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N-Quaternary Compounds

Part XVIII. Thiazolo[3,2-a]pyridinium-3-oxides

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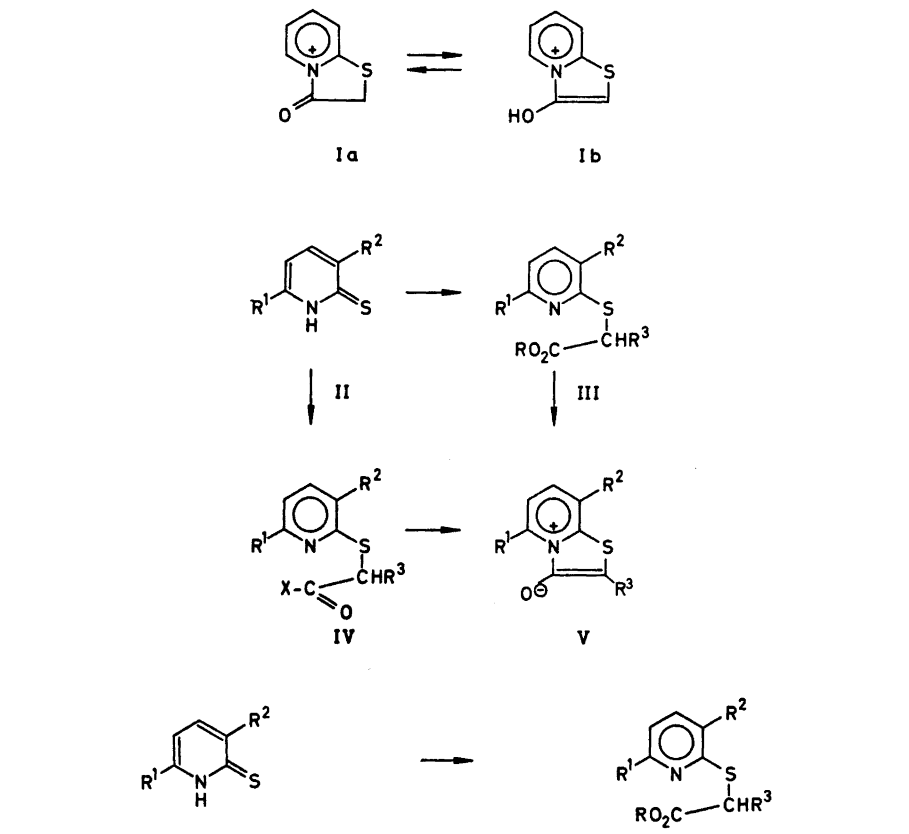
Pyrid-2-thiones react with α-halo acid halides with the formation of thiazolo[3,2-a]pyridinium-3-oxide derivatives. Such derivatives are also obtained by acid catalyzed cyclisation of α-2-pyridylthioalkanoic acids and esters or by dehydration in acetic anhydride. A pyridyl-α-methyl group for steric reasons reduces the cyclisation tendency. Cyclic products from β- or γ-pyridylthioalkanoic acids were not obtained. NMR studies showed a pH dependent tautomerism between the enolic 3-hydroxythiazole and the corresponding ketone. The thiazoles readily undergo hydrolysis and aminolysis. The amides in TFA liberate the amines with reformation of the thiazole. In this way L-alanine was acylated and recovered without racemisation.

Acylation in pyridine type solvents goes through a highly reactive intermediate acyl-pyridinium complex. Cyclic acylium compounds such as Ia should be stabilized in the tautomeric structure Ib. Little work has been done on such compounds. Besides the pyridine (I) only the quinoline analogue and a few benzothiazoles have been synthesized.[1–3] As a natural extension of our studies [4] over thiazolo[3,2-a]pyridinium-8-oxides, investigation of this relatively labile system was undertaken.

The 3-hydroxythiazole system was synthesized by acetic anhydride cyclisation of α-2-pyridylthioalkanoic acids, or by condensation between pyrid-2-thiones and α-haloacyl halides, these methods being analogous to those reported [1–3] for the synthesis of I. In addition it was found that α-2-pyridylthioalkanoic acids and esters could be cyclised by simple acid catalysis. The synthetic reactions leading to the 3-hydroxythiazole system are summarized below.

The intermediate pyridylthioacids (III) were prepared by condensation between haloalkanoic acids and pyrid-2-thiones in aqueous alkali or by heating the halo acids with the α-lactams in a solvent such as toluene.

From the 6-desmethyl thiolactam (IIb) and α-bromophenylacetic acid a mixed product of the acid (IIIf) and the 3-hydroxythiazole (Vf) was obtained. On prolonged heating both acids and esters (III) from IIb were cyclised under



II a $R^1=H$, $R^2=H$
b $R^1=H$, $R^2=OH$
c $R^1=CH_3$, $R^2=OH$

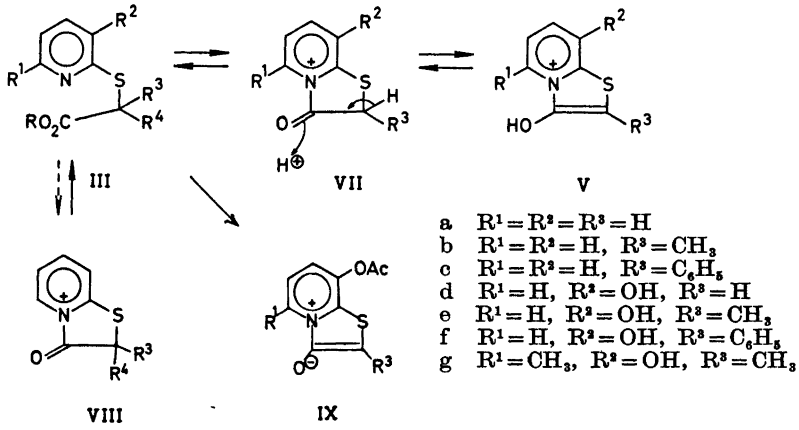
III a $R^1=R^2=R^3=R=H$
b $R^1=R^2=H$, $R^3=CH_3$, $R=H$
c $R^1=R^2=H$, $R^3=C_6H_5$, $R=H$
d $R^1=H$, $R^2=OH$, $R^3=R=H$
e $R^1=H$, $R^2=OH$, $R^3=CH_3$, $R=H$
f $R^1=H$, $R^2=OH$, $R^3=C_6H_5$, $R=H$
g $R^1=CH_3$, $R^2=OH$, $R^3=CH_3$, $R=H$
h $R^1=CH_3$, $R^2=OH$, $R^3=C_6H_5$, $R=H$
i $R^1=CH_3$, $R^2=OH$, $R^3=p\text{-}NO_2C_6H_4$, $R=H$

VI a $R=-(CH_2)_2-$
b $R=-(CH_2)_3-$
c $R=-(C(CH_3)_2)-$

the influence of the HBr formed. There was no sign of cyclisation of the 6-methyl pyridine derivatives (IIIg–i) because of steric interaction between the methyl group and the carboxy group, as well as *peri* interaction between R^1 and the 3-hydroxy group in the thiazole (V). Nor was there any tendency for cyclisation if the side-chain contained more than one carbon between

the S and the carboxy group (VI a and b) or when the methylene carbon was disubstituted (VIc). In a similar way it was shown that α-(3-hydroxy-2-pyridylthio)propionic acid in chloroform could be cyclised by saturating the solution at 0° with dry HCl. Acid catalysis in these cyclisations is reminiscent of the cyclisation of 2-pyridylthio-β-keto or β-aldehyde derivatives in concentrated acids.[4]

In the anhydride cyclisations the pyridylthiocarboxylic acids were dissolved in pyridine-acetic anhydride (1:1) and left in the cold. Formation of the bicyclic product is accompanied by yellow to red coloration depending on the nature of the substituent R^3. Cyclisation of the higher homologues VIa and VIb to 6- and 7-membered rings could not be effected presumably because these rings would lack aromatic stabilization. The experimental findings agree with our failure to cyclise corresponding γ-aldehydes.[4] The cyclisation of the isobutyric acid (VIc) also failed. This shows that the initially formed acylpyridinium derivative (VII) for stabilization must be able to tautomerize to the aromatic thiazole (V).

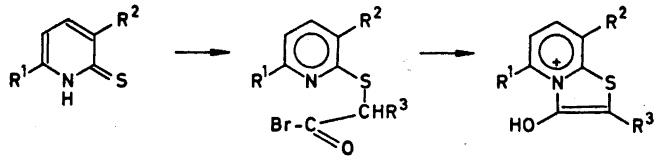


a $R^1=H$, $R^3=C_6H_5$
b $R^1=CH_3$, $R^3=C_6H_5$
c $R^1=CH_3$, $R^3=p\text{-}NO_2C_6H_4$

Acetic anhydride dehydration of III (R=H) gave two types of products. In the absence of a pyridyl-3-hydroxyl group the thiazolo[3,2-a]pyridinium-3-oxide (V) was formed. The 3-hydroxypyridines were monoacetylated. All these substances in the mass spectra gave peaks corresponding to the molecular ions. From spectroscopic evidence as discussed below the acetylated products have been assigned structure IX.

Treatment of pyrid-2-thiones with α-bromoacyl bromides in solvents such as benzene/acetone or THF under anhydrous conditions immediately precipitated the 3-hydroxythiazolo[3,2-a]pyridinium salts (V). Structural confirmation follows from spectroscopy. The NMR spectrum (Table 1) in TFA of the product from pyrid-2-thione and α-bromopropionyl bromide showed

the methyl group as a singlet at 7.29 τ, *i.e.* in the aromatic region for a methyl group. The IR spectrum in KBr showed a broad OH band in the 2800 – 3200 cm^{-1} region and no carbonyl absorption. Treatment of the 6-methyl derivative (IIc) with α-bromopropionyl bromide in THF at 0° gave a two-component



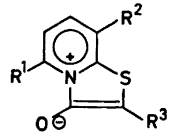
II X V

product. The NMR spectrum in TFA showed a 2-methyl group at 7.35 τ for the bicyclic structure (V) (Table 1), and a methyl doublet at 8.30 τ ($J = 7$ cps) with a methine quartet at 5.60 τ in agreement with X or a δ-lactone over the phenolic oxygen. Integration of the NMR spectrum gave the ratio 2:1, the major component being the thiazole (V). The carbonyl absorption was at 1790 cm^{-1} (KBr), as would be expected for the acid bromide (X). Addition of water furnished the corresponding pyridylthiopropionic acid (IIIg). The reluctance to cyclisation again must be ascribed to steric interaction with the pyridyl-6-methyl group as found in the cyclisation of β-ketosulphides.[4] For β-bromopropionyl bromide the reaction stopped after *S*-alkylation in agreement with the failure to cyclise the corresponding acid in acetic anhydride.

The mechanism suggested for the condensation between chloroacetyl chloride and pyrid-2-thione is initial *N*-acylation followed by cyclisation.[3] However, pyrid-2-thione is *S*-acetylated by acetyl chloride as reported.[3] The product has λ_{max} at 293 mμ (0.1 N NaOH). The longwave UV maxima for 2-methiopyridine and 1-methylpyrid-2-thione at 293 mμ and at 341 mμ respectively [5] confirm *S*-acylation. Attempts to rearrange 2-acetylthiopyridine to the *N*-acyl isomer met with no success. The failure to rearrange the *S*-acetyl derivative would suggest initial *S*-alkylation in agreement with other data [6] which show that sulphur is more nucleophilic towards saturated carbon than towards multiple bonded carbon. Further experimental evidence in favour of initial *S*-alkylation comes from the isolation of the acid bromide (X) through the sterical hindrance introduced to cyclisation by the 6-methyl group, and the reaction with the β-bromopropionyl bromide which gave the *S*-alkyl acid bromide. In the case of the α-haloacyl halides, however, the reaction rate is much enhanced as compared with α-haloacids. The rate increase could in part be due to higher electropositive character on the 2-carbon in the acyl halides as compared to the corresponding acids. But a more likely explanation seems to lie in the participation of both halogen substituted carbons in the reaction.

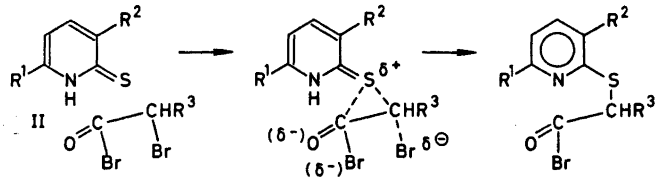
A pH dependent equilibrium exists between 3-hydroxythiazoles and the tautomeric acyl pyridinium derivatives. This was demonstrated by NMR studies. In TFA the methyl group in Ve resonates as a singlet at 7.30 τ and is therefore attached to an aromatic ring. In deuterium oxide the methyl

Table 1. NMR in TFA.

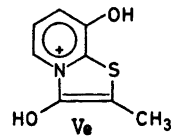


Comp.	Substituents			Chemical shift in τ values									
				In TFA					In D_2O				
	R^1	R^2	R^3	R^1	H^6	H^7	R^2	R^3	R^1	H^6	H^7	R^2	R^3
Va	H	H	H	[a c] 0.83	1.2–2.2			1.52	1.2–2.2				
Vb	H	H	CH_3	[a] 0.90	1.4–2.2			7.29	1.2–2.2				8.30
Vc	H	H	C_6H_5	[c] 0.86	1.5–2.5			2.33					
Vd	H	OH	H	[b] 0.67–2.17			—	0.67–2.17	1.37–2.20			—	
Ve	H	OH	CH_3	[b] 1.33	2.08–2.35		—	7.30	1.58	1.80–2.20		—	8.38
Vg	CH_3	OH	CH_3	[b] 6.86	2.26	1.93	—	7.35	7.16	2.23	2.00	—	7.65
IXa	H	OAc	C_6H_5	[d] 0.97	1.65–2.15		7.36	2.35					
IXb	CH_3	OAc	C_6H_5	[d] 6.69	2.39	1.91	7.45	2.35					
IXc	CH_3	OAc	p-$NO_2C_6H_4$	[d] 6.72	2.40	1.95	7.43	2.40					

[a] Br-anion. [b] HBr salt. [c] Zwitterion [d] Recorded in $CDCl_3$.

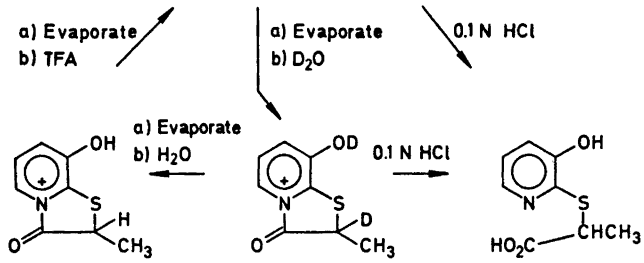


XI XII X



Ve

TFA: CH_3 at 7.30 τ (singlet)



XIIIb XIIIa IIIe

H_2O: CH_3 at 8.40 τ (doublet)

D_2O: CH_3 at 8.38 τ (singlet)

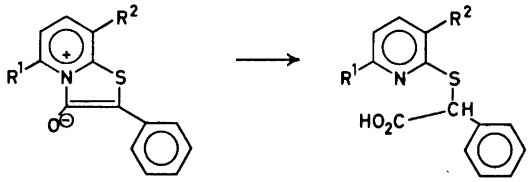
TFA: CH_3 at 8.25 τ (doublet, $J = 7$ cps)

group appears as a singlet at 8.38 τ and in water as a doublet at 8.40 τ ($J = 7$ cps). Evaporation of the water solution and redissolution in TFA gave the same NMR spectrum as of the original thiazole. The intermediate must be assigned the tautomeric keto structures XIIIa and XIIIb, respectively. For comparison, the chemical shift in TFA for the acid, obtained by hydrolysis in 0.1 N HCl, was 8.25 τ (IIIe). In deuterium oxide the methyl group in IIIe appeared as a doublet at 8.25 τ. Therefore the methine proton is not exchanged as in the case of the bicyclic product (XIII).

A betaine formulation is used for the products obtained by cyclisation in acetic anhydride. Thus these products are insoluble in nonpolar solvents, soluble to various degrees in polar organic solvents, but not very soluble in water with which they slowly react. 2-Methylthiazolo[3,2-a]pyridinium-3-oxide (Vb), however, is an exception in that it is readily soluble in solvents

such as benzene and carbon tetrachloride. The molecule forms a stable 1:1 adduct with acetic acid. In the IR spectrum in CCl_4 the carbonyl absorption is at 1715 cm^{-1} as in acetic acid itself. Duffin and Kendall [1] have reported similar properties for corresponding anhydro quinoline derivatives of α-thiopropionic and α-thiobutyric acids. Passing dry HCl through a chloroform solution of the adduct precipitated the hydrochloride of the betaine.

The 2-alkylthiazoles are rapidly hydrolyzed in aqueous media. The 2-aryl derivatives are more resistant to hydrolysis no doubt because of resonance stabilization from the phenyl ring. The relative stabilities of 2-phenyl derivatives were studied in aqueous alkali and acid. The thiazoles have their long wave UV maxima in acid solution at 330 – 340 mμ and the acids (III) at 310 – 325 mμ. The rate of hydrolysis was therefore conveniently followed by change in UV absorption. The reactions were run at 25°. After 40 min the respective hydrolysis percentages for Vc, IXa, and IXb were 50, 60, and 90 in 0.1 N HCl; in 0.1 N NaOH the respective figures were 5, 15, 75. The greater stability towards alkaline hydrolysis is understood by the 3-oxygen being negatively charged in alkaline solution. The difference between IXa and IXb in hydrolysis rates is largely caused by different *peri* interaction between the 3- and 5-substituents in agreement with their relative ease of formation.

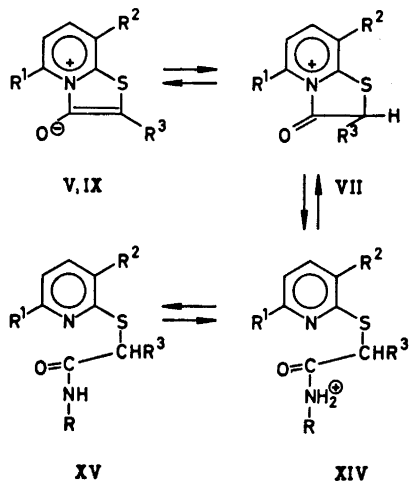


III

V c $R^1=R^2=H$
IX a $R^1=H$, $R^2=OAc$
IX b $R^1=CH_3$, $R^2=OAc$

Acylation of amines has also been looked at. The compounds carrying a hydrogen or an alkyl group in the 2-position react very readily. Thus Vb with aniline gave the corresponding anilide (XV a) in 95 % yield. In the 8-acetoxy derivatives (IX) both acetylation by the phenolic acetate and acylation by the acylpyridinium group occur. In contrast to the normal resistance of amides to hydrolysis the amines from XV are readily liberated. Thus dissolution of XV a in cold TFA leads to immediate recyclisation to the corresponding 3-hydroxythiazole as shown by the appearance in NMR of an aromatic 2-methyl group at 7.30 τ. L-Alanine could be acylated with Vb and was regenerated in TFA without racemisation.

The IR spectra of the betaines exhibit no OH absorption and no typical carbonyl absorption. The *O*-acetylated products (IX) show a carbonyl band at 1775 – 1785 cm^{-1}. All the anhydro compounds have a strong band at 1600 – 1640 cm^{-1} which could be ascribed to the Δ^2-double bond, but this also coincides with the region for pyridine absorption.



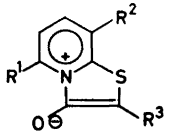
XV a $R^1=R^2=H$, $R^3=CH_3$, $R=C_6H_4$
b $R^1=R^2=H$, $R^3=CH_3$, $R=CH_2CHCO_2H$
c $R^1=R^2=H$, $R^3=R=C_6H_5$
d $R^1=CH_3$, $R^2=OH$, $R^3=R=C_6H_5$

Because of instabilities in aqueous solvents the UV spectra were recorded in acetic acid, methanol and in TFA (Table 2). The acetic acid solutions were all coloured and gave long-wave absorption maxima at 410 – 420 mμ. In methanol the maxima were around 420 mμ. The TFA solutions were colourless, however, with UV maxima at 335 – 340 mμ. The corresponding aliphatic pyridylthiocarboxylic acids absorbed in the 310 – 325 mμ region. It follows that the observed hypsochromic UV shift is not caused by hydrolytic decyclisation. Instead it must be concluded that the molecules in acetic acid are largely present as enolates and therefore are stronger acids than acetic acid. On the other hand TFA is a stronger acid and the enolate oxygen becomes protonated.

In 8-hydroxythiazolo[3,2-a]pyridinium derivatives the hypsochromic shift on going from alkaline to acid solution is of the order 15 – 20 mμ.[4] In the above case we have a shift of about 60 units. If the acetyl group in the anhydro compounds (IX) were attached to the 3-oxygen the smaller 8-hydroxy shift would have been expected. The observed shift of about 60 units clearly supports the 8-acetoxy formulation (IX).

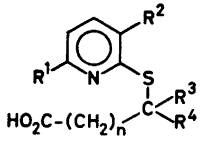
In the NMR spectra (Table 1) the 5-methyl group in the thiazoles Vf, IXb, c, are found in the region 6.7 – 6.85 τ. The chemical shift [4] for the 5-methyl group in 3-desoxy analogues is in the region 7.1 – 7.3 τ.[4] A 3-methyl group causes a downfield shift to 6.8 – 6.9 τ due to *peri* interaction. The deshielding of the 5-methyl-hydrogen nuclei in the 3-hydroxythiazoles must also be due to *peri* interaction, but the deshielding could well be enhanced by oxygen anisotropy.

Table 2. UV absorption.



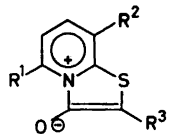
Comp.	Substituents			MeOH				AcOH				TFA	
	R^1	R^2	R^3	λ	log ε	λ	log ε	λ	log ε	λ	log ε	λ	log ε
Va	H	H	H	255	3.80	422	4.10	258	3.85	415	4.15	334	4.01
Vc	H	H	C_6H_5	260	3.74	418	4.08	262	3.80	414	4.11	334	4.00
IXa	H	AcO	C_6H_5	268	3.85	418	3.95	269	3.79	411	3.99	340	3.88
IXb	CH_3	AcO	C_6H_5	266	3.70	418	3.99	268	3.68	414	4.12	340	3.90
IXc	CH_3	AcO	*p*-$NO_2C_6H_4$	266	3.81	425	4.20	269	3.75	421	4.18	341	3.96

Table 3.



Comp.	Substituents					Method	Yield %	M.p. °C	Molecular formula	Found				Calc.			
	R^1	R^2	R^3	R^4	*n*					C	H	N	S	C	N	H	S
IIIb	H	H	CH_3	H	0	a	69	72—73	$C_8H_9NO_2S$	52.63	5.08	7.80	17.49	52.48	4.92	7.65	17.49
IIId	H	OH	H	H	0	a	87	200 (dec.)	$C_7H_7NO_3S$	45.56	4.20	7.36	17.41	45.40	3.81	7.56	17.31
IIIe	H	OH	CH_3	H	0	a	93	161 (dec.)	$C_8H_9NO_3S$	48.06	4.77	6.72	15.87	48.23	4.55	6.56	16.09
IIIg	CH_3	OH	CH_3	H	0	b	90	177—179	$C_9H_{11}NO_3S$	50.56	5.33	6.44	14.83	50.69	5.20	6.57	15.04
IIIh	CH_3	OH	C_6H_5	H	0	a	88	200—201	$C_{14}H_{13}NO_3S$	61.25	4.50	5.12	11.74	61.07	4.73	5.09	11.67
IIIi	CH_3	OH	*p*-$NO_2C_6H_4$	H	0	a	84	169—173 (dec.)	$C_{14}H_{12}N_2O_5$	52.87	3.48	8.96	—	52.46	3.75	7.83	—
VIa	H	H	H	H	1	b	55	67—68	$C_8H_9NO_2S$	52.55	5.11	7.40	17.44	52.44	4.92	6.57	17.49
VIb	H	H	H	H	2	b	47	81—82	$C_9H_{11}NO_2S$	54.95	5.76	7.08	16.20	54.83	5.58	7.11	16.25
VIc	H	H	CH_3	CH_3	0	b	50	79—80	$C_9H_{11}NO_2S$	54.80	5.76	6.95	16.48	54.83	5.58	7.11	16.25

Table 4.



Comp.	Substituents			Method	Yield %	Solv. for recryst.	Appearance	M.p. °C	Molecular formula	Found				Calc.			
	R^1	R^2	R^3							C	H	N	S	C	H	N	S
Va	H	H	H	a	94	—	yellow	175—185	C_7H_6ClNOS	44.60	3.27	8.08	18.32	44.80	3.20	8.00	18.60
Vb	H	H	CH_3	a, c	86	—	»	>220	C_8H_8BrNOS	39.19	3.27	5.49	12.69	39.02	3.25	5.68	13.01
Vb	H	H	CH_3	b	94	Benzene/ pet.ether	»	54—56	$C_8H_7NOS \cdot C_2H_4O_2$	52.99	4.98	6.11	14.46	53.33	4.89	6.22	14.22
Vc	H	H	C_6H_5	b	58	EtOH	reddish yellow	183—185	$C_{13}H_9NOS$	68.54	4.11	6.17	13.68	68.72	3.96	6.17	13.92
Vd	H	OH	H	a	90	—	greenish yellow	>220 [b]	$C_7H_6ClNO_2S$	41.13	2.81	6.80	10.92	41.26	2.94	6.88	10.81
Ve	H	OH	CH_3	a, c	88	—	»	>220 [b]	$C_8H_8BrNO_2S$	36.73	3.12	5.18	12.38	36.64	3.08	5.34	12.23
Vg	CH_3	OH	CH_3	a [a]													
IXa	H	OAc	C_6H_5	b	49	EtOAc/ EtOH	reddish yellow	182—183	$C_{15}H_{11}NO_3S$	62.84	3.82	4.95	11.22	63.10	3.89	4.91	11.24
IXb	CH_3	OAc	C_6H_5	b	75	EtOH	red	187—188	$C_{16}H_{13}NO_3S$	64.05	4.22	4.59	10.40	64.20	4.38	4.68	10.71
IXc	CH_3	OAc	p-$NO_2C_6H_4$	b	69	HOAc	reddish brown	246—247	$C_{16}H_{12}NO_2O_5S$	55.63	3.48	7.81	9.21	55.81	3.51	8.14	9.31

[a] The product was a mixture of Vf and the non-cyclic acid bromide. [b] Decomposition.

EXPERIMENTAL

Paper chromatography and TLC on silica gel GF_{254} in BuOH:EtOH:NH_3:H_2O (4:1:2:1) and BuOH:HOAc:H_2O (100:22:50) were used. The UV data were recorded on a Perkin-Elmer model 137-UV spectrophotometer and the NMR data on a Varian A-60A instrument.

2-Pyridylthiocarboxylic acids from pyrid-2-thiones (III, VI). Method (a). The pyrid-2-thione (0.1 mol) was dissolved in cold N NaOH (200 ml, 0.22 mol) and the halogeno-carboxylic acid (0.11 mol) added portionwise to the stirred solution. The resultant solution was heated to 60 – 80° and kept at this temperature for 1 – 4 h. The progress of the reaction was followed by chromatography. The cold solution was then brought to pH 4 – 5 and the precipitated solid collected and recrystallized.

Method (b). The pyrid-2-thione (0.1 mol) was dissolved in toluene (200 ml) by heating to about 70°. The halogeno acid (0.11 mol) was then added portionwise with stirring and the solution heated under reflux for 2 – 4 h. Again chromatography was used to follow the progress of the reaction. The product formed was separated from the solution, usually as a yellowish-brown oil. The solvent was decanted from the cold reaction mixture and the residual material dried *in vacuo*. These salts could be made to crystallize from acetic acid. The free base was prepared by dissolution in N NaOH (110 ml) and adjustment of pH to 4 – 5 as under method (a).

The solvents used for recrystallizations were benzene/petroleum ether/hexane in variable ratios depending on the compound or H_2O/MeOH, 3:1.

Synthesis of thiazolo[3,2-a]pyridinium-3-oxides (V, IX). (a) The pyrid-2-thione (0.02 mol) was dissolved in benzene-acetone (1:1) or THF (20 – 30 ml) containing acetic anhydride (1 ml). To this stirred, ice-cold solution was added dropwise a halo acid halide (0.03 mol). After about 5 min the reaction mixture was heated to 50° and kept at this temperature for 5 – 10 min. The yellow crystalline reaction product was filtered off from the cold reaction mixture and was pure enough for analysis after washing with acetone.

(b). The α-2-pyridylthiocarboxylic acids (0.01 mol) were dissolved in dry pyridine (10 ml) and acetic anhydride (10 ml) added. Those carboxylic acids with an α-aryl group immediately gave rise to reddish coloration, the others to a yellowish-green coloration. The anhydro compounds crystallized out from the reaction solution on standing. The products could be recrystallized from organic solvents.

(c). A solution of the pyrid-2-thione (0.02 mol) and α-halo acid (0.02 mol) in toluene (250 ml) was heated under reflux. Chromatography after 2 h showed that the pyrid-2-thione had become alkylated. On further heating this product gradually disappeared with the formation of the bicyclic thiazole. The cyclisation was complete after 48 h. The yellowish solid (4.6 g, 71 %) was filtered off from the cold reaction mixture.

The reaction with the ethyl ester proceeded in the same way.

α-2-Pyridylthiopropionanilide (XV a). 3-Hydroxy-2-methylthiazolo[3,2-a]pyridinium acetate (2.25 g, 0.01 mol) was dissolved in aniline (10 ml) in the cold. After 30 min the decolorized solution was evaporated at reduced pressure and the residue crystallized from benzene-hexane; yield 90 %, m.p. 78 – 79°. (Found: C 64.82; H 5.30; S 12.81. Calc. for $C_{14}H_{14}N_2OS$: C 65.12; H 5.42; S 12.40.) NMR in TFA: 8.39 τ (doublet, CH_3-CH), 5.52 τ (quartet, $CH-CH_3$), 2.2 – 3.3 τ (aromatic protons).

α-2-Pyridylthiophenylacetanilide (XV c). 2-Phenylthiazolo[3,2-a]pyridinium-3-oxide (1.1 g, 0.005 mol) was dissolved in aniline (5 ml) and the solution heated at 50°. The reddish colour had disappeared after 18 min, when the solution was evaporated at reduced pressure and the residual oil crystallized from ethanol; yield 1.4 g (89 %), m.p. 102 – 104. (Found: C 71.25; H 5.00; N 8.75. Calc. for $C_{19}H_{14}N_2OS$: C 71.54; H 5.04; N 8.80.) NMR in TFA: 4.35 τ (CH-Aryl), 2.2 – 3.3 τ (aromatic protons).

α-(3-Hydroxy-6-methyl-2-pyridylthio)phenylacetamide (XV d) and acetanilide from IXb. 8-Acetyl-5-methyl-2-phenylthiazolo[3,2-a]pyridinium-3-oxide (1.5 g, 0.005 mol) was dissolved in aniline (5 ml) and the red solution heated to 80°. After 30 min the now yellow solution was evaporated and the residue triturated several times with hot water. Acetanilide crystallized out from the water extracts on cooling; yield 0.5 g (78 %).

The yellowish solid, insoluble in water, was crystallized from ethanol-ether (4:1); yield 1.5 g (87 %), m.p. 175 – 185° (decomp.). (Found: C 68.96; H 5.34; N 7.61. Calc. for

$C_{20}H_{18}N_2O_2S$: C 68.57; N 5.14; N 8.00.) NMR in TFA: 7.20 τ (CH_3–aryl), 4.3 5 τ (–CH–aryl), 2.2–3.3 τ (phenyl protons), 1.98–2.35 τ (pyridine protons).

α-(2-Pyridylthio)propionalanide (XV b). 3-Hydroxy-2-methylthiazolo[3,2-a]pyridinium acetate (2.3 g, 0.01 mol) and L-alanine (3.1 g, 0.035 mol) were mixed and heated to 100° when a melt appeared to be formed. The yellow coloration was gone after about 7 min. The reaction mixture was then triturated with benzene (10 ml) and unreacted alanine filtered off. The title compound crystallized out on addition of petroleum ether to the benzene solution. The whitish solid could be recrystallized from benzene-hexane (3:2); yield 2.0 g (80 %), m.p. 156–164° (decomp.). (Found: C 52.25; H 5.67; N 10.86. Calc. for $C_{11}H_{14}N_2O_3S$: C 51.97; H 5.51; N 11.02.) NMR in TFA: 8.6 and 5.4 τ (two sets of doublets and quartets due to CH_3–CH of alanine), 8.40 γ (doublet, CH_3–methine), 5.82 τ (quartet, CH-methyl), 2.1–3.0 τ (pyridine protons).

Hydrolysis. The product was dissolved in a little TFA and the solution evaporated after a short time. Repeated extractions with benzene removed the reformed thiazole. The remaining L-alanine had specific rotation $[\alpha]_D^{20} = +14.6°$ ($c = 2$ in 5 N HCl).

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