

## N-Quaternary Compounds

### Part IV. Stereoselective Sulphoxide Formation

KJELL UNDHEIM

*Chemical Institute, University of Oslo, Oslo 3, Norway*

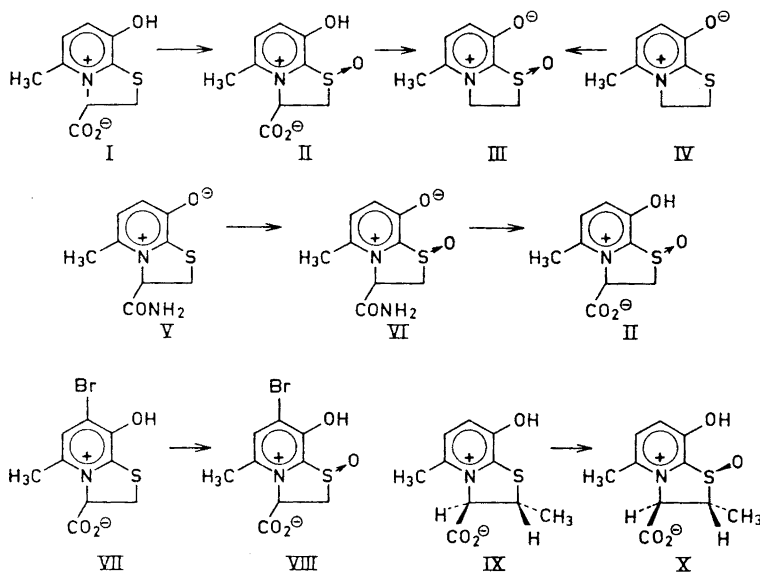
VEGARD NORDAL

*Research Division, Nyegaard & Co. A/S, Oslo, Norway*

Peracid oxidation of L-(-)-8-hydroxy-5-methyldihydrothiazolo [3,2-a]pyridinium-3-carboxylate leads mainly to the *cis* sulphoxide. The assignment of the sulphoxide configuration is based on chemical evidence and on NMR data. Decarboxylation under mild conditions removes the original asymmetric center and gives a strongly dextrorotatory sulphoxide enantiomer assigned the (*S*)-configuration.

Optically active sulphoxides can be made by the technique developed by Anderson<sup>1</sup> in which a Grignard reagent reacts with a diastereomeric sulphinate ester according to an S<sub>N</sub>2 mechanism with inversion of the configuration taking place at the sulphur. This method is widely used.<sup>2</sup> Recently, Cope<sup>3</sup> has reported that racemic sulphoxides can be resolved *via* a platinum complex containing optically active  $\alpha$ -methylbenzylamine. Alternatively, racemic sulphoxides containing a suitable functional group can be resolved by preparing covalent or ionic diastereomeric derivatives followed by fractional crystallisation and chemical cleavage of the optically resolved diastereomer as described by Phillips<sup>4</sup> in the first paper to appear on optical activity in sulphoxides. A variation of this approach is the oxidation of a sulphide containing an asymmetric center in the molecule so that the pair of diastereomers obtained by oxidation can be directly separated by crystallisation.<sup>5</sup> Asymmetric oxidation of sulphides by fermentation using growing aerobic cultures of *Aspergillus niger* have been reported to yield sulphoxides of variable optical purity,<sup>6</sup> while chemical oxidations with optically active peracids generally lead to low optical purity<sup>7</sup> and are hardly a useful preparative method. We now can report on a stereoselective oxidation of a class of sulphides which leads to sulphoxides of high optical purity.

In our original structural studies<sup>8</sup> on 8-hydroxy-5-methyldihydrothiazolo [3,2-a]pyridinium-3-carboxylate (I) we noticed that the oxidation of I with hydrogen peroxide in formic acid leads to a diastereomeric sulphoxide ratio of 9:1. The course of the reaction can be followed by paper chromatography when the two diastereomers are separated and can be seen as blue fluorescent spots in UV light. The reaction, carried out at room temperature, is essentially complete after one hour. In acetic acid the reaction was exceedingly slow and when forced by heating gave rise to the decarboxylated sulphoxide III. Excess sodium metaperiodate in cold aqueous solution for one week gave similar results.



The rate of oxidation in trifluoroacetic acid was as in formic acid. Addition of perchloric acid to formic acid reduced the time for the completion of the oxidation from 60 to 15 min. With perchloric acid in acetic acid the time required was 3 h while in aqueous solution only 50 % of the thioether had reacted after 4 h. The oxidation in methanesulphonic acid, a solvent recommended for the preparation of peracids,<sup>9</sup> required only 5 min. When the performic acid was largely pregenerated by addition of hydrogen peroxide to the formic acid 5–6 h before the sulphide, the reaction time at room temperature was reduced to about 15 min. The rate of oxidation showed the expected rate increase with temperature. At 60° in formic acid the reaction was complete in 10 min, at 90° in 5 min. The isomer ratio was invariably 9:1 which indicates that reaction takes place by the same or similar mechanisms. The observed rate differences follow roughly the expected rate differences for the formation of peracids.<sup>10</sup> In methanesulphonic acid no other carboxylic acid is present than the carboxyl group in the molecule to be oxidized which therefore could participate in the reaction.

Oxidation of the bromo derivative (VII) in formic acid gave the same sulphoxide isomer ratio as in the case of the acid (I) above. The major isomer was readily purified by fractional crystallisation. If steric approach control caused by the carboxy group is important, *i.e.* if the peracid attacks the sulphur from the side of the ring opposite to the carboxy group, a *trans* substituent on the C<sub>2</sub>-carbon might be expected to affect the isomer ratio. Therefore the *trans*-2-methyl derivative<sup>11</sup> (IX) was oxidized as above. However, the sulphoxide product consisted of 90–95 % of the one isomer, most likely the *cis* isomer. The amide (V) should not be able to form a peracid intermediate as is possible for the acid derivatives. Therefore the steric importance of the amido group should become evident from the relative dominance of the *trans* isomer formed. The isomer ratio observed was 3:2.

The isomers were readily separated by fractional crystallization. The major isomer was hydrolysed to the corresponding acid (II) without isomerisation of the sulphoxide group, by diazotisation with nitrous acid. In this way the major component was found identical with the major acid sulphoxide component, the opposite of what was to be expected for steric approach control.

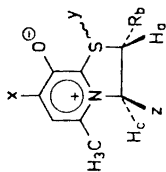
The studies of the reaction rate and isomer composition were done on the DL- form of the acid (I) since this is synthetically readily available.<sup>11</sup> The amide was made by aminolysis of the corresponding methyl ester<sup>11</sup> or by treatment of the corresponding nitrile<sup>11</sup> with ammonia.

The NMR spectra of the compounds studied are given in Table 1. The protons of the thiazoline ring resonate in an ABX system. The methine-proton of the bromo acid (VIII) is found as a doublet at 3.40  $\tau$ , the methylene protons as a sextet at 5.45 and 5.85  $\tau$ . The proton at the higher value appears in a quartet,  $J_{vic}=7.5$  and  $J_{gem}=14.5$  cps. Since the thiazoline ring is nearly planar,  $J_{vic}=7.5$  cps must be ascribed to *cis* protons while  $J_{vic}=0$  cps must be due to *trans* protons. Therefore as shown in Table 1 H<sub>a</sub> resonates at 5.45, H<sub>b</sub> at 5.85 and H<sub>c</sub> at 3.40  $\tau$ . The major isomer of the sulphoxide (II) had a very similar NMR spectrum. The amide sulphoxide isomers (VI) show marked differences in the methylene region. The major isomer has these protons resonating in a sextet as the acids above. In the other isomer these protons were found in what appears to be a fairly compressed doublet or triplet centered at 5.73  $\tau$ . These protons therefore have about the same chemical shifts. The spectrum is very similar to those of the unoxidized thioethers (I, VII, V). In the *trans* methyl derivative (X) the same marked downfield shift of the 2a-proton is seen as in the major isomer series and therefore X has the same stereochemistry.

If the H<sub>a</sub> proton is *cis* both to the carboxyl and the sulphoxide group its chemical shift should be at a lower field than that of the H<sub>b</sub> *trans* proton. In a *trans* sulphoxide configuration it seems more reasonable to expect that the chemical shifts would be nearly the same since both protons now each have one *cis* electronegative group in a neighbouring position.

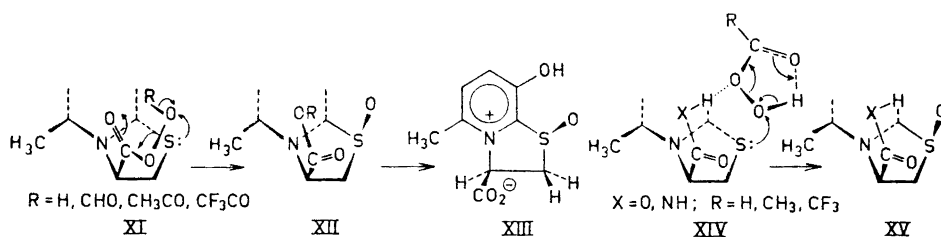
From the NMR data and the chemical evidence above, the major sulphoxide isomers can be assigned a *cis* configuration. The selective *cis* oxidation in the acid derivatives means that the carboxy group participates in the reaction through internal delivery of the peracid group which first becomes

Table 1. NMR spectra in TFA



Comp.	Substituents				Chemical shift in $\tau$							Coupling constants in cps.				
	x	y	z	R	2a	2b	3c	5	6	7	$J_{ab}$	$J_{ac}$	$J_{bc}$	$J_{6,7}$	$J_{\text{CHr-H}}$	
I	H	—	CO <sub>2</sub> H	H	5.73	—	3.67	7.22	2.58	2.15	—	0	—	9.0	—	
II	H	O	CO <sub>2</sub> H	H	5.48	5.88	3.32	7.02	1.90	1.60	14.5	0	7.05	9.0	—	
VII	Br	—	CO <sub>2</sub> H	H	5.72	—	3.73	7.25	2.30	—	—	—	—	—	—	
VIII	Br	O	CO <sub>2</sub> H	H	5.45	5.85	3.40	7.07	1.63	—	14.5	0	7.5	—	—	
V	H	—	CONH <sub>2</sub>	H	5.88	5.63	3.67	7.30	2.62	2.25	13.0	2.0	8.0	—	—	
VI cis	H	O	CONH <sub>2</sub>	H	5.32	5.78	3.28	7.05	2.00	1.85	14.5	0	7.5	9.0	—	
VI trans	H	O	CONH <sub>2</sub>	H	5.73	—	3.40	7.10	1.92	1.65	—	—	—	9.0	—	
IX	H	—	CO <sub>2</sub> H	CH <sub>3</sub>	5.30	8.25	4.05	7.22	2.53	2.20	—	—	—	—	—	
X	H	O	CO <sub>2</sub> H	CH <sub>3</sub>	5.18	8.4	3.67	7.07	1.85	1.58	—	0	—	9.0	8.0	
IV	H	—	H	H	6.17	—	4.90	7.28	2.68	2.35	—	—	8.0	9.0	—	
III	H	O	H	H	5.98	—	4.38	7.03	2.00	1.68	—	—	8.0	9.0	—	

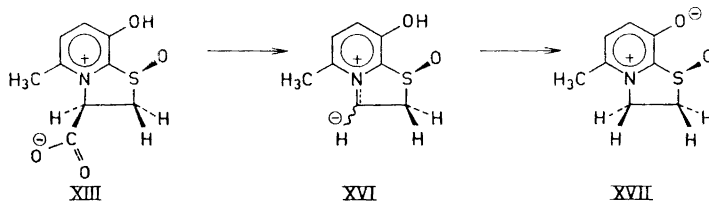
attached to the carboxy group. The latter could be oxidized to a peracid or form an acyl peroxide with the peracid used. Since sulphoxide formation involves a nucleophilic attack by sulphur onto the peroxide oxygen involving a concerted electronic displacement,<sup>12</sup> the peroxy group in XI would be correctly spaced for intramolecular *cis* oxidation of the sulphur. This explanation, however, must be excluded in the case of the amide (VI). A more likely explanation, therefore, is an association due to hydrogen bonding between the carboxy group and the peracid (XIV) favourable for interaction between the electrophilic peracid oxygen and the sulphur atom on the side of the carboxy group. In the case of the amide this association must be weaker than in the carboxy derivatives because of the difference in isomer ratios observed.



The expected rate promoting effect by the carboxy group in such a mechanism seems balanced by the electronic deactivation by the carboxy group since all compounds including the decarboxy derivative (IV) were oxidized at similar rates.

Jonsson<sup>13</sup> has very recently shown that dihydrothionaphthalene-3-carboxylic acid gives almost pure *trans*-product with hydrogen peroxide and sodium metaperiodate. A mechanism which involves attack from the structurally less hindered side opposite to the carboxyl group is proposed. Dinitrogen tetroxide was found to give mainly the *cis*-isomer explained by a dinitrogen tetroxide complex with the sulphide.

Removal of the original asymmetric carbon center at the 3-position in the pure diastereomeric sulfoxide (XIII) by decarboxylation should lead to an optically pure sulfoxide enantiomer. To effect the decarboxylation, the sulfoxide should be present in the zwitterionic form (XIII) shown below. A weak acid such as acetic acid was therefore chosen.



Thus heating XIII in acetic acid at 60° quickly furnished the sulfoxide enantiomer (XVII) the racemic form of which was prepared by performic

acid oxidation of the thioether (IV). In stronger acids such as formic acid and dilute HCl little or no decarboxylation occurred, explained by protonation of the carboxylate group.

The very mild conditions used to effect decarboxylation would not be expected to racemize the sulphoxide.<sup>2b,14</sup> It was crystallized as the perchlorate from water,  $[\alpha]_D^{20} = +260$  (H<sub>2</sub>O); recalculated for free base this corresponds to  $[\alpha]_D = +402^\circ$ .

The optically active acid (I),  $[\alpha] = -130$  (NaOH), used in this work, is not absolutely optically pure.<sup>15</sup> It can be synthesized from L-cysteine<sup>16</sup> and therefore has the *R*-configuration. The reaction mechanism outlined above demands that the *cis* sulphoxide at the sulphur should have the (*S*)-configuration, and therefore the sulphoxide (XIII) has the (1*S*,3*R*) configuration. The decarboxylated sulphoxide (XVII) therefore has the (*S*)-configuration.

However, as there might be some ambiguity attached to the assignment of the above configuration in the sulphoxides, the final conclusion must await the results from X-ray analysis.

#### EXPERIMENTAL

Paper chromatography or TLC on silica gel in the systems BuOH:EtOH:NH<sub>3</sub>:H<sub>2</sub>O (4:1:2:1) and BuOH:HOAc:H<sub>2</sub>O (100:22:50) have been used throughout this work.

*Oxidation of L-(-)-8-Hydroxy-5-methyl-dihydrothiazolo[3,2-a]pyridinium-3-carboxylate.*  
a) The title compound<sup>16</sup> (1.65 g, 0.075 mole) was dissolved in formic acid (160 ml) and 35 % hydrogen peroxide (0.15 mole) added. The solution was left in the cold overnight. Paper chromatography in the acetic acid system showed the reaction product to consist of two components, *R<sub>F</sub>* at 0.11 and 0.14, in the relative ratio 9:1 for convenience named the  $\alpha$ -form and the  $\beta$ -form, respectively. The formic acid was evaporated at reduced pressure below 40° to prevent decomposition. The residual oily material was dissolved in water (30 ml) and left in the cold. A greyish-white solid (0.50 g) was obtained, m.p. 165° (decomp.). Chromatography showed this to be the pure  $\alpha$ -form. The filtrate was then diluted with ethanol (30 ml) and left in the cold. Another 0.70 g of the pure  $\alpha$ -form was obtained. Evaporation of the filtrate, redissolution in water (5 ml) and addition of ethanol (5 ml) produced another 0.10 g of the pure  $\alpha$ -form. Chromatography of the filtrate showed this to contain about equal amounts of the diastereomers. Recrystallisation of the  $\alpha$ -form from water gave m.p. 170° (decomp.).  $[\alpha]_D = +169$  (*c* = 0.2 in water). (Found: C 47.45; H 4.05; N 6.10 Calc. for C<sub>9</sub>H<sub>9</sub>NO<sub>4</sub>S: C 47.56; H 3.99; N 6.17).

b) Sodium metaperiodate: The title compound (0.10 g) was dissolved in an aqueous solution (15 ml) of sodium metaperiodate (0.11 g). After one day at room temperature very little sulphoxide had been formed. Another 1.10 g of sodium metaperiodate was then added gradually over 6 days. The reaction was then complete and the product was largely decarboxylated.

The sulphoxide of the DL-acid (I)<sup>11</sup> was preparatively synthesized as under a). It decomposed in the 170° region as the above diastereomer, but the exact melting point or decomposition point in these sulphoxides is difficult to determine as they decompose gradually on heating.

*7-Bromo-8-hydroxy-5-methyl-1-oxodihydrothiazolo[3,2-a]pyridinium-3-carboxylate (VIII).* 7-Bromo-8-hydroxy-5-methyl-dihydrothiazolo[3,2-a]pyridinium-3-carboxylate<sup>17</sup> (2.9 g, 0.01 mole) was dissolved in formic acid (200 ml) and 35 % H<sub>2</sub>O<sub>2</sub> (2 ml) added. The solution was left at room temperature for 3½ h, evaporated at reduced pressure below 40° and the residual oil dissolved in water (5 ml). Greyish-yellow solid was slowly precipitated; yield 2.4 g (76 %), m.p. 160° (decomp.). Recrystallisation from water gave the pure major isomer, m.p. > 250° (decomp.). (Found: C 34.74; H 2.96; N 4.33. Calc. for C<sub>9</sub>H<sub>8</sub>BrNO<sub>4</sub>S: C 34.67; H 2.63; N 4.58).

Table 2. Rate studies on the oxidation of DL-8-hydroxy-5-methylidihydrothiazolo[3,2-a]-pyridinium-3-carboxylate (0.01 mole) in the solvents below, containing 35 %  $H_2O_2$  (0.2 ml) at room temperature. The time for completion of the reaction and the isomer ratio were determined by paper chromatography.

Solvent, ml	Time in minutes	Isomer ratio $\alpha/\beta$	Remarks
HCO <sub>2</sub> H 20	60	9/1	
TFA 20	60	9/1	
HOAc 20	—		Little or no reaction after 24 h
HOAc 18 HClO <sub>4</sub> 2	180	9/1	
HCO <sub>2</sub> H 18 HClO <sub>4</sub> 2	15	9/1	
H <sub>2</sub> O HClO <sub>4</sub> 2	—		50 % reacted after 4 h
HOAc 18 HCO <sub>2</sub> H 2	—		Very slow. Hardly any product after 24 h
MeSO <sub>2</sub> H 20	5	9/1	

*3-Carboxamido-5-methylidihydrothiazolo[3,2-a]pyridinium-8-oxide (V).* a) 3-Carbo-methoxy-8-hydroxy-5-methylidihydrothiazolo[3,2-a]pyridinium chloride (100 g) was dissolved in anhydrous methanol (2500 ml) and ammonia passed through the refluxing solution for 8 h. Chromatography showed that no reaction had taken place. Water (25 ml) was therefore added to the solution and the solution refluxed for another 8 h while ammonia was bubbled through the solution. Chromatography after 3 h showed that about 70 % of the ester had been converted to the amide. Concentrating the solution to about 800 ml precipitated the amide (30.7 g), m.p. 260, which after recrystallisation from water melted at 270° (decomp.). (Found: C 51.01; H 4.80; N 13.45; S 15.50. Calc. for C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>S: C 51.41; H 4.79; N 13.32; S 15.22).

b) 3-Cyano-5-methylidihydrothiazolo[3,2-a]pyridinium-8-oxide hydrobromide<sup>11</sup> (1.1 g, 0.004 mole) was dissolved in 0.88 aq. NH<sub>3</sub>. After standing for 3 days at room temperature the precipitated amide (0.68 g, 85 %) was collected. The precipitated material was chromatographically pure.

When the methyl ester of the L-acid was heated with ammonia as above the amide obtained was completely racemised.

*3-Carboxamido-5-methyl-1-oxodihydrothiazolo[3,2-a]pyridinium-8-oxide (VI).* 30 % Hydrogen peroxide (17 ml, 0.15 mole) was added at room temperature to a solution of 3-carboxamido-5-methylidihydrothiazolo[3,2-a]pyridinium-8-oxide (22.0 g, 0.1 mole) in formic acid (400 ml). The temperature rose to 35° where it remained for about 1 h. The solution was allowed to stand at room temperature overnight and evaporated at 30–35° at reduced pressure, leaving a pale yellow oil. Chromatography (BuOH:AcOH:H<sub>2</sub>O, 100:22:50) showed an intensity ratio of 3:2 for the two fluorescent spots ( $R_F=0.19$  and 0.25) obtained. This material was dissolved in water (70 ml) and the solution left in the cold overnight. Whitish solid (4.4 g), m.p. 260–65° (decomp.)

was obtained. Chromatography showed this to be 90–95 % of the isomer with  $R_F=0.19$ . Addition of ethanol (70 ml) to the filtrate slowly precipitated more solid with the above composition (7.1 g), m.p. 255–65° (decomp.). The combined fractions were recrystallized (by heating to 70°) from water (350 ml); yield 7.1 g, m.p. 255–75° (decomp.). Chromatography showed this to be practical pure isomer with  $R_F=0.19$ . (Found: C 47.55; H 4.53; N 12.50. Calc. for  $C_9H_{10}N_2O_3S$ : C 47.77; H 4.45; N 12.35).

The other sulphoxide isomer could be obtained by concentrating the filtrates and repeated recrystallisation of the solid precipitated, m.p. 275° (decomp.).

*Hydrolysis of the amide sulphoxide (VI)*. Sodium nitrite (0.11 g, 0.0015 mole) was added in small portions over 20 min to a stirred solution of the  $\alpha$ -form of the amide sulphoxide (VI) (0.17 g, 0.00075 mole) in water (1.7 ml), acetic acid (3 ml) and sulphuric acid (2.1 ml) at 0–5°. After the addition was completed, the reaction was stirred for another 90 min at this temperature. The solution was then diluted with water (40 ml), extracted with 90 % phenol (3×11 ml), the phenol extracts washed with water, ether (100 ml) added, the ethereal solution extracted with water (3×20 ml), the aqueous extracts washed with ether to remove any phenol and evaporated. The residual oil (0.13 g) was dissolved in water (3 ml) and some isopropanol added when the  $\alpha$ -form of the acid sulphoxide crystallised out.

Chromatography after the hydrolysis showed only the presence of the  $\alpha$ -form.

*Oxidation of DL-trans-2,5-dimethyl-8-hydroxydihydrothiazolo[3,2-a]pyridinium-3-carboxylate (IX)*. The title compound (1.1 g, 0.005 mole) was dissolved in formic acid (100 ml) and 35 % hydrogen peroxide (1 ml) added. The solution was left at room temperature overnight, evaporated at reduced pressure below 35–40° and the residual oil dissolved in water (10 ml). As no precipitate was formed, ethanol (10 ml) was added. Some of the sulphoxide (0.11 g) was slowly precipitated, m.p. 125° (decomp.). Addition of ethanol (20 ml) to the filtrate furnished another crop of the sulphoxide (0.40 g). (Found: C 49.55; H 4.73; N 5.55. Calc. for  $C_{10}H_{11}NO_5S$ : C 49.78; H 4.60; N 5.81).

Chromatography of the reaction mixture showed that the oxidation was essentially completed after 60 min and that the sulphoxide formed consisted of 90–95 % of the one isomer.

*DL-8-Hydroxy-5-methyl-1-oxodihydrothiazolo[3,2-a]pyridinium perchlorate (III)*. 5-Methyl-dihydrothiazolo[3,2-a]pyridinium-8-oxide (5.0 g, 0.03 mole) was dissolved in formic acid (460 ml) and 30 % hydrogen peroxide (5.1 ml, 0.045 mole) added. The solution was left at room temperature for 1 h when chromatography showed the reaction to be complete. After evaporation to dryness at reduced pressure at 20–25° the gummy residue was dried *in vacuo* overnight. As the oily material did not solidify it was dissolved in water (7 ml) and 70 % perchloric acid (3.6 ml, 0.033 mole) added. Standing in the cold precipitated a solid (4.8 g, 48 %), m.p. 168–70° (decomp.). The white crystalline perchlorate after 3 recrystallisations from water had m.p. 168–72° (decomp.). (Found: C 34.14; H 3.85; N 5.10; S 11.23. Calc. for  $C_8H_{10}ClNO_6S$ : C 33.87; H. 3.55; N 4.94; S 11.31).

Behaviour in acetic acid: Part of this material was heated for 3 h at 60° in acetic acid. Chromatography showed only traces of degradation products formed.

(+)-8-Hydroxy-5-methyl-1-oxodihydrothiazolo[3,2-a]pyridinium perchlorate (XVII). The  $\alpha$ -isomer from the sulphoxide of the L-acid (1.0 g, 0.0046 mole) was added to acetic acid (100 ml) and the reaction stirred at 60° for 1 h. The solution was then treated with a little charcoal, filtered and the filtrate evaporated. 0.9 g of the residue was dissolved in water (5 ml) and 70 % perchloric acid added dropwise to pH 1. The solution was concentrated to about 1 ml and left in the cold. The crystalline solid (0.57 g) obtained decomposed in the region 190–207°.  $[\alpha]_D^{20} = +260$  ( $c=1.9$  in  $H_2O$ ). Calculated for free base this corresponds to  $[\alpha]_D = +402$ .

Chromatography showed this product to be the same as the above sulphoxide (III).

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