

## N-Quaternary Compounds

### Part XXXV.<sup>1</sup> Solvolysis of Thiazolo[3,2-a]pyridinium-3-oxides

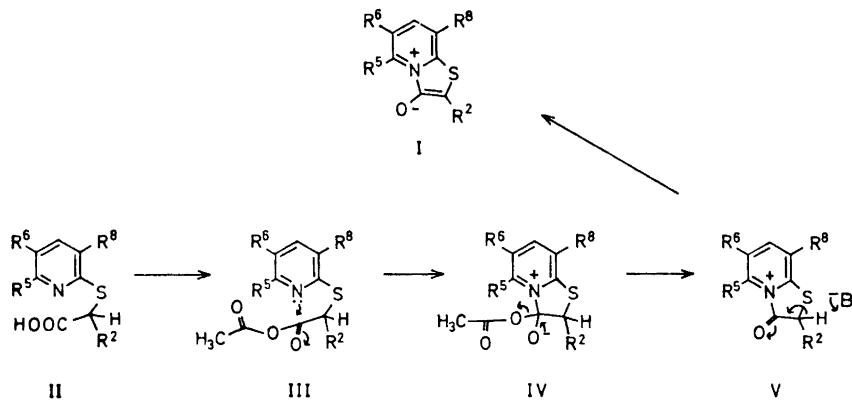
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2-Arylthiazolo[3,2-a]pyridinium-3-oxides in acid and alkaline solutions have been investigated. Steric repulsion between 3- and 5-substituents accelerates the hydrolysis. In acid solution the hydrolysis rates increase with electron donating substituents. Most compounds are more resistant to hydrolysis in alkaline solution. Light absorption data and rate constants for nitro-pyridines and a pyrimidine are interpreted to mean that the hydrolysis in alkaline solution takes place after initial pseudo-base formation.

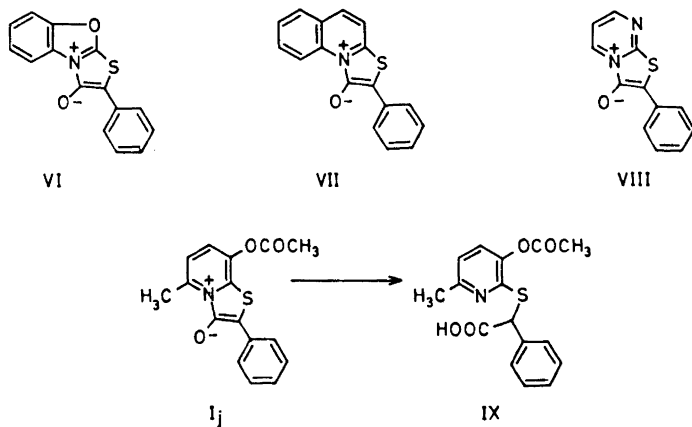
2-Alkylthiazolo[3,2-a]pyridinium-3-oxides are rapidly hydrolysed in aqueous media while 2-phenyl analogues are less reactive because of resonance stabilisation from the phenyl ring.<sup>2</sup> The preparation of an additional series of 2-aryl derivatives is described in this report and their properties in acid and alkaline solutions have been studied.

The thiazolo[3,2-a]pyridinium-3-oxides were synthesised by condensation of a pyrid-2-thione and an  $\alpha$ -halocarboxylic acid followed by cyclisation of the intermediate  $\alpha$ -2-pyridylthioalcanoic acid. Cyclisation of the thioalcanoic acids is apparent by the highly coloured products being formed. The reaction was run in a solution of acetic anhydride and pyridine. Without base catalysis the reaction was slow. A mixed anhydride intermediate (III) seems most likely. The formation of the latter from acetic anhydride is favoured by base induced dissociation of the thioalcanoic acid. A base will also promote the tautomerism of the lactam V to the aromatic thiazole I (Scheme 1). Mixed anhydride formation with ethyl chloroformate in pyridine and the related carboxyl activation by dicyclohexylcarbodiimide in pyridine also gave the cyclic product (I). When the pyridine carried no 6-substituent and was activated by another electron releasing group, cyclisation was achieved by heating in toluene alone. For comparative purposes other heterocyclic systems were included in this study.  $\alpha$ -2-Benzoxazolylthiophenylacetic acid was not cyclised to VI under the usual conditions while a quinoline (VII) and a pyrimidine (VIII) were readily formed.



Scheme 1.

The 3-hydroxypyridines on cyclisation form an acetate. The ester formation could take place either on the 3- or the 8-phenolic oxygen. This question was settled by selective hydrolysis of a 5-methyl derivative at 20°C in 0.1



Scheme 2.

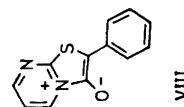
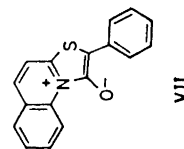
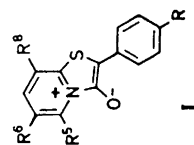
N HCl in dilute acetone (1 : 1). The choice of a 5-methyl derivative was directed by the accelerating effect exerted by a 5-substituent on the hydrolysis of the ring (see below). The resultant product was identified as the acetate IX. The original acetate is therefore the 8-acetoxy derivative I<sub>j</sub> as had previously been suggested from spectroscopic studies.<sup>2</sup>

Some light absorption characteristics of the prepared thiazoles in acid and alkaline solution are given in Table 1. Hydrolysis rates as discussed below, however, show that some of the compounds will be partly hydrolysed before

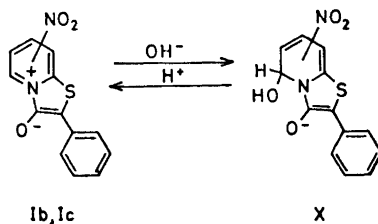
Table I. Absorption spectra in 0.1 N HCl and 0.1 N NaOH in aqueous dioxan (1 : 1).

Comp.	Substituents				0.1 N HCl in aq. dioxan (1 : 1)				0.1 N NaOH in aq. dioxan (1 : 1)							
	R <sup>5</sup>	R <sup>6</sup>	R <sup>8</sup>	R	$\lambda$ nm	log $\epsilon$	$\lambda$ nm	log $\epsilon$	$\lambda$ nm	log $\epsilon$	$\lambda$ nm	log $\epsilon$				
I a	H	H	H	H	432	4.1	283	3.8	235	4.1	436	4.2	283	3.9	238	4.1
b	H	H	NO <sub>2</sub>	H	436	3.9	338	3.8	248	3.8	494	3.9	328	3.9	255 <sup>a</sup>	3.7
c	H	NO <sub>2</sub>	H	H	455	4.0	285	4.1	254	3.9	382	3.8	305 <sup>a</sup>	3.8	230	3.9
d	H	H	CH <sub>3</sub>	H	432	4.1	283	3.8	233	4.1	455	3.9	296	3.8	232	4.0
e	H	H	OAc	H	432	4.0	283	3.7	238	4.1	428	4.1	283	3.9	235	4.1
f	H	H	H	OCH <sub>3</sub>	443	4.1	355 <sup>a</sup>	3.6	275 <sup>a</sup>	3.9	444	4.2	285	3.9	242	4.2
g	H	H	H	NO <sub>2</sub>	472	4.1	290 <sup>a</sup>	3.9	242	4.1	472	4.1	290	3.8	250 <sup>a</sup>	3.9
h	CH <sub>3</sub>	H	H	H	448	—	—	—	—	—	455	4.1	290	3.9	237	4.1
i	CH <sub>3</sub>	H	OC <sub>2</sub> H <sub>5</sub>	H	448	—	—	—	—	—	450	4.1	290	3.8	242	4.0
j	CH <sub>3</sub>	H	OAc	H	465	—	—	—	—	—	430	4.0	317	3.6	225 <sup>a</sup>	3.9
k	CH <sub>3</sub>	H	H	NO <sub>2</sub>	494	—	302	—	256	—	494	4.4	290 <sup>a</sup>	3.5	223	3.9
VII					488	4.1	307	4.0	269	3.8	488	4.3	307	3.9	269	3.8
VIII					475	3.9	288	3.9	238	4.0	449	—	347	—	238	4.4

<sup>a</sup> Shoulder.



a spectrum could be recorded. The logarithms of the extinction coefficients are therefore only given with the first decimal figure or are omitted in specially reactive compounds. With the exception of compounds Ib, Ic, and VIII the positional maxima are little affected by 0.1 N HCl and 0.1 N NaOH. This strongly indicates that the phenolic group is also largely dissociated in 0.1 N HCl. In stronger acidic solutions hypsochromic shifts were seen with much increased hydrolysis rates. The isomeric nitro-pyridines Ib and Ic undergo bathochromic shifts for the highest wavelength band of 60 and 80 nm, respectively, from acid to alkaline pH. The absorption maxima in acid solution are in the region observed for the other analogues. The anomalously high wavelength maxima at alkaline pH require a molecular change. The most likely explanation is pseudo-base formation<sup>3</sup> caused by the additional activation of the electron deficient pyridinium system by the nitro group. By analogy<sup>4</sup> to other simple pyridinium derivatives the hydroxyl anion is assumed to add to the unsubstituted 5-position as indicated in Scheme 3. The reaction is reversible if acid is added after a short time. The pyrimidinium derivative VIII, on the other hand, undergoes a hypsochromic shift (25 nm) with increase in pH. The electron deficiency in the pyrimidine should be similar to that in the nitro-pyridines and therefore lead to pseudo-base formation by hydroxyl addition to the 5- or the 7-position.



Scheme 3.

Some of the compounds investigated were found to undergo rapid reaction in aqueous solution. Solutions of the compounds were therefore made up in dioxan. These solutions were mixed with equal volumes of 0.2 N acid or base immediately before commencement of the measurements. The dioxan also keeps in solution the less water soluble compounds. The hydrolysis was followed by the decrease in absorption in the 430–490 nm region where the acids (II) formed are transparent. The results are shown in Table 2. The expected first-order kinetics for the hydrolysis was observed in acid solution.

Table 2. Rate constants for the hydrolysis at 20°C in 0.1 N HCl (dioxan:water = 1 : 1) measured by the change in light absorption at the highest wavelength absorption maxima (Table 1).

	I											VII	VIII
	a	b	c	d	e	f	g	h	i	j	k		
$\times 10^4 \text{ sec}^{-1}$	2.03	0.24	0.15	1.93	1.50	7.97	0.15	88.85	41.45	46.20	2.41	3.50	0.83

From Table 2 it is seen that the 5-methyl analogues Ih–Ik fall into a series with a much higher rate constant than the respective members of the desmethyl series Ia–Ig. The methyl group in the 8-isomer (Id) in contrast to the 5-isomer (Ih), however, hardly affects the rate constant relative to the parent desmethyl compound. The higher hydrolysis rates in the 5-methyl series are therefore ascribed to steric repulsion between the 3- and 5-substituents. The closeness of these groups in the planar aromatic structure increases the energy of the system with decrease in activation energy for hydrolysis. A calculation based on the increase in the rate constant shows the 5-methyl group to decrease the activation energy by 1.8 kcal/mol. In the quinoline VII *peri*-interaction seems a likely explanation for the observed increase in the rate constant relative to the parent pyridine Ia.

The series Ia, If, and Ig only differ in the nature of the 4-substituent in the phenyl ring. The methoxy substituent (If) increases the hydrolysis rate, whereas the nitro substituent (Ig) decreases the rate relative to the unsubstituted compound (Ia). The hydrolysis rate therefore increases with an electron releasing substituent. From Table 2 it is also evident that variations in the nature of the 6- and 8-substituents affect the rate constants in such a way that electron donating substituents increase the rate constant while electron attracting substituents have the opposite effect. In both these cases the transmitted electronic effect will affect the tautomeric ratio between the one-form of the lactam and its enol. In the absence of increased steric interaction electron donating substituents would be expected to stabilise the one-form of the molecule relative to the enol. In the one-form, the molecule is present in the reactive acylpyridinium form. Any substituent, therefore, which will increase the concentration of the latter tautomer, will promote hydrolysis.

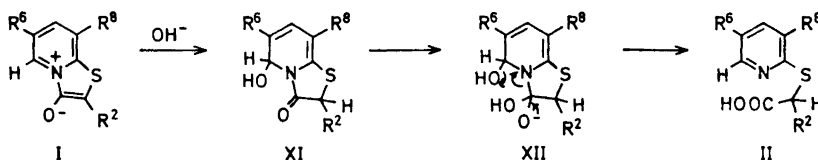
Increase in acid concentration increases the hydrolysis rates as verified for the 8-methyl derivative Id. The half life in 0.02 N HCl, 0.1 N HCl, and 0.5 N HCl was 170 min, 60 min, and 17 min, respectively.

In alkaline solution the compounds will exist as betaines presumably with partial delocalisation of the negative charge from the phenolate oxygen over the thiazolo ring. Attack by hydroxyl ions is less favourable and most compounds were resistant to hydrolysis in 0.1 N NaOH in dilute dioxan (1 : 1) at 20°C. The pyrimidine VIII and the 8-nitropyridine Ib, however, were rapidly hydrolysed (Table 3). The 6-nitropyridine Ic and the nitrophenyl derivative Ig reacted more slowly. The 5-methyl homologue Ik was even less reactive than Ig. First-order kinetics was observed.

Table 3. Rate constants for the hydrolysis at 20°C in 0.1 N NaOH (dioxan : water = 1 : 1) measured by the change in light absorption at the highest wavelength absorption maxima (Table 1).

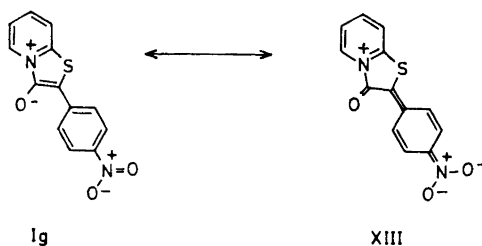
	I			VIII
	b	c	g	
$k \times 10^4 \text{ sec}^{-1}$	1.54	0.17	0.26	25.67

From Table 3 it is seen that the rate constant for the 8-nitro derivative (Ib) is almost ten times that of the 6-nitro derivative (Ic) and is further increased by a factor of about seventeen in the case of the pyrimidine (VIII). The electron withdrawing or localisation effects, however, should be similar in these analogues. The light absorption data (Table 1), however, show that these compounds (Ib, Ic, and VIII) are present as pseudo-bases in alkaline solution. The observed rate differences are therefore attributed to hydrolysis of the respective pseudo-bases. The intermediate in the base hydrolysis is formed by  $\text{OH}^-$  addition to the carbonyl group to form a tetrahedral carbon.



Scheme 4.

Assuming a nearly planar 5-pseudo-base (XII) intermediate the 3- and 5-substituents will be eclipsed. In contrast to the 8-substituent a bulky 6-substituent will by its non-bonded interaction with the 5-substituent increase the 3,5-steric repulsion and thereby increase the activation energy. Pseudo-base formation by addition to the 5-position might also be expected to be less favourable for the 6-isomer than for the 8-isomer while there is little steric difference in formation of a 7-adduct. The rate data therefore are consistent with formation of the 5-pseudo-base. The pyrimidine VIII carries no 6-substituent and has a higher rate constant than the 8-nitro-pyridine isomer (Ib) which suggests that the pseudo-base formation at least in part occurs in the 7-position.



Scheme 5.

The absorption spectrum of the *para*-nitrophenyl derivative Ig shows little shift with pH within the limits studied (Table 1). This would appear to exclude the pseudo-base as a dominant species in the solution studied. The ready hydrolysis in alkaline solution is best explained by the conjugative effect of

the nitro group. The negative charge from the phenolate oxygen is thereby to a large degree delocalised over the nitrophenyl system and thus the 3-carbon is more susceptible for nucleophilic attack.

## EXPERIMENTAL

The light absorption measurements were done on a CARY-14 instrument.

*Kinetic measurements.* The hydrolysis rates were studied at 20°C in 0.1 N NaOH and 0.1 N HCl in dioxan:water (1 : 1 v/v). The solutions were made up immediately before measurements by mixing equal volumes of a dioxan solution of the compound under investigation with aqueous 0.2 N base or acid. The rate of hydrolysis was determined by measuring the decrease in the long wave-length absorption band (Table 1). Concentrations were  $1-3 \times 10^{-4}$  M. Rate constants were determined from log-plots of concentration against time.

*Thiazolo[3,2-a]pyridinium-3-oxides (I).* The pyrid-2-thione (0.01 mol), the  $\alpha$ -bromo-phenylacetic acid (0.01 mol), and sodium bicarbonate (0.04 mol) were dissolved in water (25 ml) and the solution stirred at 50°C until the evolution of carbon dioxide had ceased (about 2 h). The solution was then acidified with acetic acid, extracted with chloroform or ethyl acetate, the extracts washed, dried and evaporated. The  $\alpha$ -(2-pyridylthio)phenylacetic acids (II) were thus obtained as an oily material. In some cases the acids were purified and crystallised. In most cases, however, the crude products were reacted further.

For cyclisation the acid was dissolved in 10–20 ml of pyridine, depending on the solubility, followed by addition of an equal volume of acetic anhydride. The solution became rapidly deeply coloured due to the cyclic product. The solutions were generally left overnight at 5°C and the crystalline precipitate collected. In some cases the material was pure enough for elemental analysis but was usually recrystallised from an organic solvent. Details are given in Table 4.

Table 4.

Comp. <sup>a</sup>	Yield %	Solv. recryst.	Appearance	M.p. °C	Molecular formula	Found			Calc.		
						C	H	N	C	H	N
I b	80	—	Dark green	270–273	C <sub>13</sub> H <sub>8</sub> N <sub>2</sub> O <sub>3</sub> S	57.11	2.88	10.07	57.35	2.96	10.29
c	52	—	Dark red	284–290	»	57.47	3.08	10.13	»	»	»
d	50	EtOAc	Red	190–191	C <sub>14</sub> H <sub>11</sub> NOS	69.36	4.48	5.60	69.68	4.59	5.80
f	53	Toluene	Red	191–193	C <sub>14</sub> H <sub>11</sub> NO <sub>2</sub> S	65.43	4.15	5.74	65.35	4.31	5.44
g	91	HCO <sub>2</sub> H	Dark red	350	C <sub>13</sub> H <sub>8</sub> N <sub>2</sub> O <sub>3</sub> S	57.28	3.34	10.34	57.35	2.96	10.29
h	50	EtOAc	Red	166–167	C <sub>14</sub> H <sub>11</sub> NOS	69.59	4.54	5.86	69.68	4.59	5.80
i	59	EtOAc	Red	178–180	C <sub>16</sub> H <sub>15</sub> NO <sub>2</sub> S	67.41	5.29	4.91	67.34	5.30	4.91
k	67	Pyridine	Dark red	318–320	C <sub>14</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub> S	58.75	3.53	9.89	58.73	3.52	9.78

<sup>a</sup> Data for compounds I a, I e and I j have previously been reported.<sup>2</sup>

$\alpha$ -(2-Benzoxazolylthio)phenylacetic acid. Attempted synthesis of thiazolo[3,2-b]benzoxazolium-3-oxide (VI). The title acid was prepared as the pyridine II from 2-mercapto-benzoxazole in 53 % yield, m.p. 140–142°C (dilute ethanol). (Found: C 62.91; H 4.12; N 4.69. Calc. for  $C_{15}H_{11}NO_3S$ : C 63.14; H 3.89; N 4.91).

The acid was not cyclised in pyridine-acetic acid under the conditions described above for the formation of I.

2-Phenylthiazolo[3,2-a]quinolinium-3-oxide (VII) was prepared as above from quinoline-2-thione and  $\alpha$ -bromophenylacetic acid in 94 % yield. The red crystalline material, after recrystallisation from toluene, had m.p. 198–199°C. (Found: C 73.46; H 3.92; N 5.10. Calc. for  $C_{17}H_{11}NOS$ : C 73.62; H 4.00; N 5.06).

2-Phenylthiazolo[3,2-a]pyrimidinium-3-oxide (VIII). Condensation between pyrimidin-2-thione and  $\alpha$ -bromophenylacetic acid as described for the pyridines yielded  $\alpha$ -(2-pyrimidylthio)phenylacetic acid in 90 % yield; m.p. 143–145°C (decomp.) (dilute ethanol). (Found: C 58.31; H 3.33; N 11.42. Calc. for  $C_{12}H_{10}N_2O_2S$ : C 58.52; H 4.09; N 11.37).

The acid thus prepared (1.0 g, 0.004 mol) was dissolved in pyridine (5 ml) and acetic anhydride (5 ml) added. The reddish solution was left at 5°C for 24 h. The red crystalline precipitate, yield 0.9 g (98 %), recrystallised from ethyl acetate had m.p. 218–220°C (Found: C 63.07; H 34.49; N 12.18. Calc. for  $C_{12}H_8N_2OS$ : C 63.14; H 3.53; N 12.27).

#### REFERENCES

1. Part XXXIV. Lie, R. and Undheim, K. *J. Chem. Soc. Perkin Trans. 1* 1973. *In press*.
2. Undheim, K. and Tveita, P. O. *Acta Chem. Scand.* 25 (1971) 5.
3. Albert, A. *Advan. Heterocycl. Chem.* 1 (1963) 167.
4. Schofield, K. *Hetero-aromatic Nitrogen Compounds. Pyrroles and Pyridines*, Butterworths, London 1967, p. 236.

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