pmr results clearly show the presence of two spectral processes: one (B) with a $\Delta G^{\ddagger}$ of 4.4 ± 0.1 kcal/mol (at −177°) and the other (C) with a $\Delta G^{\ddagger}$ of 4.9 ± 0.1 kcal/mol at −168°. At −165°, k_B/k_C is about 15.[11]

The detection of one spectral process in the ^{13}C spectrum, and two processes in the ^{1}H spectrum, is consistent with the twist boat as the ground conformation of I. It rules out the boat, chair, and skew forms as sole conformations, as well as 1:1 mixtures of a chair (or skew form) and a boat (or twist boat). It does not exclude the presence of small concentrations (<10% at low temperatures) of conformations other than the twist boat.

The likely degenerate interconversion paths for the twist boat are as follows: (1) pseudorotation *via* the boat, (2) pseudorotation *via* the skew form, and (3) interconversion of the boat, as obtained in path 1, into the chair.[12] It will be assumed in the following discussion that the boat, the skew form, and the chair are present in unobservable concentrations at low temperatures. Spectral process B cannot correspond to path 3, since this leads to a complete averaging, in disagreement with experiment. If B corresponds to path 1, C can be path 2 or 3, and this statement remains true if 1 and 2 are interchanged. In either case, process A observed in the ^{13}C spectrum is not simple, but corresponds to the sum of processes B and C seen in the ^{1}H spectrum. However, since $k_B \gg k_C$, processes A and B should have about the same free energies of activation, as found experimentally. Whether process B involves path 1 or 2 can in principle be determined experimentally or by accurate strain-energy calculations.

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(11) No attempt has been made at precise line-shape analysis of these spectra because of the very rapid increase in the line width resulting from dipole–dipole relaxation in the temperature range −165 to −178°. Nevertheless, the changes in line shapes are qualitatively in agreement with the scheme shown in Figure 1. It is planned to carry out a line-shape analysis on suitably deuterated derivatives of I, which should give much sharper lines than I itself.

(12) Although path 3 suffers from rather large internal angle strains,[1] it has very little eclipsing strain, and thus cannot be dismissed, in the absence of quantitative calculations, for process C.

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Erratum. Tautomerism of Nucleic Acid Bases

Sir:

Recently several papers from this laboratory indicated that cytosine and guanine exist in their minor tautomeric forms to the extent of 15% at room temperature in neutral aqueous solution.[1-4] This conclusion was based on a detailed analysis of the unusual selective line broadening observed for the cytosine H_5 and guanine H_8 nuclear magnetic resonance signals.

(1) G. C. Y. Lee, J. H. Prestegard, and S. I. Chan, *Biochem. Biophys. Res. Commun.*, **43**, 435 (1971).

(2) G. C. Y. Lee, J. H. Prestegard, and S. I. Chan, *J. Amer. Chem. Soc.*, **94**, 951 (1972).

(3) G. C. Y. Lee and S. I. Chan, *J. Amer. Chem. Soc.*, **94**, 3218 (1972).

(4) S. I. Chan and G. C. Y. Lee, *Proc. Jerusalem Symp. Quantum Chem. Biochem., 4th, 1971*, 277 (1972).

In view of the important implications of the above findings, we felt compelled to confirm these observations. Unfortunately, we have found it impossible to duplicate the basic experimental data reported earlier, even though identical methods were used to purify the samples. The purification of the nucleotide derivatives was essential to this work since many of the compounds were known to be contaminated with paramagnetic impurities, which could lead to the observed line broadening. Subsequently we have found that a number of samples, whose data were reported, were not purified as stated in the earlier publications, and, in addition, that some of the control experiments were carried out incorrectly.

The following additional experiments were undertaken in light of the above observations. (a) Guanine and cytosine derivatives were purified using both Dowex 50W-8X and Chelex-100 cation exchange resins. (b) Cytidine was purified by recrystallization from ethanol–water mixtures. Both the recrystallized samples and those purified using the chelating resin Chelex-100 gave sharp nuclear magnetic resonance signals.

Under certain conditions, however, broad guanine H_8 and cytosine H_5 proton line widths were obtained for samples passed through Dowex 50W-8X columns. In the case of 2′-GMP at pD 6.0, a temperatue of 18°, and at 220 MHz this residual line width was 5.5 Hz. The addition of 4×10^{-6} *M* EDTA to a 0.03 *M* solution sharpened the resonance. Since it was initially suggested that EDTA caused line narrowing by catalysis of the exchange between tautomeric structures, the line narrowing should depend only on the EDTA concentration and should be independent of the nucleotide concentration. This was not observed. Instead it was found that the amount of EDTA required to sharpen the line depended on the nucleotide concentration. This immediately suggested that the line broadening was induced by a paramagnetic impurity. Cu^{2+} is the most likely candidate, as suspected earlier by us.[1] More recently, in fact, Kearns, *et al.*, have shown that all the experimental data can be reproduced by adding 10^{-5}–10^{-6} *M* Cu^{2+} to 0.05 *M* solutions of 2′-GMP and 5′-CMP.[5]

In summary, then, it appears that the line broadening previously attributed to tautomerism can be traced to the presence of paramagnetic impurities in the samples, the most likely being Cu^{2+}.

One of us (S. I. C.) would like to apologize to the scientific community for permitting this fiasco.

(5) Y. P. Wong, K. L. Wong, and D. R. Kearns, *Biochem. Biophys. Res. Commun.*, in press.

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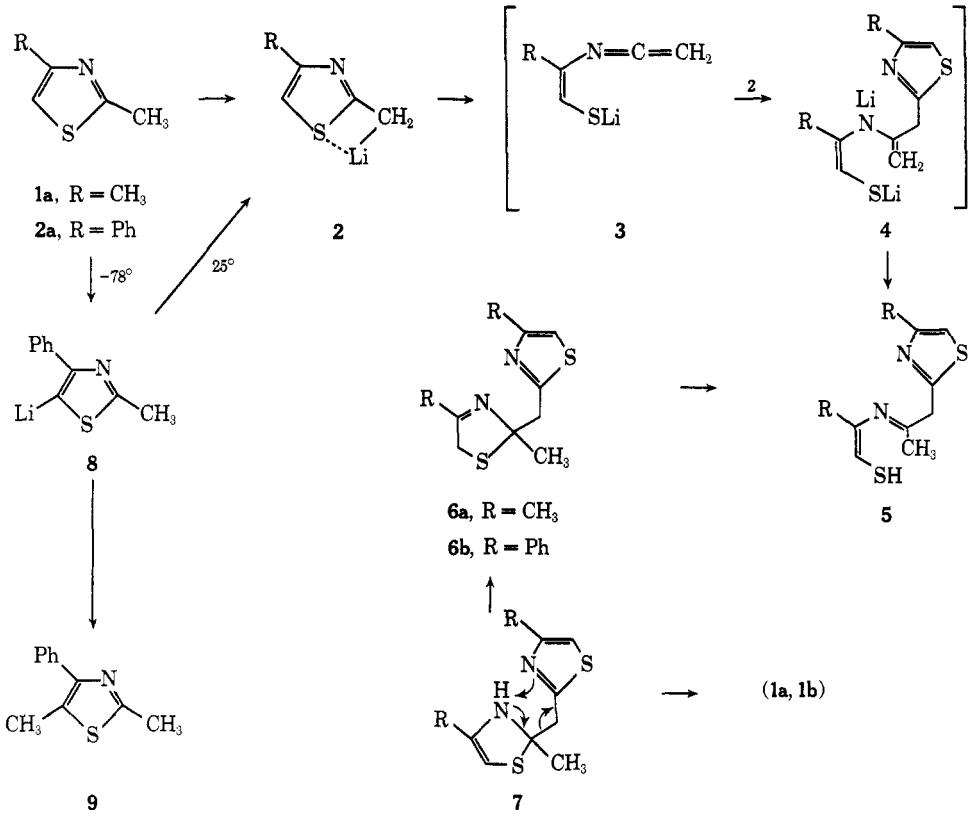
Chemistry of Metalated Heterocycles. Rearrangement and Dimerization of Lithiothiazoles, Thiadiazoles, and Oxadiazoles

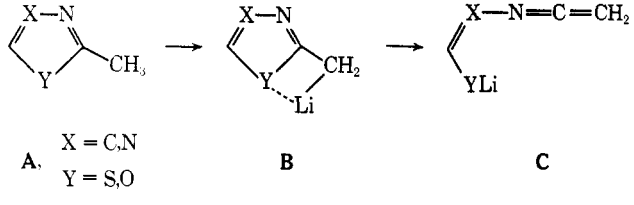
Sir:

We wish to report a remarkable property of metalated aromatic heterocycles bearing the structural feature A.

Scheme I



It has been observed that their lithio salts, B, although stable at low temperatures (< −50°), slowly and efficiently rearrange to the ketenimine C, as the temperature of their solutions (THF–hexane) rises to ambient. These ketenimine intermediates are too fragile to be isolated primarily because of their electrophilic nature and their rapid reaction with unrearranged carbanion B. Nevertheless, their presence is adequately confirmed by the isolation of dimers derived from B and C. This represents the first report of such behavior



despite the extensive literature pertaining to metalation of heterocyclic compounds.[1]

The rearrangement–dimerization was demonstrated with three different heterocyclic systems: thiazoles (**1**), 1,3,4-thiadiazoles (**10**), and 1,3,4-oxadiazoles (**11**), all conforming to the structural features in A. Treatment of 2,4-dimethylthiazole (**1a**) with *n*-butyllithium (THF, −78°) gave the corresponding lithiated derivative **2**. That the latter was indeed the lithiomethyl salt **2** was confirmed by addition of methyl iodide at −78° providing, after work-up, 2-ethyl-4-methylthiazole[2,3] in 90% yield. If, however, a solution of **2** was allowed to warm to room temperature in the absence of an added electrophile, the dimer **6a** was isolated, after quenching, in 85% yield [bp 35° (0.02 Torr); ir (film) 1665, 1530 cm^{-1}; nmr ($CDCl_3$) δ 6.8 (s, 1), 3.81 (AB q, J = 18 Hz, 2), 3.5 (s, 2, S-CH_2C=N), 2.4 (s, 3), 2.1 (s, 3), 1.8 (s, 3); *m/e* 226 (M^+, 5%)].[4] When **6a** was heated above 150°, quantitative reversal to the starting thiazole **1a** occurred (presumably *via* the tautomer **7**) which is the most likely reason for this behavior being thus far undetected. The sequence was repeated with 4-phenyl-2-methylthiazole (**1b**). Alkylation of its lithio salt with methyl iodide at −78° gave **9** (94.8%) and 2-ethyl-4-phenylthiazole (5.2%). The latter was derived from alkylation of **2**, indicating that metalation of **1b** occurs predominantly at the 5 position (**8**). However, when the solution containing **8** was allowed to reach room temperature, the corresponding dimer **6b** was isolated (90%) after aqueous work-up [oil, nmr ($CDCl_3$) δ 8.0–7.7 (m, 4), 7.6–7.2 (m, 7), 4.21 (AB q, J = 19 Hz, 2), 3.7 (s, 2), 1.9 (s, 3)]. It is interesting to note that the initially formed lithio derivative **8** (kinetically favored at 0 to −78°) rearranges to the side-chain lithio salt **2** prior to ring cleavage and dimerization.[5] The facile thermal reversal of **6b** to **1b** (*via* **7**) was also noted when the former was subjected to distillation at 135–145°.

This property of metalated thiazoles (**2**) can be readily

(1) J. M. Mallan and R. L. Bebb, *Chem. Rev.*, **69**, 693 (1969); A. Hetzheim and K. Mockel, *Advan. Heterocycl. Chem.*, 7, 183 (1966); L. L. Bambas, "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Vol. 4, Wiley-Interscience, New York, N. Y., 1952, p 81; W. Baker and W. D. Ollis, *Quart. Rev., Chem. Soc.*, **11**, 15 (1957); J. M. Sprague and A. H. Land, *Heterocycl. Compounds*, **5**, 484 (1957); H. Gilman and J. W. Morton, *Org. React.*, **8**, 258 (1954).

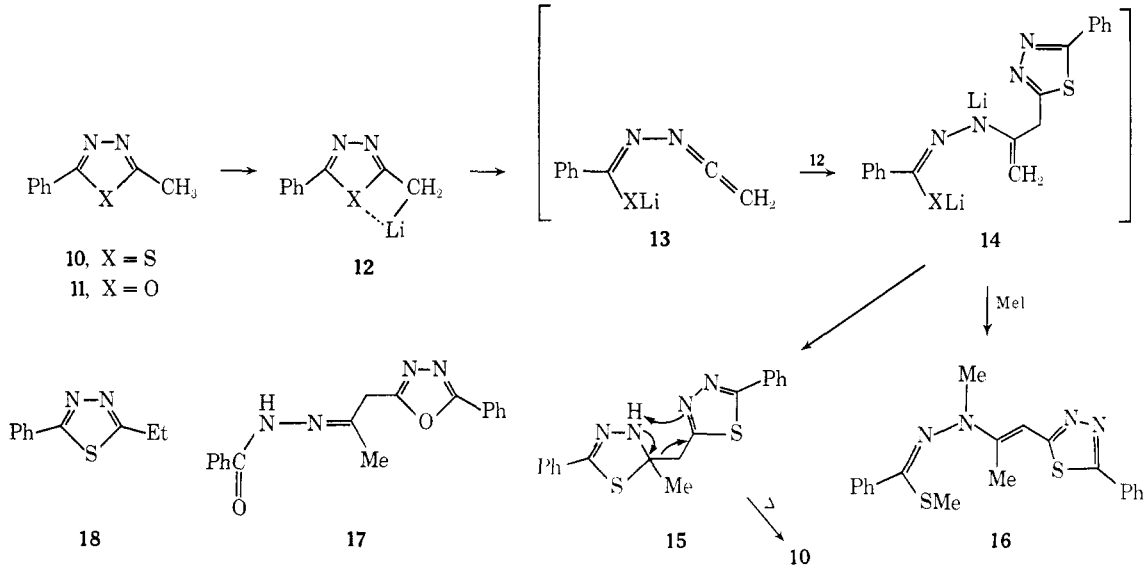
(2) F. Asinger, M. Thiel, and L. Schroder, *Justus Liebigs Ann. Chem.*, **610**, 49 (1957).

(3) Alkylation of the 2-methyl group in thiazoles *via* its lithio salt has been reported: J. Crousier and J. Metzger, *Bull. Soc. Chim. Fr.*, 4134 (1967).

(4) All new compounds gave satisfactory elemental analyses.

(5) A study on the site of metalation in thiazoles including deuterium isotope effects will be published shortly.

Scheme II

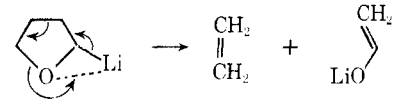


explained by assuming that the ring opening is assisted by a strong lithium–sulfur complex slowly producing the ketenimine intermediate **3** (see Scheme I). Since the ketenimine is a highly receptive electrophile,[6,7] the remaining lithio salt **2** adds to the cumulative system forming the adduct **4**. Quenching leads to the open-chain mercaptoamine **5** which expectedly tautomerizes to the cyclic form **6** (and/or **7**). Attempts to trap the dilithio adduct **4** with suitable electrophiles (MeI, D_2O) repeatedly led to complex mixtures of products, including low molecular weight and foul-smelling sulfur compounds. Successful interception of intermediates, however, was achieved in the thiadiazole system **10**.

Addition of *n*-butyllithium (THF, −78°) to the thiadiazole **10** followed by introduction of methyl iodide at the low temperature gave *via* **12** the 2-ethyl derivative **18** in 97% yield. If the experiment was repeated without addition of methyl iodide and the solution allowed to reach room temperature, the dimer **15** was isolated in 75% yield after quenching [mp 144–145°; ir (KBr) 3310, 1465, 1460 cm^{-1}; nmr ($CDCl_3$) δ 8.1–7.9 (m, 2), 7.8–7.3 (m, 8), 6.6 (NH, exchangeable with D_2O), 5.70 (AB q, J = 17 Hz, 2), 1.9 (s, 3); *m/e* 352 (M^+, 1%)]. When methyl iodide was added to the room temperature solution of **12** and the reaction stirred overnight and then quenched, the bright yellow crystalline compound isolated (47%) was characterized as the intercepted open-chain dimer **16**[8] [mp 149–151°; ir (KBr) 1590, 1500 cm^{-1}; nmr ($CDCl_3$) δ 8.1–7.8 (m, 4), 7.6–7.2 (m, 7 includes vinyl H), 2.5 (s, 3), 2.4 (s, 3), 2.2 (s, 3); λ^{CH_3CN} 406 nm; *m/e* 380 (M^+)]. This experiment provided direct proof for the existence of **14** and lent strong support for similar intermediates (**4**) in the thiazole series. As before, heating the dimer **15** at 150–160° resulted in complete reversion to the monocyclic thiadiazole **10**.

Reaction of 2-methyl-5-phenyloxadiazole (**11**) with butyllithium under similar conditions afforded the dimer **17** [35%; mp 136–138°; ir (KBr) 3240, 1635, 1530 cm^{-1}; nmr ($CDCl_3$) δ 9.1 (NH, exchangeable with D_2O), 8.2–7.7 (m, 4), 7.7–7.3 (m, 6), 4.1 (s, 2), 2.1 (s, 3); λ^{CH_3CN} 316 nm; *m/e* 320 (M^+, 12%)]. The dimer **17** was thermally stable and showed little or no tendency to revert back to the starting oxadiazole.[9]

It may be concluded at this time that the rearrangement of lithiated heterocycles of the type B is a general phenomenon which may be operating in many other systems (Scheme II). The strength of the lithium–oxygen and lithium–sulfur complex in B is apparently temperature dependent resulting in normal carbon–carbon alkylations at low temperatures while undergoing ring rupture at higher temperatures. The nearest analogy to this study may be found in the cycloreversion of lithiotetrahydrofuran to ethylene and the enolate of acetaldehyde.[10]



Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work and to the National Science Foundation.

(6) For a review on the chemistry of ketenimines, see G. R. Krow, *Angew. Chem., Int. Ed. Engl.*, **10**, 435 (1971).

(7) Carbanion–ketenimine rearrangements have been noted by us in the cycloaliphatic series; dihydro-1,3-oxazines [A. I. Meyers, *et al.*, *J. Org. Chem.*, **38**, 36 (1973)]. Unpublished observations in this laboratory have also included the carbanion rearrangement of other cyclic imino ethers and thioethers (2-oxazolines and 2-thiazolines), but this phenomenon in heteroaromatic systems was, frankly, unexpected.

(8) This compound slowly underwent a structural change in chloroform solution to other products which were not investigated.

(9) The heterocycles used in this study were obtained as follows: **1a**, purchased from Aldrich Chemical Co.; **1b**, G. Vernin, J. P. Aune, H. J. Don, and J. Metzger, *Bull. Soc. Chim. Fr.*, 4523 (1967); **10**, M. Ohta, *Yakugaku Zasshi*, **73**, 1127 (1953); **11**, H. Weidinger and J. Krantz, German Patent 1,067,439 (1958); *Advan. Heterocycl. Chem.*, **7**, 183 (1966).

(10) R. B. Bates, L. M. Kroposki, and D. E. Potter, *J. Org. Chem.*, **37**, 560 (1972), and earlier references cited; P. Tomboulian, D. Amick, S. Beare, K. Dumke, D. Hart, R. Hites, A. Metzger, and R. Nowak, *ibid.*, **38**, 322 (1973).

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