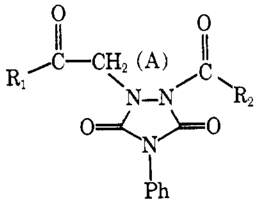
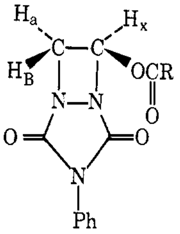
Table II

Nmr Data[a]





Compd	R1	R2	A	Compd	R	Ha	Hb	Hx	J_{AB}	J_{AX}	J_{BX}
3	9.56 (s, 1)	2.60 (s, 3)	4.80 (s, 2)	11	b	4.20[c] (m)		6.19 (m)			
5	2.10 (s, 3)	2.52 (s, 3)	4.78 (s, 2)	14	2.64 (d, 6)	4.58 (q, 1)	4.29 (q, 1)	6.56 (q, 1)	10	6	5
8	9.60 (s, 1)	4.97 (s, 2)	4.72 (s, 2)		2.23 (d, 6)						
10	9.66 (s)	b	4.78 (s)	17	1.20 (s, 9)	4.60 (q, 1)	4.27 (q, 1)	6.49 (q, 1)	10	6	5
13	9.57 (s, 1)	4.15 (m, 1)	4.79 (s, 2)								
		1.25 (d, 6)									
16	9.53 (s, 1)	1.37 (s, 9)	4.63 (s, 2)								

[a] In chloroform-d_1 with 1% TMS as internal standard. Values reported in δ units. N-Phenyl protons appeared in the δ 7.41–7.50 region for all compounds. Abbreviations used are s, singlet; d, doublet; q, quartet; m, multiplet. [b] Complex multiplet absorption in the δ 7.2–7.8 region was observed for the two phenyl groups. [c] Complex absorption pattern for both protons.

Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.73; H, 4.76; N, 15.27. Found: C, 56.83; H, 4.80; N, 15.33.

1-Formylmethyl-2-chloroacetyl-4-phenyl-1,2,4-triazoline-3,5-dione (**8**) precipitated upon pouring the reaction mixture into 250 ml of stirred hexane. Nmr spectra of the crude material indicated no polymer formation. Purification was effected by twice recrystallizing the crude product from hexane–methylene chloride: yield 0.80 g (95%); mp 157–158°; ir (KBr) 2880 (w), 2745 (w), 1810 (s), 1760–1710 cm^{-1} (s, b).

Anal. Calcd for $C_{12}H_{10}ClN_3O_4$: C, 48.91; H, 3.42; N, 14.26. Found: C, 49.00; H, 3.58; N, 14.20.

Separation of **1-formylmethyl-2-benzoyloxy-4-phenyl-1,2,4-triazoline-3,5-dione** (**10**) and **3-phenyl-6-benzoyloxy-1,3,5-triazabicyclo[3.2.0]hepta-2,4-dione** (**11**) has not yet been achieved, and their structural assignments have been tentatively made based on the nmr spectrum of the mixture, total yield 0.11 g (13%).

1-Formylmethyl-2-(2-methylpropionyl)-4-phenyl-1,2,4-triazoline-3,5-dione (**13**) and **3-phenyl-6-(2-methylpropionyloxy)-1,3,5-triazabicyclo[3.2.0]hepta-2,4-dione** (**14**) appeared as an oil after evaporation of the solvent. The mixture was dissolved in the minimum amount of methylene chloride necessary to attain solution followed by addition of the minimum amount of hexane necessary to cause slight cloudiness. The solution was allowed to stand at room temperature for 2–3 days, resulting in fractional crystallization (**14** precipitated first) of the solids. The procedure was repeated several times in order to obtain pure samples of each product.

Data for **13** follow: yield 0.50 g (60%); mp 100–101°; ir (KBr) 2870 (w), 2750 (w), 1800 (m), 1735 (s, b), 1720 cm^{-1} (s, shoulder).

Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53. Found: C, 58.29; H, 5.36; N, 14.45.

Data for **14** follow: yield 0.50 g (6.3%); mp 163–164°; ir (KBr) 1780 (m), 1755 (s), 1720 cm^{-1} (s).

Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53. Found: C, 58.00; H, 5.31; N, 14.36.

1-Formylmethyl-2-(2,2′-dimethylpropionyl)-4-phenyl-1,2,4-triazoline-3,5-dione (**16**) and **3-phenyl-6-(2,2′-dimethylpropionyl)-1,3,5-triazabicylo[3.2.0]hepta-2,4 dione** (**17**) were purified using the same procedure employed for **13** and **14**, substituting hexane–ether as the solvent pair.

Data for **16** follow: yield 0.31 g (36%); mp 135–136°; ir (KBr) 2880 (w), 2740 (w), 1780 (m), 1740 (s), 1720 (s), 1700 cm^{-1} (s).

Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.30; H, 5.79; N, 13.69.

Data for **17** follow: yield 0.30 g (36%); mp 171–172°; ir (KBr) 1780 (m), 1750 (s), 1725 cm^{-1} (s).

Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.18; H, 5.70; N, 13.89.

Vinyl trifluoroacetate (**18**) was allowed to stand with **1** for 96 hr at 60°. Approximately 80% of **1** was recovered unreacted along with 10% of a tan solid, which appeared to be an oligomeric decompositon product of **1**.

Registry No.—**3**, 33981-32-7; **5**, 34050-55-0; **8**, 33981-33-8; **10**, 34050-56-1; **11**, 33981-34-9; **13**, 33981-35-0; **14**, 33981-36-1; **16**, 34050-57-2; **17**, 33981-37-2.

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Intramolecular Catalysis in the Aminolysis of Thiol Esters

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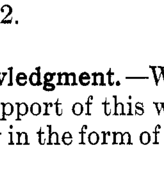
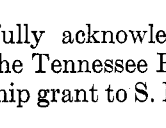
Although the aminolysis of esters has received considerable study, only one example of intramolecular amine-catalyzed aminolysis in water has been reported.[3] We report here the first example of intramolecular amine-catalyzed aminolysis of a thiol ester in water. 2-Pyridyl thiolacetate (**1a**) was chosen as the thiol ester because the pyridyl nitrogen is in a favorable geometric position to act as a general base and because thiol esters of 2-thiopyridone have an unusually high reactivity in



1a



1b

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[2] To whom inquiries should be addressed.

[3] (a) T. C. Bruice and S. M. Felton, *J. Amer. Chem. Soc.*, **91**, 2799 (1969); (b) S. M. Felton and T. C. Bruice, *ibid.*, **91**, 6721 (1969).

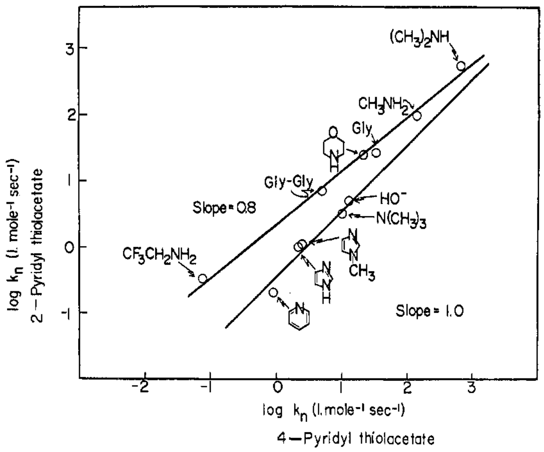

Figure 1.—A plot of the log of the second-order rate constants (k_n) for the reaction of bases with 2-pyridyl thiolacetate *vs.* the same function for 4-pyridyl thiolacetate.

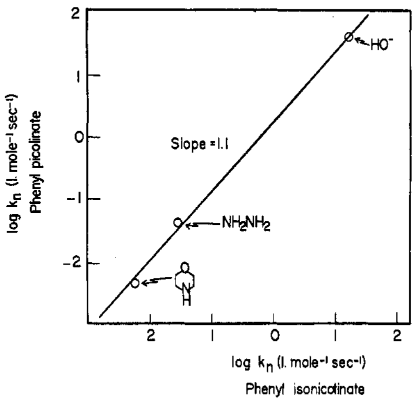

Figure 2.—A plot of the log of the second-order rate constant (k_n) for the reaction of bases with phenyl picolinate *vs.* phenyl isonicotinate. The data for hydroxide ion and hydrazines are from ref 3b.

peptide synthesis.[4] The second-order rate constants (k[B][E]) for the reaction of hydroxide ion and a series of primary, secondary, and tertiary amines with **1a** and 4-pyridyl thiolacetate (**1b**) were obtained. Log k_n for the reaction of **1a** is plotted *vs.* log k_n for **1b** in Figure 1. This plotting technique is a means of comparing nucleophilicities which normalizes scattering of points due to steric effects, electronic effects, etc.[5] In this case it compares the nucleophilicity of a series of nucleophiles toward **1a** and **1b**. **1b** was chosen for comparison because it is structurally similar to **1a** but the pyridyl nitrogen is too distant from the reaction site to be involved in catalysis. Inspection of Figure 1 reveals that the nucleophiles fall on two distinct lines. Hydroxide ion and the tertiary amines fit a line of slope 1, while the primary and secondary amines fit a line of slope 0.8. The slopes in plots of this nature are related to the Brønsted β coefficient; *i.e.*, a slope of 1.0 indicates that the β is the same for both esters and a slope different from 1 indicates that the β values are different for the two esters. Thus, the plot shown in Figure 1 indicates that the mechanism associated with the tertiary amines and hydroxide ion is the same for both thiol esters, while the mechanisms of the reaction of the primary and secondary amines appear different for each thiol ester. The reaction of hydroxide ion and the tertiary amines with both thiol esters must proceed *via* nucleophilic attack at the carbonyl group. **1b** reacts with the primary and secondary amines by the same mechanism as the tertiary amines, while the reactivity of the primary and secondary amines is enhanced over the tertiary amines for **1a**. This enhanced reactivity of amines containing dissociable protons can be attributed to intramolecular general base assistance. The intramolecular general base mechanism could involve the pyridyl nitrogen with a transition state as pictured in **1a** or it could involve the sulfur after a rapid *S*- to *N*-acyl shift with a transition state as shown in **1b**. The mechanism involving sulfur as a general base is ruled out because the basicity of the sulfur is extremely low,[6] negating its role as a general base catalyst. Thus the preferred mechanism for the intramolecular general base catalyzed reaction of the primary and secondary amines with **1a** is the one involving proton removal by the pyridyl nitrogen.

Phenyl picolinate (**2a**) was examined by this same plotting technique in an attempt to find a further example of intramolecular amine-catalyzed aminolysis of an ester in water. The logarithms of the second-order rate constants for the reaction of **2a** and phenyl isonicotinate (**2b**) with a primary amine, a secondary amine, and hydroxide are plotted in Figure 2. Figure 2 shows that all points lie on a line of slope 1.1. This indicates that the amines react *via* the same mechanism as hydroxide ion with both esters. Since hydroxide ion cannot react *via* an intramolecular mechanism, it follows that the reaction of the amines with **2a** is not proceeding *via* an intramolecular amine-catalyzed mechanism. Thus, Bruice and Felton's previous suggestion[3b] that the pyridyl nitrogen cannot get close enough to the incoming amine to remove a proton is probably correct.

Experimental Section

Materials.—The amines or their hydrochlorides were purified as described elsewhere.[3b] 2-Pyridyl thiolacetate (**1a**),[7] phenyl picolinate (**2b**),[3b] and phenyl isonicotinate (IIb)[3b] were prepared according to literature procedures.

4-Pyridinium Thiolacetate Hydrochloride.—To 5.56 g (0.05 mol) of 4-mercaptopyridine dissolved in 600 ml of acetone a slight molar excess of acetyl chloride was added. After several minutes yellow crystals formed. The reaction mixture was allowed to stand at room temperature for 30 min and then the yellow crystals were filtered off and recrystallized from acetonitrile: melting point could not be determined because the salt decomposed on heating; ir (KBr) 1710 (C=O). Calcd for C_7H_8NOSCl: C, 44.32; H, 4.26; S, 16.90. Found: C, 44.16; H, 4.06; S, 16.76.

Kinetics.—Reaction rates were determined spectrophotometrically in water at 30° by a previously published procedure.[3b] The ionic strength was maintained at 1 *M* by adding KCl. The change in absorbance was followed at 324, 342, 290, and 240 nm for **1a**, **1b**, **2a**, and **2b**, respectively.

Registry No.—4-Pyridinium thiolacetate hydrochloride, 34224-19-6.

Acknowledgment.—This research was supported from a grant from the National Institutes of Health.

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[6] R. A. Jones and A. R. Katritzky [*J. Chem. Soc.*, 3610 (1958)] report the pK_a of 2-thiopyridone to be −1.38.

[7] H. Kato, K. Tanaka, and M. Ohta, *Bull. Chem. Soc. Jap.*, **39**, 1248 (1966).