tion of that of Baganz and Rüger.[20] Thioformamide[21] and tribromoacetone[22] were combined in ether and kept cold for 2 days, and the resulting solid was thoroughly washed to give 4-dibromomethyl-4-hydroxy-Δ^2-thiazoline hydrobromide, mp 120–123°. Following Baganz and Rüger,[20] the hydrobromide was treated with sulfuric acid to give 4-dibromomethylthiazole, mp 89–90° (hexane), which was hydrolyzed to **6**: mp 59–61° (lit.[23] 65–66°); nmr ($CDCl_3$) δ 8.31 (d, 1, $J_{2,5}$ = 1.9 Hz, 5-H), 8.98 (d, 1, $J_{2,5}$ = 1.9 Hz, 2-H), 10.13 (s, 1, CHO).

1-(4-Thiazolyl)ethanol (7).—Treatment of **6** with methylmagnesium bromide gave 90% of the alcohol **7**: bp 164–165° (55 mm); nmr ($CDCl_3$) δ 1.57 (d, 3, J = 6.3 Hz, $CHCH_3$), 4.08 (s, 1, CHOH), 5.05 (q, 1, J = 6.3 Hz, $CHCH_3$), 7.20 (d, 1, $J_{2,5}$ = 1.9 Hz, 5-H), 8.53 (d, 1, $J_{2,5}$ = 1.9 Hz, 2-H).

1-(4-Thiazolyl)ethyl Chloride (8).—Alcohol **7** was converted to chloride **8** using phosphorus pentachloride in 74% yield: nmr ($CDCl_3$) δ 1.90 (d, 3, J = 6.8 Hz, $CHCH_3$), 5.28 (q, 1, J = 6.8 Hz, $CHCH_3$), 7.32 (d, 1, $J_{2,5}$ = 2.0 Hz, 5-H), 8.75 (d, 1, $J_{2,5}$ = 2.0 Hz, 2-H). Decomposition occurs on attempted distillation.

Anal. Calcd for C_5H_6ClNS: C, 40.68; H, 4.09; Cl, 24.02; N, 9.49. Found: C, 40.82; H, 4.33; Cl, 24.22; N, 9.28.

Kinetic Procedures.—Absolute ethanol was prepared by the method of Lund and Bjerrum.[24] Four volumes of absolute ethanol were diluted with one volume of water. Rate constants were determined in three different fashions. Method A was by maintenance of a static pH. This method is particularly convenient when measurements are made near room temperature and half-lives are reasonably short. A Radiometer automatic titration apparatus was used, consisting of a no. TTT 1c automatic titrator, a no. ABU 1c autoburet (with a 2.5-ml buret), a TTA 3c titrator assembly, and a no. SBR 2c recorder. A 49-ml sample of the reaction medium was brought to temperature in the reaction cell in a constant-temperature bath. Reaction was initiated by injecting, *via* syringe, *ca.* 0.0005 mol of substrate dissolved in 1 ml of 80% ethanol–20% water into the reaction cell. The reaction solution was maintained at a constant apparent pH of 7.5 by the automatic addition of 0.30 *M* potassium hydroxide in 80% ethanol. The recorder plotted a continuous curve of the addition of base *vs.* time.

Alternatively, standard aliquot techniques (method B) or sealed ampoules (method C) were used. First-order rate constants were computed using the nonlinear least squares program, LSKIN 1.[25]

Registry No.—**1**, 40982-18-1; **2**, 41040-84-0; **3**, 41040-85-1; **4**, 40982-30-7; **5**, 40982-31-8; **6**, 3364-80-5; **7**, 41040-89-5; **8**, 3364-77-0; 2-chlorothiazole, 3034-52-4; acetaldehyde, 75-07-0; 2-bromothiazole, 3034-53-5; thioformamide, 115-08-2; tribromoacetone, 3770-98-7; 4-dibromomethyl-4-hydroxy-Δ^2-thiazoline hydrobromide, 41040-92-0; 4-dibromomethylthiazole, 41040-93-1; methyl bromide, 74-83-9.

(20) H. Baganz and J. Rüger, *Chem. Ber.*, **101**, 3872 (1968).
(21) H. Erlenmeyer and K. Menzi, *Helv. Chim. Acta*, **31**, 2071 (1948).
(22) C. Rappe, *Ark. Kemi*, **21**, 503 (1963).
(23) M. Erne, F. Ramirez, and A. Burger, *Helv. Chim. Acta*, **34**, 143 (1951).
(24) H. Lund and J. Bjerrum, *Ber.*, **64**, 210 (1931).
(25) D. F. DeTar and C. E. DeTar, "Computer Programs for Chemistry," Vol. 1, D. F. DeTar, Ed., W. A. Benjamin, New York, N. Y., 1968, Chapter 6.

Transmission of Substituent Effects in Heterocyclic Systems. Rates of Solvolysis of Substituted Thiazolylethanol Derivatives[1,2]

DONALD S. NOYCE* AND STEVEN A. FIKE

Department of Chemistry, University of California, Berkeley, California 94720

Received April 3, 1973

The rates of solvolysis for several substituted 1-(5-thiazolyl)ethanol derivatives have been measured in 80% ethanol and are compared with similar studies on other heterocycles. For the group 1-(2-X-5-thiazolyl)ethyl chlorides, reaction rates are well correlated by σ_p^+ for the substituents X. Similar correlation is observed for the solvolysis rates of 1-(5-X-2-thiazolyl)ethyl chlorides. These results are discussed in terms of the application of molecular orbital calculations relevant to the thiazole system.

In continuing studies from these laboratories[2–6] on the modes of transmission of substituent effects in heteocyclic systems, we have examined the relative reactivities of a number of substituted thiazoles.

There have been a few previous investigations of the application of the Hammett equation to thiazole derivatives. Imoto, Otsuji, and coworkers[7,8] have measured saponification rates for substituted ethyl thiazolecarboxylates and the dissociation constants of the corresponding acids. Moderately satisfactory correlation with Hammett σ values was observed; however, the value of ρ was occasionally surprising.

Our previous studies have shown that the solvolysis reaction is a useful probe for examination of heterocyclic systems[4,9] and that reactivities can often be related to parameters obtained from molecular orbital calculations. Metzger, *et al.*,[10] have recently summarized the results of a number of different molecular orbital calculations on thiazole. All of the various levels of approximation agree that the susceptibility to electrophilic aromatic substitution is in the order position 5 > position 4 > position 2; however, there is not agreement as to reactivity relative to benzene. Our studies[2] have shown that the order relative to benzene is 5-thiazolyl > 4-thiazolyl $\simeq$ phenyl > 2-thiazolyl.

Effect of Substituents.—We have prepared a number of 2-substituted 1-(5-thiazolyl)ethanols (A), and have measured the rates of solvolysis of the respective chlorides or *p*-nitrobenzoates. The large differences in reactivity dictated the use of different leaving groups. A pair of 5-substituted 1-(2-thiazolyl)ethanols (B) has likewise been examined.

In the case of series A, the measured rates are col-

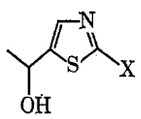
(1) Supported in part by a grant from the National Science Foundation, GP-6133X.
(2) Previous paper: D. S. Noyce and S. A. Fike, *J. Org. Chem.*, **38**, 3316 (1973).
(3) D. S. Noyce and R. W. Nichols, *J. Org. Chem.*, **37**, 4306, 4311 (1972).
(4) D. A. Forsyth and D. S. Noyce, *Tetrahedron Lett.*, 3893 (1972).
(5) D. S. Noyce and H. J. Pavez, *J. Org. Chem.*, **37**, 2620, 2623 (1972).
(6) D. S. Noyce and C. A. Lipinski, *J. Org. Chem.*, **37**, 2615 (1972).
(7) E. Imoto and Y. Otsuji, *Bull. Univ. Osaka Prefect., Ser. A*, **6**, 115 (1958); *Chem. Abstr.*, **53**, 3027*h* (1959).
(8) Y. Otsuji, T. Kimura, Y. Sugimoto, E. Imoto, Y. Omori, and T. Okawara, *Nippon Kagaku Zasshi*, **80**, 1024, 1297 (1959).
(9) D. S. Noyce and R. W. Nichols, *Tetrahedron Lett.*, 3889 (1972).
(10) R. Phan-Tan-Luu, L. Bouscasse, E. Vincent, and J. Metzger, *Bull. Soc. Chim. Fr.*, 1149 (1969).

TABLE I

RATE CONSTANTS FOR SOLVOLYSIS OF SUBSTITUTED 1-(5-THIAZOLYL)ETHANOL DERIVATIVES IN 80% ETHANOL

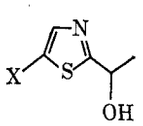
Compd solvolyzed	Leaving group	Kinetic[a] method	T, °C	10^5k, sec^{-1}	σ^+[b]	Rel rates
4 (H)	Cl	1 and 3	45.00	80.9 ± 0.7[c]	0.00	1.00
2 (2-Cl)	Cl	1 and 3	25.00	2.25 ± 0.1	0.114	
		1 and 3	45.00	23.4 ± 0.5		0.29
		1	60.00	95.0		
7 (2-CH_3)	Cl	3	25.00	385 ± 10		
6	OPNB		25.00	0.001[d]		
7	Cl		45.00	6070[c]	−0.311	75
6	OPNB	2	75.00	0.558 ± 0.007		
		2	110.00	17.2 ± 0.5		
10 (2-SCH_3)	OPNB	2	45.00	1.88 ± 0.04		
	OPNB	1	75.00	40.9		
	Cl		45.00	79,700[e]	−0.604	9,800
13 (2-OCH_3)	OPNB	1	45	12.9 ± 0.5		
	Cl		45.00	5.5 × 10^6[e]	−0.778	68,000

[a] Kinetic methods have been described previously (ref 3 and 4): 1, the usual aliquot technique; 2, using sealed ampoules; 3, at constant pH. [b] Reference 11. [c] Reference 21. [d] Extrapolated from rates at higher temperatures. [e] Calculated; see text.



A

1, X = Cl
3, X = H
5, X = CH_3
9, X = SCH_3
12, X = OCH_3



B

14, X = H
17, X = CH_3
20, X = SCH_3

lected in Table I. From the rates for 1-(2-methyl-5-thiazolyl)ethyl chloride (**6**) and 1-(2-methyl-5-thiazolyl)ethyl *p*-nitrobenzoate (**7**) we calculate a k_{Cl}/k_{OPNB} rate ratio of 3.8 × 10^5. Consideration of other compounds where k_{Cl}/k_{OPNB} ratios are available suggests using k_{Cl}/k_{OPNB} = 4.25 × 10^5. This ratio has been used to construct a relative sequence at 45° (column 7, Table I). A plot of these data against Brown's σ_p^+ substituent constants[11] gives a very high quality correlation (c.c = 0.998) and a ρ of −6.2.

Recently, Forsyth and Noyce[4] have pointed out that rate correlations for a number of heterocyclic systems are excellent with σ_p^+ in strictly defined and limited structural situations. In those cases where there is direct conjugation in the classical valence bond representation between the developing carbonium ion site and the site of attachment of the substituent, the correlation with Brown's electrophilic subtituent constants,[11] σ_p^+, is excellent; further, the magnitude of ρ is directly related to charge distribution as determined from CNDO/2 calculations.[4] This generalization manifested itself in furans, benzofurans, thiophenes, and here in thiazole.

To further extend these observations we have examined a limited number of 5-substituted 1-(2-thiazolyl)ethanol derivatives (series B).

The measured rate data are given in Table II, and relative rates are tabulated in column 7 of Table II. These data are very smoothly correlated also with σ_p^+ substituent constants. The value of ρ as determined from these three compounds (**5**, **13**, **17**) is −6.26. This value of ρ is very similar to that obtained for series A. This fact is in accord with the very similar values

(11) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4079 (1958).

TABLE II

RATE CONSTANTS FOR SOLVOLYSIS OF SUBSTITUTED 1-(2-THIAZOLYL)ETHANOL DERIVATIVES IN 80% ETHANOL

Compd solvolyzed	Leaving group	Kinetic[a] method	T, °C	10^5k, sec^{-1}	σ^+[b]	Rel rates
15 (5-H)	Cl		45.00	0.464[c]	0.00	1.00
18 (5-CH_3)	Cl	1	45.00	34.4 ± 0.7	−0.311	74
21 (5-SCH_3)	Cl	3	0.00	31.3 ± 0.8		
		3	25.00	452 ± 4		
			45.00	2830[d]	−0.604	6100

[a] See footoote *a*, Table I. [b] Reference 11. [c] Reference 2. [d] Extrapolated from data at lower temperatures.

of the changes in regional charge, Δq, calculated for these two isomeric thiazole moieties.[3,4]

Thus, in those limited siutations where direct conjugation, in a classical valence bond sense, is permissible, substituent constants from benzene appear applicable to substituted thiazoles.

Experimental Section[12]

1-(2-Chloro-5-thiazolyl)ethanol (1) has been reported previously.[2]

1-(2-Chloro-5-thiazolyl)ethyl Chloride (2).—Thionyl chloride (36 ml) was stirred at 0° in an ice bath while 1-(2-chloro-5-thiazolyl)ethanol (5.54 g) in 10 ml of dry ether was slowly added. After being stirred for 0.5 hr, the bath was removed and stirring was continued for an additional 1 hr. After reducing the volume of 15 ml on a rotary evaporator, the remaining solution was diluted with 100 ml of water. The stirred solution was brought to pH 9 by the slow addition of 1 *N* sodium hydroxide. The layers were separate and the aqueous layer was extracted with 2 × 30 ml of ether. The combined ether layers were then washed with 50 ml of 0.05 *N* sodium hydroxide, dried over anhydrous magnesium sulfate, and filtered. Removal of the ether on a rotary evaporator gave a yellow oil which was distilled to yield 3.19 g (52%) of the pure chloride **2**: bp 150° (75 mm); nmr ($CDCl_3$) δ 1.88 (d, 3, J = 7.0 Hz, $CHCH_3$), 5.29 (q, 1, J = 7.0 Hz, CHCl), 7.64 (s, 1, 4-H).

Anal. Calcd for $C_5H_5Cl_2NS$: C, 32.98; H, 2.77; N, 7.69; S, 17.61. Found: C, 33.12; H, 2.58; N, 7.88; S, 17.45.

1-(5-Thiazolyl)ethanol (3) and **1-(5-thiazolyl)ethyl chloride** (4) have been reported.[2]

1-(2-Methyl-5-thiazolyl)ethanol (5).—Ether (100 ml) was

(12) Melting points and boiling points are uncorrected. Routine ir spectra were recorded using a Perkin-Elmer Infracord Model 137. Nmr spectra were obtained using a Varian Associates Model T-60 spectrometer. Elemental analyses were determined by the Chemical Analytical Services Laboratory, College of Chemistry, Berkeley, Calif.

stirred at 0°[13] under a nitrogen atmosphere while 2-methylthiazole[16] (6.0 g, 0.06 mol) in 50 ml of ether was added dropwise from a dropping funnel. Simultaneously, *n*-butyllithium (0.066 mol, 41 ml in hexane) was added from a second dropping funnel. The thiazole was kept in slight excess during the 40-min addition period. After the addition was complete, the golden solution was stirred for an additional 15 min. Acetaldehyde (11.35 ml, 0.20 mol) was rapidly added, and an exothermic reaction ensued which resulted in a short period of gentle reflux. The ice bath was removed, and the solution was stirred for 15 min before quenching with 125 ml of cold water. The two layers were separated, and the aqueous layer was extracted with 3 × 50 ml of methylene chloride. The combined organic layers were dried over anhydrous magnesium sulfate and filtered. Removal of the solvent on a rotary evaporator yielded 8.33 g g (97%) of a crude yellow oil having excellent spectral properties for the alcohol **5** and essentially free of the isomeric 1-(2-thiazolyl)propan-2-ol: bp 89.5–90.0° (0.1 mm);[17] nmr ($CDCl_3$) δ 1.53 (d, 3, J = 6.5 Hz, $CHCH_3$), 2.60 (s, 3, 2-CH_3), 5.05 (q, 1, J = 6.5 Hz, $CHCH_3$), 5.50 (s, 1, OH), 7.30 (s, 1, 4-H).

1-(2-Methyl-5-thiazolyl)ethyl *p*-nitrobenzoate (**6**) was prepared in the usual way by treating the lithium salt of **5** with *p*-nitrobenzoyl chloride. The ester **6** was purified by chromatography on silica gel: mp 49–50°; nmr ($CDCl_3$) δ 1.82 (d, 3, J = 6.7 Hz, $CHCH_3$), 2.68 (s, 3, 2-CH_3), 6.42 (q, 1, J = 6.7 Hz, $CHCH_3$), 7.67 (s, 1, 4-H), 8.20 (s, 4, phenyl H).

Anal. Calcd for $C_{13}H_{12}N_2O_4S$: C, 53.41; H, 4.14; N, 9.58; S, 10.97. Found: C, 53.45; 4.11; N, 9.52; S, 10.69.

1-(2-Methyl-5-thiazolyl)ethyl chloride (**7**) was prepared by treating the alcohol **5** with phosphorus pentachloride in methylene chloride. Work up in the usual manner yielded 2.3 g (75%) of a light yellow oil which was eluted from a 20-cm column of silica gel with 1 l. of hexane to give the pure chloride **7**: nmr ($CDCl_3$) δ 1.83 (d, 3, J = 6.5 Hz, $CHCH_3$), 2.60 (s, 3, 2-CH_3), 5.22 (q, 1, J = 6.5 Hz, $CHCH_3$), 7.38 (s, 1, 4-H).

Anal. Calcd for C_6H_8ClNS: C, 44.58; H, 4.99; Cl, 21.93; N, 8.66. Found: C, 44.79; H, 5.05; Cl, 21.78; N, 8.77.

2-Methylthiothiazole (**8**).—Methyl mercaptan (16 ml) was added to 1 equiv of sodium methoxide in methanol (200 ml) at 0°. 2-Chlorothiazole (17.6 g) was added with 0.01 g of potassium iodide. After heating under reflux for 18 hr, the reaction mixture was diluted with water (400 ml) and extracted with ether. The ethereal extracts were dried ($MgSO_4$) and distilled to afford **8**: a colorless oil; 14.3 g, 74%; bp 89–90° (5 mm) [lit.[18] 68° (2 mm)]; nmr ($CDCl_3$) δ 2.66 (s, 3, SCH_3), 7.12 (d, 1, $J_{4,5}$ = 3.4 Hz, 5-H), 7.57 (d, 1, $J_{4,5}$ = 3.4 Hz, 4-H).

1-(2-Methylthio-5-thiazolyl)ethanol (**9**).—2-Methylthiothiazole (13.1 g, 0.1 mol) was metalated with *n*-butyllithium at 0°. Work-up in the usual fashion afforded 10.9 g (63%) of slightly impure alcohol **9**. This was further purified by elution through a 30-cm silica gel column with 1 l. of 70% hexane–30% ether: bp 174–180° (5 mm); nmr ($CDCl_3$) δ 1.51 (d, 3, J = 6.3 Hz, $CHCH_3$), 2.61 (s, 3, SCH_3), 4.97 (s, 1, OH), 5.05 (q, 1, J = 6.3 Hz, $CHCH_3$), 7.27 (s, 1, 4-H).

Anal. Calcd for $C_6H_9NOS_2$: C, 41.11; H, 5.18; N, 8.00; S, 36.58. Found: C, 41.02; H, 5.07; N, 7.92; S, 36.60.

1-(2-Methylthio-5-thiazolyl)ethyl *p*-nitrobenzoate (**10**) was prepared by treating the lithium salt of **9** with *p*-nitrobenzoyl chloride. The crude **10** was recrystallized from hexane to give a pure sample: mp 90.5–91.0°; nmr ($CDCl_3$) δ 1.80 (d, 3, J = 6.6 Hz, $CHCH_3$), 2.67 (s, 3, SCH_3), 6.33 (q, 1, J = 6.6 Hz, $CHCH_3$), 7.60 (s, 1, 4-H), 8.18 (s, 4, nitrophenyl H).

Anal. Calcd for $C_{13}H_{12}N_2O_4S_2$: C, 48.14; H, 3.73; N, 8.63; S, 19.77. Found: C, 48.22; H, 3.85; N, 8.56; g, 19.62.

2-Methoxythiazole (**11**).—The procedure used was a modification of that devised by Gronowitz for the synthesis of 5-methoxythiazole.[19]

Potassium iodide (0.01 g), cupric oxide (3.73 g, 0.0466 mol), and 2-chlorothiazole (10.0 g, 0.084 mol) were added to a solution of sodium (6.0 g, 0.26 mol) in 75 ml of anhydrous methanol. The mixture was stirred at reflux for 2 hr before cooling. The resulting dark solution was filtered, diluted with an equal volume of water, and then extracted with 3 × 40 ml of ether. The combined ether layers were dried ($MgSO_4$) distilled to give 4.76 g (50%) of pure 2-methoxythiazole: bp 49–50° (17 mm); ir (neat) 2950, 1535, 1475, 1240; 1190 cm^{-1}; nmr ($CDCl_3$) δ 4.00 (s, 3, OCH_3), 6.55 (d, 1, $J_{4,5}$ = 3.85 Hz, 5-H), 7.01 (d, 1, $J_{4,5}$ = 3.85 Hz, 4-H).

Anal. Calcd for C_4H_5NOS: C, 41.72; H, 4.38; N, 12.16 Found: C, 41.52; H, 4.51; N, 11.99.

1-(2-Methoxy-5-thiazolyl)ethanol (**12**).—Metalation of **11** was carried out at 0°. After 10 min a threefold excess of acetaldehyde was added. Work-up in the usual fashion gave 2.3 g (35%) of the clear, liquid alcohol **12**: bp 144° (19 mm); nmr ($CDCl_3$) δ 1.50 (d, 3, J_{CH,CH_3} = 6.8 Hz, $CHCH_3$), 3.96 (s, 3, OCH_3), 4.08 (s, 1, OH), 4.90 (q, 1, J_{CH,CH_3} = 6.8 Hz, $CHCH_3$), 6.80 (s, 1, 4-H),

1-(2-Methoxy-5-thiazolyl)ethyl *p*-nitropenzoate (**13**) was prepared in the usual fashion in 51% yield: mp 96–97°; nmr ($CDCl_3$) δ 1.75 (d, 3, $CHCH_3$), 4.03 (s, 3, OCH_3), 5.25 (q, 1, J = 6.8 Hz, $CHCH_3$), 7.13 (s, 1, 4-H), 8.17 (s, 4, nitrophenyl H).

1-(2-Thiazolyl)ethanol (14) has been reported.[2,20]

1-(2-Thiazolyl)ethyl Chloride (**15**).—Conversion of alcohol **14** to the chloride **15** was accomplished using thionyl chloride. Work-up and distillation afforded 42% chloride **15**: bp 84–85° (36 mm); nmr ($CDCl_3$) δ 1.90 (d, 3), 535 (q, 1), 7.25 (d, 1), 7.67 (d, 1).

Anal. Calcd for C_5H_6ClNS: C, 40.68; H, 4.09; Cl, 24.02; N, 9.49; S, 21.72. Found: C, 40.50; H, 4.07; Cl, 23.98; N, 9.60; S, 21.53.

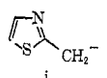
5-Methylthiazole (**16**).—Metalation of 2-chlorothiazole with butyllithium at −45°, followed by treatment with methyl iodide, gave a mixture of 2-chlorothiazole and 2-chloro-5-methylthiazole.[21]

This mixture (14.5 g 50:50 by nmr) was directly reduced by a procedure similar to that used by McLean and Muir for the reduction of 2-chlorothiazole.[22] The mixture (14.5 g) in 50 ml of glacial acetic acid was stirred with heating. When the temperature reached 60°, zinc dust (15.0 g, 0.23 g-atom) was added. The solution was heated under reflux for 4 hr and cooled. The resulting solution was neutralized with dilute ammonium hydroxide and steam distilled. The first 100 ml of distillate was extracted with 3 × 30 ml of ether. The combined ether extracts were dried ($MgSO_4$) and concentrated giving 6.82 g of the mixture. The mixture was separated on a spinning-band column by distilling the thiazole at atmospheric pressure then reducing the pressure to distil the remaining 5-methylthiazole to give 3.0 g (55%) of pure 5-methylthiazole (**16**): bp 64–66° (25 mm) [lit.[23] bp 70–72° (41 mm)]; nmr ($CDCl_3$) δ 2.42 (d, 3, $J_{4\text{-H},5\text{-}CH_3}$ = 1.2 Hz, 5-CH_3), 7.55 (q, 1, $J_{4\text{-H},5\text{-}CH_3}$ = 1.2 Hz, 4-H, incompletely resolved), 8.60 (s, 1, 2-H).

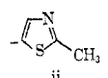
1-(5-Methyl-2-thiazolyl)ethanol (**17**).—Metalation of 5-methylthiazole at −80° using butyllithium was followed by addition of a threefold excess of acetaldehyde. Work-up in the usual fashion afforded alcohol **17** in 49% yield: bp 124–126° (5 mm); nmr (CCl_4) δ 1.54 (d, 3, J_{CH,CH_3} = 6.5 Hz, $CHCH_3$), 2.40 (d, 3, $J_{4\text{-H},5\text{-}CH_3}$ = 1.7 Hz, 5-CH_3), 4.90 (s, 1, OH), 5.06 (q, 1, J_{CH,CH_3} = 6.5 Hz, $CHCH_3$), 7.26 (q, 1, $J_{4\text{-H},5\text{-}CH_3}$ = 1.7 Hz, 4-H).

Anal. Calcd for C_6H_9NOS: C, 50.32; H, 6.34; N, 9.78; S, 22.39. Found: C, 50.50; H, 6.36; N, 9.51; S, 22.32.

(13) The reaction of 2-methylthiazole with a strong base has two major modes of reaction. A methyl proton can be removed which will form the reactive ion i, or the most reactive ring proton can be removed which will form the reactive ion ii. We have observed that at −80° *n*-butyllithium



i



ii

reacts with 2-methylthiazole to yield a mixture of anions which further reacts with acetaldehyde to give a mixture of products (42% through i and 58% through ii by nmr). On the other hand, at 0° at least 95% of the reaction goes through ring proton abstraction to give products from ion ii. This work agrees well with the trend reported by Crousier and Metzger[14] on similar studies involving reaction of i and ii with methyl iodide. The situation is very complex as shown by the recent studies of Meyers and Knaus.[15]

(14) J. Crousier and J. Metzger, *Bull. Soc. Chim. Fr.*, 4134 (1964).

(15) A. I. Meyers and G. N. Knaus, *J. Amer. Chem. Soc.*, **95**, 3408 (1973).

(16) A. Hantzsch, *Justus Liebigs Ann. Chem.*, **250**, 257 (1899).

(17) Crousier and Metzger[14] report a 6:1 mixture of **5** and 1-(2-thiazolyl)propan-2-ol, bp 132–134° (11 mm), and the nmr spectra of both isomers from reaction of butyllithium and 2-methylthiazole at −60°.

(18) P. Bastianelli, M. Chanon, and J. Metzger, *Bull. Soc. Chim. Fr.*, 1948 (1967).

(19) G. Borgen, S. Gronowitz, R. Dahlbom, and B. Holmberg, *Acta Chem. Scand.*, **20**, 2539 (1966).

(20) J. Beraud and J. Metzger, *Bull. Soc. Chim. Fr.*, 2072 (1962).

(21) The studies of Crousier and Metzger[14] indicate that incomplete alkylation is not surprising.

(22) J. McLean and G. D. Muir, *J. Chem. Soc.*, 383 (1942).

(23) H. Erlenmeyer and P. Schmidt, *Helv. Chim. Acta*, **29**, 1957 (1946).

1-(5-Methyl-2-thiazolyl)ethyl Chloride (18).—This chloride was prepared from alcohol **16** using phosphorus pentachloride to give a 67% yield of crude **18**. This was further purified by chromatography on silica gel to give 54% colorless chloride **18**: nmr ($CDCl_3$) δ 1.91 (d, 3, J_{CH,CH_3} = 7.0 Hz, $CHCH_3$), 2.41 (d, 3, $J_{4\text{-}H,5\ CH_3}$ = 1.1 Hz, 5-CH_3), 5.27 (q, 1, J_{CH,CH_3} = 7.0 Hz, $CHCH_3$), 7.33 (q, 1, $J_{4\text{-}H,5\text{-}CH_3}$ = 1.1 Hz, 4-H).

Anal. Calcd for C_6H_8ClNS: C, 44.58; H, 4.99; Cl, 21.93; N, 8.66; S, 19.84. Found: C, 44.43; H, 5.01; Cl, 21.94; N, 8.73; S, 19.74.

5-Methylthiothiazole (19).—Methyl mercaptan (27.7 ml, 0.5 mol) was added to 1 equiv of sodium methoxide in 175 ml of methanol at 0°. 5-Bromothiazole (32.8 g, 0.2 mol)[24] and 0.01 g of potassium iodide were added, and the solution was heated under reflux for 5 hr. The resulting clear solution and white precipitate wee taken up in 100 ml of water. The aqueous solution was then extracted with 3 × 200 ml of ether. The combined ether layers were dried ($MgSO_4$) and concentrated to give an oil which was distilled under reduced pressure to give 6.85 g (26%) of pure 5-methylthiothiazole (**19**): bp 132–134° (50 mm); nmr ($CDCl_3$) δ 2.47 (s, 3, SCH_3), 7.75 (s, 1, 4-H), 8.82 (s, 1, 2-H).

Anal. Calcd for $C_4H_5NS_2$: C, 36.61; H, 3.85; S, 48.93. Found: C, 36.76; H, 4.07; S, 49.10.

(24) H. C. Beyerman, P. H. Berben, and J. S. Bontekoe, *Recl. Trav. Chim., Pays-Bas*, **73**, 325 (1954).

1-(5-Methylthio-2-thiazolyl)ethanol (20).—Metalation of **18** with butyllithium at −80° and addition of a threefold excess of acetaldehyde afforded crude **20**. Distillation afforded pure **20** in 79% yield: bp 106.0–106.5° (0.2 mm); nmr ($CDCl_3$) δ 1.58 (d, 3, J = 6.2 Hz, $CHCH_3$), 2.45 (s, 3, SCH_3), 5.02 (s, 1, OH), 5.02 (q, 1, J = 6.2 Hz, $CHCH_3$), 7.42 (s, 1, 4-H).

Anal. Calcd for $C_6H_9NOS_2$: C, 41.12; H, 5.18; S, 36.59. Found: C, 41.03; H, 5.09; S, 36.32.

1-(5-Methylthio-2-thiazolyl)ethyl Chloride (21).—Treatment of **20** with phosphorus pentachloride in methylene chloride and isolation gave **21** in 96% yield as a light yellow oil. Further purification to obtain a sample for kinetic studies was accomplished by chromatography on silica gel: nmr ($CDCl_3$) δ 1.92 (d, 3, J = 6.7 Hz, $CHCH_3$), 2.48 (s, 3, SCH_3), 5.25 (q, 1, J = 6.7 Hz, $CHCH_3$), 7.53 (s, 1, 4-H).

Kinetic Procedures.—Kinetic procedures have been reported previously.[3]

Registry No.—**1**, 40982-18-1; **2**, 40982-19-2; **5**, 20155-81-1; **5** lithium salt, 40982-21-6; **6**, 40982-22-7; **7**, 40982-23-8; **8**, 5053-24-7; **9**, 40982-25-0; **9** lithium salt, 40982-26-1; **10**, 40982-27-2; **11**, 14542-13-3; **12**, 40982-28-3; **13**, 40982-29-4; **14**, 40982-30-7; **15**, 40982-31-8; **16**, 3581-89-3; **17**, 40982-32-9; **18**, 40982-33-0; **19**, 40982-34-1; **20**, 40982-35-2; **21**, 40982-36-3; 2-methylthiazole, 3581-87-1; acetaldehyde, 75-07-0; *p*-nitrobenzoyl chloride, 122-04-3; methyl mercaptan, 74-93-1; 2-chlorothiazole, 3034-52-4; 5-bromothiazole, 3034-55-7.

Transmission of Substituent Effects in Heterocyclic Systems. Rates of Solvolysis of Substituted 1-(4-Thiazolyl)ethyl Chlorides[1,2]

DONALD S. NOYCE* AND STEVEN A. FIKE

Department of Chemistry, University of California, Berkeley, California 94720

Received April 3, 1973

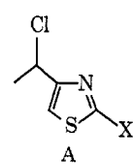
Electrophilic substituent constants, σ_m^+, have been found unacceptable for correlating the relative rates of solvolysis of 1-(2-substituted 4-thiazolyl)ethyl chlorides in 80% ethanol. Likewise, σ_m is also unsatisfactory. These data are discussed in light of several other heterocyclic systems, where similarly poor correlations have been found. It is suggested that judicious comparison of appropriately substituted pyridines and thiazoles provides an excellent working model for treatment of these substituent effects. Limited results on the rates of solvolysis of 1-(4-substituted 2-thiazolyl)ethyl chlorides support these conclusions.

This paper reports an examination of the effectiveness of substituents in promoting the solvolysis reaction of 1-(4-thiazolyl)ethyl chloride. This system is of particular interest as it relates to other five-membered heterocyclic systems and the failure of electrophilic substituent constants to reproduce adequately relative reactivities when the substituent and the reacting side chain are in a nonconjugating, or "pseudo-meta," relationship.

Earlier papers from these laboratories pointed out that Brown's electrophilic substituent constants,[3] *i.e.*, σ_m^+, do not provide a suitable basis for correlation in analogous furans,[4] benzofurans[5] and benzothiophenes.[6] It is only coincidental that σ_m^+ is satisfactory in the case of thiophene derivatives.[7] Further, σ_m^+ likewise fails to correlate substituent effects on the rate of solvolysis of 6-substituted 2-(2-pyridyl)-2-chloropropanes.[8] It was suggested that an independent set of substituent constants is needed for this structural situation.

Imoto and Otsuji, *et al.*,[9,10] have reported the application of the Hammett equation to the rates of saponification of ethyl 2-substituted 4-thiazolylcarboxylates and, with the dissociation constants of the corresponding acids, they obtained generally good correlations with σ_m except for the 2-amino substituent. It is interesting to note that this was the only substituent they studied with a very strong resonance capability.

We have previously examined a series of 1-(5-thiazolyl)ethanol derivatives,[2,11] and observed that σ_p^+ usefully correlates the relative reactivity of this series. The present results of rate measurements on a series of substituted 1-(4-thiazolyl)ethyl chlorides (A) are



A

2, X = H
4, X = CH_3
7, X = C_6H_5
11, X = Br
14, X = SCH_3

(1) Supported in part by a grant from the National Science Foundation, GP-6133X.

(2) Previous paper: D. S. Noyce and S. A. Fike, *J. Org. Chem.*, **38**, 3318 (1973).

(3) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

(4) D. S. Noyce and H. J. Pavez, *J. Org. Chem.*, **37**, 2620, 2623 (1972).

(5) D. S. Noyce and R. W. Nichols, *J. Org. Chem.*, **37**, 4306, 4311 (1972).

(6) D. A. Forsyth and D. S. Noyce, *Tetrahedron Lett.*, 3893 (1972); D. A. Forsyth, Ph.D. dissertation, University of California, Berkeley, 1973.

(7) D. S. Noyce, C. A. Lipinski, and R. W. Nichols, *J. Org. Chem.*, **37**, 2615 (1972).

(8) D. S. Noyce and J. A. Virgilio, *J. Org. Chem.*, **38**, 2660 (1973).

(9) E. Imoto and Y. Otsuji, *Bull. Univ. Osaka Prefect. Ser. A.*, **6**, 115 (1958); *Chem. Abstr.*, **53**, 3027*h* (1959).

(10) Y. Otsuji, T. Kimura, Y. Sugimoto, E. Imoto, Y. Omori, and T. Okawara, *Nippon Kagaku Zasshi*, **80**, 1024, 1297 (1959).

(11) D. S. Noyce and S. A. Fike, *J. Org. Chem.*, **38**, 3316 (1973).