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N-Quaternary Compounds

Part XV. The Thiazolo[3,2-a]pyridinium-8-oxide System

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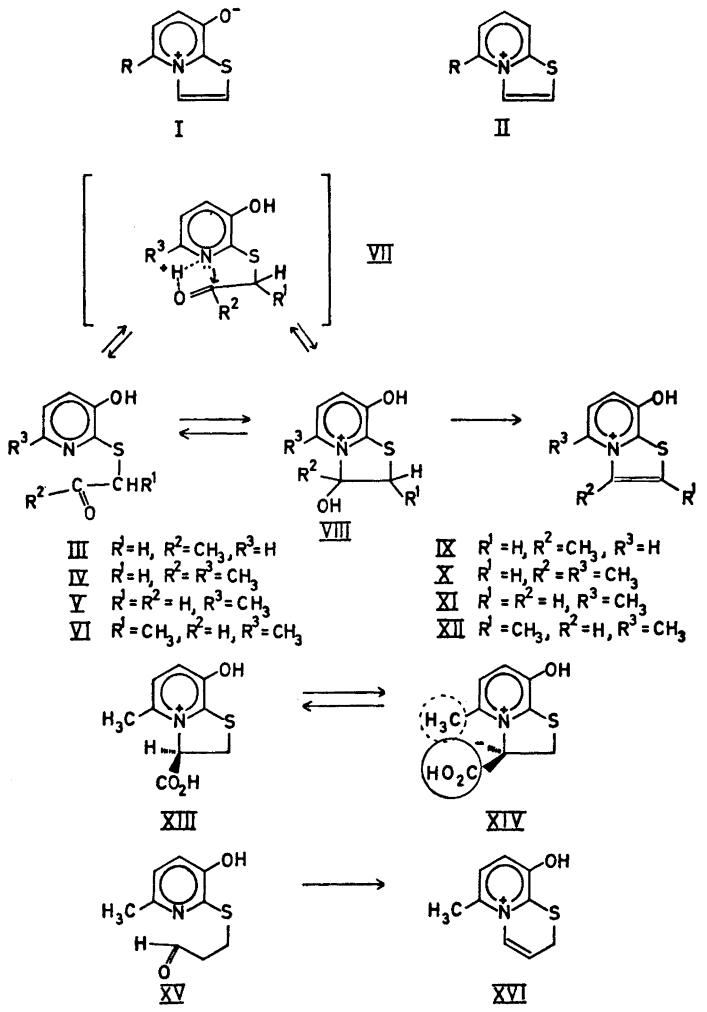
This paper describes the synthesis of the thiazolo[3,2-a]pyridinium-8-oxide system by acid catalyzed cyclisation of 3-hydroxy-2-thiopyridyl-β-carbonyl derivatives. The cyclisation rate is sensitive to interaction between the carbonyl substituent and the 6-pyridyl substituent. Corresponding γ-carbonyl derivatives were not cyclised to pyridinium derivatives. No cyclisation over the phenolic oxygen with water elimination was observed, although NMR in solution and IR in the solid state showed that the β-carbonyl derivatives largely existed in the hemiacetal or hemiketal forms. Dimethyl or diethyl acetals on heating gave the corresponding cyclic phenolic acetals. The cyclisation tendency for a γ-carbonyl derivative was less.

Electrophilic substitution readily takes place in 5- or- 7-position as shown by bromination. Reduction of the bromo derivatives with zinc in deuterioacetic acid gave the deuterio analogues. Deuterations in the 2- and 3-positions were achieved in alkaline deuterium oxide. Possible reaction mechanisms in the direct deuteration are discussed.

In the preceding report[1] it was shown that a 3-hydroxydihydro[1,3]thiazino[3,2-a]pyridinium-9-oxide derivative under the influence of strong acids could be dehydrated and rearranged to a thiazolo[3,2-a]pyridinium-8-oxide (I). In this paper we describe a more general approach to the thiazolo system.

The simple thiazolo[3,2-a]pyridinium cation (II) was only recently reported.[2–4] Simple betaines, however, have not been described. The first preparation[2] of this cation was achieved by acid catalyzed cyclisation of β-ketosulphides derived from pyrid-2-thione. We have found that simple betaines can be formed under similar reaction conditions from pyrid-2-thiones containing a hydroxyl group in the 3-position. There is no ring formation over the phenolic oxygen.

The cyclisation mechanism could be thought of as proton addition to the carbonyl oxygen followed by nucleophilic attack from the annular nitrogen onto the carbonyl carbon. Strongly acid conditions are used, however, and therefore the basic nitrogen must be protonated and less reactive. It seems more likely that the reactive species is monoprotonated with the proton



situated somewhere between the nitrogen and the carbonyl oxygen as indicated in VII. In such a model the carbonyl carbon is still activated towards nucleophilic attack while the nitrogen is less deactivated as a nucleophile.

The cyclisation of III in cold sulphuric acid was complete in a few hours. The 6-methyl derivative (IV), however, required 80° for 2 days and the yield obtained was much lower. The isomeric aldehyde (VI) was readily cyclised in the cold. Steric interaction between the two methyl groups as discussed below therefore accounts for the reluctance of IV to cyclisation. Such interaction is not present in III and VI.

Water elimination from VIII can be assumed to be the rate determining step in the overall reaction while the formation of VIII is a fast and reversible

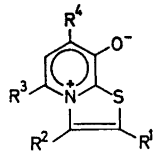
process. This assumption is supported by the findings that 3-desoxydihydrothiazoles corresponding to VIII are extremely readily formed by cyclisation of corresponding β-bromo-α-2-pyridylthioethane derivatives.[5] Also the NMR absorption (see below) of a 5-methyl group, when the 3-position is substituted, indicates no serious interaction. In the same way the non-bonded interaction between R^2 and R^3 in VIII for smaller size groups should be only moderate. During water elimination, however, the two substituents will become coplanar and occupy *peri* positions. Thus in X the repulsion arising by the close proximity of the methyl groups distorts the molecule and forces the methyl groups apart and out of plane whereby it becomes dissymmetric. The observed *peri* interaction is analogous to what has been described for naphthalene and homologues [6] and has also been used by us [7] to explain the optical stability of XIII. The methine proton on the chiral carbon in this compound is rapidly exchanged with deuterium without racemisation of the molecule. The 5-desmethyl analogue of XIII could not be prepared optically active. The explanation advanced [8] is that the intermediate carbanion (XIV) cannot easily invert through a planar transition state due to steric repulsion between the carboxy group and the methyl group in a planar state.

The steric interaction between the two methyl groups in 3- and 5-position in X is also evident from the NMR spectra recorded in TFA (Table 1). The methyl groups in compounds IX, XI, and XII are found in the 7.1 – 7.2 τ region while in the above compound the methyl groups are at 6.81 and 6.87 τ. The downfield shift must be ascribed to van der Waals repulsion since it is known [9] that disturbance of the electron cloud symmetry around the hydrogen nucleus leads to deshielding effects which are measurable in NMR. The same downfield shift of the signal from the 3-methyl group is evident in compound XXVI, which carries a bromine in the interacting *peri* position although part of this effect could be due to bromine anisotropy.

In contrast to the ease of cyclisation in the β-carbonyl derivatives, stands the reluctance of the γ-carbonyl derivative (XV) to ring formation under the above experimental conditions. At least the 4H-thiazine ring is acid stable [1] and this would also be expected to be true for the 2H-isomer (XVI). The reason for the failure to form a thiazine, therefore, must be sought in the different energy states of the fully aromatic thiazoles and the non aromatic thiazine structures. These results correspond well to what has been found for acid catalyzed cyclisation of α- and β-carboxylic acids in pyridylthioether series.[10]

The carbonyl sulphides (III – VI, XV) were synthesized from the respective thiolactams by condensation with bromoacetone and with acetals of α- or β-bromoaldehydes. The *S*-alkylation with primary and secondary alkyl halides in cold alkoxide requires 1 – 2 h, while bromoacetone reacts as added. The α-bromoacetals require reflux in methanolic sodium methoxide for 3 – 4 days. In DMF the reaction was much quicker and gave a higher yield of the desired product. The bulkiness of the acetal group probably changes the mechanism in the *S*-alkylation from a S_N2 reaction to a S_N1 reaction in agreement with the large rate increase on changing to a more polar solvent. In the β-bromo derivative the bulky acetal group is one methylene group further away from the carbon undergoing substitution and the reaction rate is much enhanced.

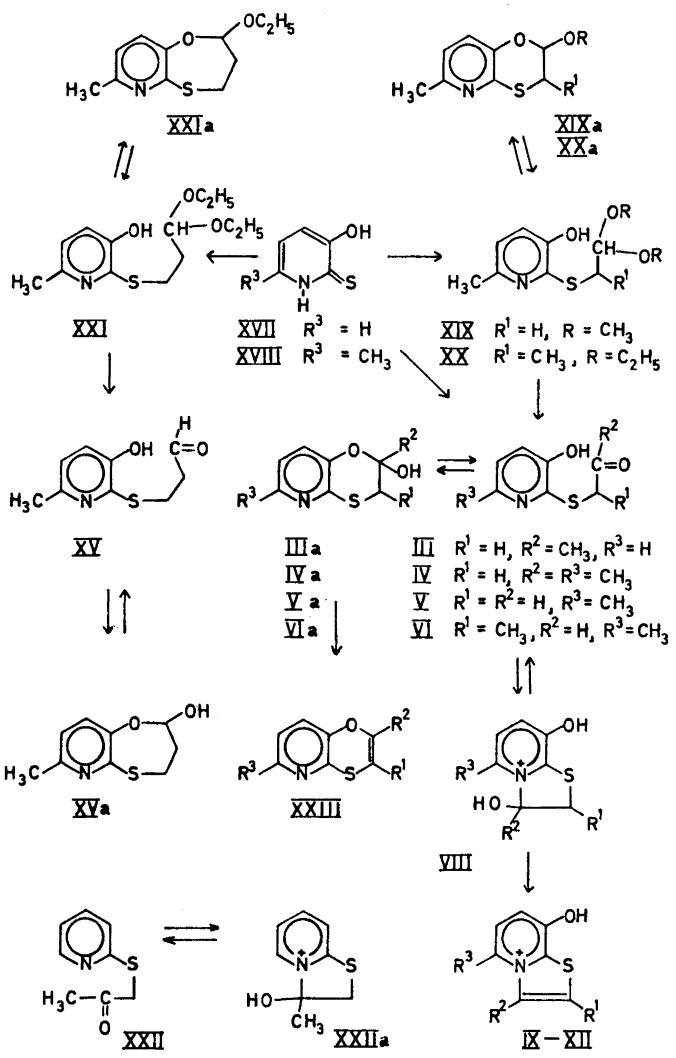
Table 1. NMR spectra in TFA.



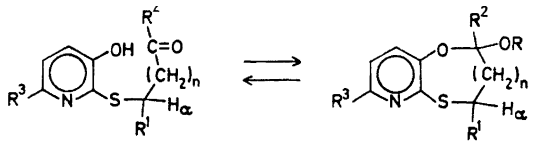
Substituent					Chemical shift in τ value				
Comp.	R^1	R^2	R^3	R^4	2	3	5	6	7
IX	H	CH_3	H	H	2.15	7.10	1.41	2.14	2.20
XXX	D	CH_3	H	H	—	7.10	1.41	2.14	2.20
XXIX	H	CH_3	D	D	2.15	7.10	—	2.14	—
X	H	CH_3	CH_3	H	2.26	6.79	6.86	2.48	2.48
XXI	D	CH_3	CH_3	H	—	6.79	6.86	2.48	2.48
XXVII	H	CH_3	CH_3	D	2.26	6.79	6.86	2.48	—
XI	H	H	CH_3	H	1.34	1.13	6.92	1.96	1.96
XXXII	D	D	CH_3	H	—	—	6.92	1.96	1.96
XII	CH_3	H	CH_3	H	7.19[a]	1.89	7.10	2.41	2.41
XXVIII	CH_3	H	CH_3	D	7.19[a]	1.89	7.10	2.41	—
XXXII	CH_3	D	CH_3	H	7.19	1.89	7.10	2.41	2.41
XXIV	H	CH_3	CH_3	Br	2.26	6.86	6.81	2.26	—
XXV	CH_3	H	CH_3	Br	7.16	1.82	7.05	2.17	—
XXVI	H	CH_3	Br	Br	2.10	6.72	—	1.79	—

[a] The methyl group in the 2-position and the proton in the 3-position couple, $J=1.5$ cps.

In the acid induced cyclisation of the carbonyl derivatives there is no evidence in the products formed for phenolic oxygen participation. Such a reaction over the phenolic oxygen would lead to an oxathiazanaphthalene ring system (XXIII). This is true also in the case where the *N*-quaternisation cyclisation reaction leads to serious steric interaction between the methyl groups in the 3- and 5-positions (IV → X). This tendency parallels the cyclisation of the corresponding β-halo ethers which give the dihydrothiazolo-pyridinium system rather than *O*-alkylation.[5] On the other hand, NMR shows that these molecules can be partly present as cyclic hemiketals or hemiacetals in solution. From Table 2 it can be seen that in NMR the protons in the side-



chain in the cyclic (IVa) and in the open form (IV) will be non-equivalent. Thus the protons of the methyl group of the side-chain in IV are shifted from 7.70 τ to 8.26 τ on cyclisation, the $S-CH_2$-protons from 6.05 τ to 6.75 τ, the geminal coupling constant being $J = 13$ cps in the bicyclic structure. Proton integration shows that the ratio of open over cyclic structure is 2:3 in both TFA and $CDCl_3$. In III only the cyclic form is present in the above solvents. The aldehyde proton of VI is absent and the molecule therefore is fully cyclic. The chemical shift for the $S-CH$-proton is at about 6.5 τ while the $O-CH$-proton is found at about 4.5 τ. These appear as unresolved peaks and therefore there is a mixture of *cis* and *trans* isomers. In the case of the γ-aldehyde (XV)



	Substituents					Chemical shift in τ values								
Comp.	R^1	R^2	R^3	R	*n*	H_4	H_5	R^1	Hα	R^2	R^3	$2H_n$	R	Open cyclic
III	H	CH_3	H	—	0									0:1
IIIa	H	CH_3	H	H	0	2.21[a]	2.33	6.05	6.15	7.97	1.67	—	—	
IV	H	CH_3	CH_3	—	0	2.98[b]	3.15	6.05	6.05	7.70	7.56	—	—	2:3
IVa	H	CH_3	CH_3	H	0	2.98[b]	3.15	6.75	6.93	8.26	7.56	—	—	
V	H	H	CH_3	—	0									
Va	H	H	CH_3	H	0	2.95[b]	3.14	5.45	5.85	5.98	7.58	—	—	0:1
VI	CH_3	H	CH_3	—	0									
VIa	CH_3	H	CH_3	H	0	3.00[b]	3.18	8.60[1]	6.3—6.8	4.4—4.8	7.58			0:1
XV	H	H	CH_3	—	1	2.05[a]	2.45	6.4—6.9		0.19	7.16	6.7		3:1
XVa	H	H	CH_3	H	1	2.45	2.70	6.4—6.9		3.40	7.13	6.4—6.9		
XIX	H	H	CH_3	—[c]	0	3.00[b]	3.20	6.5—6.8		5.47	7.55	—	6.62	7:1[d]
XIXa	H	H	CH_3	CH_3	0	3.05	3.26	6.7—6.9		4.75	7.55	—	6.48	
XX	CH_3	H	CH_3	—[c]	0	2.94[b]	3.18	8.75	6.0—6.5	5.50	7.57	—	6.3, 8.8	1:1
XXa	CH_3	H	CH_3	C_2H_5	0	3.05	3.15	8.75	6.0—6.3	4.95	7.57	—	6.3, 8.8	
XXI	H	H	CH_3	—[c]	1	2.95[b]	3.15	6.8	6.8	5.35	7.56	8.0	6.3, 8.8	1:0
XXIa	H	H	CH_3	G_2H_5	1								6.3, 8.8	

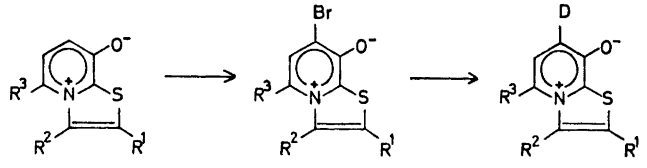
[a] Spectrum recorded in TFA. [b] Spectrum recorded in $CDCl_3$. [c] Acetal. [d] Ratio after distillation was 0:1.

the ratio between open and cyclic structure is 3:1 showing that a 7-membered ring is less favourable. The NMR spectra, however, do not rule out that the cyclisation is over the nitrogen (VIII), the intermediate in the conversion to thiazoles (IX – XII), since such intermediates should show the same type of proton non-equivalence in NMR. Therefore the acetone derivative of pyrid-2-thione (XXII) was made.[2] Its NMR spectrum was recorded in $CDCl_3$ and in $CDCl_3$ containing a few drops of TFA. The SCH_2 group appeared as a singlet at about 5.4 τ. This does not support a cyclic structure over nitrogen. Further evidence for a cyclic structure over oxygen is provided by the observed volatility of corresponding acetals (XIXa, XXa) since the ionic intermediates such as VIII would not be volatile. Therefore the concentration of VIII is either too small at any time to be seen by NMR or the rate of its interconversion with the acyclic form on the NMR time scale is so fast that it cannot be recorded. By analogy the higher homologue (XV) has been formulated in the same manner, but no proof for this is offered.

In the solid state in KBr the IR spectra of the acetonyl derivatives (III and IV) exhibit carbonyl absorption at 1700 cm^{-1}, but the intensities are only about half those of the strongest bands in the spectra. These substances therefore exist as mixtures of open and cyclic forms. The aldehyde (VI) shows no carbonyl absorption and is therefore cyclic as found by NMR in solution. More surprising is the lack of CO absorption in the spectrum of the isomeric γ-aldehyde (XV) which therefore must exist as the 7-membered hemiacetal (XVa).

The products obtained from the condensation reactions between α-bromoacetals and the thiolactam (XVIII) were mixtures of acyclic and cyclic forms. Thus the product from the dimethyl acetal of bromoacetaldehyde gave two signals in NMR from the acetal methine proton, *viz.* at 5.47 and 4.75 τ (ratio 7:1). The product lost methanol on distillation and in the NMR spectrum the methine proton signal at 5.47 τ was absent. Thus the distillation product has the bicyclic structure XIXa. The α-methyl isomer in the same way was found to be a mixture of XX and XXa. The higher homologue (XXI), however, showed no sign of cyclisation under these conditions and was distilled unchanged.

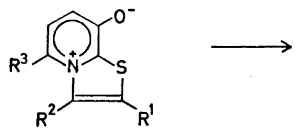
Dihydrothiazolo[3,2-a]pyridinium-8-oxides readily undergo electrophilic substitution in contrast to the cation itself.[11] Thus bromination takes place in the 5- or 7-position, the substitution pattern being governed by the phenolic oxygen in the 8-position. In the same way both the thiazoles X and XII with



X	XXIV	$R^1 = H, R^2 = R^3 = CH_3$	XXVII	$R^1 = H, R^2 = R^3 = CH_3$
XII	XXV	$R^1 = CH_3, R^2 = H, R^3 = CH_3$	XXVIII	$R^1 = CH_3, R^2 = H, R^3 = CH_3$
IX	XXVI	$R^1 = H, R^2 = CH_3, R^3 = Br$	XXIX	$R^1 = H, R^2 = CH_3, R^3 = D$

bromine in acetic acid furnished the respective 7-bromo derivatives (XXIV, XXV) which were resistant to further bromination under the above experimental conditions. In the 60 Mc NMR spectrum the two protons in the pyridine ring in the 5-methyl derivatives (X, XII) have about the same chemical shift and therefore appear as a singlet around 2.5 τ. In the corresponding dihydrothiazole series a normal AB pattern is present.[11] The NMR spectrum of the brominated thiazole derivatives above therefore does not tell whether the bromine has entered the 6- or 7-position but by analogy with the corresponding dihydrothiazolo series, where the substitution pattern has been proved by both chemical means [11] and by X-ray crystallography,[12] the bromination products have been assigned structures XXIV and XXV. The 5-desmethyl derivative (IX) was brominated in methanol due to low solubility in acetic acid. With one equivalent of bromine chromatography showed the presence of at least three components. Two of these were identified as the starting material and the dibrominated product (XXVI). The use of 2 equiv. of bromine gave a homogeneous product. Under these conditions, therefore, it was not possible to prepare selectively a mono-bromo derivative and therefore it is not known whether the 5- or the 7-position is the more reactive.

The brominated products could be quantitatively debrominated with zinc in acetic acid. In the same way the compounds can be deuterated using deuterioacetic acid (XXVII–XXIX). Attempts to carry out deuteration directly with electrophilic substitution using deuteriosulphuric acid at elevated temperatures met with little success. On the other hand, in alkaline deuterium oxide, the aromatic thiazole hydrogen in both the 2-methyl and 3-methyl derivatives were quickly exchanged with deuterium (XXX–XXXII). Since the environment for the protons in the 2- and 3-positions should be different one could expect different rates of deuteration at these positions. This was tried crudely by dissolving XI in deuterium oxide but no exchange took place. Addition of a small drop of N NaOH to the solution caused exchange of both hydrogens (XXXIII) before the NMR spectrum could be recorded. Therefore the rates are fast and probably similar. Experimentally the deuteration was followed by NMR by observing the disappearance of the signals from the protons undergoing substitution.



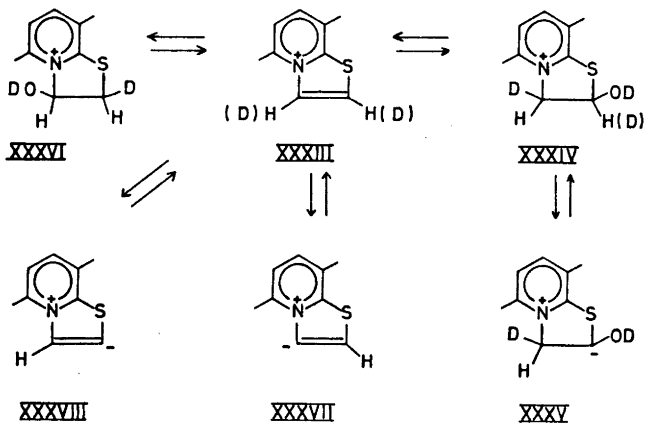
IX–XII

XXX $R^1 = D, R^2 = CH_3, R^3 = H$
XXXI $R^1 = D, R^2 = R^3 = CH_3$
XXXII $R^1 = CH_3, R^2 = D, R^3 = CH_3$
XXXIII $R^1 = R^2 = D, R^3 = CH_3$

The π-electrons in the thiazole double bond, not part of the pyridine ring, must be strongly localized to the heteroatoms, and the double bond must be electrophilic because of the quaternary nitrogen. Support for this conclusion can be found in the resistance of the thiazole ring to bromination and to

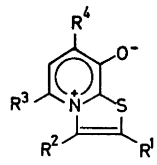
deuteration in deuteriosulphuric acid. The electron deficiency in the pyridinium ring, on the other hand, is partly overcome by the 8-oxide group.

The mechanism of the deuteration has not so far been established. One possibility is reversible addition-elimination to the double bond in the thiazole by deuterium oxide. The double bond is presumably more polarized towards the quaternary nitrogen. The deuterium oxide therefore adds at the 2-position (XXXIV) and gives back the anhydro compound deuterated in the 3-position. The 2-position is also rapidly deuterated. Addition to the double bond in the other direction would therefore seem likely. This would lead to the adduct XXXVI, however, which corresponds to the intermediate (VIII) in the cyclisation of β-carbonylthiopyridyl derivatives (III – VI). Previously we have postulated rapid interconversion of VIII and III – VI with dehydration as rate determination. The absence of any ring-opened derivatives (III – VI) in the reaction excludes the intermediate XXXVI, nor did the carbonyl derivatives cyclise under these conditons. The adduct XXXIV, however, is plausible. Thus we have found [13] that certain sulphoxides of dihydrothiazoles under the influence of acids are dehydrated to the corresponding thiazoles. The intermediate in this dehydration corresponds to XXXIV.



A deuteration mechanism involving addition-elimination to an electrophilic double bond has been suggested for the deuteration of β-phenylindenone [14] and related compounds such as chalcone and ethyl cinnamate.[15] In these compounds the deuterations were effected with deuterioethanol in the presence of sodium ethoxide. The deuteration here was said not to involve ionization of the α-vinyl hydrogen to form a carbanion. In agreement with this, adduct formation, as discussed above, could well account for deuteration in the 3-position. The 2-position could then be deuterated *via* XXXV but this seems to us less likely than direct ionisation of the 2-vinyl hydrogen and formation of the carbanion XXXVIII. If this is so the 3-position could be equally well deuterated directly *via* XXXVII. In the latter case both mechanisms might be operative.

Table 3. UV Absorption of



	Substituents				N NaOH aq							
Comp.	R^1	R^2	R^3	R^4	λ	log ε	λ	log ε	λ	log ε	λ	log ε
IX	H	CH_3	H	H	344	4.00	282	3.51	274	3.58	256	3.76
X	H	CH_3	CH_3	H	361	3.95	286	3.20	277[a]	3.25	261	3.42
XI	H	H	CH_3	H	354	3.99	282	3.40			245	3.84
XII	CH_3	H	CH_3	H	355	3.93			275[a]	3.46	253	3.87
XXI	H	CH_3	CH_3	Br	365	3.66	292[a]	3.04	281	3.13	260	3.46
XXV	CH_3	H	CH_3	Br	360	3.96	293[a]	3.20	280	3.37	253	3.86
XXVI	H	CH_3	Br	Br	372	4.42	305	3.72	296	3.69	265	4.02

Table 3. (cont.)

	Substituents				N HCl aq									
Comp.	R^1	R^2	R^3	R^4	λ	log ε	λ	log ε	λ	log ε	λ	log ε	λ	log ε
IX	H	CH_3	H	H	327	4.18	317	4.08	274	3.26	265	3.27	2.39	3.95
X	H	CH_3	CH_3	H	343	4.17	3.32[a]	4.08	276*	3.08	268	3.15	2.43	4.16
XI	H	H	CH_3	H	333	4.11	3.24[a]	4.05	271	3.91	263	4.06	2.43	4.33
XII	CH_3	H	CH_3	H	334	4.00	324[a]	3.94	275	3.28	267	3.36	240	3.90
XXIV	H	CH_3	CH_3	Br	344	3.88	330[a]	3.69	283	3.09	273	3.15	239	3.89
XXV	CH_3	H	CH_3	Br	335	4.15	324[a]	3.99	283	3.23	273	3.23	241	4.13
XXVI	H	CH_3	Br	Br	352	4.02	339[a]	3.84	295	3.42	284	3.45	246	4.07

[a] Shoulder.

The UV spectra, recorded in acid and alkaline solutions, are characterized by a number of bands (Table 3).

The highest wavelength band shows a bathochromic shift of 15 – 25 units on going from acid to alkaline solution while the band at the next highest wavelength suffers a hypsochromic shift of 30 – 40 units. The compound with a methyl group in the 5-position and no substituent in the 3-position (XI and XII) have the highest wavelength band at about 355 mμ (NaOH) and at 334 mμ (HCl). A methyl group in the 2-position (XII) hardly affects the position of this absorption band. However, in the compound without the 5-methyl group (IX) the absorption maxima are at 344 and 227 mμ, respectively. In the molecules with *peri* interaction between the two substituents in the 3- and 5-position a red shift is observed of about 5 units in NaOH and about 10 units in HCl. Thus X in NaOH absorbs at 361 mμ and in HCl at 343 mμ while the respective maxima for the isomeric compound (XXII) are found at 355 and 334 mμ. A similar shift is evident by comparison of the absorption maxima for XXIV and XXV. The shift seems even more pronounced where the *peri* interaction is between a methyl group and the larger bromine atom (XXVI).

EXPERIMENTAL

Paper chromatography and TLC on silica gel in the systems BuOH:EtOH:NH_3:H_2O (4:1:2:1) and BuOH:HOAc:H_2O (100:25:50) were used. The NMR spectra were recorded on a Varian-A60A instrument and the UV data on a Perkin Elmer UV Visirecorder 237 spectrophotometer.

1-(3-Hydroxy-6-methyl-2-pyridylthio)propanone-2 (*IV*). 3-Hydroxy-6-methylpyrid-2-thione (2.8 g, 0.02 mole) was dissolved in methanolic (50 ml) sodium methoxide (0.02 mole) and a solution of bromoacetone (2.8 g, 0.025 mole) in methanol (10 ml) added dropwise. After 1 h the solvent was evaporated, the residue suspended in water (100 ml), the suspension extracted with chloroform (3 × 25 ml), the chloroform extracts dried and evaporated leaving the title compound. This can be purified by distillation in *vacuo*, sublimation or by recrystallisation from benzene/hexane; yield 3.1 g (77 %), m.p. 97°. (Found: C 54.86; H 5.57; N 6.92; S 16.44. Calc. for $C_9H_{11}NO_2S$: C 54.82; H 5.58; N 7.11; S 16.23).

1-(3-Hydroxy-2-pyridylthio)propanone-2 (*III*) was prepared in the same way as the 6-methyl derivative from 3-hydroxypyrid-2-thione in 84 % yield; m.p. 74–76°. (Found: C 52.30; H 4.78; N 7.71. Calc. for $C_8H_9NO_2S$: C 52.50; H 4.92; N 7.65).

2-(3-Hydroxy-6-methyl-2-pyridylthio)propionaldehyde (*VI*). A solution of 3-hydroxy-6-methylpyrid-2-thione (2.8 g, 0.02 mole), potassium carbonate (3.0 g, 0.021 mole) and 2-bromopropionaldehyde diethyl acetal [16] (8.0 g, 0.04 mole) in dimethylformamide (50 ml) was heated under reflux for 15 h, the solvent distilled off at reduced pressure, the residual oily material suspended in water (50 ml), extracted with chloroform (3 × 50 ml), the chloroform extracts dried, evaporated and the residual oil distilled; pale yellow liquid, b.p. 115°/0.06 mm Hg, yield 3.9 g (64 %).

This product is the diethyl acetal of the title compound. Elementary analysis was not carried out since NMR showed that one of the ethoxy groups was partially lost with formation of the cyclic, phenolic acetal. Instead the product was hydrolysed to the aldehyde as follows: The acetal (2.8 g, 0.01 mole) was dissolved in 6 N HCl (50 ml) and the solution left in the cold overnight, the solution evaporated, the residue dissolved in water (40 ml), the water solution brought to pH 8 with potassium carbonate, the solution extracted with chloroform, the chloroform dried, evaporated and the residue crystallized from benzene; yield 1.6 g (81 %), m.p. 15°. (Found: C 55.15; H 5.70; N 7.10; S 16.24. Calc. for $C_9H_{11}NO_2S$: C 54.82; H 5.58; N 7.11; S 16.23).

2-(3-Hydroxy-6-methyl-2-pyridylthio)acetaldehyde (*V*). The dimethyl acetal was synthesized as above from bromoacetaldehyde dimethyl acetal in 59 % yield, b.p. 160°/0.07–0.1 mmHg.

Similarly the hydrolysis in cold 6 N HCl yielded the title compound in 42 % yield; m.p. 116—118°. (Found: C 52.84; H 5.03; N 7.48. Calc. for $C_8H_9NO_2S$: C 52.50; H 4.92, 7.65).

3-(3-Hydroxy-6-methyl-2-pyridylthio)propionaldehyde (*XV*). A solution of 3-hydroxy-6-methylpyrid-2-thione (2.8 g, 0.02 mole), 3-chloropropionaldehyde diethyl acetal (5 g, 0.03 mole) in ethanolic (100 ml) sodium ethoxide (0.02 mole) was refluxed for 24 h, the ethanol evaporated, the residue suspended in water (50 ml), the suspension extracted with chloroform (3 × 30 ml), the dried chloroform extract evaporated and the residual oil distilled; pale yellow oil, b.p. 155°/0.2 mm Hg, yield 2.9 g (48 %). This is the diethylacetal of the title compound.

The acetal was hydrolyzed to the aldehyde in 6 N HCl as described above for the 2-isomer; yield 76 %, m.p. 144—146°. (Found: C 55.17; H 5.67; N 6.89. Calc. for $C_9H_{11}NO_2S$: C 54.82; H 5.58; N 7.11).

2,5-Dimethylthiazolo[3,2-a]pyridinium-8-oxide (*XII*). 2-(3-Hydroxy-6-methyl-2-pyridylthio)propionaldehyde (2.0 g, 0.01 mole) was dissolved in cold, conc. sulphuric acid (10 ml) and the solution left in the cold for 24 h. The solution was then poured into cold ether (300 ml) and left in the cold for 5 h. The ether was then decanted, the residue dissolved in water (5 ml) and the product precipitated as perchlorate by dropwise addition of 35 % perchloric acid until precipitate started appearing. The zwitterion was obtained by passing an aqueous solution through a DEAE-Sephadex-A25 column. The perchlorate could be recrystallized from water while the zwitterion was recrystallized from ethyl acetate/ethanol/hexane; m.p. 206—207°, yield 1.4 g (83 %). These data are in agreement with our previously reported synthesis.

8-Hydroxy-5-methylthiazolo[3,2-a]pyridinium perchlorate (*XI*). The title compound was prepared from 2-(3-hydroxy-6-methyl-2-pyridylthio)acetaldehyde in conc. sulphuric acid in 81 % yield, m.p. 250—253°. (Found: C 36.16; H 3.17; N 5.31. Calc. for $C_8H_8NO_5SCl$: C 36.22; H 3.01; N 5.29).

3-Methylthiazolo[3,2-a]pyridinium-8-oxide (*IX*). The title compound was prepared as above from 1-(3-hydroxy-2-pyridylthio)propanone-2 in conc. sulphuric acid in 70 % yield, m.p. 216—218°. (Found: 36.24; H 3.40; S 12.04. Calc. for C_8H_7NOS: C 36.22; H 3.01; S 12.04).

3,5-Dimethylthiazolo[3,2-a]pyridinium-8-oxide (*X*). 1-(3-Hydroxy-6-methyl-2-pyridylthio)propanone-2 (2.0 g, 0.01 mole) was dissolved in conc. sulphuric acid (10 ml), the temperature slowly increased to 80° and the solution kept at 80° for 18 h. The reaction mixture was worked up as above. The yield was 0.9 g (51 %), m.p. 209—211°. (Found: C 60.00; H 5.13; N 8.09; S 17.96. Calc. for C_9H_9NOS: C 60.33; H 5.06; N 7.82; S 17.82).

7-Bromo-2,5-dimethyl-8-hydroxythiazolo[3,2-a]pyridinium bromide (*XXV*). Bromine (1.6 g, 0.01 mole) in acetic acid (3 ml) was added dropwise to a cold solution of 2,5-dimethylthiazolo[3,2-a]pyridinium-8-oxide (1.8 g, 0.01 mole) in acetic acid (15 ml). The title compound was precipitated immediately. Recrystallisation from acetic acid gave m.p. 244°, yield 2.8 g (82 %). (Found: C 31.40; H 2.38; N 3.90. Calc. for $C_9H_9NOSBr_2$: C 31.90; H 2.65; N 4.13).

7-Bromo-3,5-dimethyl-8-hydroxythiazolo[3,2-a]pyridinium bromide (*XXIV*). The title compound was prepared as above by treatment of 3,5-dimethylthiazolo[3,2-a]pyridinium-8-oxide with bromine in acetic acid; yield 71 %, m.p. 290° (decomp.). (Found: C 32.22; H 2.92; N 4.48. Calc. for $C_9H_9NOSBr_2$: C 31.90; H 2.65; N 4.13).

5,7-Dibromo-8-hydroxy-3-methylthiazolo[3,2-a]pyridinium bromide (*XXVI*). A solution of bromine (1.8 g, 0.011 mole) in methanol (5 ml) was added dropwise to a methanolic (20 ml) solution of 8-hydroxy-3-methylthiazolo[3,2-a]pyridinium perchlorate (1.3 g, 0.005 mole). After standing in the cold for 1 h the product was collected, washed with cold methanol and recrystallized from ethanol or methanol; yield 1.5 g (73 %), m.p. 250° (decomp.). (Found: C 23.70; H 1.56; N 3.47. Calc. for $C_8H_6NOSBr_3$: C 23.90; H 1.49; N 3.48).

7-Deuterio-3,5-dimethyl-8-hydroxythiazolo[3,2-a]pyridinium perchlorate (*XXVII*). Acetic anhydride (10.2 g, 0.1 mole) and deuterium oxide (2.5 g, 0.13 mole) were heated together under gentle reflux for 2 h and 7-bromo-3,5-dimethyl-8-hydroxythiazolo[3,2-a]-pyridinium bromide (0.34 g, 0.001 mole) added. To the cold solution was then added zinc powder (2 g), the reaction mixture stirred in the cold for 3 h, the zinc filtered off, the filtrate evaporated, the residue dissolved in water (1 ml) and the perchlorate of the deuterio derivative precipitated by the addition of a few drops of 35 % perchloric acid; yield 0.21 g (75 %).

7-Deuterio-2,5-dimethyl-8-hydroxythiazolo[3,2-a]pyridinium perchlorate (*XXVIII*) was prepared as above from the corresponding bromo compound in 65 % yield.

5,7-Dideuterio-9-hydroxy-3-methylthiazolo[3,2-a]pyridinium perchlorate (*XXIX*) was prepared as above from the corresponding dibromo derivative in 80 % yield.

3-Deuterio-2,5-dimethylthiazolo[3,2-a]pyridinium-8-oxide (*XXXII*). 2,5-Dimethylthiazolo[3,2-a]pyridinium-8-oxide (0.18 g, 0.001 mole) was dissolved in N NaOD by heating to 60—70°. The deuterated compound crystallized out on cooling in 73 % yield (0.13 g).

2-Deuterio-3,5-dimethylthiazolo[3,2-a]pyridinium-8-oxide (*XXXI*) was prepared as above in 78 % yield from the non-deuterated compound.

2-Deuterio-3-methylthiazolo[3,2-a]pyridinium-8-oxide (*XXX*) was prepared as above in 82 % yield from the non-deuterated compound.

2,3-Dideuterio-8-hydroxy-5-methylthiazolo[3,2-a]pyridinium perchlorate (*XXXIII*). 8-Hydroxy-5-methylthiazolo[3,2-a]pyridinium perchlorate (0.26 g, 0.001 mole) was dissolved in cold N NaOD (1 ml), the solution left in the cold for 30 min and the deuterated product precipitated as perchlorate by addition of 35 % perchloric acid; yield 0.13 g (50 %).

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