Molecular Rearrangements. Synthesis, Stability, and Rearrangements of 2-Imino-2*H*-isoxazolo[2,3-*a*]pyrimidines and 2-Aminoisoxazolo[2,3-*a*]pyrimidinium Salts

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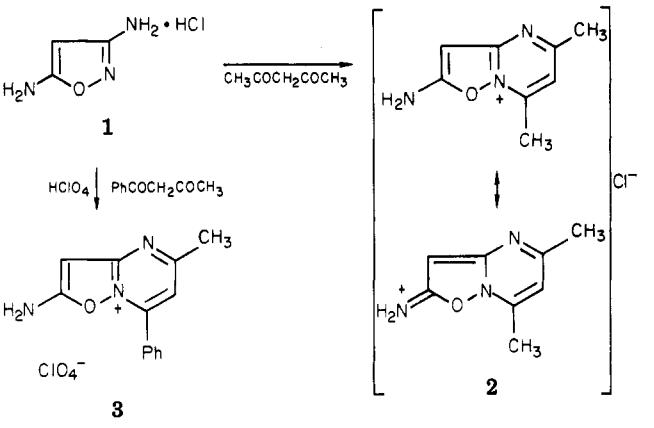
2-Amino derivatives of isoxazolo[2,3-*a*]pyrimidinium salts were prepared by the condensation of 3,5-diaminoisoxazole with acetylacetone and benzoylacetone, respectively. The free base, e.g., 2-amino-2*H*-isoxazolo[2,3-*a*]pyrimidine system, was found to be unstable and to undergo rearrangement to 2-(cyanomethylene)pyrimidine 1-oxide derivatives. Kinetic study of this rearrangement at various pH values enabled the determination of the mechanism of the reactions and the dissociation constants of these compounds. An acetyl group on the amino group inhibited the reaction. The system having a phenyl group at position 3 also proved to be resistant to this kind of decomposition. 2-Imino-3-phenyl-5,7-dimethyl-2*H*-isoxazolo[2,3-*a*]pyrimidine underwent different kinds of rearrangements upon heating with HCl, acetic anhydride, or ethanol, respectively. 3,5-Diamino-4-phenylisoxazole was prepared by two steps from 2-phenylmalononitrile.

The isoxazolo[2,3-*a*]pyrimidine system exists either as the isoxazolo[2,3-*a*]pyrimidinium salts[1] or as the reduced form.[1,2] Bearing in mind the potential pharmaceutical activity of this heterocyclic system due to its isology with pyrazolo[1,5-*a*]pyrimidines, which possess a great variety of biological activities,[3] it was interesting to study its synthesis and the stability of its derivatives. Neutralization of isoxazolo[2,3-*a*]pyrimidinium salts containing an amino group at position 2, 5, or 7 may lead to the imino derivatives of the respective reduced forms. Although the starting material 3,5-diaminoisoxazole hydrochloride (1) has been known for several years,[4] neither 2-aminoisoxazolo[2,3-*a*]pyrimidinium salts nor 2-imino-2*H*-isoxazolo-[2,3-*a*]pyrimidines were described.

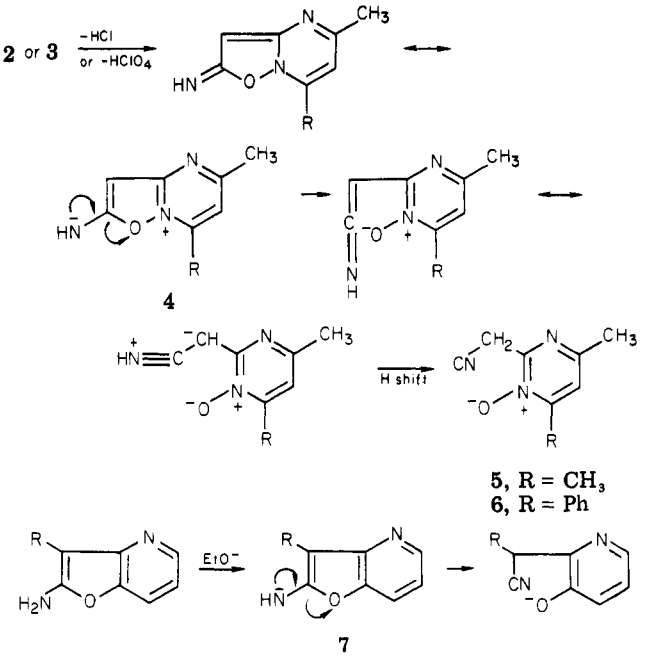
In the present work 3,5-diaminoisoxazole hydrochloride (1) yielded with acetylacetone the hydrochloride of **2**. Another 2-aminoisoxazolo[2,3-*a*]pyrimidinium salt (**3**) was obtained by using benzoylacetone in the presence of perchloric acid (Scheme I). NMR, IR, and mass spectral results were in agreement with the proposed structures.

Regioisomer **3** is assumed on the basis of previous observations[1] and is in agreement with our observations. Both **2** and **3** are stable as their salts, but as soon as they are neutralized, the five-membered ring is cleaved by rearrangement to the pyrimidine *N*-oxides **5** and **6**. The proposed mechanism for this reaction is shown in Scheme II. Recently a similar cleavage of an aminofurano[3,2-*b*]pyridine derivative on prolonged boiling with sodium ethoxide was reported.[5] It is known also that 2-aminothiophene derivatives tend to rearrange on treatment with base via the formation of a nitrile.[6] In these cases the strong base is needed for the formation of the anion **7**. However, in the present case the rearrangement is observed already at pH 3 and is complete at pH 4 in a few hours at room temperature. The dependency of the rate of rearrangement on the pH was studied, and first-order reaction rates were determined. The range of pH is that of

Scheme I



Scheme II



the first dissociation of the 2-aminoisoxazolo[2,3-*a*]pyrimidinium salts; the neutral species **4** probably rearranges, rather than the anion (Scheme II).

The rate of the reaction depends on the concentration of the neutral species **4** at the particular pH in which the reaction is performed. The first-order k_{obsd} was derived

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0022-3263/83/1948-0575$01.50/0

Table I. Observed Rate Constants of Rearrangements of 2-Aminoisoxazolo[2,3-*a*]pyrimidinium Salts 2 and 3 at 21 °C at Various pH Values (Phosphate + Acetate 0.45 M Buffers)

compd	pH	k_{obsd}	pK_a	k_1
2	6.00	$(1.38 \pm 0.05) \times 10^{-2}$	6.27 ± 0.2	0.04 ± 0.02
	5.50	$(5.75 \pm 0.05) \times 10^{-3}$		
	5.00	$(2.0 \pm 0.05) \times 10^{-3}$		
	4.50	$(6.5 \pm 0.05) \times 10^{-4}$		
3	6.89	$(5.29 \pm 0.05) \times 10^{-2}$	7.27 ± 0.2	0.23 ± 0.1
	6.55	$(2.88 \pm 0.05) \times 10^{-2}$		
	6.00	$(9.10 \pm 0.05) \times 10^{-3}$		
	5.50	$(3.00 \pm 0.05) \times 10^{-3}$		

at various pH values by plotting the logarithm of the change in UV absorption during the course of the reaction vs. time. It was assumed that the rearrangement is slow, compared to the dissociation (eq 1), where AH^+ is the

$$AH^+ \overset{K_a}{\rightleftharpoons} H^+ + A \xrightarrow{k_1} B \qquad (1)$$

protonated species (**2** or **3**), A is the neutral species (**4**), and B is the resulting pyrimidine *N*-oxide (**5** or **6**). K_a and k_1 are the dissociation and reaction constants, respectively. By using eq 2 (see Experimental Section) both the dissociation constant K_a and the first-order reaction constant k_1 could be determined (see Table I). The pK_a values of **2** and **3** are around 7. This value is close to that which is obtained for the stable analogue **18**, which is described below. This fact suggests that the neutral species **4** is the reactive species rather than the anion (Scheme II).

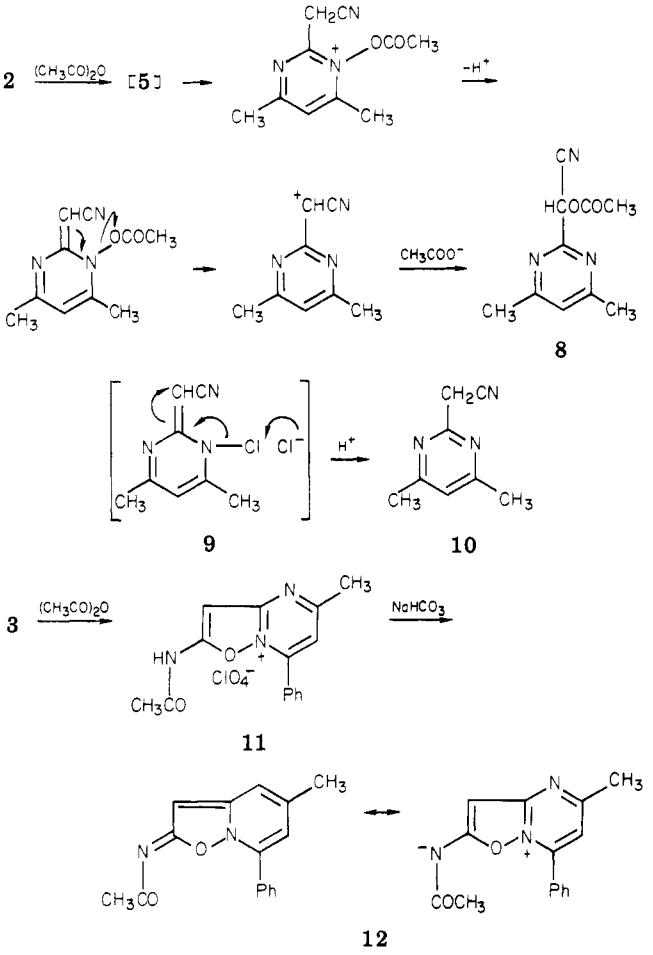
It was difficult to assign the structure of **5** because the IR showed an extremely weak absorption for a C≡N bond, and the two methyl groups gave one signal, even in the 300 MHz spectrum. However, both the existance of a C≡N group and the nonequivalence of the methyl groups were proved by ^{13}C NMR.

It was anticipated that acetylation of the amino group in **2** and **3** will cause stabilization of the 2-imino-2*H*-isoxazolo[2,3-*a*]pyrimidine system by stabilizing the negative charge on the nitrogen of structure **4**. However, on treatment of **2** with acetic anhydride products **8** and **10** were isolated. It appears that under conditions necessary for acetylation, even in the absence of any base, rearrangement of **2** to **5** occurred followed by the common rearrangement that occurs in *N*-oxides of pyrimidine on treatment with acetic anhydride, leading to **8**. A mechanism for the formation of **10** is suggested in Scheme III. The *N*-acetoxy group is replaced by an *N*-chloro derivative (**9**) which is reduced probably by the formation of chlorine.

Compound **3** was stable enough to produce the acetylation product **11** which upon neutralization gave 2-(acetylimino)-2*H*-isoxazolo[2,3-*a*]pyrimidine (**12**). The bicyclic system in **12** proved to be stable in many solvents.

In order to prepare the unknown 3-phenyl-3,5-diaminoisoxazole (**15**), we reacted phenylmalononitrile with hydroxylamine. The product of this reaction was cyanoacetamidoxime (**13**). The C≡N group in **13** was characterized by C^{13} NMR as it failed to show a C≡N band in the IR spectrum. Upon acetylation, **13** yields an *O*-acetyl derivative (**14**). The amidoxime **13** was easily cyclized to the diaminoisoxazole (**15**) by aqueous NaOH in a quantitative yield. Compound **15** showed two different signals

Scheme III



for the NH_2 protons and reacted with acetic anhydride to yield a diacetyl derivative (**16**). Upon electron impact it gives a parent peak of m/e 104. This fragment is probably the benzonitrilium cation which might be obtained via phenylaziridine imine. The latter fragment is also a considerable fragment (m/e 131, 48%) as shown in Scheme IV. A similar fragmentation was also observed in 3,5-diamino-4-phenylpyrazole.[7]

On treatment of **15** with acetylacetone in the presence of HCl it gave 2-amino-5,7-dimethyl-3-phenylisoxazolo-[2,3-*a*]pyrimidinium chloride (**17**), which upon neutralization with bicarbonate gave a stable 2-imino-2*H*-isoxazolo[2,3-*a*]pyrimidine derivative (**18**). The latter was stable in water at all pHs. On treatment with aqueous NaOH it yielded an insoluble stable sodium salt. The salt **17** could be regenerated from the sodium salt **19** by acidification with HCl. The pK_a of deprotonation was 11.37 and the pK_a of protonation was 7.12.

Acid hydrolysis of **18** which was intended to isolate the unknown 2-oxo-2*H*-isoxazolo[2,3-*a*]pyrimidine derivative (**20**) resulted in the formation of the alcohol **22**. The hydrolysis product is probably obtained but is unstable and rearranges as shown in Scheme V. The α-pyrimidinylacetic acid derivative **21** which is unstable under these conditions undergoes decarboxylation to **22**.

2-Imino-2*H*-3-phenyl-5,7-dimethylisoxazolo[2,3-*a*]pyrimidine (**18**) yielded on boiling in ethanolic HCl, two products (**23** and **24**). The chloro derivative **23** is probably formed by a mechanism similar to that shown in Scheme V. Treatment with acetic anhydride gave the acetoxy

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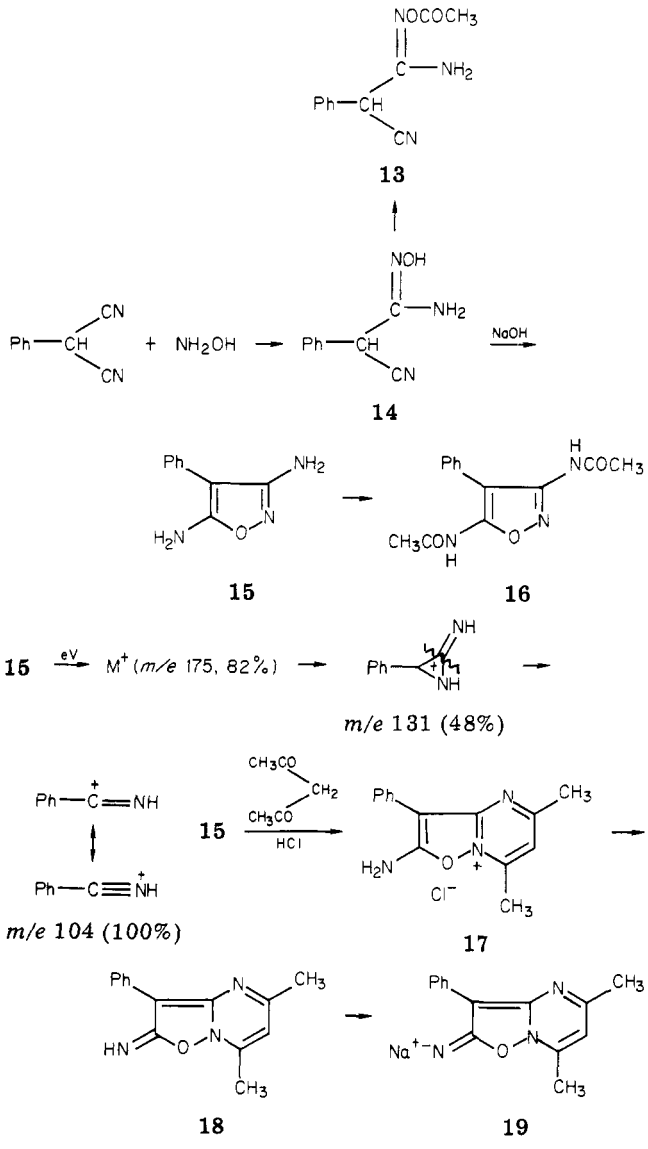
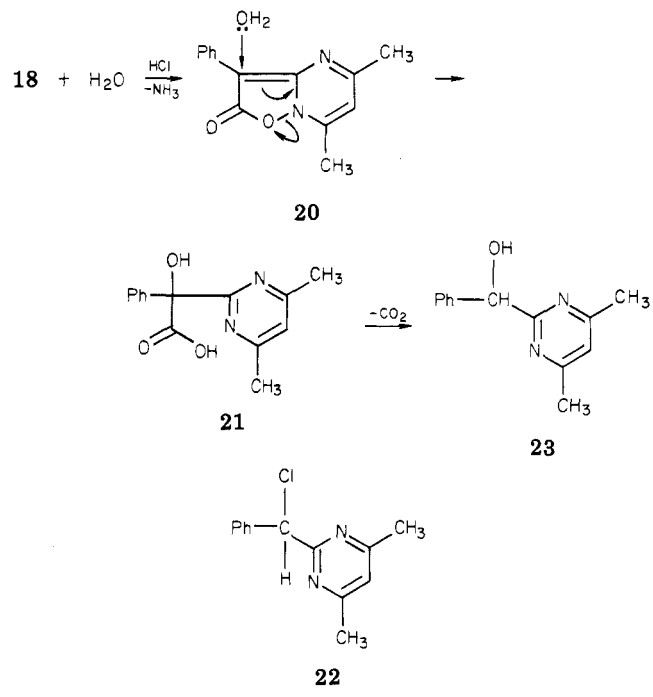
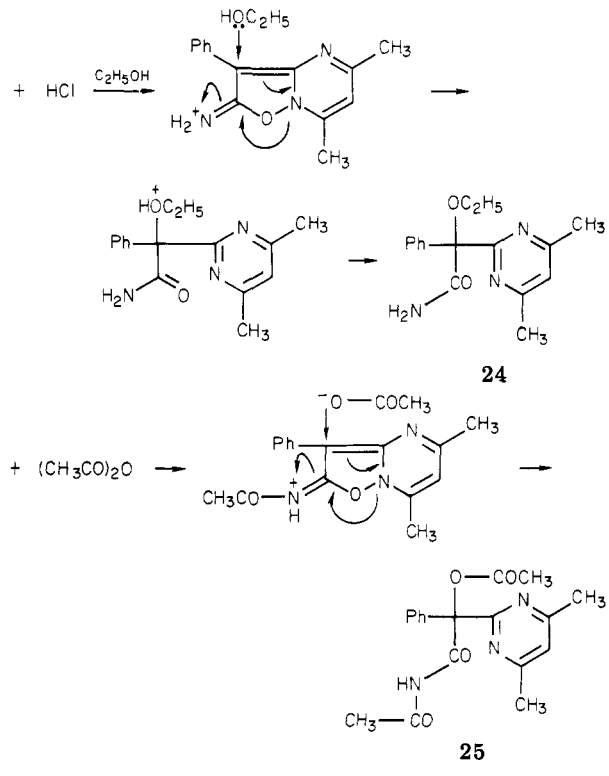
Scheme IV



Scheme V



Scheme VI



imide **25**. Mechanisms of rearrangements leading to **24** and **25** are suggested in Scheme VI.

In summary it may be concluded that stability of the neutral 2-imino-2*H*-isoxazolo[2,3-*a*]pyrimidines is achieved either when a phenyl group is located at position 3 or when the intramolecular rearrangement is blocked by substituting the hydrogen on the side chain nitrogen by an acetyl group. The system that does not have a phenyl group at position 3 is not stable as a neutral species and rearranges to pyrimidine *N*-oxide **5** or **6**. A 2-oxo derivative of the 2*H*-isoxazolo[2,3-*a*]pyrimidine system is also not stable and undergoes another kind of ring cleavage, yielding various kinds of pyrimidine derivatives (e.g., rearrangement of **20** to **22** and **23**). Ethanolic HCl and acetic anhydride caused rearrangements in which the amide group of the system was retained (e.g., rearrangements of **18** to **24** and **25**).

Experimental Section

Melting points were taken with Thomas-Hoover apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer spectrophotometer, model 157. UV and visible spectra with a Varian Techtrone spectrophotometer, Model 635. NMR spectra either with a Varian T-60 or with a Bruker WH-300 spectrometer with Me_4Si as an internal reference. Mass spectra were taken with a Varian MAT-311 spectrometer. When column chromatography was used, the mixture was dissolved in CH_2Cl_2 and mixed with a small amount of silica gel (Merck, 70–230 mesh). The solvent was evaporated, and the residue was placed on top of a silica gel column and eluted with a suitable solvent. Unless stated otherwise petroleum ether is of a boiling range of 40–60 °C.

2-Amino-5,7-dimethylisoxazolo[2,3-*a*]pyrimidinium Chloride (2). Freshly prepared 3,5-diaminoisoxazole hydrochloride (1,[4] 5.0 g) was dissolved in 2-propanol (90 mL) with heating. Acetylacetone (14 mL) was added, and the mixture was boiled for 4 min. The product which separated on cooling was collected and recrystallized from 2-propanol: mp 142 °C dec; 5.7 g (70%). The hydrochloride analyzes for a monohydrate: IR (Nujol) ν_{max} 3360 (NH_2), 1665 cm^{-1} (C=N^+); H^1 NMR (Me_2SO-d_6) δ 9.76 (br s, NH_2), 7.26 (s, CH), 5.90 (s, CH), 2.73 (s, CH_3), 2.60 (s, CH_3); UV (CH_3CN) λ_{max} 315 nm (ϵ 2985), 274 (17 210). Anal. Calcd for $C_8H_{10}N_3OCl \cdot H_2O$: C, 44.14; H, 5.52; N, 19.31; Cl, 16.32.

Found: C, 43.98; H, 5.59; N, 19.62; Cl, 16.25.

2-(Cyanomethylene)-4,6-dimethylpyrimidine 1-Oxide (5). The hydrochloride **2** (2.17 g) was stirred for 30 min in 20% $KHCO_3$ solution (10 mL). The rearrangement product was collected and recrystallized from 2-propanol: mp 65 °C; 1.1 g (67%); IR (Nujol) ν_{max} 2225 cm^{-1} (vw, C≡N); H^1NMR ($CDCl_3$) δ 7.19 (s, CH), 4.25 (s, CH_2CN), 2.53 (s, $2CH_3$); C^{13} NMR ($CDCl_3$) 155.55, 153.42, 150.82, 121.29, 114.42 (C≡N), 77.35 (CH_2CN), 22.99 (CH_3), 17.36 ppm (CH_3); UV (H_2O) λ_{max} 290 nm (ϵ 1990), 258 (7646); UV (CH_3CN) 315 nm (ϵ 2780), 270 (10430); mass spectrum, *m/e* (relative intensity) 163 (M^+, 57), 147 (M − 16), 41), 108 (73), 80 (40), 67 (56), 44 (100), 41 (71). Anal. Calcd for $C_8H_9N_3O$: C, 58.91; H, 5.51; N, 25.75. Found: C, 58.72; H, 5.49; N, 25.34.

2-Amino-5-methyl-7-phenylisoxazolo[2,3-*a*]pyrimidinium Perchlorate (3). Benzoylacetone (2.0 g) was dissolved in acetic acid (5 mL). 3,5-Diaminoisoxazole hydrochloride (1,[4] 1.0 g) and 70% $HClO_4$ (2 mL) were added, and the mixture was heated to boiling. The precipitate which separated on cooling was recrystallized from ethanol: 0.6 g (40%); exploded at 107 °C; IR (Nujol) ν_{max} 3280 (NH_2), 1670 (C=N^+), 1600 cm^{-1} (C=N); H^1 NMR (Me_2SO-d_6) δ 9.50 (br s, NH_2), 9.16–7.65 (m, Ph), 7.50 (s, CH), 6.00 (s, CH), 2.73 (s, CH_3). This salt decomposes to **6** on dissolving in CH_3CN. Anal. Calcd for $C_{13}H_{12}N_3O_5Cl$: C, 47.93; H, 3.71; N, 12.90. Found: C, 47.70, H, 3.53; N, 12.62.

2-(Cyanomethylene)-4-methyl-6-phenylpyrimidine 1-Oxide (6). The perchlorate **3** (0.65 g) was stirred for 60 min in 20% $KHCO_3$ (12 mL). The solid which was formed was collected and recrystallized from 2-propanol: 0.2 g (44%); IR (Nujol) ν_{max} 2230 cm^{-1} (vw, C≡N); H^1 NMR ($CDCl_3$) δ 7.93–7.36 (m, Ph), 7.25 (s, CH), 4.25 (s, CH_2CN), 2.56 (s, CH_3); UV (CH_3CN) λ_{max} 343 nm (ϵ 3570), 279 (8940), 250 (33 170). Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.65. Found: C, 69.18; H, 5.06; N, 18.53.

Reaction of 2 with Acetic Anhydride. 2-Amino-5,7-dimethylisoxazolo[2,3-*a*]pyrimidinium chloride (**2**, 2.0 g) was heated in acetic anhydride (7 mL) almost to boiling (115 °C). At this temperature an exothermic reaction started which proceeded for a few minutes. The solution was then boiled for additional 3 min, cooled, introduced into a 5% $NaHCO_3$ solution (120 mL), and stirred for 30 min. The products were extracted with CH_2Cl_2. The solvent was evaporated, and the residue was subjected to silica gel column chromatography. The products were eluted with ethyl acetate–petroleum ether (2:3). The first fraction was α-acetoxy-α-(4,6-dimethylpyrimidin-2-yl)acetonitrile (**8**). It was recrystallized from 2-propanol: 0.4 g (22%); mp 64 °C; IR (Nujol) ν_{max} 2240 (w, C≡N), 1745 cm^{-1} (C=O); H^1 NMR ($CDCl_3$) δ 7.00 (s, CH), 6.36 (s, CH), 2.46 (s, $2CH_3$), 2.20 (s, CH_3CO); UV (CH_3CN) λ_{max} 244 nm (ϵ 3880). Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.39; H, 5.51; N, 20.33.

The second fraction was 2-(cyanomethylene)-4,6-dimethylpyrimidine (**10**): 0.08 g (6%); mp 79 °C (lit.[8] mp 80 °C); H^1 NMR ($CDCl_3$) δ 6.93 (s, CH), 3.96 (s, CH_2CN), 2.43 (s, $2CH_3$); UV (CH_3CN) λ_{max} 247 nm (ϵ 3970). Anal. Calcd for $C_8H_9N_3$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.38; H, 6.18; N, 27.67.

2-(Acetylamino)-5-methyl-7-phenylisoxazolo[2,3-*a*]pyrimidinium Perchlorate (11). Acetic anhydride (2 mL) was added to 2-amino-5-methyl-7-phenylisoxazolo[2,3-*a*]pyrimidinium perchlorate (**3**, 2.1 g). The exothermic reaction which started proceeded for a few minutes. Ethanol (5 mL) was added with cooling. The product which separated was collected and recrystallized from ethanol: 0.3 g (13%); exploded at 165 °C; IR (Nujol) ν_{max} 1725 cm^{-1} (C=O); H^1 NMR (Me_2SO-d_6) δ 12,00 (br s, NH), 8.30–7.70 (m, Ph + CH), 7.16 (s, CH), 2.90 (s, CH_3), 2.36 (s, CH_3); UV (CH_3CN) λ_{max} 326 nm (ϵ 43 500), 255 (17 500). Anal. Calcd for $C_{15}H_{14}N_3O_6Cl$: C, 48.98; H, 3.81; N, 11.43. Found: C, 48.72; H, 4.07; N, 11.59.

2-(Acetylimino)-5-methyl-7-phenyl-2*H*-isoxazolo[2,3-*a*]-pyrimidine (12). 2-(Acetylamino)-5-methyl-7-phenylisoxazolo-[2,3-*a*]pyrimidinium perchlorate (**11**) (0.15 g) was dissolved in hot water (90 °C, 7 mL). The mixture was cooled to 50 °C, and 5% $NaHCO_3$ solution (2 mL) was added. The crystals which separated on cooling were collected: 0.1 g (94%); mp 144 °C; IR (Nujol) ν_{max} 1635 cm^{-1} (C=O); H^1 NMR ($CDCl_3$) δ 7.9–7.4 (m, Ph), 6.60 (s, CH), 6.50 (s, CH), 2.60 (s, CH_3), 2.16 (s, CH_3); UV (CH_3CN) λ_{max} 328 nm (ϵ 29 400), 272 (14 000), 257 (13 400). Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.41; H, 4.90; N, 15.72. Found: C, 67.60; H, 4.80; N, 15.78.

2-Cyano-2-phenylacetamidoxime (13). 2-Phenylmalononitrile (1.42 g) was dissolved in methanol (14 mL). Hydroxylamine hydrochloride (0.69 g) was added. The mixture was stirred, and a solution of KOH (0.57 g) in methanol (7 mL) was added dropwise during 25 min. The precipitated KCl was filtered off. The solution was cooled overnight and the product precipitated. An additional crop was obtained on evaporation of the solvent and trituration with ether. The two crops were combined and recrystallized from 2-propanol: 1.14 g (65%); mp 149 °C; IR (Nujol) ν_{max} 3170 cm^{-1} (NH_2); H^1 NMR (Me_2SO-d_6) δ 9.92 (s, NOH), 7.33 (s, Ph), 5.60 (br s, NH_2), 4.90 (s, CH); C^{13} NMR (Me_2SO-d_6) 147.73 (C=NOH), 133.07, 130.24, 127.75, 127.34 (Ph), 117.46 ppm (C≡N); mass spectrum, *m/e* (relative intensity) 175 (M^+, 41), 158 (M − 17, 100), 141 (6), 117 (94), 91 (18). Anal. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.73; H, 5.19; N, 24.12.

3,5-Diamino-4-phenylisoxazole (15). The acetoamidoxime derivative **13** (0.44 g) was stirred with 5% aqueous NaOH (5 mL) for 2 min. The material dissolved, and the product started to precipitate. It was collected and recrystallized from ethyl acetate–petroleum ether: mp 145 °C; 0.47 g (94%); IR (Nujol) ν_{max} 3120 cm^{-1} (NH_2); H^1 NMR (Me_2SO-d_6) δ 7.26 (s, Ph), 6.26 (br s, NH_2), 4.90 (br s, NH_2); C^{13} NMR (Me_2SO-d_6) 167.86, 167.25, 130.20, 127.70, 126.33, 124.34, 87.45 ppm; UV (CH_3CN) λ_{max} 265 nm (ϵ 9120); mass spectrum, *m/e* (relative intensity) 175 (82), 131 (48), 117 (19.50), 104 (100); pK_a (of first protonation) 2.38. Anal. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.61; H, 5.40; N, 23.48.

***O*-Acetyl-2-cyano-2-phenylacetamidoxime (14).** 2-Cyano-2-phenylacetamidoxime (**13**, 0.35 g) was boiled for 1 min in acetic anhydride (1 mL). The mixture was cooled, and ether (4 mL) was added. The crystals which separated were collected and washed with ether: mp 105 °C; 0.28 g (64%); IR (Nujol) ν_{max} 3260 (NH), 1730 cm^{-1} (CO); H^1 NMR (Me_2SO-d_6) δ 7.35 (br s, Ph), 5.03 (s, CH), 2.03 (s, CH_3CO); mass spectrum, *m/e* (relative intensity) 217 (2), 175 (71), 158 (66), 130 (31), 116 (100), 103 (52), 89 (45). Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.88; H, 5.18; N, 19.52.

3,5-Diacetamido-4-phenylisoxazole (16). 3,5-Diamino-4-phenylisoxazole (**15**) (0.35 g) was dissolved in acetic anhydride (0.7 mL). The solution was boiled for 30 s and cooled, ether (6 mL) was added, and the product which precipitated was collected and recrystallized from CH_3CN: mp 182 °C; 0.32 g (60%); IR (Nujol) ν_{max} 3200 (NH), 1680 cm^{-1} (CO); H^1 NMR ($CDCl_3$–Me_2SO-d_6, 1:1) δ 9.90 (br s, NH), 7.30 (br s, (Ph), 2.03 (s, $2CH_3CO$); UV (CH_3CN) λ_{max} 238 nm (ϵ 10 700). Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.23; H, 5.05; N, 16.21. Found: C, 60.43; H, 5.15; N, 16.00.

2-Imino-2*H*-3-phenyl-5,7-dimethylisoxazolo[2,3-*a*]pyrimidine (18). 3,5-Diamino-4-phenylisoxazole (**15**, 0.35 g) was dissolved in THF (4.5 mL). Acetylacetone (0.25 mL) and concentrated HCl (0.28 mL) were added, and the solution was stirred for 1 h. The precipitated hydrochloride (**17**) was collected and washed with ether. The neutral base (**18**) was obtained by stirring the hydrochloride in 5% $NaHCO_3$ solution (7 mL) for 1 h. It was collected by filtration and recrystallized from 2-propanol: mp 118 °C; 0.39 g (85%); IR (Nujol) ν_{max} 3080 cm^{-1} (NH_2); H^1 NMR ($CDCl_3$) δ 7.70–7.20 (m, Ph), 7.03 (s, NH), 6.23 (s, CH), 2.46 (s, CH_3), 2.40 (s, CH_3); mass spectrum, *m/e* (relative intensity) 239 (50), 222 (100), 207 (13.70), 196 (20), 146 (7.80), 128 (28.90), 108 (32); UV (CH_3CN) λ_{max} 321 nm (ϵ 3310), 273 (10 230); pK_{a_1} = 7.12, pK_{a_2} = 11.37. Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48. Found: C, 70.50; H, 5.95.

Determination of Dissociation Constants. Several solutions of different pH values were prepared in acetate/phosphate buffer 0.025 M (1:1). The extinction coefficient (ϵ) of the substance was measured at pH values corresponding to the range from 15% to 85% ionization. The acidic dissociation constant was determined from the equation $pK_a = pH + \log (\epsilon_{A^-} - \epsilon)/(\epsilon - \epsilon_A)$, where ϵ_{A^-} and ϵ_A are the extinction coefficient of the union and the neutral molecule, respectively. the pK_a of protonation was determined from the equation $pK_a = pH - \log (\epsilon_{BH^+} - \epsilon)/(\epsilon - \epsilon_B)$, where ϵ_{BH^+} and ϵ_B are the extinction coefficient of the cation and the neutral molecule, respectively. Thus pK_a's of **18** were found to be 11.37 and 7.12 for the acidic and the basic dissociations, respectively.

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The pK_a of protonation of **15** was determined in the same way and was found to be 2.38.

Rearrangement of 18 in Aqueous HCl. A 0.24-g sample of **18** was boiled for 40 min in 1 N HCl (5 mL). The solution was cooled and rendered alkaline with a 5 N KOH solution (5 mL). The product which separated (**22**) was collected and recrystallized from cyclohexane: 0.15 g (65%); mp 80 °C; IR (Nujol) ν_{max} 3340 cm^{-1} (OH); H^1 NMR ($CDCl_3$) δ 7.60–7.20 (m, Ph), 6.83 (s, CH), 5.77 (s, CH), 5.10 (br s, (OH), 2.41 (s, $2CH_3$); UV (CH_3CN) λ_{max} 248 nm (ϵ 4260) [lit:[9] mp 80 °C; IR (Nujol) ν_{max} 3400 cm^{-1} (OH); H^1 NMR ($CDCl_3$) δ 7.60–7.20 (m, Ph), 6.85 (s, CH), 5.78 (s, CH), 5.10 (s, OH), 2.42 (s, $2CH_3$)].

Rearrangement of 18 in Ethanolic HCl. A 0.48-g sample of **18** was boiled for 5 h in 2.25 N ethanolic HCl (10 mL). The solution rendered alkaline with a 5 N KOH solution (6 mL). The product was extracted with benzene (10 mL, three times). The solid product (**24**) which separated on concentration of the solvent to 5 mL was collected and recrystallized from 2-propanol: 0.32 g (56%); mp 196 °C; IR (Nujol) ν_{max} 3140 (NH), 1680 cm^{-1} (C=O); H^1 NMR ($CDCl_3$) δ 7.40–7.03 (m, Ph), 7.15 (s, CH), 6.15 (br s, CH), 3.38 (q, CH_2), 2.65 (s, $2CH_3$), 1.30 (t, CH_3); UV (CH_3CN) λ_{max} 245 nm (ϵ 3770). Anal. Calcd for $C_{16}H_9N_3O_2$: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.66; H, 6.41; N, 14.72.

Upon evaporation to dryness **23** was obtained. The residue was recrystallized from cyclohexane: 0.08 g (17%); mp 110 °C; H^1 NMR ($CDCl_3$) δ 7.76–7.23 (m, Ph), 6.86 (s, CH), 6.10 (s, CH), 2.44 (s, $2CH_3$) [lit:[9] mp 112 °C; H^1 NMR ($CDCl_3$) δ 7.75–7.25 (m, Ph), 6.90 (s, CH), 6.10 (s, CH), 2.48 (s, $2CH_3$)].

Rearrangement of 18 in Acetic Anhydride. A 0.48-g sample of 2-imino-2*H*-3-phenyl-5,7-dimethylisoxazolo[2,3-*a*]pyrimidine (**18**) was boiled for 1 min in acetic anhydride (0.9 mL). $CHCl_3$ (10 mL) was added on cooling, and the solution was stirred for 1 h with 5% $NaHCO_3$ solution (35 mL). The $CHCl_3$ layer was separated, dried on Na_2SO_4, and was evaporated, and the residue was subjected to silica gel column chromatography. The product (**25**) was eluted with ethyl acetate–petroleum ether (2:3) and recrystallized from 2-propanol: 0.17 g (22%); mp 153 °C; IR (Nujol) ν_{max} 3140 cm^{-1} (NH), 1730, 1695 cm^{-1} (C=O); H^1 NMR ($CDCl_3$) δ 13.10 (br s, NH), 7.63–7.20 (m, Ph), 6.96 (s, CH), 2.50 (s, $2CH_3$), 2.43 (s, CH_3), 2.33 (s, CH_3); UV (CH_3CN) λ_{max} 248 nm (ϵ 4130). Anal. Calcd for $C_{18}H_{19}N_3O_4$: C, 63.33; H, 5.61; N, 12.31. Found: C, 63.47; H, 5.47; N, 12.19.

Kinetic Study of the Rearrangement of 2 in Various pH Values. Aliquots of 0.30 mL of a freshly prepared 1×10^{-3} M solution of **2** in CH_3CN were introduced into 3.0 mL of buffer (phosphate + acetate, 0.5 M) in a quartz cell, and the course of reaction was followed by the change in absorption at 280 nm. The plot of ln (OD – OD$_\infty$) vs. time, where OD and OD$_\infty$ are the optical density during the reaction and at the end of the reaction, respectively, gave k_{obsd}. Thus, with the symbols of eq 1, the rate is $dB/dt = k_1[A]$ as well as $dB/dt = k_{obsd}([AH^+] + [A])$, and $[AH^+]/[A] = [H]^+/K_a$ (from definition of K_a). Therefore:

$$\frac{k_1}{k_{obsd}} = \frac{[H]^+}{K_a} + 1 \qquad (2)$$

or

$$\frac{1}{k_{obsd}} = \frac{[H^+]}{K_a k_1} + \frac{1}{k_1}$$

By plotting $1/k_{obsd}$ vs. $[H^+]$, or preferably by using eq 2, k_1 and k_a could be determined. Results for k_{obsd}, k_1 and k_a are given in Table I. First-order behavior was observed within the range from pH 4.5 to 6.

Kinetic Studies of the Rearrangement of 3 at Various pHs. Aliquots of 0.30 mL of a freshly prepared 1×10^{-3} M solution of **3** in 0.01 N HCl were introduced into 3.0 mL of buffer (acetate + phosphate, 0.5 M) in a quartz cell. The course of reaction was followed as above for **2**, and the constants were determined by the same way. Results and experimental data are given in Table I. First-order behavior was observed within the range from pH 5.5 to 6.9.

Registry No. **1**, 4264-07-7; **2**, 84041-07-6; **3**, 84041-09-8; **5**, 84041-10-1; **6**, 84041-11-2; **8**, 84041-12-3; **10**, 32691-58-0; **11**, 84041-14-5; **12**, 84041-15-6; **13**, 84041-16-7; **14**, 84041-17-8; **15**, 84041-18-9; **16**, 84041-19-0; **17**, 84041-20-3; **18**, 84041-21-4; **22**, 32416-43-6; **23**, 32416-44-7; **24**, 84050-06-6; **25**, 84041-22-5; acetylacetone, 123-54-6; benzoylacetone, 93-91-4; 2-phenylmalononitrile, 3041-40-5.

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Relatively Fast Solvolytic Reactions of 1-Adamantyl Mesylate. Further Development of the Y_{OTs} Scale of Solvent Ionizing Power and the N_{OTs} Scale of Solvent Nucleophilicity

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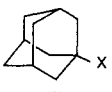
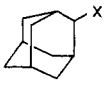
Solvolytic rate constants for 1-adamantyl mesylate in binary aqueous mixtures of ethanol, methanol, acetone, and trifluoroethanol are reported. Reactions with half-lives varying from ca. 50 min to ca. 0.3 s are followed directly at 25 °C by convenient conductimetric methods. Additional kinetic data for solvolyses of 2-adamantyl sulfonates in aqueous methanol are also reported. Logarithms of solvolysis rates for 1-adamantyl tosylate, obtained from tosylate/mesylate rate ratios, correlate linearly (slope of 1.06 ± 0.03) with logarithms of solvolysis rates for 2-adamantyl tosylate. Therefore, very similar scales of solvent ionizing power for tosylates (Y_{OTs}) may be defined by log $(k/k_0)_{AdOTs} = mY_{OTs}$, where m = 1.0 and AdOTs refers to either 1- or 2-adamantyl tosylate. Y_{OTs} values for ten pure solvents (*tert*-butyl alcohol, 2-propanol, ethanol, methanol, trifluoroethanol, hexafluoroisopropyl alcohol, and water and acetic, formic, and trifluoroacetic acids) are compared with the $E_T(30)$, π^*, and α empirical solvation parameters; there is a satisfactory correlation between Y_{OTs} and $E_T(30)$ but substantial scatter in a Y_{OTs} vs. π^* plot. Additional values of the solvent nucleophilicity parameter N_{OTs} are also calculated.

Solvolyses of 1- and 2-adamantyl substrates (I and II)



(I)



(II)

have played a central role in recent progress in mechanistic aspects of solvolysis reactions.[1-4] The relatively rigid, caged structure of the adamantyl skeleton allows system-

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