THE NOVEL DIHYDROTHIAZOLO[3,2-a]PYRIDINIUM-8-OLATE AND CLOSELY RELATED SYSTEMS; SYNTHESES AND REACTIONS

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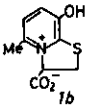
Abstract - This review covers the chemistry of the dihydrothiazolo[3,2-a]pyridinium-8-olate system, of its quinoline homologues, of amino- and nitro-dihydrothiazolo[3,2-a]pyridinium derivatives, of the dihydrothiazolo[3,2-c]pyrimidinium-8-olate system, and of the thiazolo[3,2-a]pyridinium-8- and -3-olate systems as developed in the author's laboratories. The dihydrothiazoles are formed by cyclisations over thio-azines. Asymmetric induction has been achieved in Michael adducts with thiolactams. Stereochemistry and mechanisms in adduct and cyclisation reactions have been elucidated; anchimeric involvement of the sulfur has been demonstrated. Optically active 3-carboxydihydrothiazoles are available from (R)-cysteine and oxidized furfurals; other α-pyridino acids are similarly prepared. Syntheses of thiazoles are described. Electrophilic substitution occurs readily in azinium-olates. Regiospecific deuteriations are described. N-Vinylpyridine-2-thiones are conveniently prepared from dihydrothiazoles. Photolysis of pyridinium-olates yielded the valence isomeric aziridines which are rearranged to α-pyridinones. Anchimeric assistance in oxidation of 3-carboxydihydrothiazoles yielded mainly the 1,3-cis oxide; ready decarboxylation of optically active reactant yielded the sulfoxide enantiomer. The N-chloroacetyl protecting group in peptides is removed by reaction with 3-nitropyridine-2-thione and cyclisation in cold TFA to the thiazolo[3,2-a]pyridinium-3-olate. Relevant X-ray data from structure analyses, pK_a values, NMR data, and ionisation potentials in structure analyses in the gas phase, are discussed.

Introduction

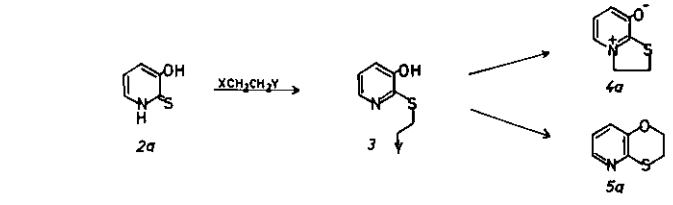
The chemistry of the thiazolo- and dihydrothiazolo[3,2-a]pyridinium-8-olate system and related systems was initiated by the isolation of a strongly blue fluorescent substance from bovine liver hydrolysates;[1] the substance was shown to have the unique pyridine salt structure 1, 5-methyl-8-hydroxydihydrothiazolo-[3,2-a]pyridinium-3-carboxylate. The literature up to 1965, when our work was started, contained no information on these systems. The development of this field of chemistry since that time will be covered in this review.

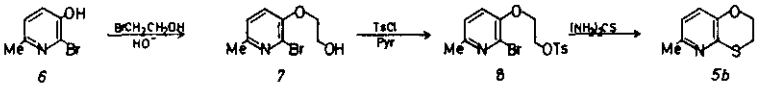
Syntheses of dihydrothiazolo[3,2-a]pyridinium-8-olates and analogues:



1b

Scheme 1

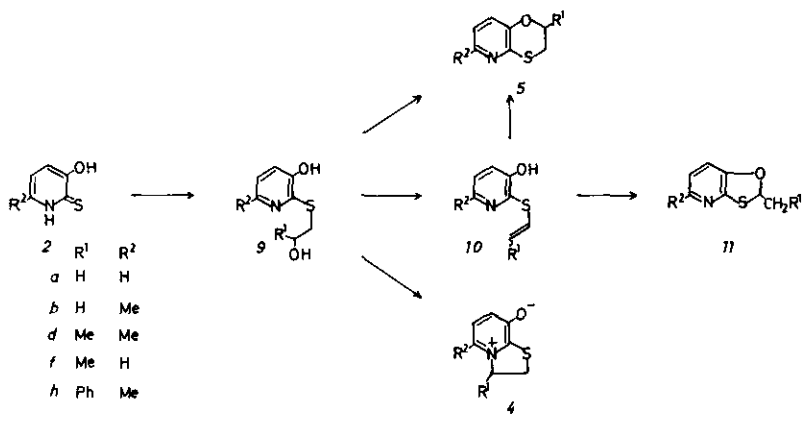




The thiazolo- and dihydrothiazolo[3,2-a]pyridinium-8-olate ring system can in principle be constructed from a preformed 2-thiopyridine or from a thiazolo derivative; both approaches have been developed.[3-6] Simple cationic derivatives had been prepared by the first approach from 2-thiopyridines; the parent cation from pyridine-2-thione and 1,2-dibromoethane,[7] and thiazolo cations by acid catalyzed cyclisation of 2-(2-oxoethylthio)pyridines.[8,9] In the preparation of a dihydrothiazole the 3-hydroxypyridine-2-thione 2 is treated with a difunctional ethane. After initial reaction on the sulfur either of the remaining nucleophilic sites may react;[10] cyclisation to the dihydrothiazolo[3,2-a]pyridinium-8-olate 4 or to the isomeric 2,3-dihydro[1,4]oxathieno[3,2-b]pyridine 5 can be envisaged. Cyclisations in the absence or presence of a base, however, almost exclusively favour

five-membered ring formation 4, and the oxathiene 5 is not seen in the reaction products. The latter, however, has been prepared by a modified process.[11] Thus, 2-bromo-3-hydroxy-5-methylpyridine 6 was O-alkylated with bromohydrin in aqueous alkali; the phenolic group at high pH is dissociated which favours O- rather than N-alkylation. Subsequent tosylation and thiation gave 5b.[11]

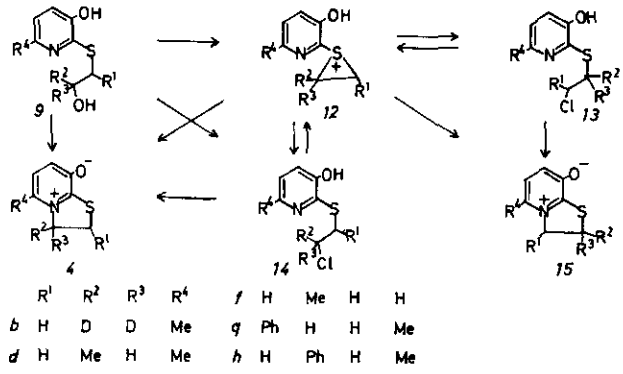
Scheme 2



Recently we have found, however, that cyclisation of 2-(2-hydroxyethylthio)-3-hydroxypyridines in concentrated sulfuric or polyphosphoric acid favours six-membered ring formation (Scheme 2); the dihydrothiazole 4 is not affected by the reaction conditions.[12] Presumably cyclisation over the pyridine nitrogen is prevented by its protonation in the strong acid media. Direct cyclisation of 9 to 5 is postulated since the reaction product did not contain the [1,3]oxathiolo[4,5-b]-pyridines 11, which are the major products on cyclisation of the alkenylthio derivatives (10; R^1 = alkyl) in strong acid media.[13] The phenyl homologue (10h), however, may go via the styryl derivative due to the ease of water elimination and since styrylthio derivatives, in contrast to the alkyl analogues, are cyclised almost exclusively to the oxathiene 5;[12] this constitutes a convenient synthesis of 2-aryl derivatives of 5 especially since the arylvinyl derivatives 10 are readily available.[14] In a weak acid, e.g. acetic acid, S-vinyl derivatives are cyclised to the dihydrothiazoles 4.[13,14]

Both the nitrogen and the sulfur in 9 are correctly spaced for neighbouring group participation in any reaction on C2 of the S-side-chain. Collapse of the former anchimeric complex leads directly to the dihydrothiazole 4, whereas collapse

Scheme 3

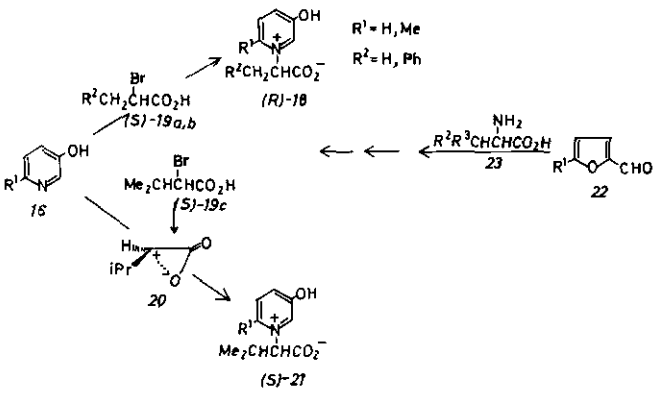


of the latter leads to an episulfonium intermediate 12 which must undergo further transformations; this is shown for some 2-(2-hydroxyethylthio)pyridines (Scheme 3).[14] Direct substitution of the β-hydroxy group with cyclisation is effected by heating 9 in acetic or formic acid. Reactions in thionyl chloride, however, yielded isomeric products. The α,α-dideuterioethylthio derivative 9b in thionyl chloride gave a mixture of the dihydrothiazole 4b and the chloro compound 14b as for direct substitution reactions, ratio 6:1. When this mixture was heated in ethyl acetate the dihydrothiazoles 4b and 15b were obtained in the ratio 20:1. Consequently some of the chloro compound 14b has been cyclised via an episulfonium intermediate 12. A methyl substituent on C2 of the side-chain or on C6 decreases the tendency for cyclisation; the major products from 9d and 9f were the chloro derivatives 14 and the rearranged 13, ratio 3:2. Similarly the phenyl analogues 9g and 9h gave the chloro derivatives 14 and 13 in the ratios 1:2 and 2:1, respectively. On heating the phenyl substituted reaction products, cyclisation gave almost exclusively the 3-phenyldihydrothiazole; for the α-phenyl reactant 9g this corresponds to complete rearrangement.

Ring opening of the substituted episulfonium intermediate is expected to occur in such a way that the nucleophile adds to the more stabilized incipient carbonium ion. In the reaction with the pyridine nitrogen, however, the latter must add cis with respect to the sulfur. This stereochemical course seems possible if the C-S bond is stretched or almost broken so that the sulfur holds the partially charged carbon from some distance. This mechanism implies configurational inversion in the cyclisation; the stereochemical course has been investigated

using optically active α-bromo acid.[15] In principle, however, the reaction might be complicated by the possibility for anchimeric assistance from the carboxy group resulting in configurational retention. The influence of the carboxy group was elucidated in a separate study of the Menschutkin reaction between 3-hydroxypyridines and optically active carboxylic acids (Scheme 4).[16]

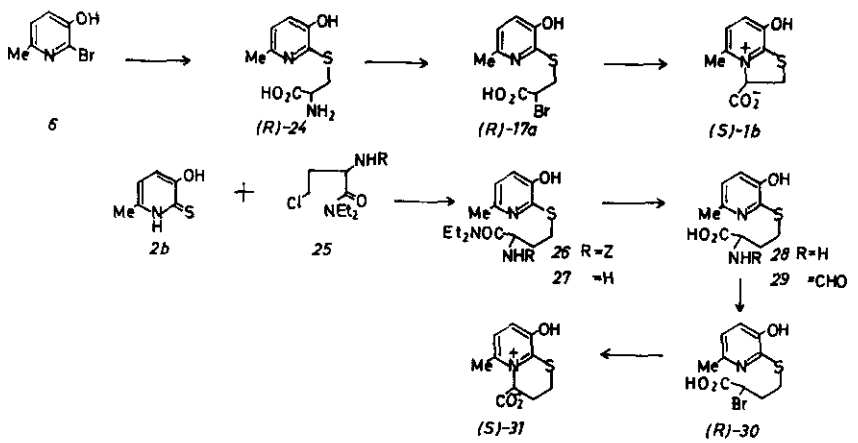
Scheme 4



The reactions with the α-bromo acids proceed by inversion of the configuration if C3 in the acid carries no more than one substituent; if C3 carries two substituents the direct substitution is slowed down and anchimeric assistance from the carboxy group results in retention.[16] The stereochemical course of these reactions was ascertained by comparison with authentic α-pyridinio acids for which direct syntheses were worked out from optically active amino acids and suitably oxidized furfurals.[17,18]

Stereochemical interference from the carboxy group in the cyclisation of the (R)-2-bromo-3-(2-pyridylthio)propionic acid 17a is unlikely in view of the above results. The bromo acid is very easily cyclised and must be generated under conditions unsuitable for cyclisation (Scheme 5). For the purpose of the stereochemical studies the amino acid (R)-24 was prepared from the bromopyridine 6 and (R)-cysteine; only partial conversion was achieved. No racemisation occurred since no deuterium was incorporated into 24 when the arylation was run in the presence of D_2O. Bromination via diazotisation goes with retention. The reactive bromo compound could be extracted into ethyl acetate at pH 2.5 and was rapidly cyclised at higher pH. Bromide ion exchange with racemisation is a competitive reaction.

Scheme 5



The optical purity 65% of the product 1b is therefore consistent with high stereospecificity in the cyclisation. The stereochemical inversion in the reaction was ascertained by comparison of the product with an authentic specimen of known configuration.[6,19]

For a further elucidation of the cyclisation reaction and of the remarkable optical stability of 1b, the homologous 9-hydroxy-6-methyldihydro[1,3]thiazino-[3,2-a]pyridinium-4-carboxylate was prepared by a similar series of reactions (Scheme 5).[20] The thiopyridine 2b was reacted to a homocysteine amide, the protecting groups removed, and the formylated amino acid optically resolved as the brucine salt. Diazotisation of the amino acid 28 ($[\alpha]_D$ -18° (N HCl)) with nitrosyl bromide gave the α-bromobutyric acid 30. The latter in contrast to the α-bromopropionic acid 17a was not very reactive. Cyclisation to 31 was effected by heating the bromo acid in aqueous solution. Extensive racemisation of 30 occurred due to bromide interchange reactions; the major enantiomer of 31 ($[\alpha]_D$ $+74^\circ$ (H_2O)) was available by fractional crystallisation.[20] Its optical stability was at least as high as that of 1b.

Comparison of the dichroic absorptions of (R)-1b and the major enantiomer of the homocysteine analogue 31 (Figs. 1 and 2) shows that the signs and positions of the CD maxima both in acid and alkaline solution are in agreement, and hence 31 is assigned the (S)-configuration; it is pointed out that (R)-1b and (S)-31 both belong to the (L)-amino acid series. The strong dichroic absorption bands of the (R)-cysteine 24 and the homocysteine 28 amino acids have opposite signs in the

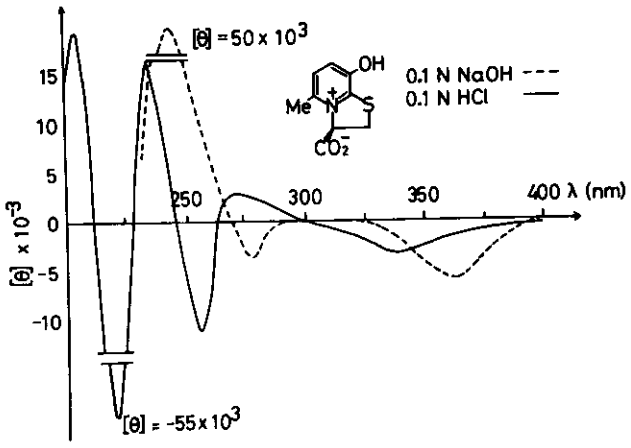


Fig. 1. CD curves: (R)-5-Methyl-8-hydroxydihydrothiazolo[3,2-a]pyridinium-3-carboxylate in 0.1 N NaOH --- and in 0.1 N HCl ——.[19]

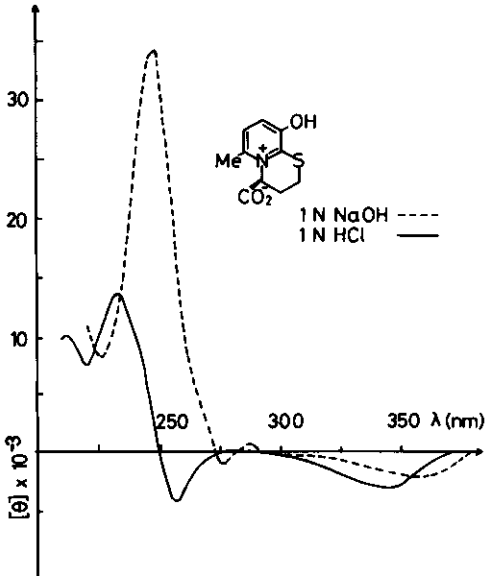


Fig. 2. CD curves: (S)-6-Methyl-9-hydroxydihydro[1,3]thiazino[3,2-a]pyridinium-4-carboxylate in 1 N NaOH --- and in 1 N HCl ——.[20]

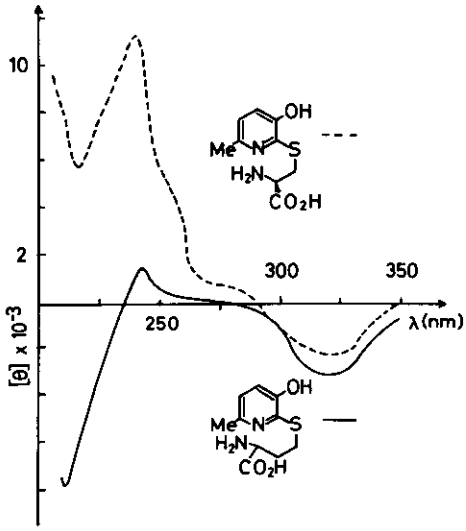
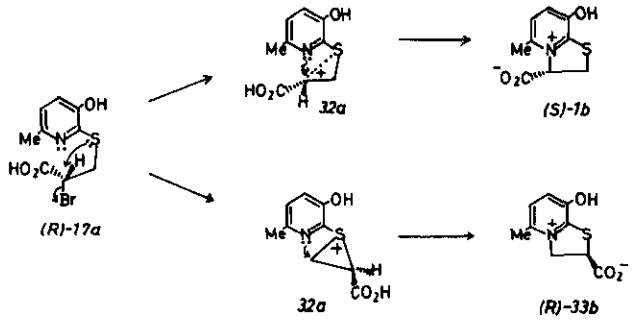


Fig. 3. CD curves: (R)-2-Amino-3-(3-hydroxy-6-methyl-2-pyridylthio)-propionic acid --- and (R)-2-amino-4-(3-hydroxy-6-methyl-2-pyridylthio)-butyric acid —— in 1 N HCl.[20]

region below ca. 225 nm where the carboxyl groups absorb; hence the major enantiomer of 28 is assigned the (R)-configuration. The assignment is further supported by the negative CD maxima below ca. 225 nm of the formylated amino acid 29 and the α-bromo acid 30.[20] From the configurations assigned it follows that the intramolecular Menschutkin reaction of 30 involves stereochemical inversion.[19,20]

Scheme 6

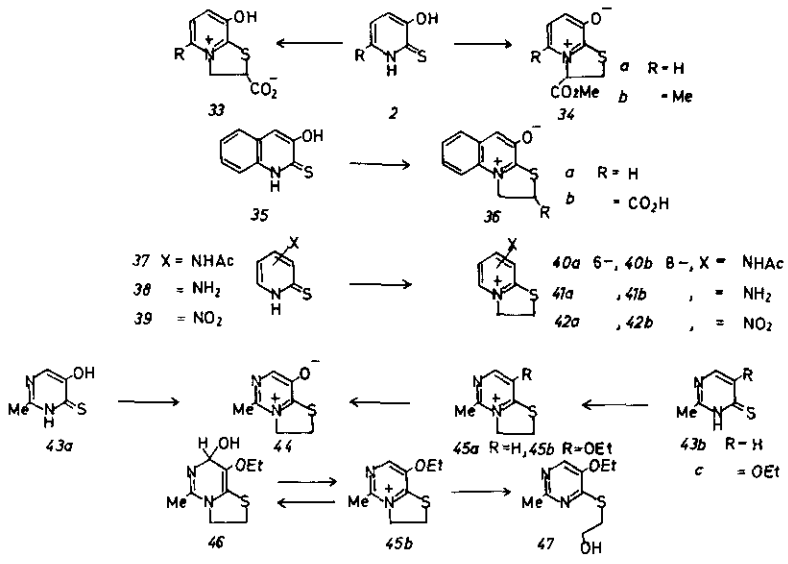


Anchimeric assistance from the sulfur in the cylisation to dihydrothiazole would be expected to yield optically active rearranged products from optically active precursors. This has been demonstrated in the cyclisation reactions of the (R)-α-bromopropionic acid 17a (Scheme 6).[15] When the reaction goes over an episulfonium intermediate the nitrogen nucleophile can attack either the methine carbon or the methylene carbon. The former reaction yields stereochemical inversion and (S)-1b; the latter reaction gives stereochemical inversion as well as rearrangement, structure (R)-33b. In fact, careful chromatography of the crude reaction product from (R)-24 after diazotisation, bromination and cyclisation gave a small amount of the 2-carboxydihydrothiazole 33b ($[\alpha]_D$ -19° (0.1 N NaOH)). Increase in the pH during the cyclisation increased the relative amount of 33b, the highest ratio for 33b:1b obtained being 2:3.[15]

The racemic modification of 2-carboxydihydrothiazoles are readily available from a pyridine-2-thione and 2,3-dibromopropionic acids (Scheme 7). Esters behave differently under alkaline conditions in that the ester function may be introduced at C3. Thus methyl 2,3-dibromopropionate in its reactions with the thiolactams 2 in the presence of sodium methoxide gave almost exclusively the 3-methoxycarbonyl isomer 34; in the presence of potassium carbonate a mixture of the 2- and 3-esters

were formed. The formation of the 3-isomer is rationalised by initial HBr elimination and subsequent Michael addition before ring closure;[3] this reaction sequence has been developed into a very convenient method for synthesizing regioselectively substituted dihydrothiazolo[3,2-a]pyridinium derivatives (see below).[4]

Scheme 7



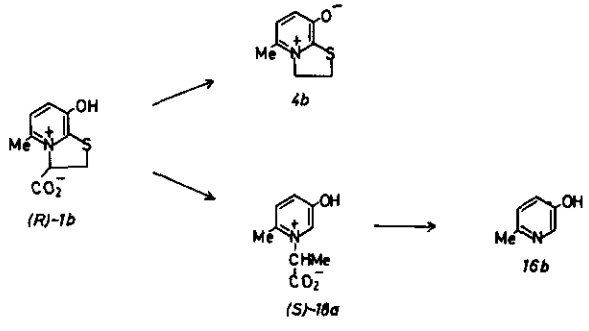
The rate of the reaction between 3-hydroxyquinoline-2-thione 35 and 2,3-dibromoethanes is less than for corresponding pyridines which can be attributed to the electronegative effect of the fused phenyl group.[21]

The 3- and 5-acetamidopyridine-2-thiones yield the dihydrothiazoles 40 with 1,2-dibromoethane.[22] 3-Aminopyridine-2-thione is also cyclised exclusively over the pyridine nitrogen to furnish 41b; the structure was confirmed by the identity with the product from hydrolytic deacetylation of the 8-acetamide 40b.[22] A strong anion exchange resin was used in the hydrolysis of 40a to 41a.[23]

The 3- and 5-nitropyridine-2-thiones react slowly with 1,2-dibromoethane due to low nucleophilicity of the sulfur. The products 42 are susceptible to nucleophilic attack at C3 with opening of the dihydrothiazole ring.[22] Reduced nucleophilicities were also to be expected for the pyrimidine-2-thiones 43 and they reacted more slowly than the corresponding pyridines; the products are the dihydrothiazoles 44 and 45.[24,25] As in the pyridines investigated, including the nitropyridines, alkylation on sulfur is the rate determining step in the reaction

sequence since the intermediate before cyclisation has not been detected in any of the reactions. In acid the stability of pyrimidine cations is such that HBr in acetic acid can be used to cleave the ethoxy group in 45b to furnish the betaine 44.[24] The importance of the phenolate group for the stabilisation of the electron deficient pyrimidinium system, however, is evident from the reactivities of the olate 44 and the O-alkyl analogue 45b towards alkali. UV monitoring of a solution of the latter in 0.1 N NaOH showed rapid competitive reactions between pseudo-base formation 46 and nucleophilic substitution at C3, 47, in analogy to the properties of the nitropyridines 42. Pseudo-base formation is reversible on acidification. The olate 44 was not affected under these conditions.[24]

Scheme 8

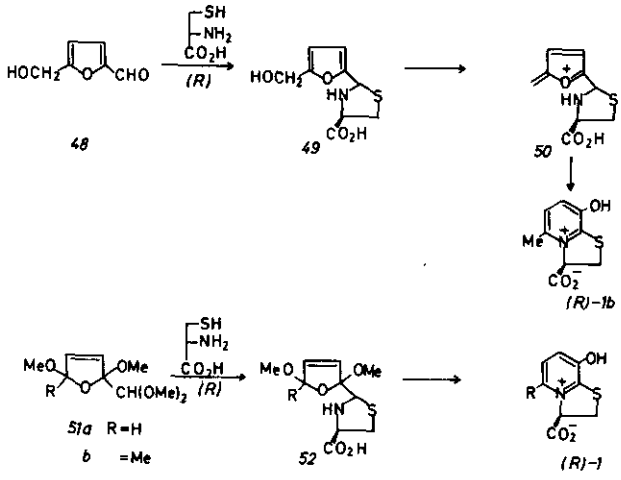


As pointed out in the introduction, optically active 5-methyl-8-hydroxy-dihydrothiazolo[3,2-a]pyridinium-3-carboxylate was originally isolated from bovine liver acid hydrolysates.[1] Its structure was determined by degradative and synthetic work, and it was shown to have the (R)-configuration. The key substances in the degradation work are shown in Scheme 8. The acid is easily decarboxylated due to the activation by the geminal positively charged pyridine nitrogen; Raney nickel desulfurisation gave the α-pyridiniopropionic acid (S)-18a which was further cleaved to 3-hydroxy-6-methylpyridine.[2]

Dissection of the structure 1b shows that the molecule can be considered as formed from the amino acid (R)-cysteine. This concept was developed into laboratory syntheses by allowing cysteine to react with suitably activated furans; it is well established that a number of carbohydrates are transformed into furans by acid catalysis. A such furan is 5-hydroxymethylfurfural which is at the right

oxidation level for the desired reaction with cysteine; in this way (R)-1b has been obtained.[6] It will be recalled (Scheme 4) that simple α-pyridinio acids can also be formed from α-amino acids and suitably oxidized furans.[17] It therefore seems likely that small quantities of this class of α-pyridinio acids as well as other pyridinium-olates are part of our diet being generated from amino acids and carbohydrates in the presence of organic acids, and are thus expected to be found in the "Browning reaction". Due to their salt nature, however, the α-pyridinio acids will not be absorbed from the gastrointestinal tract and will thus exert no pharmacological effect.

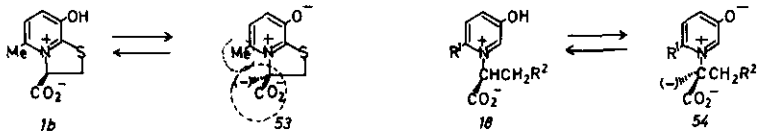
Scheme 9



The right oxidation level for the reaction with cysteine has in 5-hydroxymethylfurfural been created through the hydroxymethyl group. The reaction sequence, which is probably very complex, may be rationalised via the thiazolidine 49 (Scheme 9) which eliminates water under acid catalysis to the reactive species 50 and which is further transformed to 1b in subsequent reactions.[17] The need for a 5-α-hydroxyalkyl substituent is eliminated, if the furan ring instead is oxidized, e.g. in the 2,5-dialkoxy reactant 51. In acid solution 51 and (R)-cysteine react together to form (R)-1.[18] The yields in the reactions are low and the products are isolated by chromatography.

The dihydrothiazolo acid 1b is remarkably optically stable. Other α-pyridinio acids are readily racemised.[26] In isotope labelling experiments it was shown that the rates for base catalyzed racemisation and hydrogen-deuterium exchange in

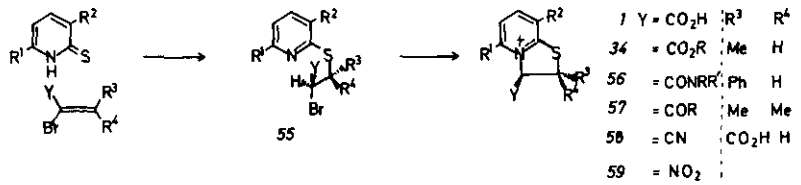
Scheme 10



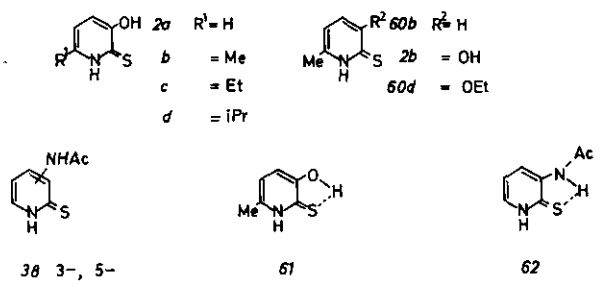
(S)-2-(3-hydroxypyridinio)propionates 18 in NaOD were similar (Scheme 10). Therefore the intermediate carbanion 54 must invert much faster than it captures a deuteron from the solvent. H3 in the dihydrothiazolo acid 1b, however, was rapidly exchanged with deuterium in 0.4 N NaOD, whereas the optical rotation remained almost constant. Rapid inversion of the carbanion 53 is therefore excluded. The non-bonded interaction between the methyl and carboxylate groups in a planar geometry will require a high activation energy for inversion of the pyramidal carbanion. The latter therefore abstracts deuterons (protons) from the solvent, from the same side as the proton was lost, faster than it can invert; hence, the configuration is retained.[26] The steric importance of the 5-methyl substituent is further supported by the finding that the desmethyl analogue 1a could not be prepared in optically active form from enantiomerically pure cysteine.[6] The optical stability of the 6-methyl homocysteine derived analogue 31 (Scheme 5) was no less than that of 1b.[20]

Pyridine-2-thiones were originally found to add to α-bromoacrylic acid and esters in the Michael fashion.[4] The α-bromine sits on a sp^2-hybridized carbon in the acrylate which becomes sp^3-hybridized in the adduct; hence the bromine becomes displaceable, resulting in cyclisation. This approach has been developed into useful regioselective syntheses of dihydrothiazolo[3,2-a]pyridinium systems.[4,27-30] Besides α-bromoacrylic acid and its derivatives other electron deficient α-bromovinyl systems are applicable, e.g. α-bromovinylketones,[31], α-bromoacrylonitrile[4] and α-bromonitroolefines (Scheme 11).[32]

Michael additions are sensitive to the nature of β-substituents which was readily seen in the present series of reactions.[4,27] Thus, the reaction between α-bromoacrylic acid and 2b proceeds in the cold. 2-Bromo-2-butenoic acid requires heating for several days.[7] The cinnamic acids are less reactive, and 2-bromo-3-methyl-2-butenoic acid failed to react. A 3-carbonyl group results in a highly



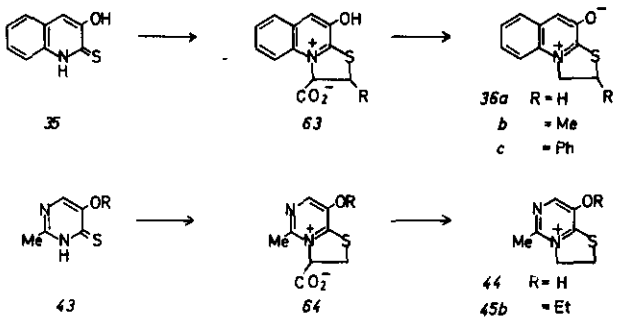
Scheme 11



active reactant.[4,27] A change in the bulkiness of the 6-alkyl substituent in 3-hydroxypyridine-2-thione had little effect on the rate of the reaction; in 4a, however, which lacks the 6-substituent the rate was significantly reduced.[29] The electron density or availability on the sulfur is therefore the most important factor for the overall rate of the reaction. This is further supported by the high reactivity of 6-methylpyridine-2-thione 60b, and the reactivity is further increased in the 3-ethoxy derivative 60d. The 3-hydroxy derivative 2b, however, is less reactive.[27] In the case of the acetamidopyridine-2-thiones the 3-isomer is much less reactive than the 5-isomer although the electronic effects should be similar.[22,33] These findings are explained by intramolecular hydrogen bonding between the phenolic hydrogen 61 or the amido hydrogen 62 and the sulfur of the thione group; this corresponds to pseudo-five-membered ring formation. The conclusion from the rate studies is in agreement with X-ray data which show strong intramolecular hydrogen-bonding for 2b in the crystalline state.[34]

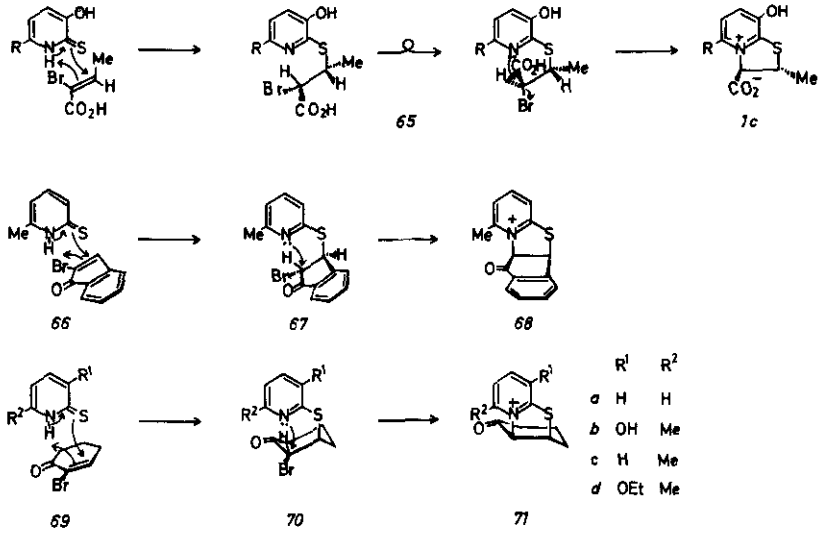
The importance of the nucleophilicity of the sulfur for the rate of the reaction is further shown in the reactions of 3-hydroxyquinoline-2-thione 35, which reacts more slowly than the pyridines with α-bromoacrylic acid. Forcing its reactions with 2-bromo-2-butenoic and -cinnamic acids gave the decarboxylated dihydrothiazolo[3,2-a]quinolinium-10-olates 36.[21] The reactivity of the pyrimidine-4-thiones 43 is further reduced; the products 64 may also contain the decar-

Scheme 12



boxylated analogues 44 and 45b since the tendency for decarboxylation is high in a highly electron deficient system.[24]

Scheme 13



In the reactions of 2 with the 2-bromobutenoic acid stereoisomers only the trans-dihydrothiazole 1c was obtained. The geometry of the product (R = Me) has been confirmed by X-ray analysis.[35] Exclusive formation of the trans-isomer was shown to be caused by rapid acid catalyzed isomerisation of (E)-2-bromo-2-butenoic acid to the (Z)-isomer under the conditions of the reaction.[27] Since the product has the trans-configuration and the cyclisation reaction proceeds by stereochemical

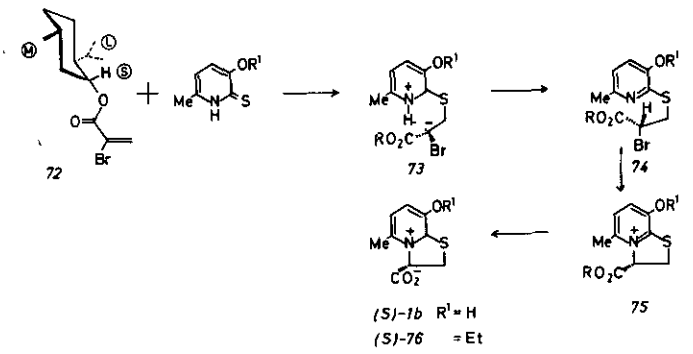
inversion (see above) the adduct formation must be suprafacial (Scheme 13). Antarafacial addition would give the cis-product which would be required to undergo almost spontaneous epimerisation, and this seems unlikely. Bromomaleic acid and its anhydride, however, react with pyridine-2-thiones to yield the trans-2,3-dicarboxy derivatives.[4,27,36] Bromofumaric acid gives the same products.[27] In these cases, however, the reaction takes another course in that dicarboxyacetylenes are formed before the Michael addition occurs.[27]

Further information on the reaction sequence and the magnitude of vicinal coupling constants for H2-H3 have been elucidated by preparing products with cis-stereochemistry. A small ring ortho-fused to C2 and C3 of the dihydrothiazole ring will for steric reasons have the cis-arrangement. This requirement is satisfied in the product 68 from 2-bromo-1-indenone and 6-methylpyridine-2-thione.[28] The suprafacial adduct 67 has the right stereochemistry for bromine displacement in the cyclisation. The vicinal coupling was 8 Hz for the ring-junction protons in 68 as compared to 0-1 Hz for other 2,3-disubstituted products assigned the trans-configuration.[28]

Models of derivatives with a six-membered ring ortho-fused at C2 and C3 of the dihydrothiazolo ring indicated that both cis- and trans-configurations are possible. Such compounds were formed from 2-bromocyclohex-2-enone (Scheme 13).[28] In accordance with the experience from the analogous series, the intermediate adduct was not seen; adduct formation is the rate determining step in the overall reaction sequence. Only one stereoisomer was formed, vicinal coupling J 7.0-7.5 Hz. Hydrogen-deuterium exchange at C3 occurred in D_2O without affecting the configuration, and in trifluoroacetic acid-d_1 there was *no exchange*. Hence, the product has the thermodynamically more stable configuration. Both the cis- and the trans-isomers apparently can assume cyclohexane conformations which would fit the observed couplings between the dihydrothiazole protons. Application of the suprafacial addition mechanism leads to the assignment of the cis-configuration. The question of relative stereochemistry was solved by X-ray analysis and the cis-configuration was confirmed.[34]

Since both the Michael addition and the cyclisation are stereochemically homogenous reactions, asymmetric induction during the sulfur addition to 2-bromopropenoic acid derivatives of chiral amines and alcohols have been investigated.[30,38] The asymmetric induction in the reactions with the α-bromoacrylamides from enantiomeric 1-phenyl-2-aminopropane and alanine ethyl ester were marginal.[30]

Scheme 14



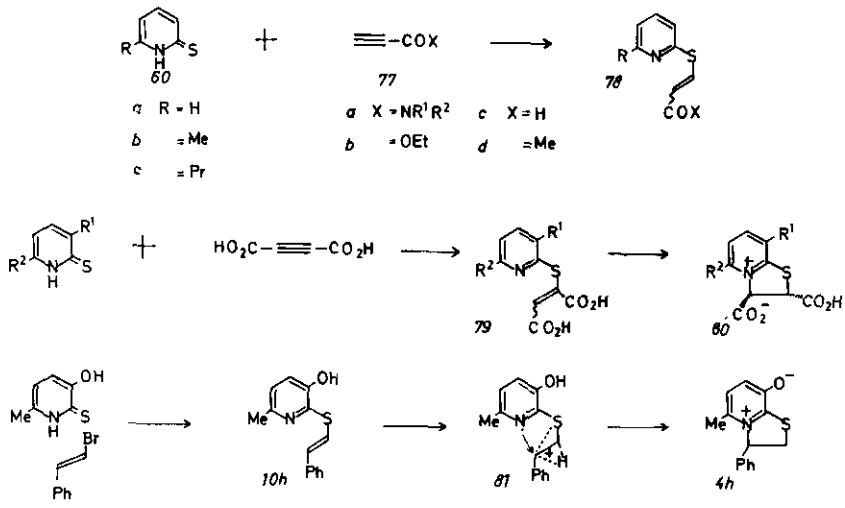
Inactive products were obtained from the α-bromoacrylates of (-)-borneol and (-)-2-octanol.[38] The optical yield was 65% (product yield 84%), however, in the reaction between 2b and (-)-menthyl α-bromoacrylate (Scheme 14).[38] The optical yield was 12% in the reaction between 3-ethoxy-6-methylpyridine-2-thione and the menthyl ester. Both products 1b and 76 had the (S)-configuration.[38]

The rate of the reaction between α-bromoacrylates and pyridine-2-thiones is sensitive to non-bonded interaction from the ester moiety; the methyl ester reacts with 2b in the cold, whereas the menthyl ester requires reflux in toluene for several days. The reaction is again fast for the O-ethyl analogue 60d where there is no phenolic hydrogen bonding. The steric induction exerted by the chiral menthyl group is therefore superimposed by hydrogen-bonding in 2b which enhances the stereochemical control.

The stereochemical course of the reaction can be rationalised by a simplified picture of steric approach control; a more complete analysis would involve evaluations of low energy transition states. In Scheme 14 suprafacial addition and inversion in the cyclisation are assumed to hold.

Michael 1:1 adducts have been found to form between pyridine-2-thiones and acetylenic amides, esters and ketones.[39,40] The S-vinyl derivatives thus formed are convenient intermediates for cyclisation reactions to thiazolo- and dihydrothiazolo[3,2-a]pyridinium derivatives (see below). The rate of adduct formation increases with the activation of the acetylenic bond by electron withdrawing substituents. The rate as well as the stereochemical course of the reaction are

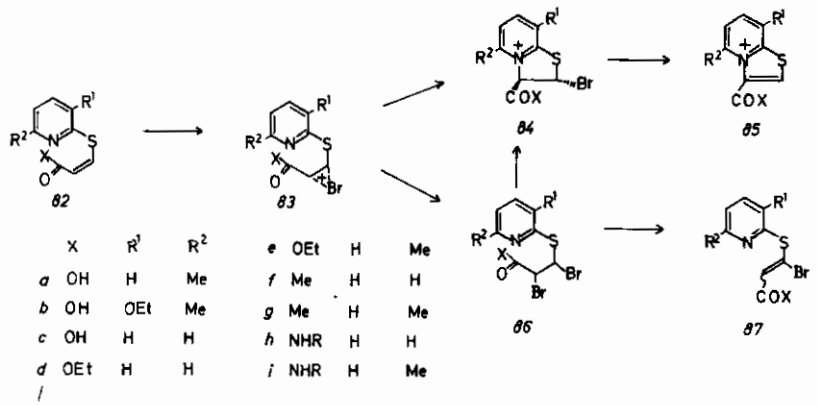
Scheme 15



affected by the pyridine 6-substituent (Scheme 15). The stereoisomer ratios corresponding to kinetic control were obtained in chloroform; the amides yielded mainly the cis-isomers, the ketones yielded the trans-isomers, and the esters yielded a slight preponderance of the cis-isomers.[40] Propynoic acid gave mainly the trans-isomer.[39,40] The adducts from the more reactive acetylenedicarboxylic acid cyclised at once to trans-2,3-dicarboxydihydrothiazolo[3,2-a]pyridinium derivatives 80.[39] The cyclisation is acid catalyzed, but in the case of the adduct 79 the electron withdrawing properties of the additional carboxy group presumably also facilitates the cyclisation. In general S-vinyl derivatives can be cyclised in acid solution;[13] thus the styryl derivative 10h is cyclised when heated in acetic acid. 10h itself is obtained by heating together 2b and β-bromostyrene in acetic acid at lower temperature than used for the cyclisation of 10h.[14]

In the reactions of S-vinyl derivatives with bromine as electrophile the nature of the products is substrate dependent.[39,41] The reaction between bromine and 3-(2-pyridylthio)propenoic acid and simple esters constitute a convenient synthetic route to the thiazolo[3,2-a]pyridinium system 85; an almost immediate precipitation of the thiazole 85 results when bromine is added to a cold chloroform solution of the propenoic acid or ester. The methyl ketone 82f gave a mixture of the thiazole 85 and the bromovinyl derivative 87; the 6-methyl derivative gave

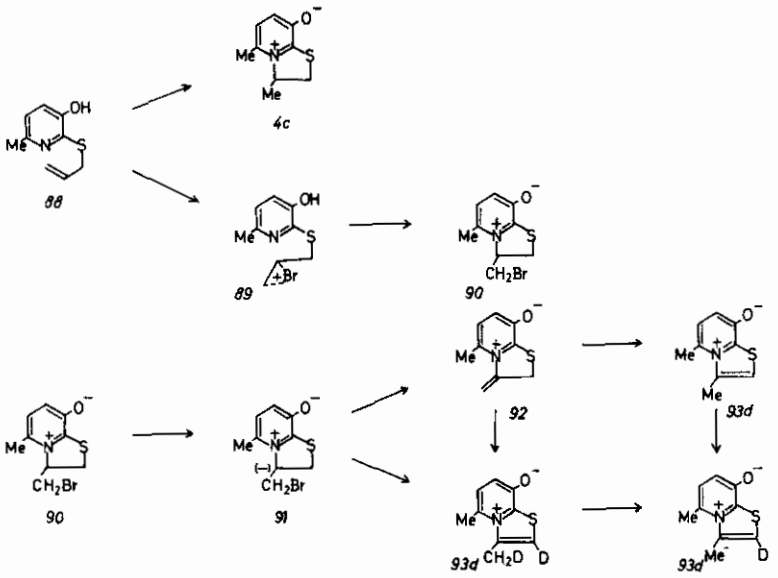
Scheme 16



	X	R^1	R^2		X	R^1	R^2
a	OH	H	Me	*e*	OEt	H	Me
b	OH	OEt	Me	*f*	Me	H	H
c	OH	H	H	*g*	Me	H	Me
d	OEt	H	H	*h*	NHR	H	H
				i	NHR	H	Me

only the bromovinyl product 87. The amides 82h gave a mixture of the trans-2-bromodihydrothiazole 84 and the bromine adduct 86; heating the mixture gave the thiazole 85. The 6-methyl substituent in 82e stopped the reaction as the adduct 86; heating the reaction mixture gave exclusively the bromovinyl derivative 87.[41] The reactions are rationalised in Scheme 16.

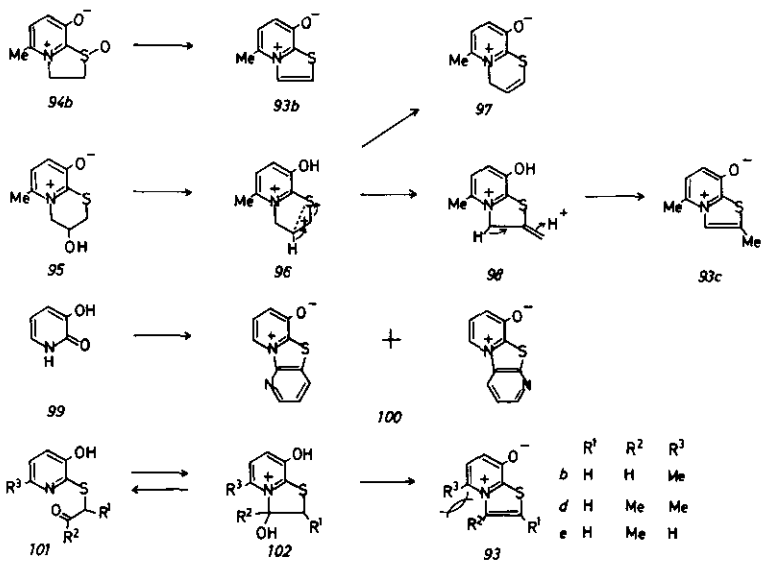
Scheme 17



Electrophilic reagents can also be used to effect cyclisation of allylic sulfides. Protonation of 88 gave the dihydroxythiazole 4c and bromination gave the corresponding bromide 90 (Scheme 17); five-membered ring formation was exclusive.[14,42]

Dihydrothiazolo[3,2-a]pyridinium salts can be ring-opened to N-vinylpyridine-2-thiones by proton abstraction from C3 (see below). In the 3-bromomethyl derivative 90, however, the 3-methylthiazole 93d was the final reaction product.[43] The methylene derivative 92 has been shown to be an intermediate. ^{1}H NMR monitoring of the reaction in 0.8 N NaOD showed deuterium incorporation at C2 and in the 3-methyl substituent. No deuterium could be detected at C2 in the starting material 90 during the reaction. At C2 in the thiazole 93d, however, rapid deuteriation occurs under the conditions of the experiment. Hence, the 3-methylene group in 92 receives its hydrogen by an intermolecular process.[43]

Scheme 18



Thiazoles are formed from the sulfoxide of dihydrothiazoles with acid catalysis after a Pummerer type rearrangement and water elimination.[13] If the 2-position contains an electronegative substituent, it may be difficult to effect oxidation of the dihydrothiazole to its sulfoxide without rearrangement and thiazole formation (see below).[44]

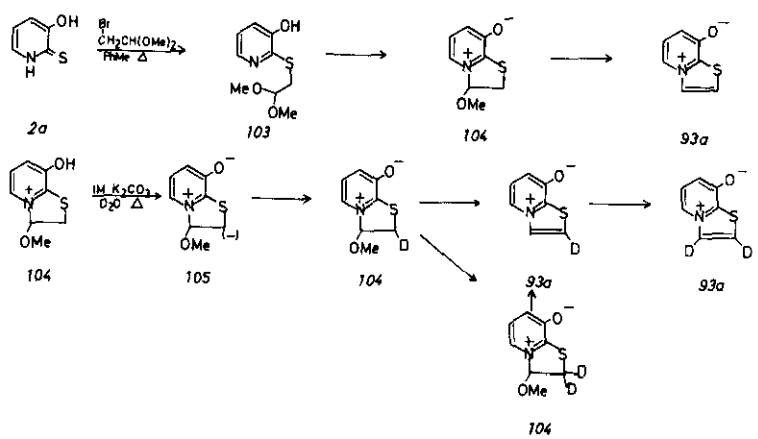
Water elimination from a 3-hydroxydihydro[1,3]thiazino[3,2-a]pyridinium-9-olate 95 in sulfuric or orthophosphoric acid has given a mixture of the 4H-thiazine 97 and the 2,5-dimethylthiazole 93c (Scheme 18). Loss of the secondary hydroxy group in 95 is facilitated by anchimeric assistance from the sulfur. The cationic intermediate can either expel a proton to yield the 4H-thiazine or rearrange to the 2-methylenedihydrothiazole 98 which subsequently suffers a prototropic shift to the thiazole.[42]

Very recently two byproducts from the thiation reaction of 3-hydroxypyridin-2-one by fusion with phosphorus pentasulfide have been identified as the ortho-fused 2,3-pyridylthiazoles 100.[45]

The most general method for the preparation of thiazolo[3,2-a]pyridinium salts consists of acid catalyzed cyclisation of 2-(2-oxoethylthio)pyridines.[5] The reaction is sensitive to steric interference from a pyridine 6-substituent. The methyl ketone 101e reacts in cold sulfuric acid whereas the 6-methyl homologue 101d requires heating; the aldehyde isomer 101b reacts in the cold. Irreversible cyclisation over the phenolic group was not observed.

The peri-interaction between the 3- and 5-substituents in the thiazole leads to disturbance of the electron cloud symmetry around the hydrogen nucleus which can be observed as deshielding effect in ^{1}H NMR. Thus, the chemical shifts for the 3,5-dimethyl protons in 93d were δ 3.1 and 3.2 (TFA), whereas the usual range is δ 2.8-2.9 in the absence of the repulsion.[5]

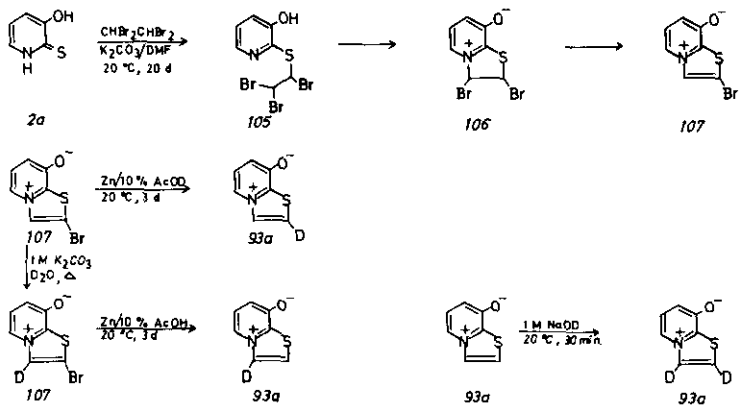
Scheme 19



When an acetal is employed instead of the oxo compounds 101 the cyclic product 104 corresponding to the adduct 102 (Scheme 18) can be isolated.[43] Thus, 3-hydroxypyridine-2-thione and bromoacetaldehyde dimethylacetal when heated together in toluene gave the 3-methoxydihydrothiazole 104. Methanol is readily eliminated by acid to the thiazole 93a. The same product was obtained on treatment of 104 with base. Normally, however, proton abstraction occurs at C3 in the dihydrothiazoles and the ring is opened to N-vinyl pyridines. Therefore a closer study of the reaction was carried out in 1 N KOD by ^{1}H NMR. Exchange of H3 in 104 was not seen during the reaction, whereas the methylene protons on C2 were gradually exchanged. The thiazole 93a was at first a mixture of the 2-deuterio and the 2,3-dideuterio derivatives, but the mixture was converted to the dideuterio derivative. The data suggest an ElcB elimination mechanism.[43]

Electrophilic and nucleophilic substitution reactions:

Scheme 20

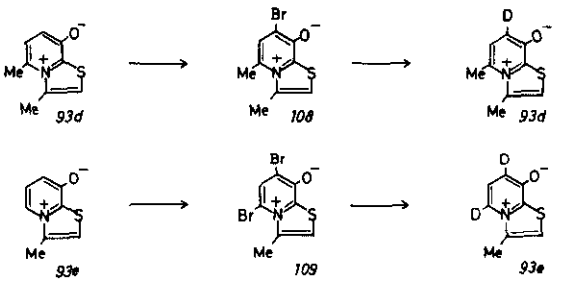


The thiazole ring in thiazolo[3,2-a]pyridinium-8-olates is not readily accessible for electrophilic substitution, whereas the pyridinium-olate moiety is highly reactive (see below). A method for the synthesis of the 2-bromo derivative 107, however, has been worked out from 1,1,2,2-tetrabromoethane (Scheme 20).[46] The reaction had to be run without heating and was slow (20 days).

Deuteriation at C2 or C3 in 93 occurs readily at similar rates by base catalysis.[5] 93a in TFA-d_1 was partly deuteriated in the pyridine ring and completely deuteriated at C2 and C3 after 5 minutes, but no significant deuteriation was seen

(^{1}H NMR) in 93a after one week in cold 10% acetic acid-$\underline{d}_1$. Hence, the bromide 107 offers a possibility for selective deuteriation in the thiazole ring. Thus, reduction of the bromide with zinc powder in 10% acetic acid-$\underline{d}_1$ gave the 2-deuterio derivative. Basically the same approach yields the 3D-isomer; the bromide was deuteriated at C3 by means of K_2CO_3 in D_2O and the bromine removed by hydrogenolysis using zinc in 10% acetic acid.[46] 2- or 3-Methyl substituted thiazoles in D_2O are also deuteriated on the unsubstituted thiazole carbon by base catalysis.[5]

Scheme 21

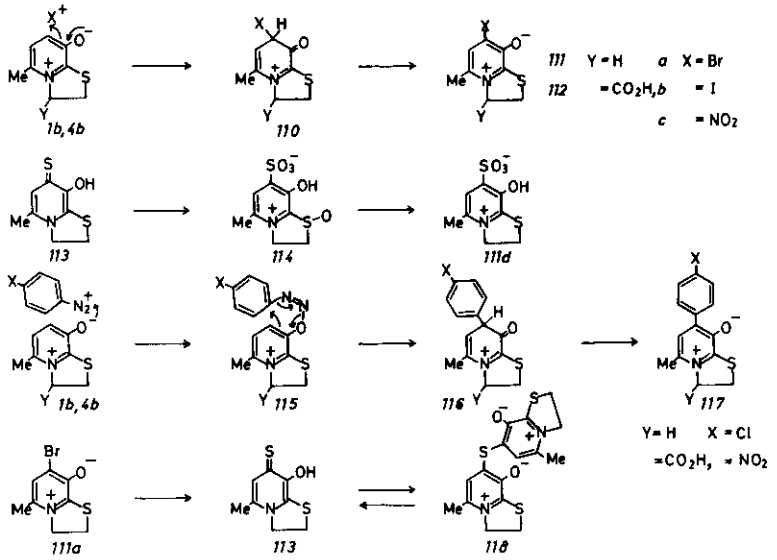


Dihydrothiazolo[3,2-a]pyridinium-8-olates readily undergo electrophilic substitution in the pyridine ring.[47,48] The thiazole analogues are similarly substituted in the pyridine ring.[5] Bromination of 5-methyl derivatives occurs exclusively in the 7-position as in the reaction of 93d to the bromide 108 (Scheme 21). In the absence of a 5-substituent bromination can occur on either C5 or C7. Regioselective substitution was not seen on simple addition of bromine to the 3-methyl derivative 93e, but the dibromide 109 was readily formed. The deuterio analogues are available by reacting the bromide with zinc in acetic acid-$\underline{d}_1$.[5]

Regioselective electrophilic substitution in the 7-position in 5-substituted dihydrothiazolo[3,2-a]pyridinium-8-olates was to be expected from activation and transition state considerations. Phenolic ortho-substitution is evident from ^{1}H NMR spectra and has been confirmed by X-ray analysis for a bromide.[35]

Bromination takes place in the presence or absence of a base (Scheme 22). Sodium iododichloride gave the iodides and nitric acid the nitrates. Direct sulfonation was not successful, but the sulfonic acid 111d was prepared indirectly by performic acid oxidation of the thiolactam 113; the initially formed sulfinyl sulfonic acid 114 was reduced to 111d by hydrogenolysis over palladium on charcoal.

Scheme 22

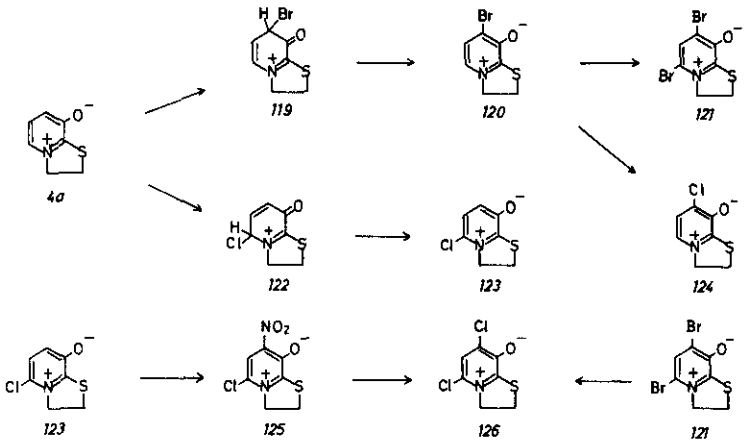


Reactions with diazonium salts resulted in arylation 117. A free radical mechanism seems excluded by the experimental conditions of the reactions. By analogy to the behaviour of aromatic diazonium salts towards nucleophiles, the first step in the reaction is formulated as covalent bond formation between the phenolate oxygen and the diazonium function, 115; subsequent pericyclic rearrangement with expulsion of nitrogen yields the observed arylated product 117.

The 7-position also corresponds to an "activated pyridine" position for nucleophilic substitution. Accordingly, thiation of the bromide 111a occurred on treatment with potassium hydrogen sulfide. Monitoring the reaction of the bromide by chromatography, showed that the dimeric sulfide 118 was present in the reaction mixture. Further reaction with potassium hydrogen sulfide, however, gave the thiolactam 113. The bromide would also react with other sulfides and no nucleophilic attack has occurred on the dihydrothiazole ring.[47]

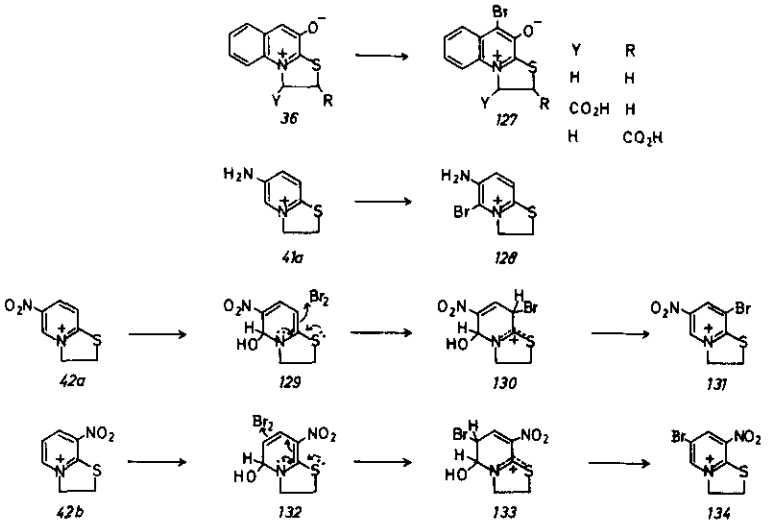
In the absence of a 5-substituent, the electrophile may enter either the 5- or the 7-position or both. Bromination at room temperature gave isomer mixtures which reacted further to the dibromide 121 (Scheme 23). Bromination in methanol at -70 °C, however, gave selectively the 7-bromide 120. On the other hand, sulfuryl chloride in dimethylformamide (DMF) at -40 °C gave the 5-chloride 123. The 7-chloro

Scheme 23



isomer 124 is available from the 7-bromide by nucleophilic substitution using sodium chloride in DMF; similarly the 5,7-dichloride could be obtained from the dibromide 121 by the sodium chloride reaction. The dichloride was also obtained from the 5-chloro-7-nitro derivative 125 by its reaction with zinc chloride in HCl. The 7-nitro derivative 125 was prepared by nitration of the 5-chloride.[48]

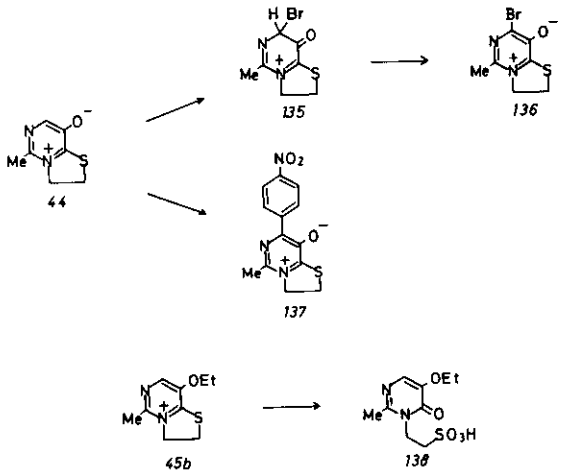
Scheme 24



The ease of electrophilic substitution in pyridinium-olate systems is further demonstrated for the quinoline analogues which were selectively brominated in the pyridine ring at C9 127 (Scheme 24).[21]

Amino substituents may also activate the pyridinium nucleus for electrophilic substitution. Thus, bromination of the 6-amino derivative 41a gave selective substitution in the 5-position 128.[33]

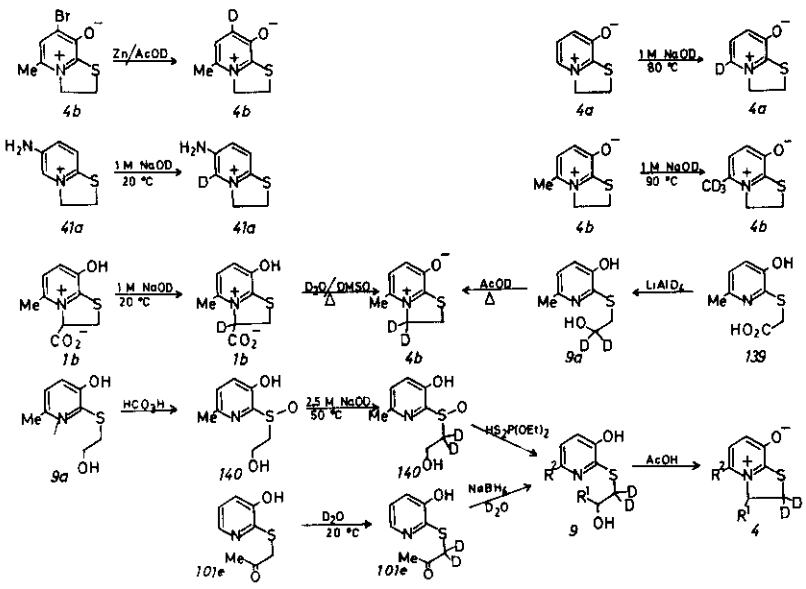
The dihydrothiazolo[3,2-a]pyridinium cation was unreactive towards electrophiles under the normal reaction conditions. The nitro substituted derivatives 42, however, are readily brominated in aqueous methanol. This observation is rationalised in terms of pseudo-base formation of the highly electron deficient nitropyridinium system. The pseudo-base formation occurs preferentially in the available α-position to the heteroatom, 129 and 132. The pseudo-bases can be regarded both as N-vinyl and S-vinyl derivatives and as such are activated for electrophilic substitution in the 8- or 6-position, respectively.[22]



Scheme 25

Bromination of the pyrimidinium-8-olate 44 also occurs readily to the 7-bromide 136. With p-nitrophenyldiazonium salts direct arylation occurs as in the pyridine analogues. In the ethoxy derivative 45b, which lacks the phenolate activation of the pyrimidine ring, the reaction instead occurs on the sulfur with oxidative ring-opening to the sulfonic acid 138; bromination of the 5-methyl substituent may also occur.[24]

Scheme 26

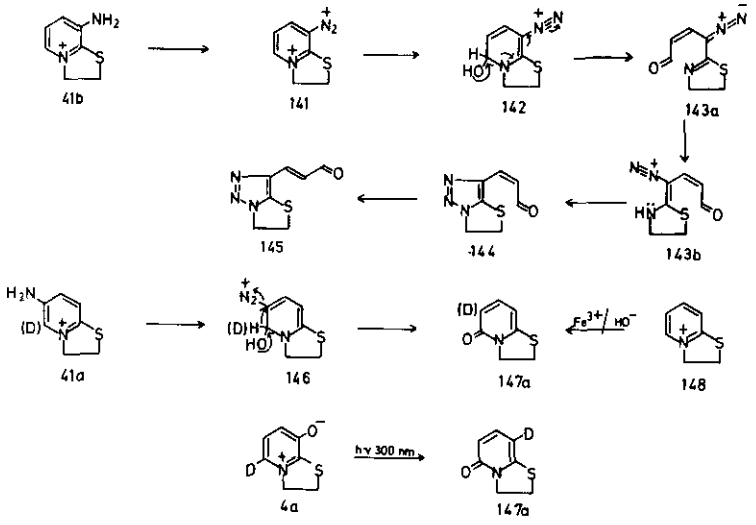


A number of deuteriated pyridinium-olates have been prepared (Scheme 26). Deuteriation in positions activated for electrophilic substitution is conveniently carried out by bromination and subsequent treatment with zinc in acetic acid-$\underline{d}_1$.[49] The 5-position has the lowest electron density and can be selectively deuteriated by hydrogen-deuterium exchange under basic conditions; the detailed conditions depend on the reactant molecule.[23] Similarly the 5-methyl substituent can be selectively labelled in NaOD.[49] H3 in the 3-carboxylate is readily exchanged in NaOD. Depending on the conditions for the decarboxylation, the 3-deuterio or the 3,3-dideuterio derivatives are obtained.[49] The latter are also available by cyclisation in acetic acid-$\underline{d}_1$ of the dideuterio alcohol from lithium aluminium deuteride reduction of the 2-(2-pyridylthio)acetate 139.

The C2 protons in the dihydrothiazole are not readily exchangeable. Labelling at C2 has therefore been achieved by deuterium insertion before ring formation. Thus the sulfide 9a was activated for deuteriation of the adjacent methylene group by sulfoxide formation 140, selectively deuteriated in NaOD, reduced back to sulfide again by means of dithiophosphoric acid O,O-diethyl ester and the sulfide cyclised in acetic acid.[50] In a slightly different approach the acetonyl derivative 101e was selectively deuteriated on the methylene carbon in D_2O and the

reduction with sodium borohydride carried out in D_2O in order to avoid deuterium exchange reactions.[50]

Scheme 27



A more electron deficient pyridine system than in the 6-and 8-nitrodihydrothiazolo[3,2-a]pyridinium derivatives, is available in the corresponding diazonium derivatives (Scheme 27). The latter were prepared from the respective amines, but underwent transformations as soon as they were formed. Diazotisation of the 8-amino isomer 41b yielded the 3-(dihydrothiazolo[3,2-e]y-triazol-7-yl)propenals; the crude product was an almost equimolar mixture of the cis- and trans-isomers which was converted to the trans-isomer 145 by acid catalysis.[22] The X-ray data of the latter show planar trans-configuration of the propenal side-chain. The atoms of the triazole ring are coplanar and the dihydrothiazole ring has an envelope conformation, C2 being 0.4 Å out of plane.[51]

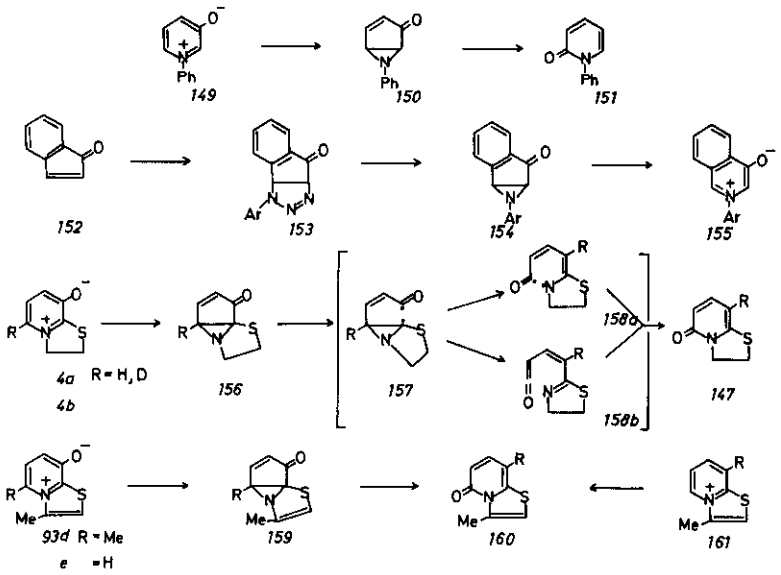
The reaction mechanism is rationalised by pseudo-base formation whereby a hydroxy group is introduced to the α-position of the heteroatom. The pyridine ring is subsequently opened for recyclisation over the diazonium group.

Pseudo-base formation in the 8-diazonio isomer 141 occurs in the para-position to the diazonium group. In the 6-isomer the para-position is occupied by the sulfur substituent and the reaction takes a different course; the amino group is lost and an oxygen function is introduced at the 5-position.[23] The pyridone structure 147a was verified by comparison with the product from alkaline potassium

hexacyanoferrate(III) oxidation of the cation 148.[23] The course of the reaction can be rationalised by initial pseudo-base formation and subsequent hydride shift to replace the diazonium function. The mechanism is supported by isotope labelling. The label from 5-deuteriated 41a was retained in the final product 147a. The coupling constant in NMR, J 7.5 Hz, is consistent with vicinal β,γ-pyridine protons. The 8-deuterio isomer, which could possibly satisfy the NMR requirements, has been prepared by photolysis of 5-deuteriodihydrothiazolo[3,2-a]pyridinium-8-olate (see below); the ^{1}H NMR data differ slightly.[23]

Photolysis:

Scheme 28



The possibility of valence isomerism for the thiazolo- and dihydrothiazolo-pyridinium-8-olates has been studied by photolysis (Scheme 28). Because of the low stability expected for the valence isomer 156 the initial work was done on simpler pyridinium-olate systems. It had been reported that one of the products from the irradiation at 350 nm of N-phenylpyridinium-3-olate 149 was its valence isomer 6-phenyl-6-azabicyclo[3,1,0]hex-3-en-2-one 150.[52] With our medium pressure Hg lamp, however, the reaction proceeded further to the N-vinylpyridin-2-one 151.[53] The valence isomerism is reversible. Thus, irradiation of 1-aryl-1a,6a-dihydro-indeno[1,2-b]arizin-6(1H)-ones 154 at ca. 255 nm gave the coloured ylides which quickly reverted to 154, but could be trapped as acid salt in which case the

isoquinolinium-4-olates 155 were obtained. The former was prepared from inden-1-one by regioselective adduct formation with phenyl azides and subsequent photolysis of the adducts using a 300 w lamp.[54]

Irradiation of 5-methyldihydrothiazolo[3,2-a]pyridinium-8-olate 4b at 350 nm produced its labile valence isomer 6-methyl-2-thia-5-azatricyclo[4.3.0.0.^{1,5}]non-7-en-9-one 156.[55] When the pyridinium-olates 4 were irradiated with the medium pressure Hg lamp the rearranged dihydrothiazolo[3,2-a]pyridine-5-one 147 was formed. Irradiation of the valence isomer 156b with the same lamp also gave the rearranged product 147b; the structure assigned to the product has been verified by X-ray analysis.[56]

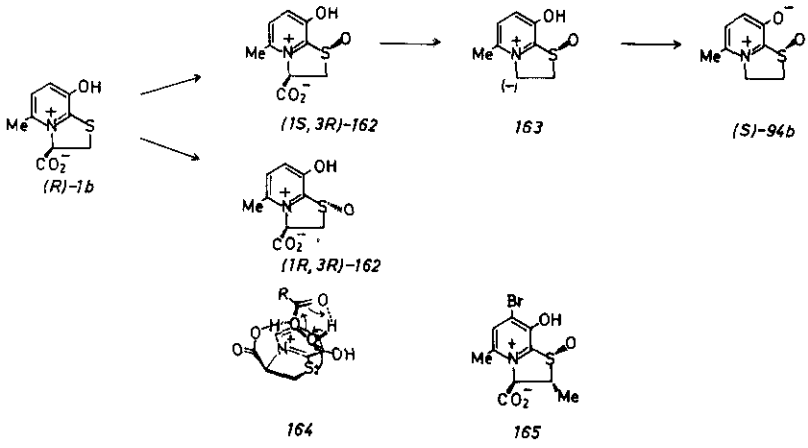
Formation of the photolabile valence isomer 156 corresponds to a photochemically allowed disrotatory ring closure in analogy to the formation of 150 from 149 as well as to the photochemically reversible isomerism between dihydroindeno-[1,2-b]azirin-6(1H)-ones 154 and the isoquinolinium isomers 155.

A comparison of the isomer pairs for 4 and 147 shows that the net effect of the photolytic transformation corresponds to an interchange of the 5- and 8-substituents. This can be rationalised by ring-opening of the valence isomer and recyclisation in a different manner. The species undergoing recyclisation may either be drawn as a biradical or perhaps better as a keten 158.

The rearrangement on irradiation of the thiazolo[3,2-a]pyridinium-8-olates 93, irrespective of the irradiation source at ca. 350 nm, proceeded right through to the lactams 160. In the case of 160e the assigned structure was verified by comparison with the product from the alkaline potassium hexacyanoferrate(III) oxidation of the corresponding cation 161.[55]

Sulfoxidation:

Peracid oxidation of dihydrothiazolo[3,2-a]pyridinium-8-olates yields sulfoxides.[2,44,57-59] Oxidation of the 3-carboxy derivative 1b gave the sulfoxide diastereoisomers in the ratio 9:1 (Scheme 29).[2] The reaction is conveniently run at room temperature in formic or trifluoroacetic acid by addition of 35% H_2O_2. In methanesulfonic acid the reaction is fast, in acetic acid very slow. Oxidation of the 2-methyl homologue of 1b is even more stereoselective. The stereochemical findings and the ^{1}H NMR data led to assignment of the 1,3-cis configuration to the major diastereoisomer.[57] The assigned stereochemistry has been confirmed by X-ray



Scheme 29

analysis of the sulfinyl bromide 165 which is formed almost exclusively in the oxidation of trans-2,5-dimethyl-7-bromo-8-hydroxydihydrothiazolo[3,2-a]pyridinium-3-carboxylate.[35,58]

Preferential formation of the cis-product implies that the 3-carboxy group participates in the reaction. If the peracid becomes associated with the 3-carboxy group through hydrogen bonding or other attractive forces (164), the peracid is correctly placed for cis-oxidation. The same steric effect results from initial formation of a mixed peracid anhydride; in methanesulfonic acid the sulfoxide formation may be preceeded by oxidation of the 3-carboxy group.

The stereoselectivity in the sulfoxidations can be used to prepare optically active sulfoxides.[57] Thus, performic acid oxidation of (R)-1b gave mainly the isomer (1S,3R)-162; the minor isomer (1R,3R)-162 was removed by crystallisation. When the major isomer was heated at 60 °C in acetic acid it was rapidly decarboxylated to the sulfinyl enantiomer (S)-94b ($[\alpha]_D$ +260° (perchloric acid salt in H_2O)). The dichroic absorption curves for (S)-94b have positive maxima at 229 and 355 nm in alkaline solution and at 223 and 315 nm in acid solution, whereas the sign of an intermediate band is pH dependent (Fig. 4).[60]

Kinetic studies of the oxidation by means of ^{1}H NMR (Table 1) show the highest rate for the 3-carboxy derivative 1b in agreement with anchimeric assistance from the carboxy group.[59] The rates for the 2-carboxy derivatives are considerably lower. The quinoline analogue 63a is much less reactive than 1b. In the amide and

the 2-carboxy derivatives the diastereoisomer ratios were close to unity. In the 2,3-dicarboxy derivative 80b, however, only one stereoisomer was seen, probably the 1,3-cis-isomer 168. When 35% H_2O_2 in formic acid is used in the oxidation of 33 and 80b mainly the thiazole 93f is obtained.[44] The reactions go over the respective sulfoxides since addition of a little water to these sulfoxides in the 85% H_2O_2-formic acid mixture resulted in formation of the thiazoles 93f.[59] Apparently the electron withdrawing 2-carboxy group under the acid conditions of the reaction promotes a Pummerer type rearrangement to form the hemimercaptal 167 which may dissociate to the minor product 169 or loose water to the major thiazole product.[44] In the 2-carboxyguinoline analogue 36b the sulfoxide is oxidatively ring-opened to

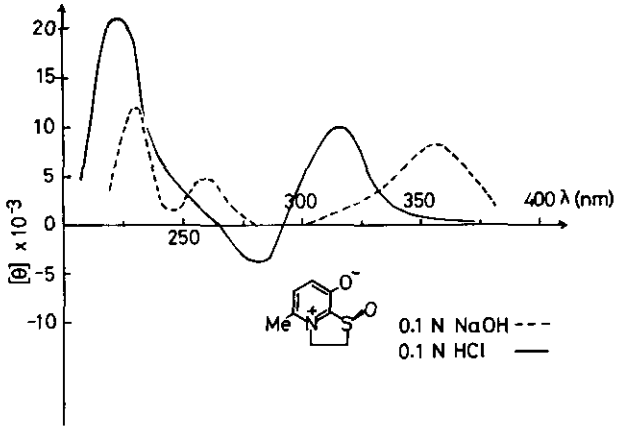
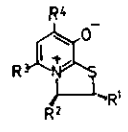


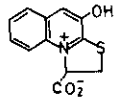
Fig. 4.

CD curves: (1S)-1-*Oxo*-5-*methyldihydro*-thiazolo[3,2-a]pyridinium-8-olate in 0.1 N NaOH --- and in 0.1 N HCl ——.[60]

Table 1. Reaction time by ^1H NMR for 80% oxidation with 85% H_2O_2 in formic acid at 4.5 °C.[59]



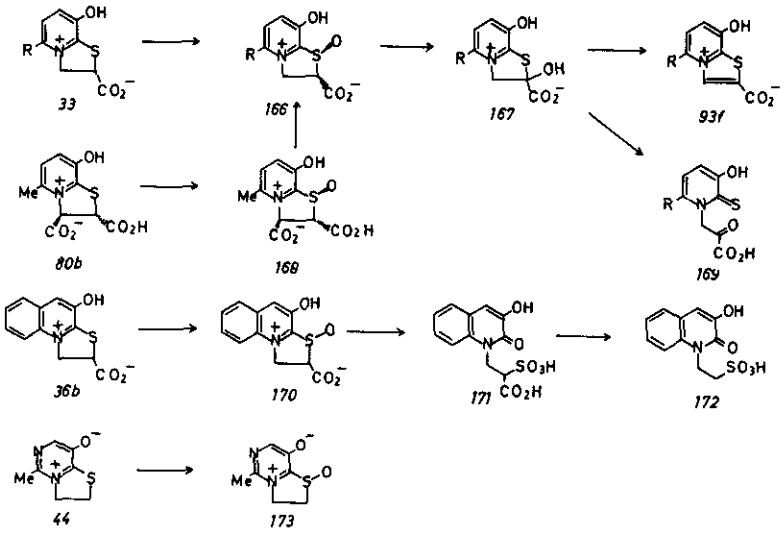
	R^1	R^2	R^3	R^4	Time, min.
1b	H	CO_2H	Me	H	10
56a	H	$CONH_2$	Me	H	14
4b	H	H	Me	H	12
112a	Me	CO_2H	Me	Br	23
80b	CO_2H	CO_2H	Me	H	75
33b	CO_2H	H	Me	H	30
33a	CO_2H	H	H	H	100



70

63a

Scheme 30

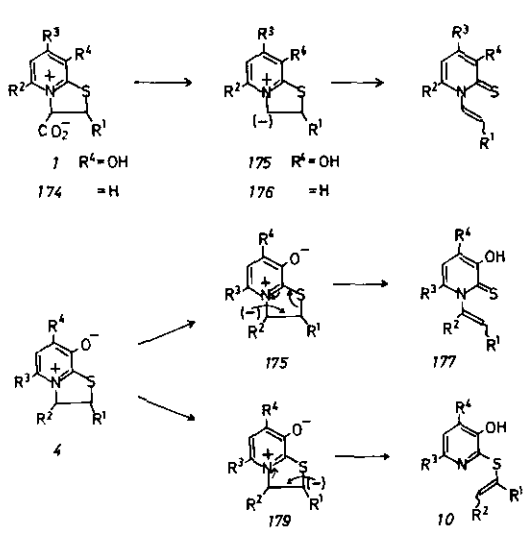


the quinolin-2-one 171.[59] This reaction has many analogies in the oxidative removal of thio-groups and insertion of hydroxy groups in electron deficient systems. Low electron density on the sulfur is also reflected in a heterogenous reaction product in the slow oxidation of the pyrimidine analogue 44 to its sulfoxide 173.[24]

Vinylation reactions:

Dihydrothiazolo[3,2-a]pyridinium-3-carboxylates are readily decarboxylated because of the geminal positively charged nitrogen in the pyridine ring. The course of the reaction after expulsion of carbon dioxide depends on the experimental conditions (Scheme 31). Pyrolytic decarboxylation in the mass spectrometer gives the corresponding N-vinylpyridine-2-thiones 177,178.[49,61,62] Preparative decarboxylative ring-opening is reached by heating a mixture of the acid in quartz sand at 150-180 °C at reduced pressure, and the product is collected after sublimation.[63] In protic media the intermediate carbanion is protonated. In the pyrolytic decarboxylation of 8-hydroxy derivatives the N-vinyl product may contain some of the betaine isomer 4, especially in the reactants with a bulky 5-substituent.[63]

The protons at both C2 and C3 in the dihydrothiazolo[3,2-a]pyridinium deriva-



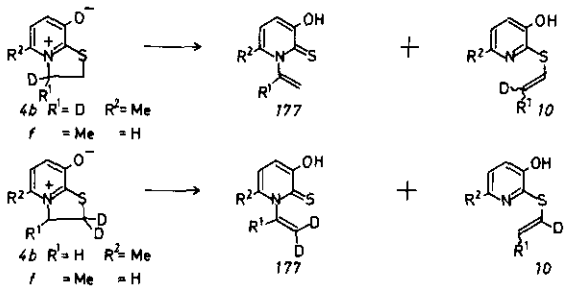
Scheme 31

tives are activated by the positively charged or partly charged adjacent heteroatoms. ^{1}H and ^{13}C NMR show that the C3 protons are the more acidic; this may, however, be changed on substitution.

Deprotonation of the betaines can be carried out preparatively in solid potassium carbonate with sublimation of the vinyl products from the reaction mixture.[64] A more convenient method, however, is the use of potassium tert-butoxide in solution.[50] Opening of the dihydrothiazole ring by nucleophilic substitution was not seen. Product analyses by ^{1}H NMR and GLC (Scheme 31) showed 98% relative yield of the N-vinyl isomer from the parent betaine 4a. In the 2-methyl-derivative 4e only the N-vinyl isomer was seen. From the 3-methyl derivative 4f, however, the S-vinyl isomer was the more important. The course of the reaction is sensitive to steric interaction from the 5-substituent; increasing bulkiness of the 5-substituent increases the relative yield of the S-vinyl isomer.

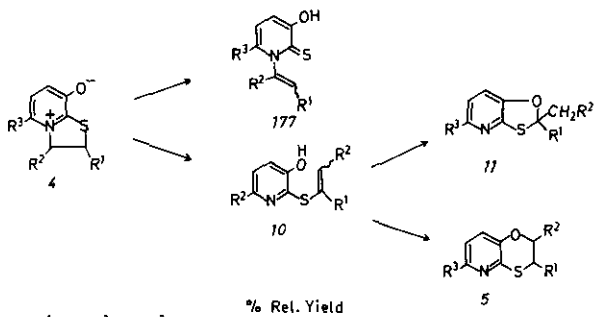
Deuterium labelling experiments support the formation of intermediate carbanion at C2 or C3 as the major route in the formation of S- or N-vinyl isomers respectively (Scheme 32). Ring-opening of the 3,3-dideuterio derivative of 4b gave only 30% retention of the deuterium label in the N-vinyl product. The N-vinyl isomer from the 3-deuteriated 3-methyl derivative contained no deuterium label,

Scheme 32



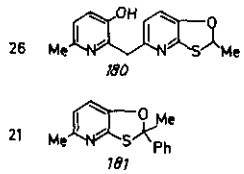
wheras ca. 30% of the deuterium label was retained in the S-vinyl isomer. There was no sign in any of the products of 1,2-deuterium shifts. The extensive loss of the deuterium label from the 3-deuteriated compounds can be attributed to a faster protonation than ring-opening of an intermediate carbanion on C3. In the N-vinyl derivatives from the 2,2-dideuterio analogues no significant loss of deuterium was seen. The S-vinyl isomer from the 3-methyl derivative was monodeuteriated. There was a noticeable isotope effect in the ring-opening reactions in that the N- ; S-vinyl isomer ratios were decreased slightly on deuteriation at C3 and increased slightly on deuteriation at C2. The labelling experiments exclude an initial carbanion at either C2 or C3, respectively as a common source for both the N- and S-vinyl isomers and is in accordance with the postulated mechanism (Scheme 32).[50]

Pyrolysis in the gas phase give other products in addition to the N- and S-vinyl derivatives.[13,65] 5-Methyldihydrothiazolo[3,2-a]pyridinium-8-olate is sublimed structurally unchanged at 230 °C/0.01 mmHg. When the betaine vapour molecules, however, are passed through a narrow quartz tube enclosed by an oven at 400 °C isomerisation reactions occur. The products are the N- and S-vinyl isomers as well as the oxathiole 11 and the dihydrooxathiene 5 isomers. The product compositions depend on the nature and positions of the substituents (Scheme 33). All four isomers are formed from the parent betaine 4a. The 2-methyl derivative 4e gave almost entirely the N-vinyl isomer, and the 3-phenyl-5-methyl isomer gave similar amounts of the vinyl isomers. Another product, obtained in 20% relative yield in the latter case, has been identified as the 2-methyl-2-phenyloxathiole 181; its generation requires an additional phenonium type rearrangement. The



Scheme 33

	R¹	R²	R³	% Rel. Yield 177	10	11	5
a	H	H	H	96	1	2	1
b	H	H	Me	23	18	29	4
e	Me	H	H	99		1	
f	H	Me	H	77	18	4	
h	H	Ph	Me	10	59	10	



26

21

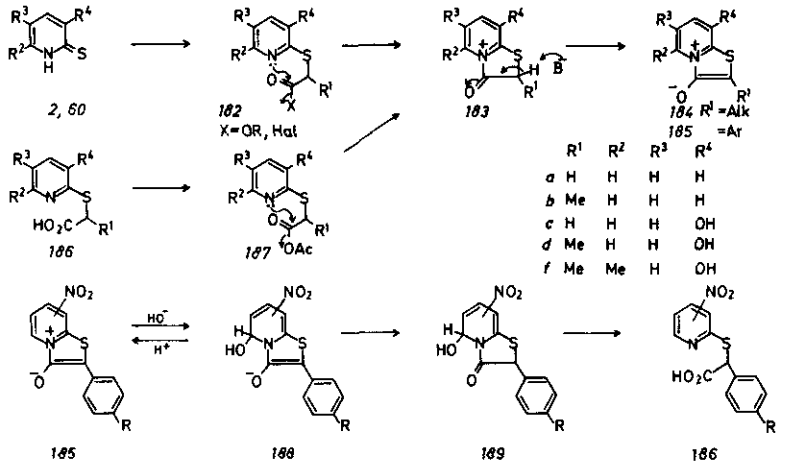
5-methyl *isomer* 4b yielded an additional dimeric condensation product 180 presumably through the reactivity of the activated methyl group.

The generation of the bicyclic products is ascribed to cyclisation reactions of their S-vinyl isomers. Separate experiments with S- and N-vinyl *isomers confirmed* cyclisation of *the former and no* reaction of the latter. It would appear that S-vinylation is more favourable at high temperature pyrolysis than in the base catalyzed vinylation reactions from dihydrothiazoles (see above).

Thiazolo[3,2-a]pyridinium-3-olates:

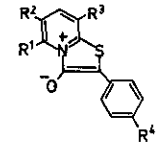
The labile thiazolo[3,2-a]pyridinium-3-olate system is isomeric with the thiazolo[3,2-a]pyridinium-8-olate system. Before our investigation was started the unsubstituted compound 184a had been synthesized from pyridine-2-thione and α-bromoacetyl bromide and by cyclisation of 2-(2-pyridylthio)acetic acid *in* acetic anhydride.[66] The former reaction requires that the sulfur nucleophile attacks preferentially, or at least irreversibly, the sp^3-hybridized bromine substituted carbon. Related is the discovery that when a pyridine-2-thione is heated with an α-halo acid or ester in the absence of base, the acid liberated from the S-alkylation catalyzes cyclisation to the thiazole 184,185 (*Scheme* 34).[67] The most convenient method for preparing the thiazoles, however, were found to be cyclisation

Scheme 34

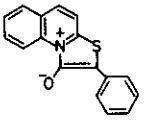


	R^1	R^2	R^3	R^4
a	H	H	H	H
b	Me	H	H	H
c	H	H	H	OH
d	Me	H	H	OH
f	Me	Me	H	OH

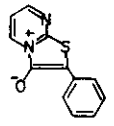
Table 2. Rate constants for the hydrolysis at 20 °C in 0.1 N HCl and in 0.1 N NaOH (dioxan: water=1:1) measured by the change in light absorption at the highest wavelength absorption maxima.[68]



		R^1	R^2	R^3	R^4	0.1 M HCl $k \times 10^4 sec^{-1}$	0.1 M NaOH $k \times 10^4 sec^{-1}$
185	*a*	H	H	H	H	2.03	
	b	H	H	NO_2	H	0.24	1.54
	c	H	NO_2	H	H	0.15	0.17
	d	H	H	Me	H	1.93	
	e	H	H	OAc	H	1.50	
	f	H	H	H	OMe	7.97	
	g	H	H	H	NO_2	0.15	0.26
	h	Me	H	H	H	88.85	
	i	Me	H	OEt	H	41.45	
	j	Me	H	OAc	H	46.20	
	k	Me	H	H	NO_2	2.41	



190 3.50

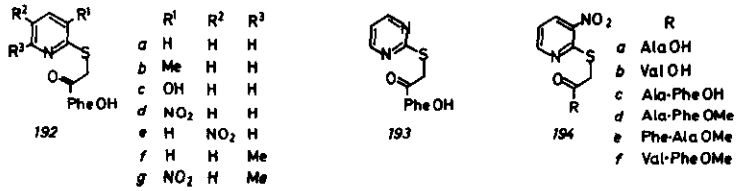


191 0.83 25.67

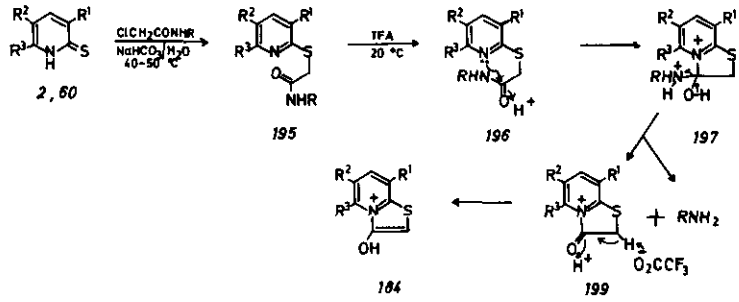
of (pyridylthio)acetic acids in acetic anhydride and pyridine. Without base catalysis the reaction is slow, which suggests a mixed anhydride intermediate; 3-hydroxypyridines are concurrently acetylated to the 8-acetoxy derivatives. Mixed

anhydride formation with ethyl chloroformate in pyridine and the related carboxyl activation by dicyclohexylcarbodiimide in pyridine also gave the cyclic product.[68] The cyclisation reaction, and the stability of the thiazole are adversely affected by a pyridine 6-substituent. The initially formed acylpyridinium salt is highly reactive but is tautomerized into the aromatically stabilized thiazole. The 2-alkylthiazoles 184, however, are rapidly hydrolyzed in aqueous media. 2-Aryl derivatives 185 are less reactive because of the additional resonance stabilisation from the aryl substituent. Kinetic studies of their solvolysis in acid solution showed first order kinetics (Table 2). The 3,5-peri-interaction in the 5-methyl derivatives accelerates the hydrolysis (185h-k). Electron donating substituents in the pyridine or phenyl ring also increase the rate. The rate is further increased with increase in acid strength. In alkaline solution the betaines are relatively resistant to hydrolysis except for the nitro derivatives; the quinoline and pyrimidine analogues are also reactive.

Compunds of this class are coloured; long-wave UV maxima were in the range 400-450 nm depending on substituents except for the nitro derivatives which in alkaline solution absorb in the 500 nm region. This finding for the nitro compounds can be explained by pseudo-base formation in alkaline solution.[68]



Scheme 35



In the presence of amines the thiazolo[3,2-a]pyridinium-3-olates undergo aminolysis. In TFA the amino adducts can be cleaved back to the original reactants.[67] This observation has been developed into a method for selective cleavage of a halogenoacetyl function, e.g. in the removal of the N-chloroacetyl group which is used as protecting group in peptide synthesis.[69] Thus the chloroacetamide and the pyridine-2-thione are initially reacted together in aqueous sodium hydrogen carbonate; the product in cold TFA undergoes cyclisation with concomitant liberation of the amine without significant racemisation (Scheme 35).

Rate studies of the cyclisation of N-(2-pyridylthio)acetyl derivatives of phenylalanine in TFA at 20 °C show that in the unsubstituted derivative 192a an equilibrium is reached between the amide and the thiazole. In the 3-hydroxy or 3-methyl pyridines the reaction was complete after 6 and 10 h respectively. For the 3-nitro derivative the reaction time was 2.5 h whereas the 5-nitro isomer did not react nor did the pyrimidine analogue 193 react. The major effect of the 3-substituent is therefore not electronic but rather steric in nature. Presumably the coplanar 3-nitro group will favour conformations of the side-chain in which the carbonyl group is close to the nitrogen. The rates for cyclisation of the valine, phenylalanine and alanine (3-nitropyridylthio)acetyl derivatives 194 and 192d increased in this order reflecting steric interaction from the α-carbon of the amino acid. The alanylphenylalanine dipeptide 194c was deacylated at about the same rate as the alanine derivative 194a. The esters behaved in the same way.

Physicochemical properties of thiazolo- and dihydrothiazolo[3,2-a]pyridinium derivatives:

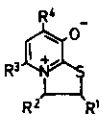
X-ray analyses show that the pyridinium ring in dihydrothiazolo[3,2-a]pyridinium derivatives is planar.[35-37] The five-membered ring has the envelope conformation with S1 and C3 coplanar (within 0.05 Å) with the pyridine ring; C2 is 0.57 and 0.60 Å out of the plane in 1-methyl-4-ethoxy-5a,6,7,8,9,9a-hexahydro-9-oxopyrido[2,1-b]benzothiazolium bromide 71d (Scheme 13) and in trans-2-carboxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate 80 (Scheme 15) respectively.[36,37] The angle between the 2,3-dicarboxy substituents in 80 is 160° corresponding to a torsion angle ca. 80° for H2-H3;[36] this explains the weak ^{1}H NMR coupling (0-Hz) generally observed in trans-2,3-disubstituted derivatives.

The cyclohexanone ring in the 2,3-cis derivative 71d has the chair confor-

mation.[37] The H2-H3 torsion angle is 41±3° which is to be compared with the vicinal proton coupling J 7.0 Hz (TFA).

In the crystals the 2,3-carboxyacid 80 exists as infinite chains by hydrogen-bonding between the 2- and 3-carboxy groups in neighbouring molecules.[36] The hydrogen is closer to the oxygen in the 2-carboxy group which therefore is the weaker acid group as would be expected from electronic considerations. The dihydrothiazolo[3,2-a]pyridinium-8-olates are strongly blue fluorescent under UV light. The long wavelength UV maxima in acid solution are in the range 330-340 nm, and there is a phenolate shift to ca. 350-360 nm in alkaline solution;[3] sulfoxidation gives hypsochromic shifts.[2] The pyrimidine analogues have similar absorptions.[24] The thiazolo[3,2-a]pyridinium-8-olates are slightly yellow but have their strong long wavelength absorption maxima in the same regions as the dihydrothiazoles.[5]

Table 3. Ionization constants from potentiometric titrations in water at 20 °C.[70]

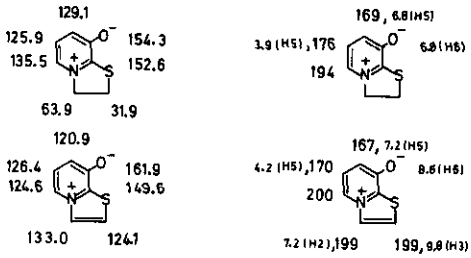


	R^1	R^2	R^3	R^4	pK_a2 ±0.02	pK_a1
4b	H	H	Me	H	4.70	
1a	H	CO_2H	H	H	4.47	1.2
1b	H	CO_2H	Me	H	4.97	1.5
33b	CO_2H	H	Me	H	4.96	2.0

The acid dissociation constants have been determined for some of the dihydrothiazoles (Table 3).[70] The pK_a values for the 3-hydroxy group in the monocyclic α-pyridino acids 18 (Scheme 4) are in the region 5.15-5.30,[70] whereas the value 4.96 has been reported for N-methylpyridinium-3-olate.[71] Similarly the pK_a 4.70 for 4b is increased to 4.97 in its 3-carboxy derivative 1b. The acid weakening effect of the carboxy group, as carboxylate, is almost the same in either the 2- or 3-position. In the 7-bromide of 1b pK_a2 is reduced to 2.85. The pK_a for the carboxy group, in the range 1.2-2.0, was not accurately determined.

Gated-(1) decouplings have been used in the interpretation and assignments of the chemical shifts in ^{13}C NMR spectra. Data for the parent betaines in the thiazole and dihydrothiazole series are given in Table 4.[46,72] The one-bond carbon-hydrogen coupling $^1J_{CH}$ is highest for the α-position in pyridines, especially on quaternisation; this corresponds to the 5-position. It is otherwise noticeable

Table 4. ^{13}C NMR data in D_2O by Gated-(1) decouplings of the parent thiazolo- and dihydrothiazolo[3,2-a] pyridinium-8-olate systems.[46,72]



that $^1J_{CH}$ for both C2 and C3 in the thiazole are of the same size which may indicate that the positive charge is shared almost equally between the two heteroatoms.

As part of our studies of organic salts on mass spectrometry the betaines 4 and 93 and their isomers have been extensively investigated.[73] Internal salts may display a molecular ion of an ambiguous structure which is isobaric with the betaine. We have found that appearance (AP) and ionisation potentials (IP) give useful information about the nature of closely related gaseous species.[74] In principle a number of uncharged isomers could be used to explain the relatively high volatility of the betaine 4b (Scheme 36). From fragmentation studies alone these species cannot be differentiated but differentiations are possible by comparative studies of fragmentation characteristics and AP/IP values.[13,49,62] Gaseous molecules with internal charge separation have been shown to be characterized by low IP's.[73] Thus the gaseous species from the betaines as a group differ from the isobaric uncharged molecules by low IP's (Scheme 36). Direct evaporation of the betaines is therefore concluded, and this is further supported by the fragmentation characteristics.[13,49] (Table 5). Thus the betaine has the molecular ion as base peak whereas the N- and S-vinyl isomers as a group are characterized by expulsion of a substituent from the β-vinyl carbon to form the base peak; the fragmentation is rationalised by formation of a thiazolo[3,2-a] pyridinium ion (Scheme 37) with little tendency for further fragmentation.[61,62] The betaine fragments similarly to the dihydrooxathiene and even more closely to its valence isomer but differs from these by ca. 1 eV in the ease of ionisation.

The low AP/IP's (ca. 7 eV) for the gaseous species from the thiazole betaines 93 are also consistent with direct evaporation.[55,75]

Scheme 36

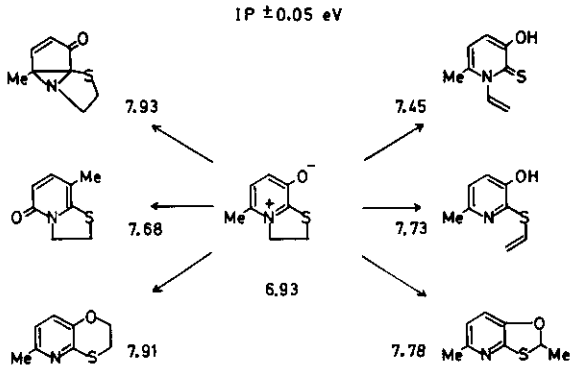
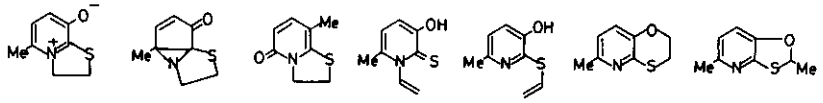


Table 5. Fragmentations and % relative intensities on electron impact (70 eV) mass spectrometry.[13]

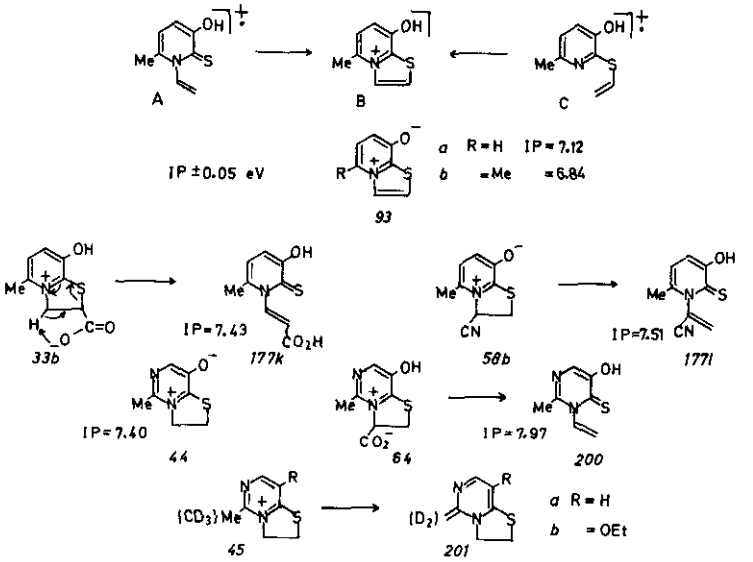


	FRAGMENTATION (% REL. INT.)						
M-	100	100	100	59	42	100	100
H	16	40	45	100	100	10	49
Me		2	1	2	5	3	86
C_2H_2	2	6	3	11	7	3	3
CO	9 (1:1)	24	41		1	7 (1:4)	
C_2H_4	9		3			26	
HCO	9	20	45	2	3	3	3
C_2H_4S		8	12				

3-Carboxydihydrothiazolo derivatives are decarboxylated in the mass spectrometer to form N-vinyl pyridines which are the volatile species.[49,62] The AP value 7.43 eV for the 2-carboxy isomer and its fragmentation are consistent with N-vinylation before evaporation; the carboxylate group acts as an internal base for proton abstraction at C3.[49,62] The data for the 3-cyano derivative 58b are also consistent with N-vinylation, presumably caused by the high acidity of H3.[49,62]

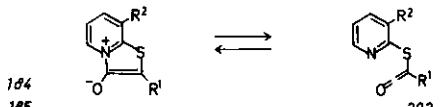
Basically the same problem exists in the volatilisation reactions of dihydrothiazolo[3,2-c]pyrimidinium salts. Both the AP/IP data and the fragmentation

Scheme 37



characteristics are in accordance with decarboxylative N-vinylation from the 3-carboxy derivative 64 and with direct evaporation of the betaine 44.[25,76] The gaseous species from the cations 45 are the corresponding anhydro-bases; this has been confirmed by isotope labelling. In the 8-ethoxy derivative 45b, however, competition exists between dealkylation to the betaine and anhydro-base formation.[76]

Several groups of mesoionic compounds have been studied by mass spectrometry and fragmentations have been explained from either the mesoionic form or from the uncharged valence isomer without knowledge about the nature of the gaseous species. We have shown, by means of AP data, however, that the sydnones are present in the gas phase predominantly as their valence isomeric N-nitroso ketenes.[77] Other mesoions may behave differently. Thus the AP's for the thiazolo[3,2-a]pyridinium-3-olates fall into two groups (Scheme 38).[78] In the absence of the 8-hydroxy group the AP's are very low, less than 7 eV. These compounds are therefore present predominantly as mesoions in the gas phase. In the 8-hydroxy series the AP's are more than 1 eV higher and these are therefore present in the gas phase in an uncharged state. Presumably the ketene is generated in the solid sample on heating and is subsequently cyclised to the mesoion except for the hydroxy derivatives

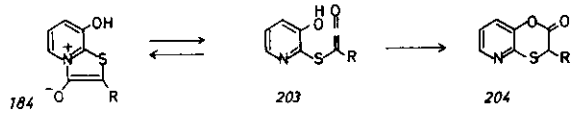


184
185

202

R^1	R^2	AP/IP ± 0.05 eV
H	H	6.92
Me	H	6.82
Ph	H	6.70
Ph	OAc	6.27

Scheme 38



184
185

203

204

R	AP/IP ± 0.05 eV
H	8.70
Me	8.60
Ph	8.42

where the reactive ketene group is trapped by δ-lactone formation.

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