198, 123, 88; exact mass calcd for $C_{19}H_{24}N_2O_3$ 328.1787, obsd 328.1788.

(2) To the carbamate (13 mg, 0.039 mmol) in chloroform (7 mL) was added iodotrimethylsilane (56 μL, 0.4 mmol), and the resulting solution was refluxed for 7 h. Methanol (5 mL) was added, and reflux was continued for 8 h. The solvents were removed by rotary evaporation, and the crude product was purified by flash chromatography (silica gel half-saturated with ammonia) using 3% methanol in chloroform as eluent and then 50% methanol in chloroform to afford pyridone **42** (7 mg) in 70% yield: R_f = 0.025 (basic SiO_2, $CHCl_3$–acetone–MeOH 50:45:5, two runs); IR (Nujol) 3149, 3121, 1651, 1600, 1152, 1119 cm^{-1}; ^1H NMR (MeOH-d_4) δ 7.66 (d, 1 H, J = 9.4 Hz), 6.44 (d, 1 H, J = 9.4 Hz), 5.46 (m, 1 H), 5.36 (q, 1 H, J = 6.6 Hz), 3.64 (br, 1 H), 3.57 (dd, 2 H, J = 8.5, 14.2 Hz), 2.86 (dd, 1 H, J = 4.8, 17.2 Hz), 2.64 (d, 1 H, J = 16.9 Hz), 2.20 (d, 1 H, J = 16.5 Hz), 2.02 (d, 1 H, J = 16.6 Hz), 1.75 (d, 3 H, J = 6.6 Hz), 1.55 (s, 3 H); mass spectrum, m/z 256 (M^+), 239, 224, 212, 200, 184, 128; exact mass calcd for $C_{16}H_{20}N_2O$ 256.1570, obsd 256.1576.

5-(Aminomethyl)-2(1*H*)-pyridinone (46). 5-Cyano-2-methoxypyridine (**44**, 2 g, 14.9 mmol), prepared by the procedure of Forrest and Walker,[27] was dissolved in 40 mL of ammonia-saturated methanol and hydrogenated over 0.8 g of Raney nickel at a pressure of 45 psi. After 3 h the catalyst was filtered, the solvent evaporated, and the crude product dissolved in 20 mL of dichloromethane. The solution was cooled (ice bath), and 4 mL of triethylamine and 2.3 mL of methyl chloroformate were added. After 2 h at rt, the solvent was removed by rotary evaporation, and the residue was dissolved in water and extracted with 3 × 10 mL of ethyl acetate. The combined organic layers were washed with water, dried, and concentrated to afford 1.6 g (55% overall yield) of the crude carbamate **45**. The carbamate (116 mg, 0.59 mmol) was dissolved in 10 mL of chloroform and refluxed for 7 h with 1.68 mL (11.8 mmol) of iodotrimethylsilane. Methanol (5 mL) was then added and gentle reflux maintained for 8 h. The reaction mixture was concentrated, and the crude product was purified by flash chromatography over ammonia-saturated silica gel, using first 3% methanol in ethyl acetate and then 25% methanol in ethyl acetate to furnish 47 mg (75%) of the pyridone **46**: R_f = 0.1 (basic SiO_2, 7% methanol in ethyl acetate); IR (Nujol) 3387, 2922, 2856, 1653, 1606, 904 cm^{-1}; ^1H NMR (D_2O) δ 7.75 (dd, 1 H, J = 2.4, 9.3 Hz), 7.66 (s, 1 H), 6.67 (d, 1 H, J = 9.3 Hz), 4.03 (s, 2 H); ^{13}C NMR (MeOH-d_4) δ 155.0, 136.3, 128.7, 110.5, 106.4, 31.2; mass spectrum, m/z 124 (M^+), 108, 96, 78, 53; exact mass calcd for $C_6H_8N_2O$ 124.0637, obsd 124.0637.

5-[(Dimethylamino)methyl]-2(1*H*)-pyridinone (48). Since the transformations employed to prepare compound **48** are routine and in part related to the methods described above, only spectral data follow: R_f = 0.15 (acetone–$CHCl_3$–MeOH 9:10:1): IR (Nujol) 2922, 1672, 1593, 1543, 1522, 1377, 1153, 1005, 949, 721 cm^{-1}; ^1H NMR (D_2O) δ 7.75 (d, 0.5 H, remaining portion of dd obscured by proton at 7.71), 7.71 (br s, overlapping signals, 1.5 H), 6.67 (dd, 1 H, J = 8.5, 1.5 Hz), 4.15 (s, 2 H), 2.62 (s, 6 H); ^{13}C NMR (MeOH-d_4) δ 155.6, 135.4, 130.4, 112.0, 100.9, 48.9, 33.1; mass spectrum, m/z 152 (M^+), 128, 108, 80, 69, 58; exact mass calcd for $C_8H_{12}N_2O$ 152.0950, obsd 152.0949.

Determination of AChE Activity. Rats were killed by decapitation. Brains were extirpated rapidly. The hippocampus was dissected out on ice according to the method of Glowinski and Iverson.[29] Samples were homogenized in ice-cold 0.32 M sucrose. Homogenates were centrifuged at 1000*g* for 10 min to remove cell nuclei and heavy debris. The supernatant was then aspirated off and spun again (12000*g*) for 20 min to form a pellet (Whittaker's P_2 fraction) that contained synaptosomes and mitochondria.[30] The pellet was resuspended in 0.32 M sucrose. A portion of this synaptosome-rich fraction was added in triplicate to ice-cold pH 7.4 Krebs–Ringer medium.

Assay of AChE was carried out according to the method described in Mantione et al.[31] Tissue homogenate was incubated for 30 min at 30 °C in a final volume of 20 μL containing 75 mM sodium phosphate buffer, pH 7.0, containing 1.5 mM [^{14}C]-acetylcholine (1.9 mCi/mmol). To each sample was added 25 μL of cold water, followed by 150 μL of tetraphenylboron solution.[32] The tubes were vortexed for 10 s and then centrifuged for 1 min. The bottom aqueous layer was quickly frozen in a dry ice/acetone bath, and the top organic layer was aspirated off. Finally, the buffer was allowed to thaw, and a 25-μL portion was counted for the amount of [^{14}C]acetate formed. The amount of residual [^{14}C]acetylcholine left in the buffer by the extraction step alone was determined by subtracting from the tissue sample values of [^{14}C]acetylcholine measured in a blank sample that contained buffer and substrate, but no tissue.

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Supplementary Material Available: ^1H NMR for **48**, **46**, **42**, **41**, **40**, **39**, **37**, **35**, **34**, **29**, **28**, **25**, and **10**/**11** and ^{13}C NMR for **25**, **24**, **18**, **17**, and **14b** (18 pages). Ordering information is given on any current masthead page.

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Reaction of Aminopropanedinitrile 4-Methylbenzenesulfonate (Aminomalononitrile *p*-Toluenesulfonate (Tosylate)) with Isothiocyanates

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Aminopropanedinitrile 4-methylbenzenesulfonate (ammoniopropanedinitrile or aminomalononitrile *p*-toluenesulfonate (tosylate)) reacts with alkyl and aryl isothiocyanates in 1-methyl-2-pyrrolidinone (NMP) to give 5-amino-2-(alkylamino)-4-cyanothiazoles and 5-amino-2-(arylamino)-4-cyanothiazoles (2,5-diaminothiazole-4-carbonitriles), respectively, which react with amidines or ortho esters to afford 7-amino-2-(alkylamino)thiazolo[5,4-*d*]pyrimidines and 7-amino-2-amino-2-(arylamino)thiazolo[5,4-*d*]pyrimidines.

Propanedinitrile (malononitrile, dicyanomethane, $CH_2(CN)_2$) and its derivatives are important compounds for the preparation of diverse substrates and for the synthesis of a wide variety of heterocycles.[1-7] Of particular

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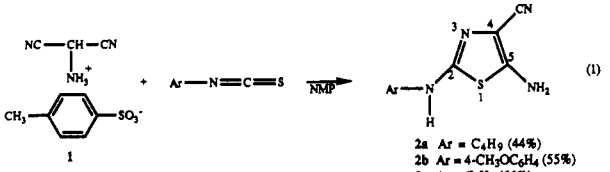
interest is the highly functional and versatile aminopropanedinitrile (aminomalononitrile),[1-4,7] which is usually employed in the more stable form as aminopropanedinitrile 4-methylbenzenesulfonate (ammoniopropanedinitrile or aminomalononitrile *p*-toluenesulfonate (tosylate), AMNT, 1).[8-12] During studies on the synthesis of new heterocycles, it was observed that AMNT (1) reacts with alkyl and aryl isothiocyanates[13] in 1-methyl-2-pyrrolidinone (NMP) to give 5-amino-2-(alkylamino)-4-cyanothiazoles (**2a**) and 5-amino-2-(arylamino)-4-cyanothiazoles (**2b–2f**) in 44–81% yields (eq 1).[14-17] The unsaturated 2-aminonitrile (*o*-

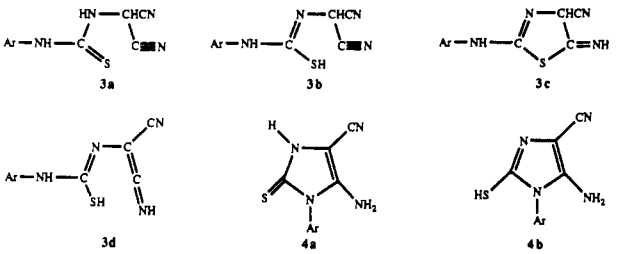


(1)

2a Ar = C_4H_9 (44%)
2b Ar = 4-$CH_3OC_6H_4$ (55%)
2c Ar = C_6H_5 (66%)
2d Ar = 4-ClC_6H_4 (58%)
2e Ar = 4-$O_2NC_6H_4$ (81%)
2f Ar = 1-$C_{10}H_7$ (74%)

aminonitrile) functionality (cf. **2**) is well-known for its versatile reactivity and for its importance in the synthesis of heterocycles.[15] It is also of interest to prepare these compounds owing to the outstanding pharmacological properties[16,17] and the diverse applications of some of their derivatives.[18]

Electron-attracting substituents on the isothiocyanates appear to enhance the yields of thiazoles **2b–2e**.[19] 1-Methyl-2-pyrrolidinone (NMP) serves as solvent and as a base to generate aminopropanedinitrile (aminomalononitrile)[8-12] and to neutralize 4-methylbenzenesulfonic acid. It is reasonable to expect the amino group of the liberated (from AMNT, 1) aminopropanedinitrile to attack the sp-hybridized carbon atom of the isothiocyanate to afford an intermediate 2-thiouracil **3a**, which cyclizes via a nucleophilic attack by sulfur at the carbon atom of a nitrile group to yield **3c**, which undergoes tautomerism to thiazole **2**. Alternatively, nucleophilic attack by sulfur at the carbon atom of an intermediate ketene imine **3d** could also lead to thiazole **2**.



X-ray crystallographic data,[20] infrared,[16,21-27] ultraviolet,[16,27] ^{13}C NMR,[28-30] and ^{1}H NMR[28-30] spectral data and mass spectrometry were used to establish the structures of thiazoles **2a–2f** and to eliminate isomeric structures of thiouracils **3a** and **3b** and of 1-substituted 5-amino-4-cyano-1,3-dihydro-2*H*-imidazole-2-thiones **4**.[13-15] The thiazoles **2a–2f** show N–H stretching in the region 3420–3160 cm^{-1} and nitrile stretching in the 2210–2195 cm^{-1} region. The secondary amino group proton shows a triplet at 7.11 ppm for 5-amino-2-(butylamino)-4-cyanothiazole (**2a**) and singlets in the 9.63–10.67 ppm region for the aryl-substituted thiazoles **2b–2f**. The primary amino group protons show singlets in the 6.50–7.16 ppm region for thiazoles **2a–2f**. 2-Aminothiazoles can exist as the amino and imino tautomers (cf. **3c**), although the former is generally predominant.[28-30] The ^{13}C NMR spectra of thiazoles **2** show resonances in the 158–160 ppm region (C-2), in the region 99–100 ppm (C-4), in the 150–153 ppm region (C-5), and in the 120–121 ppm region (C≡N).

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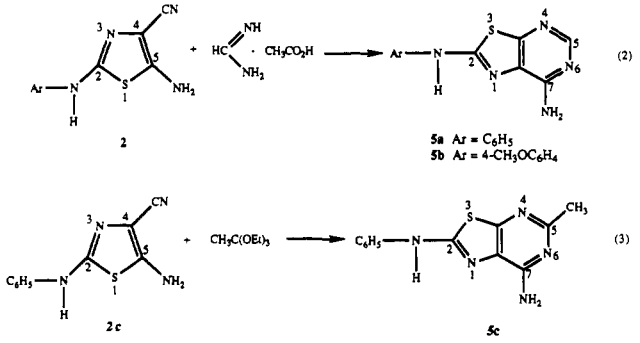
Examples of the synthetic utility of the thiazoles (2) are shown in the reactions of formamidine acetate[8b] with the unsaturated 2-aminonitrile functionality in compounds **2b** and **2c** to afford 7-amino-2-[(4-methoxyphenyl)amino]-thiazolo[5,4-*d*]pyrimidine (**5b**) and 7-amino-2-(phenylamino)thiazolo[5,4-*d*]pyrimidine (**5a**), respectively. The reaction of thiazole **2b** with triethyl orthoacetate,[17,31] followed by treatment with 8 M ethanolic ammonia,[32] gave 7-amino-5-methyl-2-(phenylamino)thiazolo[5,4-*d*]pyrimidine (**5c**). Similarly, thiazole **2c** reacted with triethyl orthoformate to give thiazolo[5,4-*d*]pyrimidine **5a**.[17,31] Compounds **5a–5c**, which represent a relatively rare family of heterocycles, are structurally similar to other bioactive compounds.[33–36]



Experimental Section

Melting points were determined in open capillary tubes with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Robertson Laboratory, Inc., Florham Park, NJ.

High-resolution mass spectra (HRMS) were obtained with a VG 7070-HF mass spectrometer (70 eV). Chemical ionization mass spectra (CIMS, 2-methylpropane) and electron impact mass spectra (EIMS) were obtained with a Finnigan 9610 GC-EI-CI mass spectrometer with a Nova 3 data system operating at an ionization potential of 70 or 100 eV.

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a General Electric Model QE 300 (300-MHz) spectrometer, and chemical shifts (δ) are reported in parts per million relative to internal tetramethylsilane (0.00 ppm). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a General Electric Model QE 300 (75.5-MHz) spectrometer, and chemical shifts are reported in parts per million relative to the central solvent (DMSO-d_6) resonance at 43.5 ppm.

IR spectra were obtained with a Perkin-Elmer 283 spectrophotometer, calibrated with the 1601 cm^{-1} absorption of polyphenylethene.

Ultraviolet spectra were obtained in ethanenitrile on a Cary 16 spectrometer.

Analytical TLC was performed on Analtech Uniplate 10 × 20 cm (250 μm thick) silica gel GF prescored glass plates, which were developed in a solvent mixture of 1:2 ethyl ethanoate/hexanes. After the solvent had risen to the top, the plates were checked under ultraviolet light and developed in a diiodine chamber to visualize the compounds.

Flash column chromatography was performed on 230–400 mesh silica gel.

The commercially available isothiocyanates were used without further purification.

General Method. Preparation of 5-Amino-2-(alkylamino)-4-cyanothiazoles and 5-Amino-2-(arylamino)-4-cyanothiazoles (2). To an aluminum foil covered 25-mL round-bottomed flask containing a solution of aminomalononitrile tosylate (AMNT, 1, 1.17 g, 4.6 mmol) and anhydrous 1-methyl-2-pyrrolidinone (NMP, 15 mL, 14.5 g, 147 mmol) was added isothiocyanate (4.6 mmol), dropwise, with stirring, at 22–24 °C. The reaction mixture was stirred at 22–24 °C for 12–20 h, diluted with 1:1 ethyl ethanoate/diethyl ether (100 mL), transferred to a separatory funnel, and washed with water (2 × 100 mL), and the layers were separated. The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo. The residue was chromatographed on silica gel (1:2 ethyl ethanoate/hexanes) to afford thiazoles (2).

***N*-(5-Amino-4-cyano-2-thiazolyl)butanamine (2a)**: 44%; mp 125–126 °C; IR (Nujol, cm^{-1}) 3340, 3320, 3220, 3210, 3180, 2205, 1610, 1240, 1080; UV (CH_3CN) λ_{max} (log ϵ) 240 (3.52), 295 (3.54); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.96 (t, 3 H), 1.41 (m, 2 H), 1.55 (m, 2 H), 3.19 (m, 2 H), 6.50 (s, 2 H), 7.11 (t, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 17.68, 23.62, 34.82, 47.06, 99.97, 121.03, 156.98, 157.88; HREIMS 196.0781 (calcd for $C_8H_{12}N_4S$ 196.0783). Anal. Calcd for $C_8H_{12}N_4S$: C, 49.00; H, 6.17; N, 28.57. Found: C, 49.22; H, 6.05; N, 28.50.

5-Amino-4-cyano-2-[(4-methoxyphenyl)amino]thiazole (2b): 55%; mp 199–200 °C; IR (Nujol, cm^{-1}) 3405, 3320, 2195, 1615, 1605, 1250, 1235, 1040; UV (CH_3CN) λ_{max} (log ϵ) 265 (4.04), 304 (4.04); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.79 (s, 3 H), 6.83 (s, 2 H), 6.97 (d, 2 H), 7.47 (d, 2 H), 9.63 (s, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 59.17, 99.68, 118.17, 120.80, 122.19, 138.56, 152.71, 157.81, 157.97; HREIMS 246.0556 (calcd for $C_{11}H_{10}N_4SO$ 246.0575). Anal. Calcd for $C_{11}H_{10}N_4SO$: C, 53.70; H, 4.10; N, 22.77. Found: C, 53.97; H, 4.24; N, 22.47.

5-Amino-4-cyano-2-(phenylamino)thiazole (2c): 66%; mp 164–165 °C; IR (Nujol, cm^{-1}) 3360, 3280, 3160, 2200, 1630, 1600, 1250; UV (CH_3CN) λ_{max} (log ϵ) 268 (3.99), 304 (4.04); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.91 (s, 2 H), 6.99–7.59 (m, 5 H), 9.84 (s, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 99.74, 120.46, 120.76, 124.94, 132.96, 145.09, 151.96, 158.49; HREIMS 216.0487 (calcd for $C_{10}H_8N_4S$ 216.0470). Anal. Calcd for $C_{10}H_8N_4S$: C, 55.59; H, 3.73; N, 25.93. Found: C, 55.84; H, 3.70; N, 25.64.

5-Amino-2-[(4-chlorophenyl)amino]-4-cyanothiazole (2d): 58%; mp 210–211 °C; IR (Nujol, cm^{-1}) 3420, 3300, 3200, 2210, 1620, 1600, 1240, 1230, 1100; UV (CH_3CN) λ_{max} (log ϵ) 272 (4.04), 306 (4.15); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.96 (s, 2 H), 7.41 (d, 2 H), 7.61 (d, 2 H), 10.00 (s, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 99.67, 120.62, 121.84, 128.13, 132.73, 143.95, 151.48, 158.69; HREIMS 250.0067 (calcd for $C_{10}H_7N_4SCl$ 250.0080).

5-Amino-4-cyano-1-[(4-nitrophenyl)amino]thiazole (2e): 81%; mp 230–232 °C; IR (Nujol, cm^{-1}) 3310, 2205, 1615, 1605, 1270, 1115; UV (CH_3CN) λ_{max} (log ϵ) 253 (3.86), 376 (4.13); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.16 (s, 2 H), 7.74 (d, 2 H), 8.2 (d, 2 H), 10.67 (s, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) 99.98, 119.71, 120.30, 129.54, 143.93, 149.91, 150.81, 159.97; HREIMS 261.0335 (calcd for $C_{10}H_7N_5O_2S$ 261.0320).

5-Amino-4-cyano-1-[(1-naphthyl)amino]thiazole (2f): 74%; mp 190–191 °C; IR (Nujol, cm^{-1}) 3300, 3180, 2200, 1630, 1590, 1240; UV (CH_3CN) λ_{max} (log ϵ) 240 (4.04), 325 (3.99); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.97 (s, 2 H), 7.55-8.37 (m, 7 H), 9.77 (s, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 99.54, 118.70, 120.76, 125.83, 126.27, 129.09, 129.50, 130.07, 137.89, 140.50, 153.33, 159.16; HREIMS 266.0603 (calcd for $C_{14}H_{10}N_4S$ 266.0626). Anal. Calcd for $C_{14}H_{10}N_4S$: C, 63.20; H, 3.79; N, 21.06. Found: C, 63.14; H, 4.00; N, 20.83.

7-Amino-2-(phenylamino)thiazolo[5,4-*d*]pyrimidine (5a) was prepared via a modification of a previously reported procedure.[8b] To a solution of 5-amino-4-cyano-2-(phenylamino)thiazole (**2c**, 100 mg, 0.46 mmol) in dry 1-methyl-2-pyrrolidinone (NMP, 7 mL, 7.23 g, 71 mmol) was added formamidine acetate (96 mg, 0.92 mmol) in one portion. The reaction solution was refluxed for 2 h, cooled, diluted with 100 mL of 2:1 ethyl ethanoate/diethyl ether solution, washed with water (3 × 100 mL), dried ($MgSO_4$), and filtered, and the solvent was evaporated in vacuo. The residue

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was purified by column chromatography with 1:1 ethyl ethanoate/hexanes to give 50 mg (44%) of pyrimidine **5a**: mp 274-276 °C; IR (Nujol, cm^{-1}) 3480, 3100, 1620, 1580; UV (CH_3CN) λ_{max} (log ϵ) 230 (4.19), 285 (4.23), 303 (4.21); ^1H NMR (300 MHz, DMSO-d_6) δ 7.11 (m, 1 H), 7.27 (s, 2 H), 7.43 (t, 2 H, J = 7.93 Hz), 7.97 (d, 2 H, J = 7.91 Hz), 8.21 (s, 1 H), 10.64 (s, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 121.78, 126.02, 132.39, 132.97, 144.36, 155.88, 158.20, 161.18, 161.25; HREIMS 243.0585 (calcd for $C_{11}H_9N_5S$ 243.0579).

7-Amino-2-(phenylamino)thiazolo[5,4-*d*]pyrimidine (5a) was also prepared (75%) from the reaction of thiazole **2c** with triethyl orthoformate (see procedure for the preparation of **5c** below).[17,31] Anal. Calcd for $C_{11}H_9N_5S$: C, 54.31; H, 3.73. Found: C, 54.34; H, 3.60.

7-Amino-2-[(4-methoxyphenyl)amino]thiazolo[5,4-*d*]pyrimidine (5b, 42 mg, 38%, mp 260-262 °C) was prepared as described above using 5-amino-4-cyano-2-[(4-methoxyphenyl)-amino]thiazole (**2b**) and formamidine acetate: IR (Nujol, cm^{-1}) 3100, 1620, 1580, 1520; UV (CH_3CN) λ_{max} (log ϵ) 228 (4.16), 292 (4.23), 300 (4.16); ^1H NMR (300 MHz, DMSO-d_6) δ 3.83 (s, 3 H), 7.00 (d, 2 H, J = 8.95 Hz), 7.19 (s, 2 H), 7.88 (d, 2 H, J = 8.86 Hz), 8.18 (s, 1 H), 10.47 (s, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 59.17, 118.09, 123.45, 137.82, 155.58, 157.98, 158.51, 161.55, 174.49; HREIMS 273.0673 (calcd for $C_{12}H_{11}N_5OS$ 273.0684). Anal. Calcd for $C_{12}H_{11}N_5OS$: C, 52.73; H, 4.06. Found: C, 52.81; H, 3.89.

7-Amino-5-methyl-2-(phenylamino)thiazolo[5,4-*d*]pyrimidine (5c).[17,31] Ethanoic anhydride (0.23 mL, 25 mg, 0.24 mmol) was added to a round-bottom flask containing thiazole **2c** (100 mg, 0.46 mmol) and triethyl orthoacetate (5 mL, 4.4 g, 30.9 mmol). The mixture was refluxed for 1 h and cooled, and the unreacted triethyl orthoformate was removed under vacuo. To the residue (a red oil) was added 10 mL of 8 M ethanolic ammonia,[32] and the mixture was stirred at 22-24 °C for 24 h and filtered to afford pyrimidine **5c**. Recrystallization from petroleum ether/propanone gave 57 mg (48%) of pyrimidine **5c** (mp 277-278 °C): IR (Nujol, cm^{-1}) 3100, 2980, 1610, 1040; UV (CH_3CN) λ_{max} (log ϵ) 233 (4.08), 290 (4.16); ^1H NMR (300 MHz, DMSO-d_6) δ 2.35 (s, 3 H), 7.06 (s, 2 H), 6.98-7.98 (m, 5 H), 10.42 (s, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 25.15, 117.66, 121.84, 126.22, 128.96, 132.45, 140.50, 154.00, 156.49, 157.83, 160.46; HREIMS 257.0760 (calcd for $C_{12}H_{11}N_5S$ 257.0760).

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Registry No. 1, 5098-14-6; **2a**, 134312-05-3; **2b**, 134312-06-4; **2c**, 134312-07-5; **2d**, 134312-08-6; **2e**, 134312-09-7; **2f**, 134312-10-0; **5a**, 134312-11-1; **5b**, 134312-12-2; **5c**, 134312-13-3; BuNCS, 592-82-5; 4-$CH_3OC_6H_4NCS$, 2284-20-0; PhNCS, 103-72-0; 4-ClC_6H_4NCS, 2131-55-7; 4-O_2NC_6NCS, 2131-61-5; $C_{10}H_7NCS$, 551-06-4; formamidine acetate, 3473-63-0.

Supplementary Material Available: ^{13}C NMR and ^1H NMR spectra of 5-amino-2-[(4-chlorophenyl)amino]-5-cyanothiazole (**2d**), 5-amino-4-cyano-2-[(4-nitrophenyl)amino]thiazole (**2e**), and 7-amino-5-methyl-2-(phenylamino)thiazolo[5,4-*d*]pyrimidine (**5c**) (6 pages). Ordering information is given on any current masthead page.

7-Aminoaziridinomitosenes: Synthesis, Structure, and Chemistry

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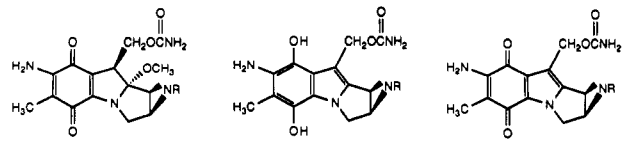
7-Aminoleucoaziridinomitosene (**2a**) has been proposed as a key intermediate in the reductive activation process for the antineoplastic agent, mitomycin C (**1a**). Little is known about **2a** and its oxidized equivalent, 7-aminoaziridinomitosene (**3a**). An expedient electrochemical procedure for **3a** and the corresponding *N*-methyl analogue **3b** has been developed. NMR spectral studies of **3a** in DMF-d_7 and DMSO-d_6 provided important information concerning the solution-state structure for this adduct. Factors controlling the aziridine ring-opening process under reductive and nonreductive conditions have been determined, as well as evidence for the intermediacy of **2a** in the reductive activation cascade of **1a**.

In most commonly accepted proposals pertaining to the mode of action of mitomycin C (**1a**), reductive activation of the antineoplastic agent is believed to generate 7-aminoleucoaziridinomitosene (**2a**), which then undergoes further reaction permitting covalent bonding of the drug to DNA.[1,2] Despite the central importance of this intermediate, few reports have focused on **2a** or its oxidized equivalent **3a**,[3] a situation fostered by the inherent reactivity of this species.[4] In this paper, we describe an expedient synthesis of 7-aminoaziridinomitosenes **3** and their spectral and chemical properties.



1a, R = H; **b**, R = CH_3 **2a**, R = H; **b**, R = CH_3 **3a**, R = H; **b**, R = CH_3

Synthesis. We have reported[5] that electrochemical reduction (−1.0 V, Pt electrode) of 1.5 mM methanolic

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