of **10** as a pale orange oil: ir (neat) 5.80 μ sharp (C=O); pmr 3.80 (s, 2, $=ClCH_2COCH_3$), 2.35 (m, 4, allylic), 2.14 (s, 3, $COCH_3$), and 1.58 (m, 6, aliphatic); mass spectrum *m/e* 278, 151 (parent minus I). This oil turned black and became viscous when exposed to air for short periods of time or when heated to 40°. Because of this sensitivity no further analytical data were obtained.

Registry No.—**8**, 21527-61-7; **10**, 51004-20-7; **11**, 51004-21-8; **12**, 36597-09-8; **13**, 18559-89-2; **15**, 51004-22-9; 1-oxa-3-azaspiro[4,4]-nonan-2-one, 19684-59-4.

References and Notes

(1) This work was supported by Grant No. 12445 of the National Science Foundation.
(2) This work formed part of the Ph.D. thesis presented by M. C. V. Z., to The Ohio State University, 1973.
(3) (a) M. S. Newman and Z. ud Din, *Syn. Commun.*, **1**, 247 (1971); (b) *J. Org. Chem.*, **38**, 547 (1973).
(4) M. S. Newman and G. Fraunfelder, *J. Org. Chem.*, **39**, 251 (1974).
(5) H. C. Brown and G. Goldman, *J. Chem. Soc.*, **84**, 1650 (1962).
(6) F. C. Whitmore, "Organic Compounds of Mercury," Reinhold, New York, N. Y., 1921, pp 67–73.
(7) L. G. Makarova in "Organometallic Reactions," Vol. 1, Wiley-Interscience, New York, N. Y., 1970, 325 ff.
(8) A. N. Nesmeyanov, A. E. Borisov, I. S. Savel'eva, and M. A. Osipova, *Izv. Akad. Nauk USSR, Otd. Khim. Nauk*, 1249 (1961); *Chem. Abstr.*, **56**, 1469c (1962).
(9) H. C. Brown and H. Nambu, *J. Amer. Chem. Soc.*, **92**, 1761 (1970).
(10) E. J. Corey and R. H. K. Chen, *Tetrahedron Lett.*, 1611 (1973).
(11) E. Hunt and B. Lythgoe, *Chem. Commun.*, 757 (1972).
(12) J. E. Baldwin and J. A. Walker, Chem. Commun., 354 (1972).
(13) T. W. Gibson and W. Erman, *J. Org. Chem.*, **37**, 1148 (1972).
(14) T. Ozeki and M. Kusaka, *Bull. Chim. Soc. Jap.*, **39**, 1995 (1966).
(15) N. C. Yang and M. J. Jorgenson, *Tetrahedron Lett.*, 1203 (1964).
(16) C. M. Starks, *J. Amer. Chem. Soc.*, **93**, 195 (1971).
(17) For an improved synthesis of **6**, see M. S. Newman and M. C. Vander Zwan, *J. Org. Chem.*, **38**, 2910 (1973).
(18) M. S. Newman and A. O. M. Okorodudu, *J. Org. Chem.*, **34**, 1220 (1969).
(19) S. M. McElvain and D. Kundiger, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 506.
(20) H. Labhart and G. Wagniere, *Helv. Chim. Acta*, **42**, 2219 (1959).
(21) O. Lorenz, *Anal. Chem.*, **37**, 101 (1965).

The Chemistry of Metalated Heterocycles. Dimerization of 2-Lithiomethyl-1,3-thiazoles, -1,3,4-thiadiazoles, and -1,3,4-oxadiazoles

G. Knaus and A. I. Meyers*

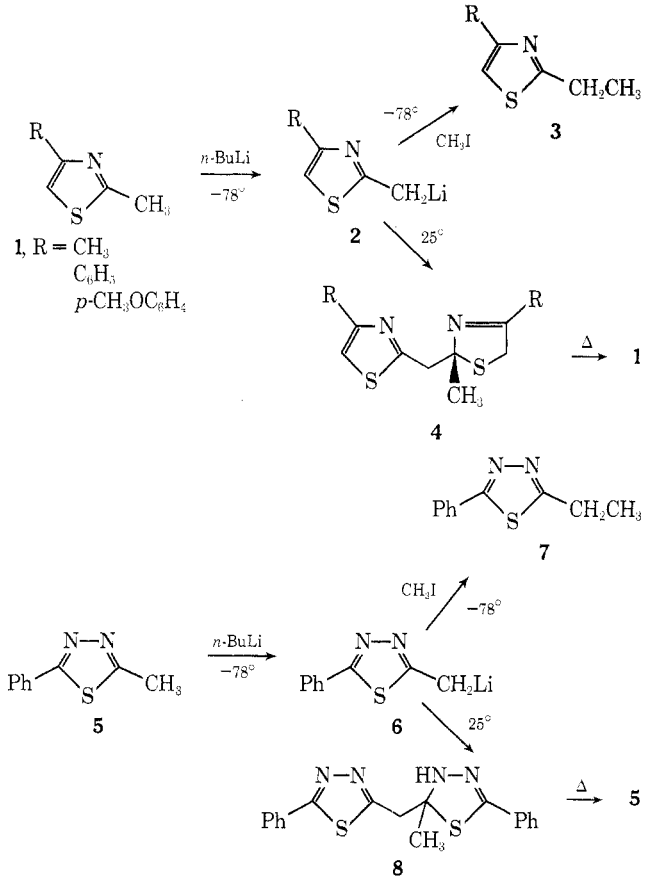
Department of Chemistry, Colorado State University, Fort Collins, Colorado 80521

Received November 12, 1973

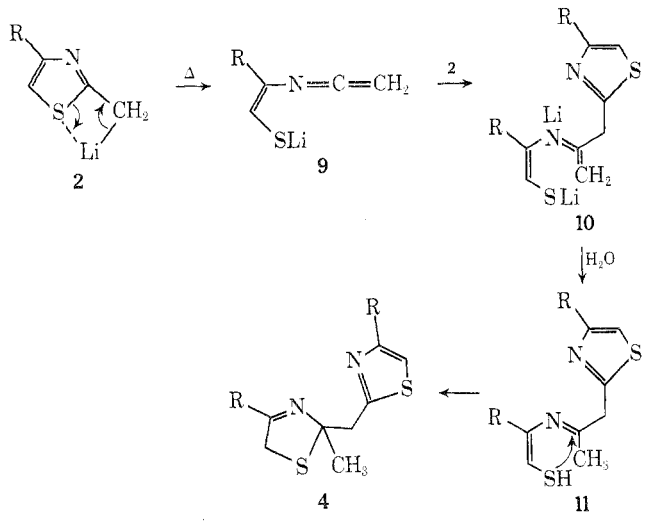
The carbanions derived from 2-methyl-1,3-thiazoles **2** are shown to retain their integrity at low temperatures by C-alkylation with alkyl halides. On the other hand, if these lithiated species are allowed to warm from −78° (their temperature of formation) to ambient temperatures, nucleophilic attack occurs with trace amounts of nonmetalated thiazole **1** producing the dimer **4**. Similar results were obtained when the 2-methyl-1,3,4-thiadiazole **5** (X = S) and the 2-methyl-1,3,4-oxadiazole **5** (X = O) were transformed into their lithio salts. These data tend to nullify the previously suggested mechanism for dimerization involving a ketenimine intermediate.

In a preliminary report[1] the behavior of thiazoles **1** and 1,3,4-thiadiazoles **5** after conversion to their respective lithio salts **2** and **6** was described. It was shown that alkylation of the lithio thiazole with methyl iodide at low temperature produced the expected 2-ethyl derivative whereas allowing **2** to warm to room temperature led to the dimer **4** in 75–90% yield. Similar behavior was noted for the lithio thiadiazole **6**, which produced, after low-temperature alkylation, the 2-ethyl derivative **7** or the dimer **8** upon warming in the absence of methyl iodide. Of further interest was the fact that the dimeric products **4** and **8** readily reversed upon heating (>150°) to the starting heterocycles. This facile dimerization of the lithiated heterocycles and their subsequent reversion to monomers has apparently escaped detection despite the extensive literature pertaining to metalation of heterocycles.[2] The purpose of the present paper is not only to report further details regarding the dimerization of lithio heterocycles but to offer a mechanism for this process.

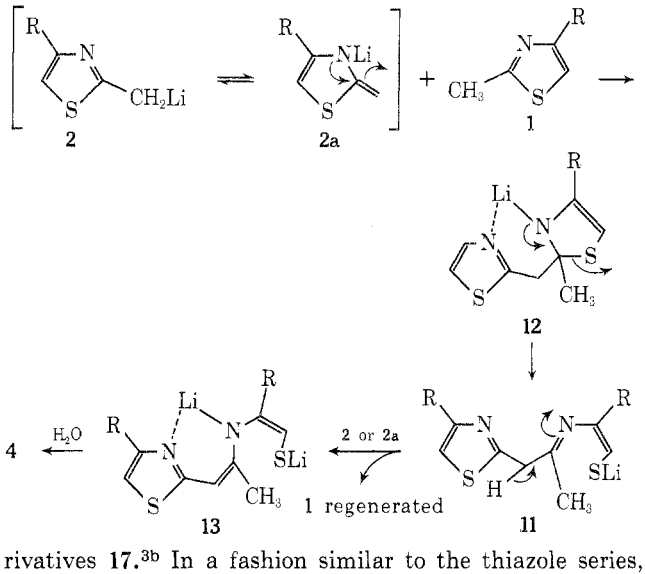
In the case of the thiazole system **1**, the dimer **4** may be envisioned as forming through two different mechanisms (Schemes I and II). The lithio thiazole may rearrange upon warming from −78° to 25° to the thiolithio ketenimine **9**, which is attacked as it is formed by unrearranged lithio thiazole, leading to the adduct **10**. Quenching of the solution would produce the thiol imine **11**, resulting in cyclization to the observed dimer **4**. This pathway, originally suggested for the dimer formation,[1] is based upon the analogous dimerization of oxazine and oxazoline carbanions **14** to their respective dimers **16**,[3a] Proof of the intermediacy of the ketenimine **15** was presented by isolation and characterization of the entrapped O-trimethylsilyl de-



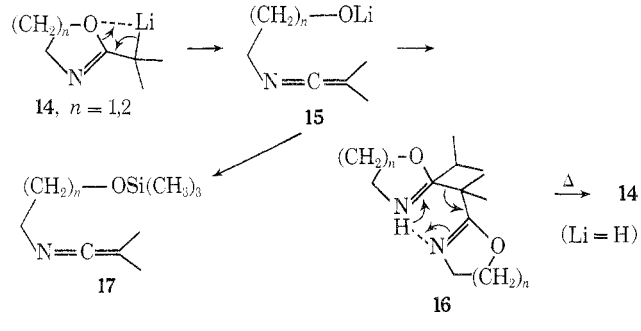
Scheme I



Scheme II

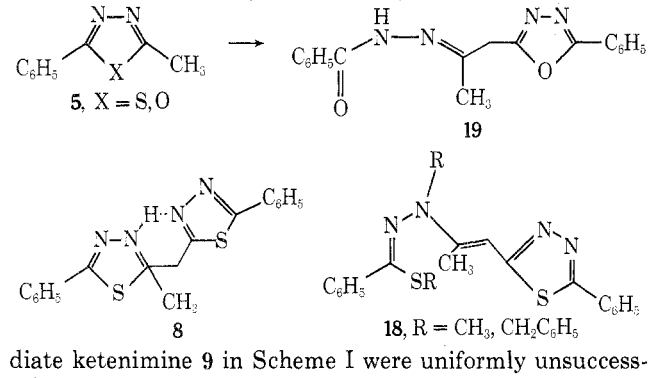


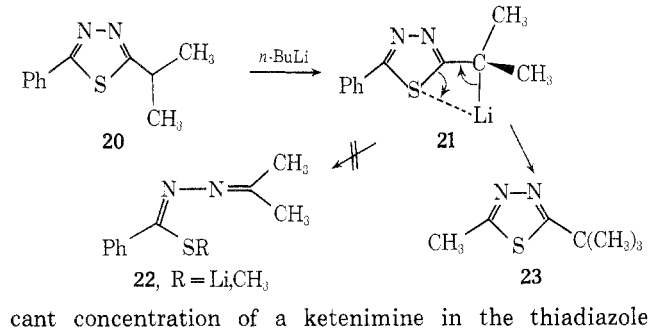
rivatives **17**.[3b] In a fashion similar to the thiazole series, **16** also underwent quantitative reversion to **14** on heating.



Another feasible pathway leading to the thiazole dimer which does not involve the ketenimine intermediate is outlined in Scheme II.[4] In this route to the dimer, the lithio methylthiazole may add directly to unmetalated thiazole, which need be present in only trace amounts, generating the adduct **12**. Rearrangement to the open-chain imine **11** provides an intermediate whose acidity toward the lithio thiazole **2** should be rather pronounced. Proton abstraction by **2** would give the dilithio intermediate **13** (the tautomer of **10** postulated in Scheme I) and regenerate the 2-methylthiazole **1** for further reaction. Attempts to trap **13** using methyl iodide gave only a complex mixture of products.

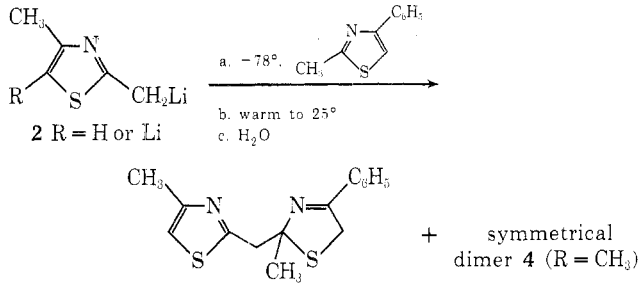
Open-chain intermediates were isolated, however, from the related 1,3,4-thiadiazole **5** (X = S) and 1,3,4-oxadiazole **5** (X = O) when their respective lithio salts were allowed to warm from −78° to room temperature. The dimer **8** derived from the thiadiazole was smoothly formed when no external electrophile was added prior to quenching, while the thio imine **18** was isolated if methyl iodide or benzyl bromide was added prior to quenching. The corresponding bicyclic dimer of the oxadiazole **5** (X = O) was not obtained after quenching with water. Rather the open-chain hydrazide **19** was isolated. Presumably, the facile ring–chain tautomerism present in the sulfur heterocycles (leading to **8**) is not as pronounced in the oxygen system owing to the lesser nucleophilic character of the *N*-acyl group in **19**. Various attempts to trap the intermediate ketenimine **9** in Scheme I were uniformly unsuccessful, as was every attempt to detect the strong ketenimine absorption (2000–2100-cm^{-1} region) in the reaction medium. Pursuing the earlier observation in the oxazoline and oxazine series[3] that a tertiary carbanion generated from these systems does not react with ketenimines owing to their bulky nature, the 2-isopropyl thiadiazole **20** was prepared and transformed into its lithio salt **21**. If the ketenimine **22** (R = Li) is indeed an intermediate, the latter should form spontaneously at or near 0° and subsequent alkylation would provide the *S*-methyl ketenimine **22** (R = CH_3). However, addition of methyl iodide to **21** at various temperatures (−78 to 25°) afforded no ketenimine **22** (R = CH_3) but only the 2-*tert*-butylthiadiazole **23** in quantitative yield. It soon became clear that any significant concentration of a ketenimine in the thiadiazole dimerization was rather doubtful and the alternate mechanism (Scheme II) should be considered. In order to test the latter mechanism, a large excess (2.5 equiv) of *n*-butyllithium was added (−78°) to 2,4-dimethylthiazole **1** (R = CH_3) and the solution was allowed to warm to room temperature prior to deuterolysis. After work-up, *only dideuterated thiazole was recovered with no evidence of any dimeric product.* Under these conditions, almost complete dianion formation resulted and the concentration of nonmetalated thiazole was nil.[5] This is in sharp contrast to the earlier experiment wherein 1.0–1.1 equiv of *n*-butyllithium was employed and undoubtedly allowed a small amount of thiazole to escape metalation.





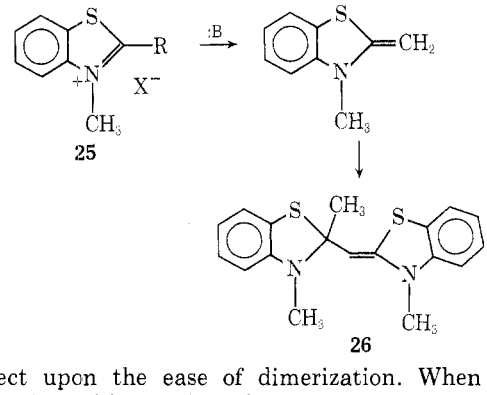
Finally, a crossover experiment involving the dilithio thiazole, generated at −78° with 1.9 equiv of *n*-butyl-

lithium, followed by addition of 2-methyl-4-phenylthiazole at −78°, gave both the unsymmetrical (**24**) and symmetrical (**4**) dimers after the mixture was allowed to rise to ambient. Similar results were obtained using only 0.9 equiv of *n*-butyllithium. One may conclude from these results that 2-lithio thiazoles **2** add to the C=N of nonmetalated thiazoles as the temperature rises to ambient and this process takes place even when the thiazoles are dilithiated.



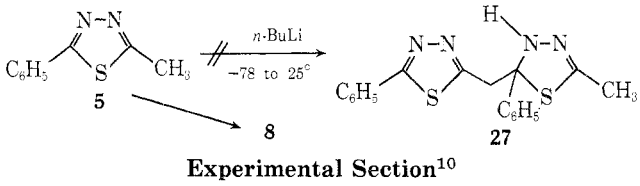
24

The mechanism depicted in Scheme II has some related precedent. It has been observed[6,7] that benzothiazolium salts **25** (R = CH_3) under basic conditions gave the dimer **26.** It was also noted that the nature of the R group had



25 **26**

an effect upon the ease of dimerization. When R was ethyl[8] or benzyl,[9] **25** did not lead to dimers of the type **26,** but only recovery of the monomeric base. Similar behavior was observed for 2-methyl-5-phenyl-1,3,4-thiadiazole (**5**) when treated with 1.0 equiv of *n*-butyllithium. The dimer derived by carbanion attack at the carbon bearing the methyl group **8** was the only product obtained and none of the dimer **27** was isolated. It would appear, therefore, that the dimerization process is quite sensitive to both steric and electronic factors at the 2 position.



5 **8** **27**

Experimental Section[10]

Metalation and Dimerization of 2,4-Dimethylthiazole (1, R = CH_3). *n*-Butyllithium (8.0 ml, 17.7 mmol) in hexane was added dropwise to a stirred solution (N_2) of 2,4-dimethylthiazole[11a] (2.00 g, 17.7 mmol) in dry tetrahydrofuran (30 ml) at −78°. The resulting wine-colored reaction mixture was stirred at this temperature for 0.5 hr and then allowed to warm to room temperature. This was stirred for a further 8 hr, poured into ice-water (100 ml), and extracted with ether (2 × 150 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated under vacuum to give a light yellow oil. Molecular distillation afforded 1.64 g (82%) of dimer **4** (R = CH_3): bp ~35° (0.02 Torr); ir (NaCl) 1665, 1530, 1465, 1440, 1420 cm^{-1}; nmr ($CDCl_3$) δ 6.77 (s, 1), 3.81 (AB q, *J* = 18 Hz, 2), 3.5 (s, 2, $SCH_2C{=}N$), 2.43 (s, 3), 2.10 (s, 3), 1.80 (s, 3).

Anal. Calcd for $C_{10}H_{14}N_2S_2$: C, 53.06; H, 6.23; N, 12.38. Found: C, 52.79; H, 6.01; N, 12.33.

Metalation and Dimerization of 2-Methyl-4-phenylthiazole (1, R = Ph). *n*-Butyllithium (4.5 ml, 7.1 mmol) in hexane was added dropwise to a stirred solution (N_2) of 2-methyl-4-phenylthiazole[11b] (1.24 g, 7.10 mmol) in dry tetrahydrofuran (30 ml) at −78°. The resulting yellow-colored reaction mixture was allowed to warm to room temperature and stirred for a further 8 hr, at which time it was dark brown in color. Quenching with water and extraction with ether, as described above, gave 1.12 g (90%) of dimer **4** (R = Ph) as a light yellow oil. Crystallization from ether–hexane (−78°) gave an almost colorless solid which melted when warmed to room temperature: nmr ($CDCl_3$) δ 8.0–7.7 (m, 4), 7.6–7.2 (m, 7), 4.30 (AB q, 2), 3.73 (s, 2), 1.91 (s, 3).

Pyrolysis of **4** (R = Ph) (0.95 g) in a molecular distillation apparatus at 150–160° for 0.5 hr, followed by distillation (0.02 Torr), gave 0.91 g (96%) of 2-methyl-4-phenylthiazole.

Metalation and Dimerization of 2-Methyl-4-*p*-methoxyphenylthiazole (1, R = *p*-$CH_3OC_6H_4$). *n*-Butyllithium (4.4 ml, 7.0 mmol) was added dropwise to a stirred solution (N_2) of **1** (R = *p*-$CH_3OC_6H_4$)[12] (1.44 g, 7.00 mmol) in dry tetrahydrofuran (25 ml) at −78°. Quenching with water and work-up as before gave 1.29 g (90%) of dimer **4** (R = *p*-$CH_3OC_6H_4$) as a light yellow oil: nmr ($CDCl_3$) δ 7.33 (A_2B_2, q, 8), 7.17 (s, 1), 4.22 (AB q, 2), 3.80 (s, 6), 3.71 (s, 2), 1.87 (s, 3).

Pyrolysis of **4** (R = *p*-$CH_3OC_6H_4$) (0.88 g) as before and distillation under vacuum (0.02 Torr) gave 0.81 g (92%) of 2-methyl-4-*p*-methoxyphenylthiazole.

Metalation and Dimerization of 2-Methyl-5-phenylthiadiazole (5). A. Quenching with Water. *n*-Butyllithium (3.6 ml, 7.9 mmol) in hexane was added dropwise to a stirred solution (N_2) of 2-methyl-5-phenylthiadiazole[13] (1.40 g, 7.95 mmol) in dry tetrahydrofuran (35 ml) at −78°. Quenching with water (at 25°) and work-up as before gave an orange solid. Recrystallization from acetonitrile–water (15:1 v/v) gave 1.04 g (74%) of dimer **8** as almost white needles: mp 144–145°; ir (KBr) 3310 (NH), 1465, 1455, 1420 cm^{-1}; nmr ($CDCl_3$) δ 8.1–7.9 (m, 2), 7.8–7.3 (m, 8), 6.66 (s, NH, D_2O exchange), 3.73 (AB q, 2), 1.87 (s, 3); mass spectrum (70 eV) *m/e* 352 (M^+, 1).

Anal. Calcd for $C_{18}H_{16}N_4S_2$: C, 61.33; H, 4.58; N, 15.90. Found: C, 61.58; H, 4.74; N, 15.85.

Pyrolysis of dimer **8** (0.58 g) in a sublimation apparatus at 150–170° (0.03 Torr) gave 0.53 g (92%) of 2-methyl-5-phenylthiadiazole.

B. Quenching with Methyl Iodide. The lithio salt was quenched with iodide (1.3 equiv) at 25° and work-up as before gave a yellow solid. Recrystallization from hot acetonitrile gave a 47% yield of dimer **18** (R = CH_3): mp 149–151°; ir (KBr) 1590, 1505, 1435 cm^{-1}; nmr ($CDCl_3$)[14] δ 8.1–7.8 (m, 4), 7.6–7.2 (m, 7), 2.50 (s, 3), 2.37 (s, 3), 2.23 (s, 3); λ_{max} (CH_3CN) 406 nm.

Anal. Calcd for $C_{20}H_{20}N_4S_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.95; H, 5.56; N, 14.59.

C. Quenching with Benzyl Bromide. The lithio salt was quenched with benzyl bromide (1.2 equiv) at 25° and work-up as before gave a yellow solid. Recrystallization from hot acetonitrile gave a 38–45% yield of dimer **18** (R = $C_6H_5CH_2$): mp 142–144°; ir (KBr) 1590, 1525, 1495, 1455, 1450, 1435 cm^{-1}; nmr ($CDCl_3$)[14] δ 8.1–7.8 (m, 4), 7.6–7.1 (m, 17), 4.10 (s, 2), 4.01 (s, 2), 2.43 (s, 3); λ_{max} (CH_3CN) 407 nm.

Anal. Calcd for $C_{32}H_{28}N_4S_2$: C, 72.18; H, 5.30; N, 10.53. Found: C, 72.35; H, 5.36; N, 10.71.

Metalation and Dimerization of 2-Methyl-5-phenyloxadiazole. *n*-Butyllithium (2.9 ml, 6.45 mmol) was added dropwise to a stirred solution of 2-methyl-5-phenyloxadiazole[15] (1.03 g, 6.44 mmol) in dry tetrahydrofuran (20 ml) at −78°. The resulting wine-colored reaction mixture was stirred for 0.5 hr (−78°) and then allowed to warm to room temperature. This was stirred for a further 8 hr, poured into ice-water (100 ml), and extracted with ether (2 × 150 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated under vacuum to give a colorless, oily solid. Upon the addition of anhydrous ether (*ca.* 20 ml), a white, crystalline solid separated and was quickly filtered. Recrystallization from acetonitrile–carbon tetrachloride (1:1 v/v) gave 0.36 g (34%) of dimer **19:** mp 135–137°; ir (KBr) 3240 (NH), 1635 (CO), 1530, 1510, 1480 cm^{-1}; nmr ($CDCl_3$) δ 9.12 (s, NH, D_2O exchange, 1), 8.2–7.7 (m, 4), 7.7–7.3 (m, 6), 4.1 (s, 2), 2.1 (s, 3); mass spectrum (70 eV) *m/e* 320 (M^+, 12).

Metalation and Methylation of 2-Isopropyl-5-phenylthiadiazole (20). *n*-Butyllithium (2.2 ml, 5.0 mmol) in hexane was added dropwise to a stirred solution (N_2) of 2-isopropyl-5-phenylthiadiazole[16] (1.02 g, 5.0 mmol) in dry tetrahydrofuran (30 ml) at −78°. The resulting wine-colored reaction mixture was then allowed to warm to room temperature. This was stirred for 8 hr, and methyl

iodide (0.90 g, 6.3 mmol) was added dropwise. This was stirred for a further 1 hr, poured into ice–water (100 ml), and extracted with ether (2 × 150 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated under vacuum to give a light yellow oil. Molecular distillation gave 0.98 g (90%) of 2-*tert*-butyl-5-phenylthiadiazole (**23**): ir (NaCl) 1470, 1460, 1430 cm^{-1}; nmr ($CDCl_3$) δ 8.1–7.8 (m, 2), 7.6–7.3 (m, 3), 1.44 (s, 9).

Anal. Calcd for $C_{12}H_{14}N_2S$: C, 66.04; H, 6.47. Found: C, 66.07; H, 6.61.

Attempted Dimerization of 2,4-Dimethylthiazole with Excess Base. *n*-Butyllithium (11.1 ml, 25.0 mmol) in hexane was added dropwise to a stirred solution (N_2) of 2,4-dimethylthiazole (1.12 g, 10.0 mmol) in dry tetrahydrofuran (25 ml) at −78°. The resulting wine-colored reaction mixture was allowed to warm to room temperature and stirred for 8 hr. Quenching with deuterium oxide and extraction with ether followed by molecular distillation gave 0.96 g (84%) of 2-deuteriomethyl-5-deuterio-4-methylthiazole: nmr ($CDCl_3$) δ 6.66 (s, 0.1 H), 2.63 (t, 1:1:1, CH_2D), 2.40 (s, 3).

Formation of Mixed Dimer 24. *n*-Butyllithium (3.2 ml, 7.3 mmol) in hexane was added dropwise to a stirred solution (N_2) of 2,4-dimethylthiazole (0.92 g, 8.1 mmol) in dry tetrahydrofuran (30 ml) at −78°. The resulting wine-colored reaction mixture was stirred for 1 hr at −78° and then a solution of 2-methyl-4-phenylthiazole (1.42 g, 8.1 mmol) in dry tetrahydrofuran (10 ml) was added. This was allowed to warm to room temperature, quenched with ice–water (100 ml) 8 hr later, and extracted with ether (2 × 150 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated under vacuum to give a yellow oil. Molecular distillation at an oil bath temperature of 105° (0.08 Torr) gave dimer **4** (R = CH_3) (36%) and 2-methyl-4-phenylthiazole (79%). Further distillation at an oil-bath temperature of 145–150° (0.08 Torr) gave mixed dimer **24** (19%) as a viscous oil: ir (NaCl) 1635, 1530, 1495, 1450 cm^{-1}; nmr ($CDCl_3$) δ 8.05–7.75 (m, 2), 7.60–7.35 (m, 3), 6.77 (s, 1), 4.33 (AB q, 2), 3.77 (s, 2), 2.43 (s, 3), 1.80 (s, 3).

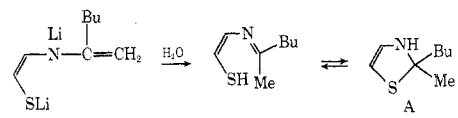
A repeat experiment using 1.90 equiv of *n*-butyllithium to form the dilithiothiazole, followed by the addition of 2-methyl-4-phenylthiazole and work-up as above, gave the symmetrical dimer **4** (32%) and the mixed dimer **24** (11%) along with starting material (82%).

Acknowledgment. The authors wish to express their gratitude to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for financial support of this work.

Registry No.—**1** (R = CH_3), 541-58-2; **1** (R = C_6H_5), 1826-16-0; **1** (R = *p*-$CH_3OC_6H_4$), 50834-78-1; **4** (R = CH_3), 41898-76-4; **4** (R = C_6H_5), 50834-81-6; **4** (R = *p*-$CH_3OC_6H_4$), 50834-82-7; **5** (X = S), 1456-72-0; **5** (X = O), 4046-03-1; **8**, 50883-40-4; **18** (R = CH_3), 41898-82-2; **18** (R = $CH_2C_6H_5$), 50834-83-8; **19**, 41898-84-4; **20**, 50834-84-9; **23**, 50834-85-0; **24**, 50834-86-1.

References and Notes

(1) A. I. Meyers and G. N. Knaus, *J. Amer. Chem. Soc.*, **95**, 3408 (1973).
(2) 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," Vol. 4, A. Weissberger, Ed., 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).
(3) (a) A. I. Meyers, E. M. Smith, and M. S. Ao, *J. Org. Chem.*, **38**, 2129 (1973); (b) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *ibid.*, **38**, 36 (1973).
(4) We wish to thank Professor S. Hunig, Wurzburg, for his comments and suggestions pertaining to this scheme.
(5) The possibility of the excess *n*-butyllithium reacting with the proposed ketenimine intermediates **9** or **22** was ruled out on two counts: (a) the high recovery (85%) of starting 2,4-dimethylthiazole and (b) products derived from such a reaction would lead to butylated thiazolines A which were sought but not found.



(6) O. Mumm, H. Hinz, and J. Diederichsen, *Chem. Ber.*, **72**, 2107 (1939).
(7) H. Larive and R. Dennilauler, *Chimia*, **15**, 115 (1961).
(8) G. H. Alt, *J. Org. Chem.*, **33**, 2858 (1968).
(9) J. Metzger, H. Larive, E. Vincent, and R. Dennilauler, *J. Chem. Phys.*, **60**, 944 (1963).
(10) All boiling points and melting points are uncorrected.
(11) (a) Aldrich Chemical Co., Milwaukee, Wis. (b) G. Vernin, J. P. Aune, H. J. M. Don, and J. Metzger, *Bull. Soc. Chim. Fr.*, 4523 (1967).
(12) B. Das, *J. Indian Chem. Soc.*, **34**, 505 (1957).
(13) M. Ohta, *J. Pharm. Soc. Jap.*, **73**, 1127 (1953).
(14) This compound slowly underwent a structural change in chloroform solution to other products which were not investigated.
(15) H. Weidinger and J. Krantz, German Patent 1,067,439 (1958).
(16) Prepared by successive metalation–methylation (at −78°) of 2-methyl-5-phenylthiadiazole.

The Chemistry of Metalated Heterocycles. The Site of Metalation of 2-Methyl-4-Substituted 1,3-Thiazoles. Electronic, Steric, and Isotope Effects

G. Knaus and A. I. Meyers*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80521

Received November 12, 1973

Metalation of 2-methyl-4-aryl-1,3-thiazoles proceeds predominantly at the C-5 position, whereas metalation of the 4-alkyl derivative occurs at the 2-methyl group. It is shown that the anions generated at −78° are the result of the respective kinetic acidities of these positions. Furthermore, at elevated temperatures, the thermodynamic acidities prevail, producing the lithio methyl anions regardless of the nature of the 4 substituent. An apparent primary kinetic isotope effect for the C-5 ring proton has been determined and agrees well with the isotope effect for other heterocyclic protons.

In the previous article[1] dealing with metalation of thiazoles **1** and related compounds, the lithio salt **2** was shown to alkylate trace quantities of the nonmetalated derivative **1** producing dimeric products **4** in high yield. This process appears only to take place if the solution of the lithiated thiazole **2** is allowed to warm from its temperature of formation (−78°) to ambient. However, if the lithiated thiazole is treated with an electrophile, E, at −78°, two alkylated products **5** and **6** are obtained. The ratio of these products is heavily dependent upon the nature of the 4 substituent, R, in the starting thiazole (Table I). Although Metzger[2] has reported, in an extensive temperature study on the metalation of 2-methylthiazole (**1**, R = H), that the two lithio salts **2** and **3** are formed independently and not through proton–metal exchange, it was felt that further evidence of this claim was necessary. In addition, examination of Table I reveals that metalation and subsequent alkylation of thiazoles containing the 4-aryl substituent leads to predominantly the 5-alkylthiazole **6**. On the other hand, when the 4 substituent is methyl, me-