Basicities of Thiazole Heterocyclic Compounds and the Reaction of 3-Methyl-2-methylimino-Δ^4-thiazolines with Ethyl Bromoacetate and 2-Bromoacetophenone

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The pK_a's of several thiazole heterocyclic compounds have been determined and represent products with significantly high values. Because of their high basicities, sometimes these compounds were able to act as not only nucleophiles but also strong organic bases. 4-Substituted-3-methyl-2-methylimino-Δ^4-thiazolines **5a-d** reacted with ethyl bromoacetate in refluxing benzene, giving the corresponding *N*-alkylated salts **8a-d**, while the products obtained from the reaction with 2-bromoacetophenone in the presence of base were pyrrolothiazines **10b-d**.

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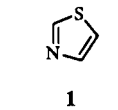
Introduction.

The thermodynamic basicity of thiazole (**1**) is very low [1]. This is due to the enhanced aromatic character of thiazole ring which is responsible for a more effective stabilization of the positive charge developing on the nitrogen atom. But, the introduction of a conjugated amino group into the 2-position of the thiazole ring markedly enhances the basicity [2]. From this point of view we have been interested in the exocyclic *N*-containing thiazole system such as 5,6-dihydroimidazo[2,1-*b*]thiazoles **4a-b**, 3-methyl-2-methylimino-Δ^4-thiazolines **5a-b**, and 6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidines **6a-b**. Actually, because of its low basicity, aromatized 3-methylimidazo[2,1-*b*]thiazole (**3**) is not converted to the corresponding betaines by reactions with electrophiles such as aryl isocyanate, aryl isothiocyanate, and carbon disulfide, while 5,6-dihydroimidazo[2,1-*b*]thiazoles **4a-b** react readily with those electrophiles to give corresponding betaines [3-6]. As part of the studies on their structures and their behavior on the reaction of the thiazole compounds, we have determined the pK_a's of thiazole heterocycles **2-6b**.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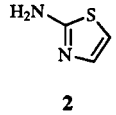
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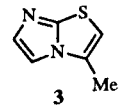
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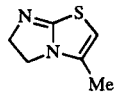
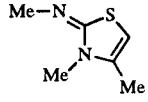

4a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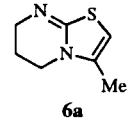
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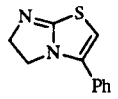
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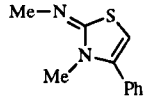
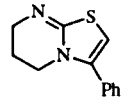

5b


6b

3-Substituted-5,6-dihydroimidazo[2,1-*b*]thiazoles **4a-b** and 6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidines **6a-b** reacted readily with α-haloketones or α-haloesters such as 2-bromoacetophenones or ethyl bromoacetate in acetone or benzene at room temperature, providing the corresponding *N*-alkylated imidazothiazolium bromides and *N*-alkylated thiazolopyrimidium bromides, respectively [7]. On the other hand, interesting results were obtained in the case of iminothiazolines **5a-b**.

Therefore, we wish to describe the basicities of compounds **2-6b** and the reaction of 4-substituted-3-methyl-2-methylimino-Δ^4-thiazolines **5a-b** with ethyl bromoacetate and 2-bromoacetophenone.

Results and Discussion.

Basicity of Thiazole Heterocyclic Compounds.

The potentiometric titration method of Albert and Serjeant has been used in this determination, so that pK_a's have been corrected for ionic-strength effects [8-10]. Because of their poor solubilities to water, the pK_a's of phenyl derivatives, **4b**, **5b** and **6b** have been measured in 50% aqueous ethanol. The pK_a's of the several heterocyclic compounds are summarized in Table I.

Table 1

pK_a Values of Thiazole Heterocyclic Compounds at 25°

Compounds	pKa Literature	pKa Found
1	2.52 [1]	
2	5.36 [2]	5.37 ± 0.05
3		5.36 ± 0.05
4a		9.81 ± 0.03
4b		7.68 ± 0.05 [a]
5a		9.97 ± 0.03
5b		7.81 ± 0.04 [a]
6a		10.31 ± 0.06
6b		9.11 ± 0.04 [a]

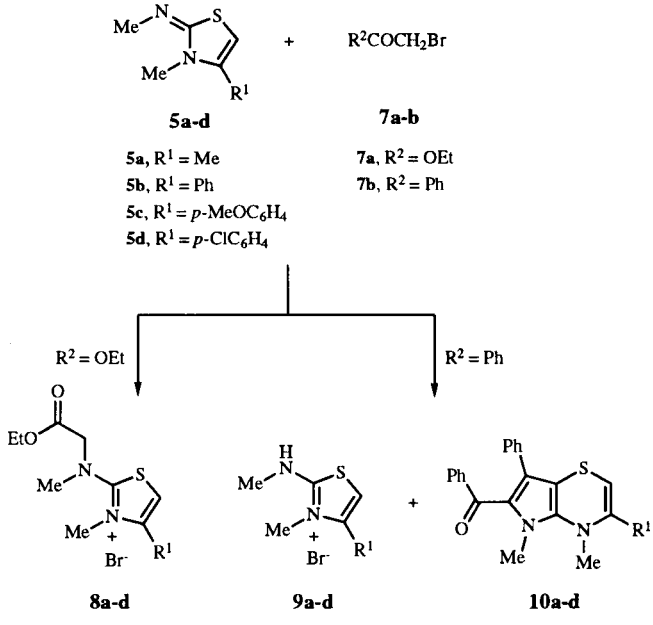
[a] In 50% aqueous ethanol.

It is shown that all thiazoles **4a-6b** have high basicities considering that the pK_a value of pyridine and triethylamine is 5.27 and 10.72, respectively. Because of this high basicity, it seems that these compounds are able to act as a strong organic base. The monocyclic compounds, **5a-b**, relative to the corresponding bicycles **4a-b**, are slightly more basic, but the thiazolopyrimidines, **6a-b**, are much more basic. That is, the basicities of saturated *N*-bridged thiazole compounds seem to increase with increasing ring size. And the pK_a values of methyl substituted thiazole compounds, **4a**, **5a** and **6a**, are higher than those of the corresponding phenyl substituted thiazole compounds, **4b**, **5b** and **6b**, respectively. These trends may be interpreted as being mainly due to polar effects. Methyl and methylene groups are electron donating and, therefore, the thiazolium ion is expected to be stabilized to a greater degree by methyl substitution and increasing ring size.

The Reaction of Iminothiazolines **5a-d** with Electrophiles.

Because of high basicity, sometimes these compounds can act not only as nucleophiles but also as strong organic bases. Evidence was found in the reaction of 3-methyl-2-methylimino-4-phenyl-Δ^4-thiazoline (**5b**) with some electrophiles. 3-Methyl-2-methylimino-4-phenyl-Δ^4-thiazoline (**5b**) reacted with ethyl bromoacetate in refluxing benzene, to produce the corresponding *N*-alkylated salt **8b**, whereas the product obtained in the reaction with 2-bromoacetophenone was not the simple *N*-alkylated compound but a mixture of 3-methyl-2-methylamino-4-phenylthiazolylium bromide (**9b**) and pyrrolothiazine **10b** (Scheme 1). The formation of the hydrobromides salt **9b** of **5b** indicates that 3-methyl-2-methylimino-4-phenyl-Δ^4-thiazoline (**5b**) acted as an organic base as well as a nucleophile in this reaction. When 3 equivalents of **5b** and 2 equivalents of **7b** were allowed to react in refluxing benzene for 2 hours, there was obrtained 30% of **9b** and 12% of **10b** with 52% recovery of **5b** on the basis of **5b** used. In this reaction, 2 equivalents of **5b** appears to be used as a base, and 1 equivalent as a nucleophile. The salt **9b** reacted readily with potassium carbonate in acetonitrile to convert to its free form **5b**. Therefore, we tried the reaction of iminothiazolines **5a-d** and 2-bromoacetophenone (**7b**) in the presence of potassium carbonate as a base. When equimolecular **5b-d** and **7b** and 2 equivalents of potassium carbonate were allowed to react in refluxing benzene for 4 hours, pyrrolothiazines **10b-d** were produced in moderate yields (58-62%). In the case of methyl derivative **5a**, we were able to monitor the yellow major spot on tlc. It was like that of pyrrolothiazine **10a**, but it was so unstable as to be decomposed even on tlc developing; consequently, we failed to isolate **10a**.

Scheme 1



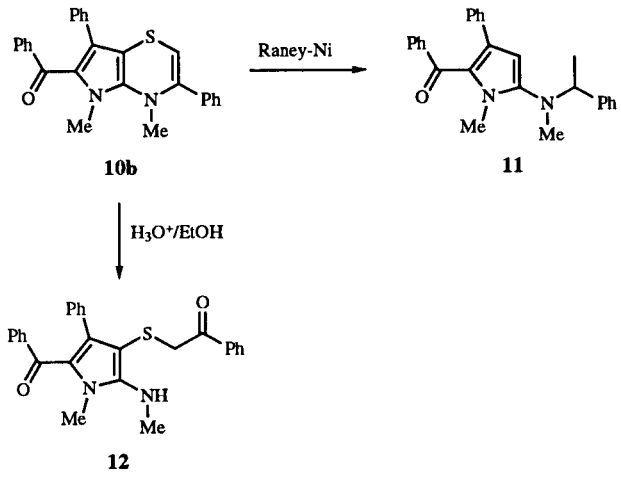
The structural elucidation of **8a-d** and **10b-d** were accomplished on the basis of spectral data and microanalyses. The ir spectra of **8a-d** showed absorption in the carbonyl stretching region of 1732-1736 cm^{-1}. The principle ^1H nmr spectra of *N*-alkylated thiazolylium salts **8a-d** showed downshifted methyl singlets and one vinyl singlet as compared with those of their corresponding thiazolines **5a-d**. The mass spectrum of pyrrolothiazine **10b** was characterized by m/z = 422 (M^+), and 407, due to the loss of a methyl group. All 27 carbon and 22 hydrogen atoms were resolved by ^1H, ^{13}C and DEPT nmr experiments (2 x CH_3, 16 x CH, 9 x C). Its principle ^1H nmr spectrum showed two methyl singlets at δ 3.87 and δ 2.98 and one vinyl singlet at δ 6.01.

Chemical Evidence in Support of Assigned Structures.

The treatment of pyrrolothiazine **10b** with Raney nickel resulted in desulfurization and reduction to give a compound **11** (Scheme 2), characterized by its ^1H nmr spectrum of a doublet at δ 1.53 and a quartet at δ 4.43 with vicinal coupling constants, J = 7.6 Hz, based on its methyl and methine in the C_5 side chain of the pyrrole ring, respectively, and a vinyl singlet at δ 5.88 assigned to C_4 H. The mass spectrum of **11** showed a molecular ion peak at m/z = 394 and a base peak at m/z = 289 due to the loss of a benzoyl group from the molecular ion.

Pyrrolothiazine **10b** was decomposed to **12** under aqueous acidic conditions (Scheme 2). Structural elucidation of **12** was accomplished on the basis of spectral data. The ir spectra of **12** showed absorption in the NH stretching region of 3360 cm^{-1}. The ^1H nmr spectrum of **12** was characterized by a deuterium oxide-exchangeable broad singlet at δ 4.40 assigned to the C_5 NH proton and a singlet at δ 3.49 assigned to the methylene proton in C_4 side chain of the pyrrole ring. The mass spectrum of **12** showed a molecular ion peak at m/z = 440.

Scheme 2



X-ray Crystal Diffraction Analysis.

In order to confirm the assigned structure, we prepared a single crystal of compound **10b**. We were able to obtain a good crystal of **10b** from acetone, and the X-ray crystal diffraction analysis of **10b** confirmed the pyrrolothiazine ring system, as depicted in Figure 1. Details of the crystallographic data are shown in Tables 2-4.

Table 2

Details of Crystallographic Data for **10b**

formula	$C_{27}H_{22}N_2OS$
fw	422.53
temperature, K	293(2)
wavelength, Å	0.71073
crystal system	triclinic
space group	P1 (no. 2)
a, Å	6.873(2)
b, Å	11.680(7)
c, Å	14.647(7)
α, deg	73.85(4)
β, deg	83.45(3)
γ, deg	72.75(4)
V, Å^3	1077.9(9)
Z	2
d_{calcd}, g/cm^3	1.302
absorption coefficient, mm^{-1}	0.172
F(000)	444
crystal size, mm	0.30 x 0.30 x 0.15
theta range, deg	1.89-24.97
index ranges	0≤h≤8, -13≤k≤13, -17≤l≤17
independent reflections	3064
refinement method	full-matrix least-squares on F^2
data to parameter ratio	2808/280
GOF on F^2	1.016
final R indices {I>2σ(I)}	R_1 = 0.0455, wR_2 = 0.1149
R indices (all data)	R_1 = 0.0476, wR_2 = 0.1170
largest diff. peak and hole	0.552 and -0.298 e.A^{-3}

GOF = $\{\Sigma w(F_o^2-F_c^2)^2/\text{No. of reflections - No. of parameters}\}^{1/2}$, $R_1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$, $wR_2 = \{\Sigma w(F_o^2-F_c^2)^2/\Sigma wF_o^4\}^{1/2}$, where $w = 1/\{\sigma^2F_o^2 + (0.0749P)^2+0.52P\}$, where $P = \{Max(F_o^2,0) +2F_c^2\}/3$

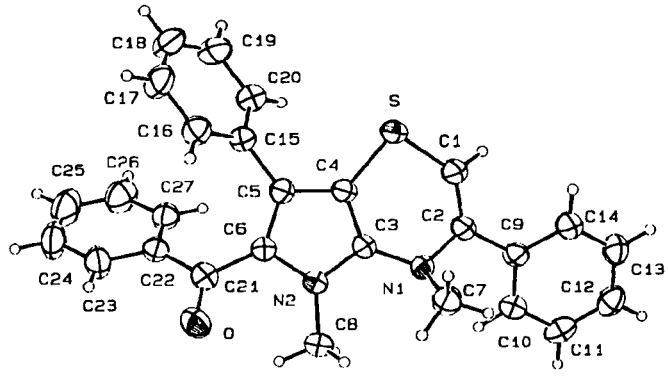


Figure 1.

Mechanism.

A plausible mechanism for the reaction of 3-methyl-2-methylimino-4-phenyl-Δ^4-thiazoline (**5b**) with 2-bromoacetophenone to give pyrrolothiazine **10b** may be represented by the sequence as shown in Scheme 3. It is likely that one molecule of 2-bromoacetophenone reacts with iminothiazoline **5b** to give *N*-alkylated adduct **13**. This *N*-alkylated adduct **13** reacts with enolate of another molecule of 2-bromoacetophe-

Table 3

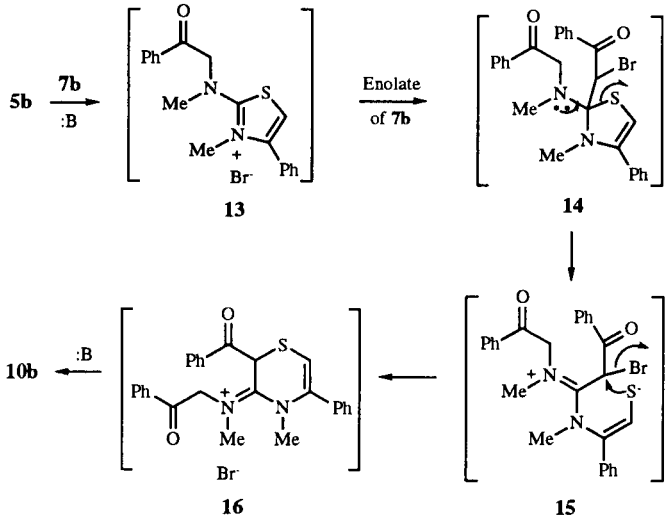
Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters (Å^2 x 10^3) for **10b**

	x	y	z	U(eq)
S	2557(1)	730(1)	4476(1)	54(1)
O	-5831(3)	3390(2)	2543(2)	65(1)
N(1)	-1034(3)	2669(2)	5302(1)	37(1)
N(2)	-2838(3)	3007(2)	3882(2)	36(1)
C(1)	2590(4)	1552(3)	5305(2)	46(1)
C(2)	990(4)	2338(2)	5624(2)	36(1)
C(3)	-1183(4)	2420(2)	4437(2)	35(1)
C(4)	235(4)	1659(2)	3971(2)	38(1)
C(5)	-539(4)	1763(2)	3101(2)	37(1)
C(6)	-2473(4)	2618(2)	3044(2)	36(1)
C(7)	-2538(4)	2345(3)	6060(2)	46(1)
C(8)	-4494(4)	4037(3)	4070(2)	48(1)
C(9)	1242(4)	2979(2)	6325(2)	36(1)
C(10)	76(4)	4180(2)	6309(2)	43(1)
C(11)	333(4)	4777(3)	6959(2)	49(1)
C(12)	1787(5)	4175(3)	7637(2)	53(1)
C(13)	2955(5)	2989(3)	7668(2)	51(1)
C(14)	2679(4)	2385(3)	7028(2)	43(1)
C(15)	439(4)	1017(2)	2415(2)	39(1)
C(16)	-597(5)	376(3)	2079(v	50(1)
C(17)	314(6)	-283(3)	1423(2)	65(1)
C(18)	2278(6)	-326(3)	1102(2)	70(1)
C(19)	3347(5)	273(3)	1447(2)	66(1)
C(20)	2442(4)	941(3)	2104(2)	49(1)
C(21)	-4001(4)	3085(2)	2323(2)	44(1)
C(22)	-3365(4)	3226(2)	1299(2)	42(1)
C(23)	-4749(5)	3232(3)	672(2)	56(1)
C(24)	-4242(6)	3407(3)	-285(2)	71(1)
C(25)	-2402(7)	3587(4)	-630(2)	74(1)
C(26)	-1039(6)	3610(3)	-25(2)	65(1)
C(27)	-1506(5)	3430(2)	938(2)	47(1)

Table 4
Bond Lengths (Å) and Angles (°) for **10b**

S-C(1)	1.744(3)	S-C(4)	1.752(3)
O-C(21)	1.232(3)	N(1)-C(3)	1.396(3)
N(1)-C(2)	1.427(3)	N(1)-C(7)	1.477(3)
N(2)-C(3)	1.365(3)	N(2)-C(6)	1.394(3)
N(2)-C(8)	1.457(3)	C(1)-C(2)	1.332(3)
C(2)-C(9)	1.481(3)	C(3)-C(4)	1.371(3)
C(4)-C(5)	1.397(4)	C(5)-C(6)	1.401(3)
C(5)-C(15)	1.486(3)	C(6)-C(21)	1.453(4)
C(9)-C(10)	1.389(4)	C(9)-C(14)	1.394(4)
C(10)-C(11)	1.379(4)	C(11)-C(12)	1.379(4)
C(12)-C(13)	1.371(4)	C(13)-C(14)	1.379(4)
C(15)-C(16)	1.381(4)	C(15)-C(20)	1.385(4)
C(16)-C(17)	1.377(4)	C(17)-C(18)	1.368(5)
C(18)-C(19)	1.367(5)	C(19)-C(20)	1.385(4)
C(21)-C(22)	1.491(4)	C(22)-C(27)	1.387(4)
C(22)-C(23)	1.392(4)	C(23)-C(24)	1.378(5)
C(24)-C(25)	1.361(5)	C(25)-C(26)	1.371(5)
C(26)-C(27)	1.382(4)		
C(1)-S-C(4)	97.43(13)	C(3)-N(1)-C(2)	115.1(2)
C(3)-N(1)-C(7)	116.2(2)	C(2)-N(1)-C(7)	113.9(2)
C(3)-N(2)-C(6)	108.7(2)	C(3)-N(2)-C(8)	123.8(2)
C(6)-N(2)-C(8)	126.4(2)	C(2)-C(1)-S	126.7(2)
C(1)-C(2)-N(1)	124.2(2)	C(1)-C(2)-C(9)	120.9(2)
N(1)-C(2)-C(9)	114.8(2)	N(2)-C(3)-C(4)	108.5(2)
N(2)-C(3)-N(1)	122.5(2)	C(4)-C(3)-N(1)	128.9(2)
C(3)-C(4)-C(5)	108.6(2)	C(3)-C(4)-S	121.6(2)
C(5)-C(4)-S	129.7(2)	C(4)-C(5)-C(6)	106.9(2)
C(4)-C(5)-C(15)	125.9(2)	C(6)-C(5)-C(15)	127.0(2)
N(2)-C(6)-C(5)	107.3(2)	N(2)-C(6)-C(21)	120.6(2)
C(5)-C(6)-C(21)	132.1(2)	C(10)-C(9)-C(14)	117.9(2)
C(10)-C(9)-C(2)	121.8(2)	C(14)-C(9)-C(2)	120.4(2)
C(11)-C(10)-C(9)	121.5(3)	C(10)-C(11)-C(12)	119.5(3)
C(13)-C(12)-C(11)	120.0(3)	C(12)-C(13)-C(14)	120.5(3)
C(13)-C(14)-C(9)	120.6(3)	C(16)-C(15)-C(20)	118.5(3)
C(16)-C(15)-C(5)	121.6(2)	C(20)-C(15)-C(5)	120.0(2)
C(17)-C(16)-C(15)	120.8(3)	C(18)-C(17)-C(16)	120.3(3)
C(17)-C(18)-C(19)	119.7(3)	C(18)-C(19)-C(20)	120.4(3)
C(15)-C(20)-C(19)	120.2(3)	O-C(21)-C(6)	120.8(3)
O-C(21)-C(22)	119.1(2)	C(6)-C(21)-C(22)	120.1(2)
C(27)-C(22)-C(23)	118.9(3)	C(27)-C(22)-C(21)	122.6(2)
C(23)-C(22)-C(21)	118.4(3)	C(24)-C(23)-C(22)	120.0(3)
C(25)-C(24)-C(23)	120.7(3)	C(24)-C(25)-C(26)	120.0(3)
C(25)-C(26)-C(27)	120.4(4)	C(26)-C(27)-C(22)	120.0(3)

Scheme 3



none generated by a base to produce thioacetal intermediate **14**. The intermediate **14** readily undergoes C-S bond cleavage giving vinyl sulfide anion **15**. Several papers have mentioned this similar type of bond breaking between carbon and heteroatoms in the heterocyclic systems [4, 11-15]. Then vinyl sulfide anion attacks the α-carbon bearing bromine to form the thiazine ring. Finally, two side chains of thiazine ring **16** are converted to the pyrrolothiazine product **10b** by intramolecular aldol condensation.

EXPERIMENTAL

General.

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. The ir spectra were recorded on a Perkin-Elmer Model 16FPC FT Infrared spectrometer. The ^1H, ^{13}C and DEPT nmr spectra were obtained on a Varian Gemini 300 spectrometer. All chemical shift values were reported in the δ scale from internal tetramethylsilane. The mass spectra (EI) were recorded on a JEOL JMS-SX-102A double focusing mass spectrometer. The resolving power was typically 1,000 and the magnet was scanned at 10 seconds per decade for full-scan mass spectra. For the high resolution mode, a resolving power of 10,000 was used. For mass spectral analysis (EI) a heated direct insertion probe was used to evaporate the samples into the source area, which was heated to 175°. A 70 eV ionization energy was used. Microanalyses were determined with a Perkin-Elmer 240 DS element analyser. Preparative liquid chromatography was performed on a Buchi B-680 MPLC system, using a column packed with Merck Kieselgel 60 (230-400 mesh).

pK_a Determination [8-10].

An Orion Model SA520 *p*H meter, which was standardized with two buffer solutions at *p*H 7.00 and 4.01, was used for potentiometric titration. The apparatus used and detailed procedure were similar to the one described by Albert and Serjeant. Standard hydrochloric acid solutions were prepared and titrated by standard methods and their concentration were 0.1033 *M* and 0.1010 *M*. Approximately 0.01 *M* solutions were prepared by dissolving 0.5 mmole of the double recrystallized heterocyclic compounds in 47.5 ml of boiled, carbon dioxide free distilled water. These solutions were titrated with standard hydrochloric acid solution. The titrants were added in portions of about 0.1 molar equivalent (0.5 ml) of the heterocycles in the solution. After each addition, the solution was stirred, and then the *p*H was determined. The pK_a values were calculated from empirical approximation given by Albert and Serjeant which the pK_a's are corrected for ionic-strength effects.

Preparation of Thiazole Heterocyclic Compounds.

3-Substituted-5,6-dihydroimidazo[2,1-*b*]thiazoles, **4a-b** [16-26], 4-substituted-3-methyl-2-methylimino-Δ^4-thiazolines, **5a-b** [27, 28], and 3-substituted-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidines, **6a-b** [29, 30] were prepared as reported in the literature.

3-Methyl-5,6-dihydroimidazo[2,1-*b*]thiazole (**4a**).

This compound was obtained as colorless crystals, mp 90-92°; ir (potassium bromide): 3276, 3067, 1566, 1406, 1297, 1247 cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.18 (s, 1H, C_2 H), 4.16

(t, 2H, J = 9.4 Hz, C_6 H), 3.68 (t, 2H, J = 9.4 Hz, C_5 H), 1.92 (s, 3H, C_3 CH_3); ^{13}C nmr (deuteriochloroform): δ 169.8, 131.8, 94.2, 60.3, 45.4, 13.6.

3-Phenyl-5,6-dihydroimidazo[2,1-*b*]thiazole (**4b**).

This compound was obtained as colorless crystals, mp 110-112°; ir (potassium bromide): 3126, 2947, 2837, 1606, 1506, 1382, 1252 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.34-7.28 (m, 5H, Ar H), 5.58 (s, 1H, C_2 H), 4.14 (t, 2H, J = 9.2 Hz, C_6 H), 3.72 (t, 2H, J = 9.2 Hz, C_5 H); ^{13}C nmr (deuteriochloroform): δ 169.8, 136.9, 130.5, 128.5, 125.9, 97.5, 60.1, 47.9.

3-Methyl-2-methylimino-4-methyl-Δ^4-thiazoline (**5a**).

This compound was obtained as colorless crystals, mp 96-97°; ir (potassium bromide): 3096, 2847, 2768, 1626, 1412, 1367, 1312 cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.38 (s, 1H, C_5 H), 3.07 (s, 3H, C_2 N-CH_3), 2.84 (s, 3H, N_3 CH_3), 1.92 (s, 3H, C_4 CH_3); ^{13}C nmr (deuteriochloroform): δ 161.5, 135.1, 91.2, 40.0, 29.9, 14.3.

3-Methyl-2-methylimino-4-phenyl-Δ^4-thiazoline (**5b**).

This compound was obtained as colorless crystals, mp 75-76°; ir (potassium bromide): 2965, 2835, 1628, 1444, 1399, 1366, 1165 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.26-7.24 (m, 3H, Ar H), 7.19-7.16 (m, 2H, Ar H) 5.62 (s, 1H, C_5 H), 3.04 (s, 3H, C_2 N-CH_3), 2.92 (s, 3H, N_3 CH_3); ^{13}C nmr (deuteriochloroform): δ 161.0, 140.6, 131.4, 128.4, 128.2, 128.0, 94.4, 40.2, 32.3.

3-Methyl-2-methylimino-4-(4'-methoxyphenyl)-Δ^4-thiazoline (**5c**).

This compound was obtained as colorless crystals; mp 73-75°; ir (potassium bromide): 3046, 1632, 1508, 1250, 1192 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.27-7.24 (d, 2H, Ar H), 6.94-6.91 (d, 2H, Ar H), 5.72 (s, 1H, C_5 H), 3.89 (s, 1H, OCH_3), 3.18 (s, 3H, C_2 N-CH_3) 3.04 (s, 3H, N_3 CH_3); ^{13}C nmr (deuteriochloroform): δ 161.9, 160.1, 141.0, 130.0, 124.2, 114.0, 94.1, 55.3, 40.6, 32.7.

3-Methyl-2-methylimino-4-(4'-chlorophenyl)-Δ^4-thiazoline (**5d**).

This compound was obtained as colorless crystals, mp 97-99°; ir (potassium bromide): 3054, 1628, 1398, 1190 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.41-7.38 (d, 2H, Ar H), 7.28-7.26 (d, 2H, Ar H) 5.81 (s, 1H, C_5 H), 3.19 (s, 3H, C_2 N-CH_3) 3.04 (s, 3H, N_3 CH_3); ^{13}C nmr (deuteriochloroform): δ 161.5, 140.0, 135.1, 130.3, 130.0, 129.8, 95.3, 40.6, 32.8.

3-Methyl-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine (**6a**).

This compound was obtained as pale pink crystals, mp 60-62°; ir (potassium bromide): 3135, 3000, 2859, 1568, 1435, 1359, 1279 cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.13 (s, 1H, C_2 H), 3.45 (t, 2H, J = 6.0 Hz, C_7 H), 3.20 (t, 2H, J = 6.0 Hz, C_5 H), 1.77 (s, 3H, C_3 CH_3) 1.71-1.63 (m, 2H, C_6 H); ^{13}C nmr (deuteriochloroform): δ 160.6, 133.7, 90.7, 44.2, 41.6, 19.2, 13.2.

3-Phenyl-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine (**6b**).

This compound was obtained as colorless crystals, mp 116-117°; ir (potassium bromide): 2990, 2876, 1599, 1490, 1441, 1363, 1274 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.39-7.34 (m, 3H, Ar H), 7.31-7.27 (m, 2H, Ar H), 5.59 (s, 1H, C_2 H), 3.55 (t, 2H, J = 5.9 Hz, C_7 H), 3.43 (t, 2H, J = 5.9 Hz, C_5 H), 1.80-1.73 (m, 2H, C_6 H); ^{13}C nmr (deuteriochloroform): δ 160.8, 139.8, 130.7, 128.8, 128.5, 128.1, 95.0, 45.0, 44.5, 19.9.

3-Methyl-2-[*N*-(2-ethoxy-2-oxoethyl)-*N*-methylamino]-4-methylthiazolylium Bromide (**8a**).

3-Methyl-2-methylimino-4-methyl-Δ^4-thiazoline (**5a**) (1.42 g, 10 mmoles) and ethyl bromoacetate (1.67 g, 10 mmoles) were refluxed in dry benzene (50 ml) for 5 hours. After cooling **8a** was filtered, 2.69 g, (87%) as colorless crystals, mp 154-156°; ir (potassium bromide): 3446, 2976, 1736, 1570, 1372, 1218, 1110 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.28 (s, 1H, C_5 H), 4.50 (s, 2H, CH_2CO), 4.19 (q, 2H, J = 8.0 Hz, CH_2CH_3), 3.89 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 1.21 (t, 3H, J = 8.0 Hz, CH_2CH_3); ^{13}C nmr (deuteriochloroform): δ 173.2, 167.4, 140.6, 108.5, 62.1, 57.0, 43.6, 37.8, 15.2, 14.0.

Anal. Calcd. for $C_{10}H_{17}BrN_2O_2S$: C, 38.84; H, 5.54; N, 9.06. Found: C, 39.10; H, 5.50; N, 8.84.

3-Methyl-2-[*N*-(2-ethoxy-2-oxoethyl)-*N*-methylamino]-4-phenylthiazolylium Bromide (**8b**).

3-Methyl-2-methylimino-4-phenyl-Δ^4-thiazoline (**5b**) (2.04 g, 10 mmoles) and ethyl bromoacetate (1.67 g, 10 mmoles) were refluxed in dry benzene (50 ml) for 5 hours. After cooling, extraction with water from the reaction mixture, purification of the aqueous layer with active carbon, and evaporation of water under reduced pressure gave the product **8b**, 3.00 g (81%) as a colorless jelly; ir (nujol): 3448, 1736, 1562 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.70-7.67 (m, 2H, Ar H), 7.61 (s, 1H, C_5 H), 4.72 (s, 2H, CH_2CO), 4.19 (q, 2H, J = 7.1 Hz, CH_2CH_3), 3.66 (s, 3H, CH_3), 3.40 (s, 3H, CH_3), 1.21 (t, 3H, J = 7.1 Hz, CH_2CH_3); ^{13}C nmr (DMSO-d_6): δ 174.3, 167.9, 143.7, 130.2, 129.1, 129.0, 128.4, 109.1, 61.6, 56.5, 43.0, 40.1, 14.0.

Anal. Calcd. for $C_{15}H_{19}BrN_2O_2S$: C, 48.52; H, 5.16; N, 7.55. Found: C, 48.73; H, 5.11; N, 7.41.

3-Methyl-2-[*N*-(2-ethoxy-2-oxoethyl)-*N*-methylamino]-4-(4'-methoxyphenyl)thiazolylium Bromide (**8c**).

3-Methyl-2-methylimino-4-(4'-methoxyphenyl-Δ^4-thiazoline (**5c**) (2.34 g, 10 mmoles) and ethyl bromoacetate (1.67 g, 10 mmoles) were refluxed in dry benzene (50 ml) for 5 hours. After cooling **8c** was filtered, 3.13 g (78%) as colorless crystals, mp 147-149 °; ir (potassium bromide): 3435, 2986, 1732, 1546, 1402, 1254 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.60-7.57 (d, 2H, ArH), 7.44 (s, 1H, C_5 H), 7.13-7.10 (d, 2H, ArH), 4.65 (s, 2H, CH_2CO), 4.23 (q, 2H, J = 8.0 Hz, CH_2CH_3), 3.83 (s, 3H, CH_3), 3.61 (s, 3H, CH_3), 3.36 (s, 3H, CH_3), 1.25 (t, 3H, J = 8.0 Hz, CH_2CH_3); ^{13}C nmr (DMSO-d_6): δ 174.2, 167.9, 160.7, 143.8, 130.7, 120.6, 114.6, 107.7, 61.6, 56.3, 55.5, 42.8, 40.1, 14.0.

Anal. Calcd. for $C_{16}H_{21}BrN_2O_3S$: C, 47.89; H, 5.28; N, 6.98. Found: C, 47.90; H, 5.22; N, 6.97.

3-Methyl-2-[*N*-(2-ethoxy-2-oxoethyl)-*N*-methylamino]-4-(4'-chlorophenyl)thiazolylium Bromide (**8d**).

3-Methyl-2-methylimino-4-(4'-chlorophenyl)-Δ^4-thiazoline (**5d**) (2.38 g, 10 mmoles) and ethyl bromoacetate (1.67 g, 10 mmoles) were refluxed in dry benzene (50 ml) for 5 hours. After cooling **8d** was filtered, 3.45 g (85%) as colorless crystals, mp 154-156°; ir (potassium bromide): 3425, 2976, 1734, 1561, 1421, 1257, 1217 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.74-7.71 (d, 2H, ArH), 7.65-7.62 (d, 2H, ArH), 7.61 (s, 1H, C_5 H), 4.68 (s, 2H, CH_2CO), 4.22 (q, 2H, J = 7.6 Hz, CH_2CH_3), 3.63 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 1.25 (t, 3H, J = 7.6 Hz, CH_2CH_3); ^{13}C nmr (DMSO-d_6): δ 174.5, 167.8, 142.7, 135.2, 131.0, 129.2, 127.3, 109.6, 61.6, 56.4, 43.1, 40.0, 14.0.

Anal. Calcd. for $C_{15}H_{18}BrClN_2O_2S$: C, 44.40; H, 4.47; N, 6.90. Found: C, 44.40; H, 4.48; N, 6.88.

Procedure for the Reaction of Iminothiazoline **5b** with 2-Bromoacetophenone.

3-Methyl-2-methylimino-4-phenyl-Δ^4-thiazoline (**5b**) (1.84 g, 9 mmoles) and 2-bromoacetophenone (1.19 g, 6 mmoles) were refluxed in dry benzene (30 ml) for 2 hours. After cooling **9b** was filtered, 0.77 g (30% on the basis of **5b**). Removal of the solvent from the filtrate and preparative liquid chromatography (hexane/ethyl acetate 8:1) gave the pyrrolothiazine **10b** (0.46 g, 12% on the basis of **5b**). Then, **5b** (0.95 g, 52% on the basis of **5b** used) was recovered by eluting with hexane/ethyl acetate 1:2.

3-Methyl-2-methylamino-4-phenylthiazolylium Bromide (**9b**).

This compound was obtained as colorless crystals, mp 190-192°; ir (potassium bromide): 3336, 3117, 2817, 1626, 1462, 1377 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.53-7.51 (m, 3H, Ar H), 7.39-7.36 (m, 2H, Ar H), 6.88 (s, 1H, C_5 H), 3.77 (s, 3H, C_2 N-CH_3), 3.18 (s, 3H, N_3-CH_3); ^{13}C nmr (deuteriochloroform): δ 169.1, 143.2, 130.8, 129.3, 129.2, 127.9, 104.2, 36.8, 33.3.

Anal. Calcd. for $C_{11}H_{13}BrN_2S$: C, 46.33; H, 4.59; N, 9.82. Found: C, 46.20; H, 4.58; N, 9.80.

Compound **9b** (0.57 g, 2 mmoles) and potassium carbonate (0.55 g, 4 mmoles) were stirred in acetonitrile (30 ml) at rt for 16 hours. After cooling to 0°, inorganic materials were filtered off. The filtrate was dried over anhydrous sodium sulfate and then decolorized with active carbon. Evaporation of the solvent under reduced pressure gave free base **5b**, 0.38 g, (93%) from **9b**.

6-Benzoyl-4,5-dimethyl-3,7-diphenyl-4*H*,5*H*-pyrrolo[3,2-*b*]-1,4-thiazine (**10b**).

This compound was obtained as orange crystals, mp 166-168°; ir (potassium bromide): 3067, 2937, 2329, 1611, 1581 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.55-7.48 (m, 4H, Ar H), 7.40-7.32 (m, 3H, Ar H), 7.17-7.12 (m, 1H, Ar H), 7.03-6.97 (m, 7H, ArH), 6.01 (s, 1H, C_2 H), 3.87 (s, 3H, CH_3), 2.98 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 186.2, 144.3, 140.5, 139.4, 136.7, 133.5, 131.1, 129.7, 128.8, 128.4, 127.6, 127.4, 127.3, 126.6, 126.4, 126.2, 106.9, 102.3, 41.7, 33.2; ms: m/z (relative intensity) 77 (14), 105 (12), 407 (100), 422 (54, M^+); hrms: (EI) Calcd. for $C_{27}H_{22}N_2OS$: 422.1453. Found: 422.1457.

General Procedure for the Reaction of Iminothiazolines **5b-d** with 2-Bromoacetophene in the Presence of Potassium Carbonate.

Iminothiazolines **5b-d** (10 mmoles), 2-bromoacetophene (10 mmoles), and potassium carbonate (20 mmoles) were refluxed in dry benzene (50 ml) for 4 hours. After cooling, inorganic materials were filtered off. Removal of the solvent from the filtrate and preparative liquid chromatography (hexane/ethyl acetate 8:1) gave the pyrrolothiazines **10b-10d**.

6-Benzoyl-4,5-dimethyl-3,7-diphenyl-4*H*,5*H*-pyrrolo[3,2-*b*]-1,4-thiazine (**10b**).

This compound was obtained in a 62% yield.

6-Benzoyl-4,5-dimethyl-3-(4'-methoxyphenyl)-7-phenyl-4*H*,5*H*-pyrrolo[3,2-*b*]-1,4-thiazine (**10c**).

This compound was obtained in 58% yield as orange crystals; mp 170-172°; ir (potassium bromide): 2938, 2843, 1757, 1615, 1510, 1404 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.50-7.45 (m, 4H, Ar H), 7.15-7.12 (m, 1H, Ar H), 7.02-6.90 (m, 9H, Ar H), 5.87 (s, 1H, C_2 H), 3.87 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 2.99 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 186.8, 160.5, 145.0, 141.2, 140.1, 134.1, 131.7, 131.5, 130.4, 130.3, 130.2, 129.7, 128.2, 128.2, 128.0, 127.2, 114.8, 105.4, 103.3, 56.0, 42.2, 33.8; ms: m/z (relative intensity) 77 (26), 105 (49), 290 (45), 321 (28), 437 (100), 452 (79, M^+); hrms: (EI) Calcd. for $C_{28}H_{24}N_2O_2S$: 452.1558. Found 452.1555.

6-Benzoyl-4,5-dimethyl-3-(4'-chlorophenyl)-7-phenyl-4*H*,5*H*-pyrrolo[3,2-*b*]-1,4-thiazine (**10d**).

This compound was obtained in 60% yield as orange crystals; mp 99-101°; ir (potassium bromide): 3054, 2938, 1678, 1609, 1551, 1472 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.48-7.45 (m, 4H, Ar H), 7.34-7.31 (m, 2H, Ar H), 7.14-7.11 (m, 1H, Ar H), 7.01-6.97 (m, 7H, Ar H), 6.03 (s, 1H, C_2 H), 3.85 (s, 3H, CH_3), 2.95 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 186.9, 143.8, 140.6, 139.9, 135.8, 134.6, 134.0, 131.8, 131.5, 130.7, 130.4, 130.3, 129.6, 128.3, 128.0, 127.2, 127.0, 108.6, 102.8, 42.4, 33.6; ms: m/z (relative intensity) 77 (24), 105 (38), 441 (100), 456 (81, M^+); hrms: (EI) Calcd. for $C_{27}H_{21}ClN_2OS$: 456.1063. Found: 456.1067.

1-Methyl-2-benzoyl-5-[*N'*-methyl-*N'*-(2-phenylethyl)]-3-phenylaminopyrrole (**11**).

Pyrrolothiazine **10b** (0.41 g, 0.98 mmoles) and freshly prepared Raney nickel (W-2) [31] (4 g) were stirred in absolute ethanol (20 ml) at 50° for 1.5 hours. In consequence, nickel filtered off. Removal of the solvent from the filtrate and preparative liquid chromatography (hexane/ethyl acetate 8:1) gave the pyrrole **11**, 0.24 g (62%) as a yellow oil; ir (deuteriochloroform): 2991, 1680, 1520, 1467, 1420, 1393 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.59-7.57 (m, 2H, Ar H), 7.45-7.30 (m, 5H, ArH), 7.19-7.17 (m, 1H, Ar H), 7.08-6.98 (m, 7H, Ar H), 5.88 (s, 1H, C_4 H), 4.43 (q, 1H, J = 7.6 Hz, CH), 3.88 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 1.53 (d, 3H, J = 7.6 Hz, CH_3); ^{13}C nmr (deuteriochloroform): δ 187.1, 149.6, 142.0, 139.8, 136.4, 135.0, 131.1, 130.0, 129.5, 128.5, 128.4, 127.7, 127.5, 127.4, 127.3, 126.0, 101.6, 62.3, 37.0, 33.3, 17.8; ms: m/z (relative intensity) 77 (13), 105 (42), 169 (23), 289 (100), 394 (40, M^+); hrms: (EI) Calcd. for $C_{27}H_{26}N_2O$: 394.2045. Found: 394.2041.

1-Methyl-2-benzoyl-3-phenyl-4-phenacylsulfanyl-4-(N'-methylamino)pyrrole (**12**).

Pyrrolothiazine **10b** (0.50 g, 1.18 mmoles), a few drops of concentrated hydrochloric acid, and 95% ethanol (30 ml) were stirred at 50° for 2 hours. Removal of the solvent from the reaction mixture and preparative liquid chromatography (hexane/ethyl acetate 5:1) gave the compound **12**, 0.42 g (82%),as a yellow oil; ir (deuteriochloroform): 3360, 3065, 2949, 1683, 1604, 1583, 1525, 1399, 1362 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.74-7.71 (m, 2H, Ar H), 7.44-7.38 (m, 5H, ArH), 7.18-6.98 (m, 8H, Ar H), 4.40 (br s, 1H, NH), 3.71 (s, 3H, CH_3), 3.49 (s, 2H, CH_2), 2.77 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 194.4, 186.2, 152.9, 139.5, 138.4, 135.5, 134.2, 133.4, 130.9, 130.8, 129.6, 128.7, 128.6, 128.5, 127.6, 127.4, 126.6, 126.4, 42.6, 35.3, 34.5; ms: m/z (relative intensity) 77 (34), 105 (25), 201 (32), 216 (50), 290 (28), 321 (99), 407 (26), 440 (100, M^+); hrms: (EI) Calcd. for $C_{27}H_{24}N_2O_2S$: 440.1558. Found: 440.1556.

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