methylene chloride (5 ml) was added a solution of ethyl chloroformate (0.325 g, 3.0 mmol) in methylene chloride (10 ml). After 10 min the reaction mixture was quenched with ethanol (2 ml). The product (0.4 g, 48%) was obtained as an oil by dry column chromatography of the residue, obtained after evaporation, on alumina eluting with chloroform: ^{1}H NMR δ 1.15 (CH_3, 3 H, t), 1.35 (CH_3, 3 H, t), 2.56 (CH_3, 3 H, s), 3.55 (CH_2, 2 H, q), 4.33 (CH_2, 2 H, q), 6.5–6.8 (H-5, H-6, and H-8, m), 7.13 (H-1, 1 H, s); significantly, there was no characteristically low-field absorption for an aromatic-type H-8.

Anal. Calcd for $C_{12}H_{17}N_3O_3S$: C, 50.87; H, 6.05; N, 14.83; S, 11.31. Found: C, 50.60; H, 6.07; N, 14.71; S, 11.57.

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Registry No.—**1**, 20010-99-5; **2**, 56488-16-5; **3**, 56488-17-6; **4**, 56488-18-7; **5**, 56488-19-8; **6**, 56488-20-1; **7**, 56488-21-2; **8**, 56488-22-3; **9**, 56488-23-4; **10**, 56488-24-5; **11**, 56488-25-6; **12**, 56488-26-7; **13**, 56488-27-8; **14**, 56488-28-9; **15**, 56488-29-0; **16**, 56488-30-3; **17**, 56488-31-4; carbon disulfide, 75-15-0; methyl iodide, 74-88-4; methyl bromoacetate 96-32-2; 2-bromoethanol, 540-51-2; bromoacetaldehyde dimethyl acetal, 7252-83-7; *p*-nitrobenzoyl chloride, 122-04-3.

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Solvolysis of Isothiazole Analogs of Cumyl Chloride. Determination of the Brown Electrophilic Substituent Constants for Isothiazole Derivatives

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Rates of solvolysis in 80% ethanol have been determined for 2-(3-isothiazolyl)-2-chloropropane, 2-(4-isothiazolyl)-2-chloropropane, and 2-(5-isothiazolyl)-2-chloropropane. From these rates and the rates of solvolysis of cumyl chlorides bearing electron-withdrawing substituents σ^+ values appropriate for the replacement of the benzene ring by an isothiazolyl moiety have been determined.

The chemistry of isothiazole, which was first prepared in 1956,[2] has recently been reviewed.[3] Electrophilic substitution occurs preferentially in the 4 position, including nitration and halogenation, but relatively few quantitative indices of the reactivity of the system are available. Nitration of phenylisothiazoles leads to substitution in the phenyl moiety.[4,5] The latter authors observed that the phenyl ring is strongly deactivated by the isothiazole ring, which is, of course, protonated by the concentrated acid of the nitration mixture.

In competitive nitrations, Dou and Metzger et al.[6] observed the following relative reactivities for the 4 position of various isothiazoles: 3-methylisothiazole, 1.0; 5-methylisothiazole, 1.7; isothiazole, 0.43. The isothiazoles were substantially less reactive than 2,4-dimethylthiazole.

The most quantitative studies are by Katritzky and his coworkers and include examination of nitration and hydrogen exchange.[7] The acid-catalyzed hydrogen–deuterium exchange of 3,4-dimethylisothiazole showed a change in the slope of the rate–acidity profile at $D_0 = -6.0$.[7] The authors concluded that the reaction at low acidities occurs on the free base and at high acidities on the conjugate acid; they estimated that the free base was 10^8 times more reactive than the conjugate acid. Hydrogen–deuterium exchange in D_2SO_4 of isothiazole and isoxazole and their 3- and 5-methyl derivatives was also studied.[8] Exchange was observed only in the 4 position. Heating with D_2SO_4 of various concentrations did not lead to any observable exchange in the 3 and 5 positions for any conditions under which the compounds were stable. Standard k_0 values for exchange at pH 0 at 100° were calculated as before,[9] with the assumption that pK_a values for isothiazoles follow the same relationship for temperature variation as pyridine. For isothiazole the calculated log k_0 value was −7.5. The authors calculated a log partial rate factor of 3.6 which, with their ρ value of −7.5, corresponds to a replacement σ_{Ar}^+ value[11] for the 4-isothiazolyl group of −0.48. In contrast to their earlier estimation,[7] the order of reactivity for the 4 positions of the 1,2-azoles is found to be pyrazole ≫ isoxazole > isothiazole (> phenyl).

Obviously, the question of the relative electrophilic reactivity of the isothiazoles is far from closed. The available quantitative data show that isothiazole's 4 position is more reactive than a phenyl position and less reactive than the 4-pyrazolyl position[8] or the 5-thiazolyl position.[6] Direct indications of the relative electrophilic reactivity of the 3 and 4 positions are absent, although it is clear that they are both significantly less reactive than the 4 position. Extrapolation from the substitution patterns of 4-substituted isothiazoles would suggest a greater reactivity for the 5 posi-

Table I
Rate Constants for Solvolysis of 2-(x-Isothiazolyl)-2-propyl Chlorides in 80% Ethanol

Compd solvolyzed	Temp, °C	10^5 k, sec^{-1} [a]	σ_{Ar}^+
2-(3-Isothiazolyl)-2-propyl chloride	45.65	20.6 ± 0.2	
	45.65	20.6 ± 0.3	
	57.5	86.9 ± 0.8	
	57.7	88.6 ± 0.7	
	74.80	343 ± 3	
	74.80	350 ± 3	
	75.00	377[b]	0.65
2-(4-Isothiazolyl)-2-propyl chloride	0.00	125 ± 2	
	0.00	127 ± 1	
	18.67	1150 ± 10	
	18.67	1150 ± 10[c]	
	25.08	2220 ± 30	
	25.08	2340 ± 50	
	75.00	211000[b]	−0.04
2-(5-Isothiazolyl)-2-propyl chloride	45.08	15.85 ± 0.06	
	45.10	16.14 ± 0.07	
	57.70	58.8 ± 0.5	
	59.00	63.2 ± 0.2	
	73.63	271. ± 1.0	
	73.63	274. ± 0.6	
	75.00	305[b]	0.67

[a] Determined at constant pH 7.5. [b] Extrapolated from measurements at other temperature. [c] Constant pH 10.

tion relative to the 3, but such a statement is subject to the pitfall of incomplete understanding of substituent effects in the isothiazole system.

We have approached this problem by examining the solvolytic reactivities of the isothiazolyl analogs of cumyl chloride, as we have done for pyridine[12] and thiazole systems.[11] Such an approach is particularly advantageous in the present circumstances as it avoids the severe series of extrapolations which Katritzky and his coworkers found necessary. It further makes accessible a reactivity index for all three of the positions of isothiazole.

Results

The results of the rate measurements in 80% ethanol are given in Table I.

From the measured rates extrapolated to 75° we calculate the replacement σ_{Ar}^+ values[11] given in the last column of Table I using the correlation equation determined earlier[12] from reactivities of some cumyl chlorides with deactivating substituents. The 4-isothiazolyl moiety is very slightly activating, while both of the other isomers are strongly deactivating compared to phenyl. These relationships are roughly similar to those observed by Katritzky et al.[8] However, there is a *significant* quantitative difference in the magnitude of the activation exerted by the 4-isothiazolyl moiety. It is the opinion of the present authors that our direct determination of a σ_{Ar}^+ value through solvolysis rate measurements is a better guide than Katritzky's value because of the necessarily severe extrapolations required in his studies. It should be noted that his extrapolation procedure gives a value[10] for thiophene (2-thienyl position, $\sigma_{Ar}^+ = -1.15$) which is very substantially more negative than the value determined from a large number of other studies.[13,14]

Experimental Section

General. All melting points and boiling points are uncorrected. Elemental analyses and high-resolution mass spectra were determined by the Analytical Services Laboratory, College of Chemistry, University of California, Berkeley, Calif. NMR spectra were recorded using a Varian T-60 spectrometer with Me_4Si as internal standard.

Isothiazole-4-carboxylic acid was prepared following the procedure of Adams and Slack,[15] mp 159–160° (lit.[15] mp 162°), and was converted to the methyl ester; mp 55° (lit.[15] mp 55°); NMR ($CDCl_3$) δ 9.18 (s, 1, H_5), 8.80 (s, 1, H_3), 3.88 (s, 3, OCH_3).

2-(4-Isothiazolyl)-2-propanol. To a stirred solution of 7.5 mmol (2.5 ml of a 3 *M* solution in ether) of methylmagnesium bromide in 30 ml of anhydrous ether, which was cooled in an ice bath, was added slowly 0.5 g (3.5 mmol) of methyl isothiazole-4-carboxylate in 10 ml of anhydrous ether. After addition was complete, the ice bath was removed, and the reaction mixture was allowed to stir at room temperature for 1 hr. The white precipitate was hydrolyzed with 20 ml of saturated ammonium chloride solution. The layers were separated, and the aqueous layer was extracted repeatedly with dichloromethane. The organic layers were combined and dried with magnesium sulfate. The solvents were evaporated to yield 0.4 g (80%) of 2-(4-isothiazolyl)-2-propanol: NMR (CCl_4) δ 8.33 (s, 1, H_5), 8.30 (s, 1, H_3), 3.95 (broad s, 1, –OH), 1.55 (s, 6, methyl protons); mass spectrum calcd for C_6H_9NOS, 143.04075; found, 143.0385.

2-(4-Isothiazolyl)-2-chloropropane. To a stirred solution of thionyl chloride (0.12 g, 1 mmol) in 12 ml of 1,2-dichloroethane was added dropwise 0.1 g (0.7 mmol) of 2-(4-isothiazolyl)-2-propanol in 6 ml of the solvent. The solution was stirred at room temperature for 1.5 hr, then the solvent and excess thionyl chloride were removed on the rotary evaporator. The residue, 0.12 g, was taken up in 2 ml of carbon tetrachloride, separated from a small amount of insoluble material, and utilized for kinetic studies without further purification: NMR (CCl_4) δ 8.42 (s, 1, H_5), 8.37 (s, 1, H_3), 1.97 (s, 6, CH_3).

2-(5-Isothiazolyl)-2-propanol. In a flame-dried flask equipped with a nitrogen inlet, a reflux condenser and drying tube, and a dropping funnel, a solution of 10 g (0.117 mol) of isothiazole in 124 ml of anhydrous ether was cooled with stirring in an ice bath. As stirring continued, 75 ml of a 2 *M* solution of butyllithium in hexane mixed with 50 ml of anhydrous ether was added dropwise. After the 1-hr addition period, the ice bath was removed, and stirring was continued for an additional 2 hr. The solution was then cooled, and 8.8 g (0.15 mol) of acetone was added cautiously. The mixture was stirred for 0.5 hr. Saturated ammonium chloride solution (100 ml) was added, and stirring was continued until both layers became clear. The layers were separated and the aqueous layer was extracted repeatedly with chloroform. The organic layers were combined and dried. The solvents were evaporated, and the residue was distilled under vacuum to yield 3.35 g (20%) of 2-(5-isothiazolyl)-2-propanol: NMR (CCl_4) δ 8.10 (d, J = 2 Hz, 1, H_3), 6.93 (d, J = 2 Hz, 1, H_4), 5.30 (br s, 1, 1 H), 1.60 [s, 6, $(CH_3)_2$-COH–]; mass spectrum calcd for C_6H_9NOS, 143.04075; found, 143.0391.

2-(5-Isothiazolyl)-2-propyl Chloride. A solution of 0.72 g (0.005 mol) of 2-(5-isothiazolyl)-2-propanol in 5 ml of carbon tetrachloride was added cautiously to a stirred solution of 0.6 g (0.005 mol) of thionyl chloride in 10 ml of carbon tetrachloride. A white precipitate formed immediately. The mixture was stirred overnight at room temperature resulting in a yellow solution with a brown suspended liquid. To this was added 0.5 g (0.005 mol) of triethylamine. After a few minutes of additional stirring, the mixture was cooled thoroughly. The mixture was filtered and the solvent was removed to yield 0.72–0.80 g (82–99%) of the desired chloride which was shown by NMR to contain a trace of the alkene but no unreacted alcohol. 2-(5-Isothiazolyl)-2-propyl chloride was used for kinetic measurements without further purification: NMR (CCl_4) δ 8.15 (d, J = 2 Hz, 1, H_3), 7.02 (d, J = 2 Hz, 1, H_4), 2.00 [s, 6, $(CH_3)_2CCl$–].

3-Tribromomethylisothiazole. 3-Methylisothiazole was prepared from commercial 5-amino-3-methylisothiazole hydrochloride by the procedure of Buttimore et al.:[16] bp 134–136° (lit.[15] bp 135–136°); NMR (CCl_4) δ 8.48 (d, J = 4 Hz, 1, H_5), 6.95 (d, J = 4 Hz, 1, H_4), 2.45 (s, 3, C_3CH_3).

A mixture of 2.5 g (0.025 mol) of 3-methylisothiazole and 14.5 g (0.77 mol) of *N*-bromosuccinimide in carbon tetrachloride (50 ml) was heated under reflux with 0.5 g of benzoyl peroxide. Heating was continued for 48 hr. At the end of this period the solution was cooled and filtered. The solvent was evaporated to yield a mixture which by NMR was shown to contain 3-tribromomethylisothiazole (95%) and 5% 3-dibromomethylisothiazole: NMR (CCl_4) 3-tribromomethylisothiazole δ 8.70 (d, J = 4 Hz, 1, H_5), 7.61 (d, J = 4 Hz,

1, H_4). 3-Dibromomethylisothiazole: δ 8.60 (d, J = 5 Hz, 1, H_5), 7.53 (d, J = 5 Hz, 1, H_4), 6.73 (s, 1, $-CHBr_2$).

Ethyl Isothiazole-3-carboxylate. The reaction residue from above, containing predominantly 3-tribromomethylisothiazole, was mixed with 25 ml of ethanol. The mixture was stirred and warmed as 0.077 mol of silver nitrate, dissolved in a minimum amount of water, was added. After 20 min heating was discontinued and the mixture was cooled. The precipitated silver bromide was removed by filtration. Sodium chloride was added to saturate the solution, and the small amount of additional precipitate was removed. The resulting solution was extracted repeatedly with methylene chloride. The organic layers were washed with 5% aqueous sodium bicarbonate solution and dried over magnesium sulfate. The solvents were evaporated, and the residue was distilled to yield 2.5 g (64% based on 3-methylisothiazole) of ethyl isothiazole-3-carboxylate: bp 140–145° (5 Torr); NMR ($CDCl_3$) δ 8.77 (d, J = 5 Hz, 1, H_5), 7.73 (d, J = 5 Hz, 1, H_4), 4.40 (q, J = 6 Hz, 2, $-COOCH_2CH_3$), 1.43 (t, J = 6 Hz, 3, $-COOCH_2CH_3$).

2-(3-Isothiazolyl)-2-propanol. To a stirred, cooled solution of 7.5 mmol of methylmagnesium bromide (2.5 ml of a 3 M solution in ether) in 20 ml of anhydrous ether was cautiously added 0.5 g (3.2 mmol) of ethyl isothiazole-3-carboxylate in 5 ml of anhydrous ether. The reaction mixture was stirred at room temperature for 0.5 hr. At the end of this period, 15 ml of saturated ammonium chloride solution was added. The layers were separated and the aqueous layer was extracted with four 20-ml portions of chloroform. The organic layers were dried over magnesium sulfate. The solvents were evaporated to yield 0.35 g (77%) of 2-(3-isothiazolyl)-2-propanol which contained a trace of nonaromatic impurity. Part of the product (0.15 g) was purified by column chromatography (chloroform and alumina) and submitted for high-resolution mass determination: NMR ($CDCl_3$) δ 8.48 (d, J = 4 Hz, 1, H_5), 7.18 (d, J = 4 Hz, 1, H_4), 6.6 (broad s, 1, –OH), 1.63 [s, 6, $-C(CH_3)_2OH$]; mass spectrum calcd for C_6H_9NOS, 143.04075; found, 143.0396.

2-(3-Isothiazolyl)-2-chloropropane. The procedure used in the preparation of 2-(5-isothiazolyl)-2-chloropropane was utilized without variation. Upon work-up, the reaction was found to yield the desired product and about 30% (by NMR) of the alkene. This mixture was solvolyzed without further purification. NMR showed multiplets in the aromatic region corresponding to the superimposed signals of the chloride and the alkene; however, the signal of the methyl protons was well resolved and occurred at δ 1.87.

Kinetic Techniques. Rate measurements were performed in 80% ethanol–water which had been prepared by dilution of four volumes of dry ethanol with one volume of water. The ethanol was dried by distillation from magnesium ethoxide according to the method of Lund and Bjerrum.[17] The water utilized was redistilled laboratory distilled water. Volumes were measured at room temperature.

Rates of all compounds were followed at constant pH maintained through automatic, recorded neutralization of generated acid with 0.3 M potassium hydroxide in 80% ethanol. Between 0.6 and 0.8 mmol of substrate was used for each run.

The apparatus was a radiometer automatic titrator consisting of a TTTlc automatic titrator, and ABUlc autoburette (with a 2.5-ml burette), and TTA3c titrator assembly and an SBR2c recorder. Radiometer electrodes, K401 calomel and 202c glass, were used.

Best least squares rate constants were determined using the LSKIN-1 program.[18]

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Registry No.—2-(3-Isothiazolyl)-2-propyl chloride, 56615-15-7; 2-(4-isothiazolyl)-2-propyl chloride, 56615-16-8; 2-(5-isothiazolyl)-2-propyl chloride, 56615-17-9; isothiazole-4-carboxylic acid methyl ester, 56133-37-0; 2-(4-isothiazolyl)-2-propanol, 56615-18-0; methyl bromide, 74-83-9; 2-(5-isothiazolyl)-2-propanol, 56615-19-1; isothiazole, 288-16-4; acetone, 67-64-1; 3-tribromomethylisothiazole, 56615-20-4; N-bromosuccinimide, 128-08-5; 3-dibromomethylisothiazole, 56615-21-5; ethyl isothiazole-3-carboxylate, 23244-32-8; 2-(3-isothiazolyl)-2-propanol, 56615-22-6.

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