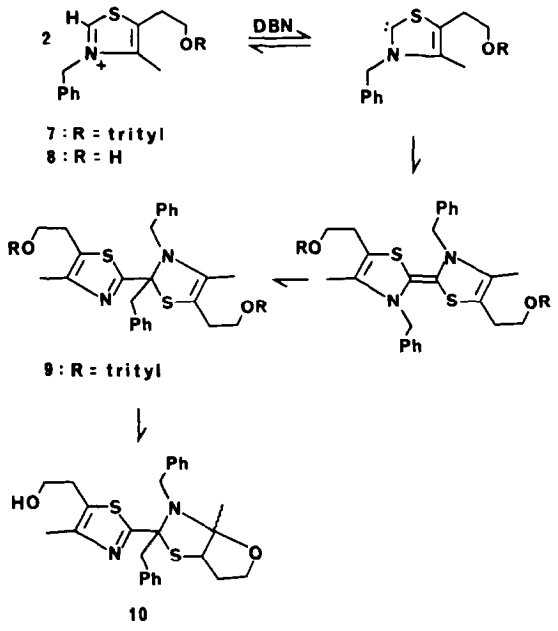
We next wished to prepare an electron-deficient ethoxycarbonyl thiazolium salt with an *N*-alkyl group which would possibly mimic the chemistry of the *N*-pyrimidinylmethyl group of thiamine—i.e., we wished to replace the *N*-methyl group of **1** with an *N*-phenylmethyl, or preferably an *N*-(4-amino-2-methylpyrimidin-5-yl)methyl, group. The 3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-5-ethoxycarbonyl-4-methylthiazolium salt yields a stable but inactive tricyclic derivative, structurally related to Metzler's tricyclic form of thiamine (*17*), in basic acetone (*18*). The 3-phenylmethyl thiazolium salt **4**, however, yields the rearranged dimer **6** via the expected ethylenic dimer **5** (see below) in good yield (Scheme 2). Although unexpected, this rearrangement was fortunate since (1) it yielded a stable and isolatable derivative rather than the oxygen-sensitive ethylenic dimer, and (2) it suggested that the 3-phenylmethyl salts of the thiamine thiazole and thiamine would yield structurally related rearranged dimer products.

We next turned our attention to salts of the thiamine thiazole. When the 3-phenylmethyl-*O*-trityl derivative of the thiamine thiazole **7** was refluxed for 1 h in acetone containing two equivalents of DBN, the rearranged dimer **9** was obtained in 50% yield (Scheme 3). Although dimer products were detected when triethylamine, rather than DBN, was used as the base, the longer reaction times (4 h) in refluxing acetone and/or the higher reaction temperatures necessary for complete reaction of the thiazolium salt led to product decomposition and lower yields. When 5-(2-hydroxyethyl)-4-methyl-3-phenylmethylthiazolium salt **8** was refluxed under identical conditions but worked up under acidic conditions, the *N,O*-ketal derivative **10** of the rearranged dimer was isolated in 75% yield (Scheme 3). The rearranged dimer **10** was isolated as a diastereomeric mixture in which the 4-methyl group is either *cis* or *trans* to the 2-phenylmethyl group. As illustrated in Scheme 3, dimer **10** must be obtained by closure of the *N,O*-ketal of the rearranged dimer **9** (R=H). We are not certain whether the *N,O*-ketal formation leading to **10** occurs during the reaction or as a result of working up the reaction mixture in acidic solution. Nevertheless, this intramolecular *N,O*-ketal formation in related $\Delta^{4,5}$-thiazoline ring systems has been reported previously (*19*).

We were faced with two further technical difficulties in determining optimal conditions for the dimerization of thiamine. First, the thiazolium form of thiamine

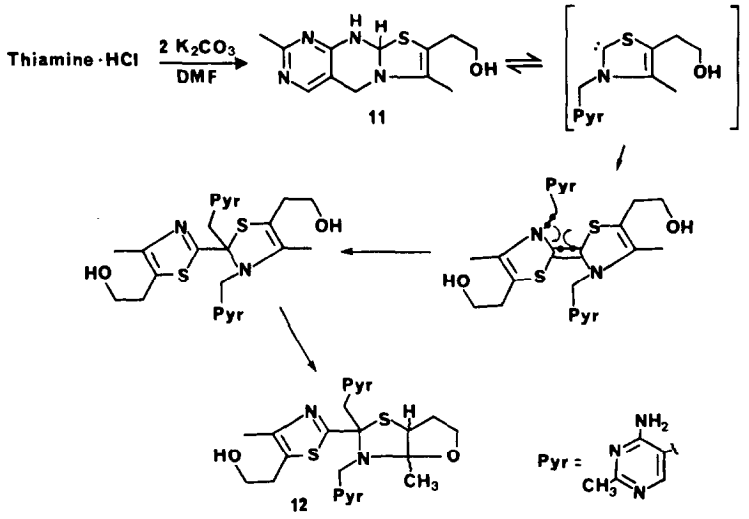


SCHEME 2

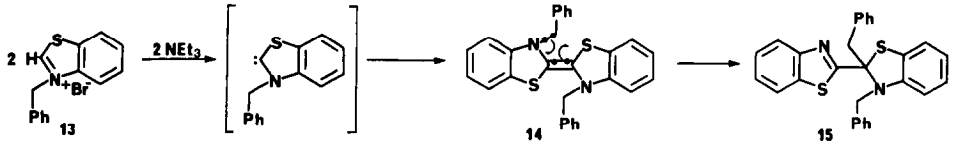


SCHEME 3

is virtually insoluble in nonaqueous solution. Second, we could not use conditions of excess base (as used for the dimerization of salts **1**, **4**, **7**, and **8**) since thiamine undergoes a unique intramolecular decomposition to the yellow form under those conditions (*17, 20*). Eventually, we found that when thiamine HCl and K_2CO_3 (two equivalents) are suspended in DMF thiamine goes into solution as its neutral tricyclic form **11**. Additionally, as we have recently reported for the tricyclic form of thiamine in basic ethanol (*18*), under these conditions in basic DMF and in the



SCHEME 4



SCHEME 5

presence of excess benzaldehyde the tricyclic form is a good catalyst of the benzoin condensation, demonstrating that the C-2 deprotonated intermediate is generated from the tricyclic form under these conditions.[6]

The rearranged dimer of thiamine **12** was thus obtained as its *N,O*-ketal by heating a suspension of dry thiamine hydrochloride and two equivalents of dry potassium carbonate in dry deoxygenated DMF (Scheme 4). As with the rearranged dimer **10**, the rearranged dimer of thiamine **12** was isolated as a mixture of diastereomers with the 4-methyl *cis* to either the 2-pyrimidinylmethyl group or the 2-thiazolyl ring.[7] Nevertheless, this diastereomeric mixture gave a characteristic elemental analysis and a mass spectrum that was consistent with the cleavage patterns of the rearranged dimers **6**, **9**, and **10** (see Experimental). In analogy to the mechanism of formation of the rearranged dimers **9** and **10**, we suggest that dimer **12** is produced as shown in Scheme 4 by 1,3-sigmatropic rearrangement of the ethylenic dimer followed by ring closure to the *N,O* ketal.

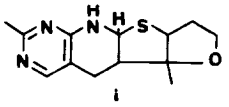
Under conditions for the synthesis of the rearranged dimers of these thiazolium salts, benzothiazolium salt **13** yields the rearranged dimer **15** in 75% yield (Scheme 5). Baldwin and his colleagues have elucidated the mechanistic details of the conversion of **13** to **15** (*12*). They demonstrated that salt **13** yields the ethylenic dimer **14** when reacted in DMF with two equivalents of triethylamine at 0°C, and when heated at 80°C in DMF the ethylenic dimer undergoes a facile 1,3-sigmatropic rearrangement to the rearranged dimer **15**. Additionally, Baldwin *et al.* report that ethylenic dimers derived from *N*-allyl- and *N*-3,3-dimethylallyl-benzothiazolium salts undergo 1,6-sigmatropic rearrangements to the corresponding rearranged dimers (*21*). Based on this literature precedent we conclude that the mechanism of formation of the rearranged dimers reported in this paper is through a facile 1,3-sigmatropic rearrangement of intermediate ethylenic dimers.

DISCUSSION

Two mechanisms have been proposed to account for the dimerization of nucleophilic carbenes (*16*). First is an indirect mechanism in which the carbene reacts

[6] When a reaction mixture of thiamine HCl (1 mM), K_2CO_3 (2 mM), and benzaldehyde (10 mM) was stirred in dry deoxygenated DMF for 5 h at 0°C, benzoin was isolated in 259% yield (based on initial thiamine).

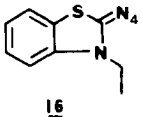
[7] The other major products isolated from this reaction are the *cis* and *trans* isomers of the *N,O*-ketal derivative *i* of the tricyclic form of thiamine:



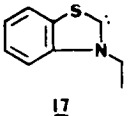
i

with a second carbene precursor followed by deprotonation to the ethylenic dimer. The second proposed mechanism is the direct reaction of two carbenes to yield the ethylenic dimer directly. One objection to this latter mechanism has been that the carbene would be too unstable to accumulate in concentrations necessary for direct dimerization. Recently, however, Lapin and Schuster have demonstrated that when potentially nucleophilic carbenes can be generated in sufficient concentrations, as in the laser photolysis of 9-diazoxanthine, direct carbene dimerization can, in fact, be observed (*22*). Additionally, Hopmann and Brugnani report pK_as of 11.7 and 12.1 for 3-methylbenzothiazolium and thiamine, respectively, as measured spectrophotometrically in basic aqueous solution (*23*); Crosby and Lienhard have demonstrated that these pK_as are decreased by as much as two to three units in more hydrophobic, nonaqueous solution (*24*). In the presence of an excess of strong base in aprotic solution (i.e., under conditions of our studies), the thiazolyl carbenes would be expected to accumulate in the concentrations necessary for a direct dimerization mechanism.

Balli *et al.* argue against a direct mechanism for nucleophilic carbene dimerization based on the following experimental results. The *N*-ethyl-2-benzothiazolyl carbene **17**, generated by the controlled decomposition of **16**, can be trapped by reagents such as acids, azides, and methanol, but even in the absence of added trapping agents the dimerization product cannot be detected (*25*). The dimerization product of **17** can be detected when *N*-alkylbenzothiazolium salts or their C-2



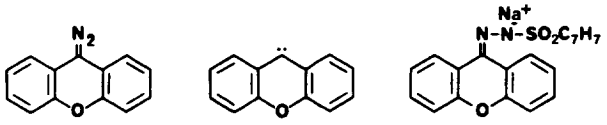
16



17

methanol addition products are refluxed in basic aprotic solution. Thus the authors conclude that the thiazolium salt is required for dimerization (*25*). But, if nucleophilic carbene **17** generated from **16** is not dimerizing, then with what is it reacting? Based on their product isolation and the chemistry reported by Quast and Hunig (*26*), the benzothiazolyl carbene is apparently reacting with **16** and/or intermediate decomposition products of **16**. An alternative explanation of the data of Balli *et al.* is that the low concentration of the benzothiazolyl carbene generated from **16** precludes its direct dimerization. Formation of dimer products will depend on the rate of decomposition of **16** to **17**, and the relative rates of reaction of the benzothiazolyl carbene with **16**, with decomposition products of **16**, or with added trapping reagents. The ethylenic dimer would not be observed when the rate of formation of the benzothiazolyl carbene is too slow, or the rate of its decomposition is too fast, to allow for generation of a high concentration.

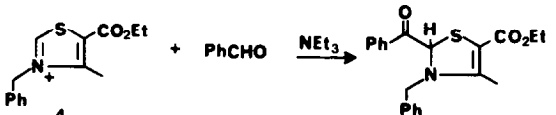
Relative carbene reactivity has also been invoked to explain seemingly conflicting results on the carbene chemistry of 9-xanthylidene **19**. During the photolysis of xanthylidene diazonium salt **18** direct dimerization of 9-xanthylidene is observed even in the presence of added alkenes (*22*). When generated from tosylhydrazone **20**, dimerization is not observed but alkene–carbene addition products can be detected and isolated (*27*). Lapin and Schuster argue that the low concentration of 9-xanthylidene generated from **20** precludes dimerization, allowing for reaction of



18 19 20

the carbene with added alkenes. With the more competent carbene precursor **18** carbene dimerization is competitive (*22*). Thus, the absence of dimerization in the system of Balli *et al.* cannot be used as evidence to exclude a direct dimerization mechanism for nucleophilic carbenes, but instead may indicate the necessity of generating sufficient concentrations of the carbene intermediate in the absence of added trapping reagents.

We have also observed selective nucleophilic carbene reactivity which excludes carbene dimerization. As has been reported in a previous paper, thiazolium salt **4** reacts with benzaldehyde in both basic methanol and basic acetone to yield the 2-benzoylthiazoline **21,** with no detectable formation of the rearranged dimer **6.**



4 21

Additionally, thiazolium salt **1** and thiamine react with aldehydes in basic aprotic or alcoholic solution to the exclusion of dimerization (*28*). Our inability to detect the ethylenic or rearranged dimers when these thiazolium salts are reacted with aldehydes in basic nonaqueous solution suggests that the thiazolyl carbenes react preferentially with aldehydes to the exclusion of dimerization. We have observed dimerization of thiazolyl carbenes only in aprotic basic solution, conditions which would be conducive to reversible generation of maximum concentrations of the thiazolyl carbenes, as would be expected for the direct dimerization mechanism.

Our major objection to an indirect mechanism for carbene dimerization is based on our ability to detect dimerization products of thiamine. As in basic ethanol and butanol (*17*), in basic DMF thiamine exists not in the thiazolium form but in the neutral tricyclic form (Scheme 4) which is a precursor to the thiamine carbene (*18*).[8] Thus in this system the thiazolium salt, whose high concentration would be

[8] One referee suggested that we might want to comment on the recent report of Sugimoto and Hirai (*29*) who claimed isolation of the thiamine-deprotonated intermediate. Although it is possible that they have isolated the thiamine dimer, we have been unable to detect thiamine dimerization products in ethanol at 0°C, i.e., under the conditions of their studies. Perhaps a more reasonable interpretation of their data is that they have actually isolated Metzler's tricyclic form of thiamine. First, the uv spectrum of their compound is not significantly different from either Maier and Metzler's (*17*) calculated spectrum of the tricyclic form (Maier and Metzler state explicitly that the actual spectrum is shifted about 3 nm to lower wavelength relative to their published spectrum) or the spectrum of the tricyclic form which we have observed [λ_{max} (log ε): 256 (4.0), 268–270 (3.8)]. More compelling evidence that Sugimoto and Hirai have isolated the tricyclic form is found in their ^{1}H NMR data. They assign the NH_2 protons as two resonances, a singlet at δ6.45 and a broad singlet at δ7.3. In our experience pyr-

necessary for an indirect dimerization mechanism, does not exist in appreciable concentrations. Dimerization of the thiamine carbene is then similar to dimerization of the nucleophilic cycloheptatrienyl (*29*) carbene under conditions in which a direct dimerization mechanism can be excluded. Based on these arguments we conclude that the more likely mechanisms for the dimerization of these thiazolium salts is via a direct mechanism.

CONCLUSION

In conclusion, our results with the dimerization of thiazolium salts can be best interpreted as direct evidence that in nonaqueous solution the carbene structure is a very important contributor to the stability and chemical reactivity of the C-2 deprotonated thiamine intermediate. Our conclusion that the thiazolyl carbenes are dimerizing through a direct mechanism is based on several lines of indirect evidence. First, in related systems, namely the 9-xanthylidene (*22*) and cycloheptatrienyl carbenes (*29*), dimerization is observed when the carbene intermediate can be generated in high concentrations even under conditions in which an indirect mechanism can be excluded. Given the pK_a of thiazolium systems as measured in basic aqueous solution and the observation that these pK_as are decreased in more hydrophobic solution, under conditions of their dimerization in strongly basic aprotic solution the thiazolyl carbenes would be expected to accumulate in sufficient concentrations for direct dimerization. Lastly, given that under conditions of its dimerization thiamine exists as its neutral tricyclic form, it is unlikely that an indirect dimerization mechanism could be operative, but instead, the direct dimerization of two carbene intermediates, each of which is nonaromatic, to give the nonaromatic ethylenic dimer appears to be the most reasonable mechanism to account for formation of the products which we have observed.

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NH_2 protons are always observed as broad resonances, either a singlet or doublet but never as one sharp and one broad resonance with the widely divergent chemical shifts they report. A more reasonable interpretation of their NMR data is that the sharp resonance at δ6.45 and the broad resonance at δ7.3 are assignable to the C-9a-H and N-H protons, respectively, of the tricyclic form of thiamine (for a reasonable model system see (*18*)). If our assignment is correct, then their interesting result is the rapid exchange of the C-9a proton of the tricyclic form without apparent detectable formation of the thiazolium form of thiamine, a result which is at least consistent with a recently proposed mechanism for formation of the thiamine carbene from the tricyclic form of thiamine (*18*).

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